MBSR During AI Therapy for Breast Cancer
NCT03253627

Protocol

11-16-2021

MINDFULNESS-BASED STRESS REDUCTION TO IMPROVE COGNITIVE FUNCTION DURING AROMATASE INHIBITOR THERAPY

A pilot, single-center randomized controlled trial of the preliminary efficacy of an eight-week, group-based Mindfulness-Based Stress Reduction intervention versus Health Enhancement Program active control to improve neural markers of changes in cognitive function in postmenopausal women receiving aromatase inhibitor therapy for breast cancer.

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
AI	Aromatase Inhibitor
BOLD	Blood-Oxygen-Level-Dependent
CFR	Code of Federal Regulations
CRF	Case Report Form
DE	Differential Expression
dMRI	Diffusion MRI
DTI	Diffusion Tensor Imaging
DNA	Deoxyribonucleic Acid
DCIS	Ductal Carcinoma In Situ
EDTA	Ethylenediaminetetraacetic Acid
FA	Fractional Anisotropy
FFR	Federal Financial Report
fMRI	Functional MRI
fcMRI	Functional Connectivity MRI
GCP	Good Clinical Practice
HEP	Health Enhancement Program
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MBSR	Mindfulness-Based Stress Reduction
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
N	Number (typically refers to participants)
NIH	National Institutes of Health
NINR	National Institute of Nursing Research
NYU	New York University
OHRP	Office for Human Research Protections
PI	Principal Investigator
PROs	Patient-Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
QC	Quality Control
RNA	Ribonucleic Acid
RNA-Seq	RNA Sequencing
ROI	Region of Interest

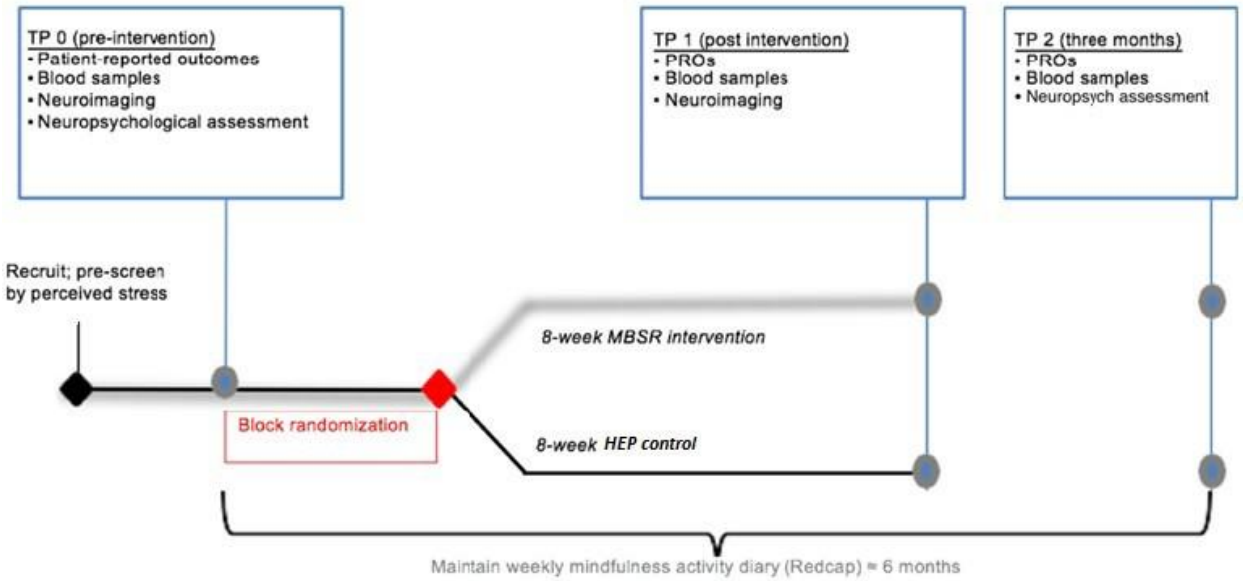
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences
US	United States

Protocol Summary

Title	Mindfulness-Based Stress Reduction To Improve Cognitive Function During Aromatase Inhibitor Therapy
Short Title	NA
Brief Summary	This study will use non-invasive neuroimaging (i.e., MRI) to examine whether Mindfulness-Based Stress Reduction (MBSR) improves neural markers of changes in cognitive function for postmenopausal women taking aromatase inhibitor (AI) therapy for breast cancer. The pilot randomized controlled trial will obtain preliminary efficacy of MBSR versus Health Enhancement Program (HEP) active control to improve neural markers of changes in cognitive function. The final sample will include 32 postmenopausal women with breast cancer. MBSR and HEP groups will meet for a matched schedule of 8 weekly 2.5-hour sessions and a one-day weekend retreat. Specimen and data collection will be done at three time points: pre-randomization (i.e., within three weeks before beginning the intervention), within three weeks after completion of the intervention, and approximately three months (+/- 1.5 weeks) post intervention. To obtain effect sizes, change scores for neuroimaging parameter estimates will be correlated with change scores for measures of neuropsychological function and affect. Differential expression of genes will be associated with change scores in neuroimaging parameter estimates.
Phase	Preliminary efficacy
Objectives	The **primary aim** is to (1) evaluate the preliminary efficacy of MBSR to improve neural markers of changes in cognitive function during AI therapy. The **exploratory, hypothesis generating aims** are to (2) describe relationships between neural markers and (a) neuropsychological function and (b) affect during MBSR; and (3) explore the moderating effect of inter-individual differences in the expression of genes involved in stress responses on neural markers of changes in cognitive function during MBSR.
Methodology	Single blind, randomized controlled trial
Endpoint	Primary endpoint: Changes in neural markers of cognitive function Exploratory endpoints: Changes in neuropsychological function and affect; moderating effect of differential expression of genes involved in stress responses
Study Duration	Three years
Participant Duration	Approximately seven months
Duration of behavioral intervention	Eight weeks
Population	Postmenopausal women with breast cancer in the New York City metropolitan area, aged 18-79
Study Sites	New York University (NYU Langone Health Perlmutter Cancer Center, Bluestone Center for Clinical Research, New York University Center for Brain Imaging)
Number of participants	40 enrolled, with 32 evaluable participants

Description of Study Intervention/Procedure	The MBSR group will receive training from a trained instructor during a group-based, 2.5-hour manualized educational activity weekly for eight weeks. Activities include body scans, gentle stretching, yoga, and mindful awareness. Participants will be asked to complete daily 45-minute mindfulness activities on days the group does not meet and a one-day weekend retreat (approximately 7 hours) to reinforce learning. The HEP group, which was developed to serve as an active control for MBSR, will receive manualized health education in physical activity, functional movement, music therapy, and nutrition—without mindfulness instruction—using similar modalities for a matched schedule with the same time requirements.
Reference Therapy	NA
Key Procedures	Functional and structural brain imaging, neuropsychological testing, patient-reported outcomes, and blood draws
Statistical Analysis	See statistical analysis plan (SAP). A formal SAP will be developed for this study in consultation with the study biostatistician. Only a general overview of study statistics is included in this protocol.

Schematic of Study Design



Note: Informed consent will be obtained after recruitment before any study procedures begin. Of the 32 subjects recruited with analyzable data, 16 will be randomly assigned to the MBSR group and 16 to the HEP group in a permuted block design, stratified by receipt of chemotherapy (i.e., two strata). Up to 40 participants will be recruited to reach this goal. See Table A (Schedule of Events) for details of specific assessments and specimens collected at each time point, as well as the intervention timeline.

1 Key Roles

John Merriman, PhD, RN, Assistant Professor
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Principal Investigator: Dr. Merriman will direct and oversee all aspects of the R00 study, ensuring that study procedures are implemented and maintained for the enrollment of participants, form development, collection of data, data management, and budget maintenance. He will have primary responsibility for oversight of data analysis, preparation of manuscripts, and the submission of annual and final reports.

Bradley Aouizerat, PhD, Professor
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Other Significant Contributor: Dr. Aouizerat is an internationally recognized expert in the fields of molecular epidemiology and molecular biology, both in laboratory methods and statistical analytic methodologies, particularly in the area of symptom management science. Dr. Aouizerat, who has collaborated productively with Dr. Merriman since 2009, will provide in-depth guidance on best practices in biospecimen handling, storage, and processing. He is the Director of the Bluestone Center for Clinical Research Biospecimen Bank, where the samples will be stored for the proposed project. He will provide guidance with respect to the planned gene expression analyses and provide Dr. Merriman access to his laboratory (for biospecimen processing) and research staff for the performance of gene expression data analyses. He will contribute to the dissemination of study findings.

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Other Significant Contributor: Dr. Fletcher is a biostatistician with more than 15 years of experience conducting evaluation research in the fields of community and public health. His methodological interests include item-response theory, differential item analysis, multilevel modeling, and analysis of longitudinal data. His substantive interests include health disparities and chronic disease. He will provide overall guidance for the planned analyses and will contribute to the dissemination of study findings.

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Other Significant Contributor: Dr. Hammer is Director of Research and Evidence-Based Practice at Mount Sinai Hospital and Adjunct Associate Professor at the College of Nursing. Her research on the role of inflammation in cancer symptoms is informative for the R00 study.

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Other Significant Contributor: Dr. Kwa is an expert in medical oncology for postmenopausal women with breast cancer. She interacts with patients at Bellevue Hospital Center and Perlmutter Cancer Center who may be potential participants in this study, and she will contribute to dissemination.

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Other Significant Contributor: Dr. Melkus is the Florence and William Downs Professor in Nursing Research, Associate Dean for Research, and Director of the Muriel and Virginia Pless Center for Nursing Research. Her expertise in conducting behavioral intervention research and serving as a career development mentor to many rising early-career scientists will benefit Dr. Merriman in the conduct of the R00 study.

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Other Significant Contributor: Dr. Milad is Director of the Behavioral Neuroscience Program and manages a neuroimaging analytic core lab for NYU School of Medicine. Exploratory neuroimaging data analyses will be conducted in the core lab.

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Other Significant Contributor: Dr. Shallcross is an expert in mindfulness-based interventions and has expertise in recruiting for behavioral interventions at the NYU Perlmutter Cancer Center.

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Other Significant Contributor: Dr. Wen is a Postdoctoral Scholar in the NYU School of Medicine under the mentorship of Dr. Mohammed Milad. Dr. Wen will collaborate with the study team for neuroimaging data analysis.

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Significance

Approximately 3.1 million breast cancer survivors are alive today.[30] Among women with hormone-receptor positive breast cancer, which accounts for 75% of cases, aromatase inhibitor (AI) therapy improves disease-free and overall survival for postmenopausal women.[1] It is typically prescribed for at least five years after surgery.[1] Symptoms experienced during this extended therapy may include **changes in cognitive function**, such as difficulty with concentration and recall.[31] These symptoms may negatively affect quality of life and ability to adhere to prescribed therapy.[32] For example, poorer attention (i.e., ability to maintain concentration) and working memory (i.e., ability to retain information for seconds or minutes to work with it) negatively impact meaningful activities such as work, achieving personal goals, and social interactions.[33-35]

AI therapy blocks conversion of androgens to estrogen through the enzyme aromatase, which is the primary source of estrogen for postmenopausal women.[1] Estrogen promotes neural and synaptic plasticity, which contributes to growth and maintenance of neurons and white matter tracts that connect them.[36,37] Objectively and subjectively measured changes in cognitive function associated with AI therapy could be mediated through changes in neural structure and function (i.e., **neural markers of cognitive changes**) due to AI-therapy induced estrogen deprivation.[7,38-40] Co-occurring **changes in affect** may be associated with cognitive changes and underlying neural markers of cognitive changes.[10,11,41] See Figure 1.

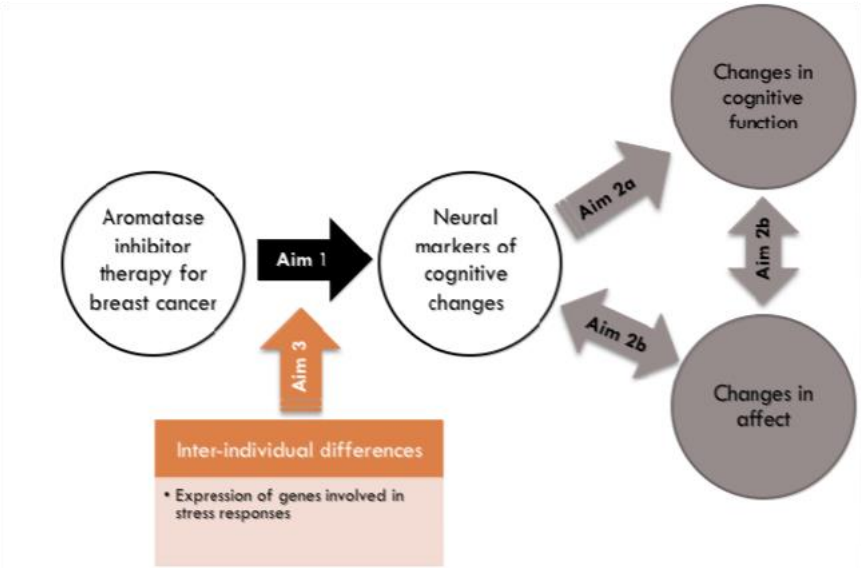

Figure 1. Relationships evaluated in the R00 study in the context of the mindfulness-based stress reduction intervention (Part II-aim 1 and exploratory aims 2a, 2b and 3)

Neural markers bridge variable findings of objective and subjective changes in cognitive function and changes in affect. For example, one functional magnetic resonance imaging (fMRI) study found lower than normal activity in the bilateral posterior parietal cortices during attention tasks in women ten years after chemotherapy plus tamoxifen, a selective estrogen receptor modulator endocrine therapy agent, compared to women with a history of breast cancer treated without chemotherapy or anti-estrogen therapy.[42] Women who received systemic therapy responded more quickly during these tasks, which reduced their accuracy and effectiveness.[42] A similar association was found in an fMRI study of women three years after chemotherapy with or without tamoxifen compared to women without breast cancer.[43] In this study, women had reduced prefrontal cortical activation during a memory encoding task but increased activity in the same brain region during memory recall.[43] In addition, they showed poorer attention, as evidenced by greater response impulsivity.[43] The researchers hypothesized that poorer attention reduced the ability to encode memories

successfully so that greater effort was needed to retrieve these poorly encoded memories.[43] The unique contribution of anti-estrogen therapy to cognitive changes in both studies was not testable, so it is unclear whether the findings were related to chemotherapy, anti-estrogen therapy, or their combination. These findings suggest that poorer attention is closely related to poorer function in other cognitive domains (slower performance, impaired memory), and that deficits may be explained by neural markers.

Relationships between AI therapy and neural markers of cognitive changes may be moderated by **inter-individual differences** in expression of genes involved in stress responses (e.g., inflammation pathways).[44] Peripheral inflammation is communicated to the brain through the vagus nerve.[45,46] In response, microglial cells in the brain produce inflammatory cytokines.[45] Central cytokines may damage neurons and neuroglia by inducing oxidative stress.[47] Damage may be less likely to be repaired due to AI-induced estrogen deprivation.

Mindfulness-based stress reduction (MBSR) is a well-tested intervention in the general population for improving stress-related outcomes.[48] Its use has been linked to neural markers associated with stress.[49] Inter-individual variability in the expression of genes involved in stress responses could moderate relationships between MBSR and neural markers during AI therapy.[50,51] Neural markers of changes in cognitive function may correspond to improved self-report and neuropsychological measures of cognitive function. Although neural deficits have been shown to improve in stressed adult populations using MBSR,[25,28] it is not known whether the intervention improves neural deficits in women taking AI therapy, which may reduce neural plasticity.

Summary. AI therapy may result in changes in cognitive function. Neural markers of cognitive changes may underlie changes in cognitive function and affect. Inter-individual differences in stress responses may be associated with variability in neural markers. The R00 study will test preliminary efficacy of an intervention targeted at modifiable stress responses to improve neural markers of changes in cognitive function during AI therapy.

Innovation

The R00 study appears to be the first to evaluate neural markers of cognitive changes in women undergoing AI therapy during an MBSR intervention targeting stress responses. Neural markers may bridge gaps in understanding of how stress reduction interventions impact more distal objective and subjective measures of cognitive function. Because cognitive function and affect are closely linked, the study will incorporate emotion processing into the cognitive neuroimaging task. Although a previous study found a significant relationship between worry and cognitive function,[10] no studies have described neural markers using a task that engages cognitive and emotion processing simultaneously in the context of a stress-reduction intervention. The R00 study will integrate genomics and neuroimaging by evaluating the moderating relationship of inter-individual differences in the expression of genes involved in stress responses on variability in neural markers.

2.2 Rationale

Adjuvant AI therapy improves disease-free and overall survival for postmenopausal women after surgery for hormone receptor-positive breast cancer.[1] Among symptoms associated with AI therapy are changes in cognitive function.[2,3] Up to 25% of postmenopausal women with breast cancer report that they experience changes in cognitive function during AI therapy.[4-7] Studies using neuropsychological tests found subtle deteriorations in verbal[2,8] and visual[2] learning and memory—as well as concentration, working memory, and executive function—for as many as a third of these patients.[9] Changes in cognitive function may be associated with changes in affect (e.g., worry,[10] depressive symptoms[7,11]). Neural markers of cognitive changes, including changes in brain function and structure, may underlie changes in cognitive function.

The investigators' recent preliminary neuroimaging work[52] to describe neural markers of cognitive changes suggests that postmenopausal women with breast cancer have inefficient cognitive-emotion processing before AI therapy, as evidenced by greater neural activity in the hippocampus (working memory) and amygdala (emotion processing) during task performance compared to controls. During AI therapy, patients show differential activation compared to controls in the dorsolateral prefrontal cortex (executive function and working memory), medial prefrontal cortices (cortical control of amygdala responses), and hippocampus.

In previous work by our group looking at changes in neuropsychological performance with AI therapy,[9] we found that, compared to controls, postmenopausal women in the first 18 months of AI therapy (a) declined in working memory and concentration performance in the first six months, recovered to baseline (i.e., pre-AI therapy) levels by one year and then had a second decline in performance in these cognitive domains through 18 months; and (b) had poorer executive function performance pre-AI therapy, then improved in executive function performance in the first six months of therapy, which matched performance improvements by controls. However, women on AI therapy then remained flat in their performance while controls continued to improve (possibly due to practice effects) through 18 months.

Taken together, women with breast cancer experienced poorer cognitive performance in some cognitive domains before AI therapy; in other cognitive domains they experienced a pattern of decline, recovery, and then a second decline. It is unclear what happens after 18 months, but other groups have noted that some women have persistent cognitive problems. These patterns of neuropsychological performance suggest that it is important to intervene before AI therapy and later in AI therapy. Since the therapy is at least 5 years, with some women receiving therapy for 10 years, intervening in the first 18 months may prevent or alleviate long-term cognitive problems.

Stress responses could partially explain relationships between AI therapy and neural markers of cognitive changes. The Mindfulness Stress-Buffering Account suggests that interventions such as Mindfulness-Based Stress Reduction (MBSR) may improve stress responses by attenuating negative appraisals of stress and reducing reactivity to stressful situations.[12] For example, mindfulness meditation improved psychological stress responses in women with breast cancer.[13-20] It improved some measures of cognitive function.[21-23] Mindfulness practices reduced physiological markers of stress responses, including inflammatory markers in women with breast cancer[13,20,24] and in stressed community adults,[25] as well as cortisol reactivity for breast cancer survivors[26] and during chemotherapy for colorectal cancer.[27] Although similar neural deficits as the investigators found in the investigators' preliminary work have been shown to improve in stressed adult populations using MBSR,[25,28] it is not known whether the intervention improves neural deficits in women taking AI therapy (estrogen, production of which is blocked by AI therapy, is neuroprotective and promotes neural plasticity[30,31]). Genetic variability was previously found to moderate the effect of MBSR on self-reported cognitive function.[29] Therefore, it is possible that inter-individual variability in the expression of genes involved in stress responses could moderate relationships between AI therapy and neural markers of cognitive changes during MBSR. Taken together, MBSR may improve neural markers of cognitive changes shown in preliminary work to be deficient in postmenopausal women before and during AI therapy for breast cancer by targeting stress responses. Neural markers of changes in cognitive function may correspond to improved self-reported cognitive function and neuropsychological function, as well as improved affect.

Hypothesis: Stress reduction, moderated by gene expression, blunts the impact of AI therapy on neural markers of changes in cognitive function, thereby improving cognitive function and affect in women with breast cancer.

2.3 Potential Risks & Benefits

2.3.1 Known Potential Risks

This study involves no more than minimal risk, as defined by federal regulations, to research participants. The probability and magnitude of harm or discomfort anticipated for this research are not greater than what the population encounters in daily life or during the performance of physical or psychological examinations or tests. The only alternative to study participation is non-participation. Non-participation will in no way affect the potential participant's medical care. An infrequent risk of study screening, enrollment, or participation is breach of confidentiality. For the MRI scan and neuropsychological testing, common risks include the possibility that participants may become frustrated or fatigued. Infrequently, some participants may become claustrophobic or anxious during a scan, and anxiety may continue even after the scan. Sometimes people feel lightheaded when they sit up after a scan. A clinically significant, unexpected disease or condition might be identified during the MRI scan as an incidental finding. Risks of completion of subjective study measures include fatigue and frustration. Common risks of blood draws include bruising, bleeding, or soreness; infrequent risks include fainting or infection. An infrequent risk of the collection of genomic information is that breach of confidentiality of genomic research data could potentially impact future insurability, employability, and reproduction plans; such a breach might have a

negative impact on family relationships and result in embarrassment. Participating in the group-based intervention may include uncomfortable social interactions for some participants, and participants may become fatigued.

2.3.2 Known Potential Benefits

Subjects may not benefit personally from being in this study. Subjects might experience reduced stress and improvements in health by participating in MBSR or HEP. The investigators hope that findings from this study lead to better understanding in the future about whether and how MBSR and HEP may improve cognitive function in women with breast cancer taking aromatase inhibitors.

3 Objectives and Purpose

The purpose of the **pilot randomized controlled trial** is to obtain preliminary efficacy of an eight-week, group-based MBSR intervention versus HEP active control to improve neural markers of changes in cognitive function in postmenopausal women receiving AI therapy for breast cancer.

3.1 Primary Objective

The **primary aim** is to (1) evaluate the preliminary efficacy of MBSR to improve neural markers of changes in cognitive function during AI therapy.

3.2 Secondary Objectives

The **exploratory, hypothesis generating aims** are to (2) describe relationships between neural markers and (a) cognitive function and (b) affect during MBSR; and (3) explore the moderating effect of inter-individual differences in the expression of genes involved in stress responses on neural markers of changes in cognitive function during MBSR.

4 Study Design and Endpoints

4.1 Description of Study Design

This study is a pilot, single-center randomized controlled trial of the preliminary efficacy of an eight-week, group-based MBSR intervention versus HEP active control (i.e., two groups, parallel design) to improve neural markers of changes in cognitive function in postmenopausal women receiving aromatase inhibitor therapy for breast cancer. Participants will be stratified in a permuted block design by receipt of chemotherapy (i.e., two strata). Data will be collected at up to three time points using a repeated measures design (i.e., pre-intervention, post-intervention, approximately three months after the intervention). The study groups will meet at New York University for MBSR or HEP. Neuropsychological, self-report, and biospecimen data collection will be conducted at the Bluestone Center, Meyers College of Nursing, or the NYU Center for Brain Imaging. Neuroimaging data will be collected at the NYU Center for Brain Imaging. A portion of the retreat will be performed at a teaching kitchen facility that will be used by the HEP trained instructor.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

As this pilot randomized controlled trial is designed to provide preliminary efficacy for a future well-powered R01 application, the primary endpoint (i.e., preliminary efficacy) will be evaluated using effect sizes for neural markers of changes in cognitive function from before to after MBSR versus HEP.

4.2.2 Secondary Study Endpoints

No secondary endpoints.

4.2.3 Exploratory Endpoints

Exploratory endpoints will include correlations between neural markers of changes in cognitive function (or baseline neural markers if no changes are found) and changes in (a) cognitive function from before to

three months after MBSR versus HEP and (b) self-reported affect from before to within three weeks after and three months (+/- three weeks) after the intervention. Exploratory endpoints will also include the moderating effect of inter-individual differences in the expression of genes involved in stress responses on neural markers of changes in cognitive function. Exploratory endpoints were chosen to gain preliminary evidence of relationships between neural markers and objectively and subjectively measured cognitive and affective phenotypes, as well as to gain preliminary evidence for underlying biological mechanisms (i.e., gene expression). See Figure 1 for a graphical representation of these relationships.

5 Study Enrollment and Withdrawal

The R00 study will enroll up to 32 evaluable participants (i.e., 16 per group) for the pilot randomized controlled trial. Up to 40 participants will be enrolled to obtain this final sample size.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1. Willingness and ability to participate in study assessments and the eight-week intervention
2. Female
3. Age 18-79
4. Able to speak and read English
5. Post-menopausal (defined as [A] amenorrhea persisting for an entire year, [B] oophorectomy or ovarian suppression/ablation, or [C] hysterectomy and age greater than 51 years)
6. Diagnosed with stage 0 (i.e., ductal carcinoma in situ [DCIS]) or stage I, II, or III breast cancer
7. Post lumpectomy or mastectomy and any re-excisions
8. Post cytotoxic chemotherapy, if prescribed
9. Taking AI therapy OR scheduled to begin AI therapy by the time of the first follow-up study assessment (i.e., TP1)
10. Written, informed consent

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Metastatic (i.e., stage IV) disease
2. Current diagnosis of a major psychiatric disorder (e.g., schizophrenia, bipolar I disorder)
3. Suicide attempt in the last ten years
4. History of hospitalization or residential treatment for psychiatric illness, eating disorder, or substance abuse within the last two years
5. Current neurological disease (e.g., Parkinson's Disease, dementia)
6. History of head trauma
7. Claustrophobia
8. MRI-incompatible head or neck tattoos
9. Unable to lie on the back
10. MRI-incompatible metal implant*

*If a potential participant reports implanted metal objects, which might be affected by MRI magnets, the study personnel or MRI technologist will screen over the phone or in person to determine whether the potential participant would be safe during the MRI scan. A current list of implants compatible with MRI will be consulted (http://www.mrisafety.com/TheList_search.asp).

5.3 Vulnerable Subjects

No special classes of people who may be considered vulnerable populations (e.g., fetuses, neonates, pregnant women, children less than 16 years of age, prisoners, institutionalized individuals) will be recruited into the study.

5.4 Strategies for Recruitment and Retention

Approximately 640-800 new postmenopausal patients with early-stage breast cancer are seen at the NYU Perlmutter Cancer Center annually. The investigators' target goal of 16 participants with evaluable data recruited in each of years one and two would be a successful recruiting rate of 3%, which is well below

the investigators' success rate of 33% of eligible patients using similar recruiting procedures for the K99 study at the University of Pittsburgh. **Inclusion of Women, Minorities, and Children:** All participants in the R00 study will be women, since breast cancer primarily affects them. Breast cancer in men is rare, accounting for less than 1% of breast cancers in the United States. Moreover, the natural history of male breast cancer is different than in women. No one will be excluded on the basis of race or ethnicity. The target enrollment for minority populations is 14 of the participants. The minority population in New York City is 25% African American, 12% Asian American, <1% Native American/Pacific Islander, and 16% mixed race. The city is 28% Hispanic/Latino of any race. A particular strength of the NYU Perlmutter Cancer Center is its diverse patient population, which includes large multiethnic, international populations comprised of medically underserved and minority women with breast cancer. No children under 18 years of age will be included in the R00 study. Breast cancer under age 21 is extremely rare, with an incidence estimated to be 0.1 per 100,000 women. AI therapy is approved for the adjuvant treatment of postmenopausal women with breast cancer. Therefore, women with breast cancer age 18 and older who meet the inclusion criteria in section 5.1 would be eligible for AI therapy and, thus, would be eligible for participation in the study.

The screening procedures for this study vary based on whether the potential participant is screened (1) directly or (2) after contact initiated via a research registry, DataCore, any form of advertisement (e.g., study flier, NYU Langone Health media services, social media), or referral from a participant in the study. For any recruitment method, the screening script will be followed throughout. It is anticipated that 120 interested potential participants will go through screening procedures and up to 40 will be enrolled to obtain a final evaluable sample size of 32. The explanation for these estimates is that (A) a number of interested participants will be unable to do MRI due to claustrophobia or MRI-incompatible metal implants, and (B) it is anticipated that a number of enrolled participants will have neuroimaging data that is not evaluable (e.g., head movement, image artifacts).

(1) Initial screening procedure for the study if screened directly: If the potential participant meets eligibility criteria as determined during the medical record review (see 5.4.1), the study team member will notify a clinician at the site (i.e., treating physician or that physician's nurse practitioner or physician assistant) of the intent for direct screening. If the clinician approves and the participant agrees to discuss the study, as determined by the clinician, the team member will screen the potential participant in person for eligibility (see final screening procedure below). If the potential participant would prefer, the study team member will call to conduct the screening or send information about the study via email.

(2) Initial screening procedure for the study after contact initiated via a research registry, DataCore, any form of advertisement (e.g., study flier, NYU Langone Health media services, social media), or referral from a participant in the study: Any study advertisements will be approved by the IRB. With clinician approval, study fliers will be posted in clinics. Patients who are interested in the study may contact study staff directly, or their clinicians may refer potential participants to study staff. Additional recruitment methods will include clinical research registries (e.g., Research Match), NYU internal recruitment email, patient letters, identification of potential participants by DataCore and contact through MyChart at NYU Langone Health, NYU Langone Health media services and social media, or referral from patients in the study. After contact is initiated via any of these methods, a study team member will determine eligibility using the final screening procedure below.

Final screening procedure common to either of the above initial screening procedures:
Potential participants must meet screening criteria on the screening form (attached). If the candidate reports an implanted metal object, the study staff or the MRI technologist will conduct further screening according to the script to determine whether the candidate will be safe in the MRI machine before being allowed to begin the study. Candidates are required to be postmenopausal to enroll in the study. However, if the MRI technologist requests a pregnancy screening, the candidate will be required to complete it before enrolling. If the potential participant is not eligible or decides not to participate, reason for ineligibility or refusal will be recorded and the screening form will be destroyed.

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Written, informed consent will be obtained at the initial assessment visit (i.e., TP0) at the Center for Brain Imaging, Meyers College of Nursing, or the Bluestone Center for Clinical Research prior to any study procedures, including study assessments, random assignment, and the intervention. After informed consent, a urine and saliva toxicology screen will be performed at each of the study time points to determine whether controlled substances or alcohol, which might affect results, have recently been consumed by the participant.

Multiple means of contact will be collected for enrolled participants, including email, mailing address, and phone number. Reminders for study visits will be sent via email, if available, or via one of the other means of contact.

5.4.1 Use of DataCore/EPIC Information for Recruitment Purposes

This study will utilize EPIC to identify potential participants. A study team member who already has (or will have been given) access to the medical record will screen for eligibility for the study. The PI and approved study staff (e.g., clinical research coordinator) will have access to these search results. During recruitment windows, medical records of patients with scheduled visits at study sites will be reviewed each workday to identify potential participants scheduled for clinic visits the following workday who meet eligibility criteria contained in the medical record. Data points reviewed will include sex, age, menopausal status, breast cancer diagnosis and staging, comorbidities and previous conditions, surgical history, breast cancer treatment history, and medication use.

Once potential subjects have been identified using EPIC, the study team member will notify the treating physician or that physician's nurse practitioner or physician assistant that they have patients potentially eligible to participate. At that point, either of the following will occur:

- Treating physician or that physician's nurse practitioner or physician assistant agrees to permit study team member to contact potential subjects on their behalf, after the clinician obtains verbal consent from the patient to be contacted as a direct approach (see screening procedure in 5.4)
- The study team will mail the IRB-approved patient letter to potential subjects, or email a flyer through MyChart, if they do not have a scheduled medical appointment after referral to our study by a clinician.
- Provide physician or that physician's nurse practitioner or physician assistant with an advertisement to provide to potential subjects

Study staff will work with DataCore to identify patients who may meet inclusion criteria. Specifically, DataCore will conduct a query in Epic to find potentially eligible patients. Data points to be searched in this query will include age, diagnoses, and medication use. The query will be run after IRB approval and as needed during the course of the study, depending on recruitment rates. Query results will be used solely for identification of patients who may be eligible for the study. Using query results, DataCore will set up an IRB-approved contact message in MyChart for distribution. The recruitment message may be repeatedly sent in MyChart up to two times at two-month intervals. Patients who respond in MyChart that they are interested in the study will be contacted by the study team, who will follow the approved recruitment procedures. The study team will discard contact information from patients who do not meet inclusion criteria or who do not wish to participate in the study. If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

Once contact is made, approved recruitment language (see script) will be used to communicate the reason for the contact, and potential participants will be asked if they are interested in participating in this study. Should the potential participant agree, the study team member will screen the participant for eligibility and provide the potential participant with information regarding next steps. Any recruitment information sent by email will utilize Send Safe email. Should a potential participant decide not to participate, reason for non-participation will be recorded and screening forms will be destroyed by shredding.

If a potential subject requests information regarding opting out of further recruitment for all research, she will be directed to email research-contact-optout@nyumc.org or call 855-777-7858.

5.5 Duration of Study Participation

The duration of study participation after informed consent is approximately seven months, which includes the three assessments (i.e., TP0, TP1, TP2) and the intervention between the TP0 and TP1 assessments. The time between initial screening and the enrollment visit (i.e. TP0) will vary depending on the speed with which a sufficient number of potential participants for randomization is recruited. The investigators plan to recruit in each cycle until a sufficient number of potential participants who meet eligibility criteria are recruited, at which point enrollment visits will be scheduled. Investigators will continue these cycles until the target sample size of evaluable participants is reached.

5.6 Total Number of Participants and Sites

Recruitment will end when 40 participants are enrolled. It is expected that approximately 40 participants will be enrolled to produce 32 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time on request. An investigator may terminate participation in the study if:

- Any adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The participant becomes claustrophobic during an MRI scan.
- The participant sustains a head injury between study visits.
- The participant has an MRI-incompatible metal object implanted between assessment visits (study personnel or an MRI technologist will determine whether any new metal implants will be safe for MRI according to the procedure described in section 5.2).
- The participant fails to attend at least 70% of intervention visits.
- The participant is lost to follow-up.

5.7.2 Handling of Participant Withdrawals or Termination

If a participant cannot be contacted for follow-up using all of the contact information collected, no further efforts will be made to contact the participant and that participant will be considered lost to follow-up. Abrupt termination of participation in the study intervention poses no safety risk to participants. As this study is minimal risk, efforts will not be made to collect safety and efficacy data after withdrawal.

If participants withdraw or are withdrawn from an intervention cycle, additional participants may be added to subsequent cycle(s) to reach recruitment targets for the number of evaluable participants.

Any data and banked specimens collected before withdrawal from the study will be retained for analysis, and no new data will be collected. If the participant requests that data and blood samples be destroyed, all paper records will be shredded, blood samples will be destroyed, and any data already processed into computer files will be removed. However, if results based on the participant's data have been submitted for publication or presentation before the request is made, the results cannot be removed from the publication or presentation.

5.7.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI and NINR, depending on who suspends or terminates the study. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

As this study will evaluate preliminary efficacy, it will not be possible to determine whether the intervention

is efficacious or futile for this population during the study. Circumstances that may warrant temporary suspension or termination or include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable with no immediate feasible plan to compensate

If the study is temporarily suspended, the study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the sponsor and/or IRB.

6 Behavioral/Social Intervention

6.1 Study Behavioral or Social Intervention(s) Description

The MBSR group will receive manualized training in mindfulness activities including body scans, gentle stretching, yoga, and mindful awareness.[48] The HEP control, which was developed to serve as an active control to MBSR, will receive manualized health education in physical activity, functional movement, music therapy, and nutrition—without mindfulness instruction.[56]

6.1.1 Administration of Intervention

MBSR will be administered in person by a trained instructor for eight weekly sessions (approximately 2.5 hours each) and a one-day (approximately 7 hours) retreat. Participants will be asked to complete daily 45-minute mindfulness activities on days the group does not meet to reinforce learning. Homework sessions will be accessible via the Internet or by CD, if preferred by a participant. MBSR activities will include walking meditation, gentle yoga, body scan, and instruction in mindfulness.

The HEP active control consists of manualized activities that will be administered by experts in physical activity, functional movement, music therapy, and nutrition using similar modalities for a matched schedule with the same time requirements. As detailed in the HEP manual, physical activity will include moderate-intensity walking and stretching; functional movement will include balance, stability, and agility; music therapy will include music making, song writing, and imagery; and nutrition will include recommended nutritional intake and how to improve participants' current diets.

The groups will be led by trained instructors who are expert community interventionists and who are contracted as consultants with NYU. The group leaders are contracted for work that they routinely do in the community. The consultants are not engaged in the research activities for this protocol (e.g., collecting data, performing recruitment). The PI and study staff approved by the IRB will oversee the protocol-related activities of the groups. In addition, the IRB-approved research study staff will be on-site during the groups to monitor all activities.

6.1.2 Procedures for Training Interventionists and Monitoring Intervention Fidelity

MBSR instructors have nationally standardized certification requirements, including familiarity with the MBSR manual. HEP instructors are considered experts in the specific health education content to be covered (e.g., nutritionist, physical therapist). Because HEP instructors have no path to certification in the HEP active control condition, the PI will review the specific sections of the HEP intervention manual with each content expert, as appropriate, to establish expectations for intervention fidelity. A study team member who is not blinded to group assignment will record intervention sessions, which will be randomly assessed by that study team member for fidelity to the manualized interventions after each cycle of the study. Specifically, the study team member will review one randomly chosen treatment session from each group (i.e., MBSR, HEP), flag any deviations from the manual, and code any deviations as equivalent or non-equivalent to the intent of the manual. If the total non-equivalent deviations from the manual are greater than 5% of activities, the PI will meet with the interventionist to evaluate the reason for deviation and whether fidelity can be maintained for the next cycle of the study. If it is determined that the interventionist cannot maintain fidelity, a replacement interventionist will be hired.

6.1.3 Assessment of Subject Compliance with Study Intervention

The investigators will track feasibility data, including willingness to complete study measures and retention rates. Participant engagement will be assessed through attendance records for MBSR or HEP sessions, and by percentage of homework completed and mindfulness activities during study participation assessed using REDCap diaries. A link to the weekly REDCap survey will be emailed to participants with a reminder to complete the diary. Participants will not be required to be computer literate or have access to a computer; therefore, if a participant will not have access to REDCap, paper diaries will be provided.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

After written informed consent, participants will complete the baseline assessment (i.e., TP0) and be randomly assigned to the MBSR or HEP group in a permuted block design stratified by receipt of chemotherapy (i.e., two strata). To reduce bias, research staff who assess participants, as well as the PI, will be blinded to group assignment. At regional community centers, the MBSR group will receive training from a trained instructor during a group-based, approximately 2.5-hour manualized educational activity weekly for eight weeks. Participants will be asked to complete daily 45-minute mindfulness activities on days the group does not meet and a one-day weekend retreat (approximately 7 hours) to reinforce learning. HEP, which was developed to serve as an active control to MBSR, will receive manualized health education, without mindfulness instruction, using similar modalities for a matched schedule with the same time requirements. Participant engagement will be assessed through attendance records, and by percentage of homework completed and mindfulness activities during study participation assessed using REDCap diaries. Assessments will be done at three time points (see Figure – MBSR Study Schema): within three weeks pre-randomization (TP0), within three weeks after completion of the intervention (TP1), and three months (+/- 1.5 weeks) post intervention (TP2). Functional and structural brain imaging will be done at the NYU Center for Brain Imaging at TP0 and TP1. Neuropsychological tests and blood draws will be completed at the Bluestone Center for Clinical Research, Meyers College of Nursing, or New York University Center for Brain Imaging at TP0 and TP2. Neuropsychological tests will not be performed at the post-intervention assessment (i.e., TP1) due to likelihood of practice effects at that interval (i.e., two months). Patient-reported outcomes (see Patient-Reported Outcomes below for detail of these study measures) will be assessed at each time point.

Demographic and Clinical Characteristics. Demographic and clinical characteristics will be collected by patient self-report at TP0 and confirmed, when possible, by medical record review. A list of concomitant medications will be collected from participants at each study visit and confirmed, when possible, by medical record review.

MRI. Functional MRI (fMRI) and diffusion MRI (dMRI) scans will be collected at TP0 and TP1 using a 3T Siemens Prisma scanner (Erlangen, Germany). Total time to obtain the neuroimaging scans is approximately one hour at each of these time points. During fMRI, participants will complete the emotional faces n-back (EFNBACK) task,[62] which engages working memory while evaluating the impact of emotional distractors. Participants will complete a resting state fMRI scan (i.e., fcMRI) before the EFNBACK to evaluate the activity of the brain in its default mode.[10,63] dMRI will evaluate white matter integrity.

Neuropsychological Function. Neuropsychological function will be evaluated with a battery of well-validated measures in the NIH Toolbox at TP0 and TP2.[57] Total time to administer these tests is approximately two hours at each of these time points.

Patient-Reported Outcomes. Patient-reported outcomes will be collected at each time point (i.e., TP0, TP1, TP2). Subjective cognitive function will be assessed with the Patient Assessment of Own Functioning Inventory,[58] Attentional Function Index,[33] and PROMIS-Cognitive.[59] Affect will be assessed with the PROMIS measures[60] and subjective measures of worry (i.e., Three-Item Worry Index,[61] Cancer-Specific Worry Index[10]). Fatigue and sleep disturbance will be assessed with the PROMIS measures.[60] Self-reported stress will be assessed with the Perceived Stress Scale.[55] Dispositional mindfulness will be measured with the Mindful Attention Awareness Scale (MAAS).[78] Total time to administer the self-report

measures is approximately 30 minutes.

Blood draws. Blood will be drawn to obtain data on variability in genes and gene products. Universal precautions will be used during blood collection and banking. At each assessment time point (i.e., TP0, TP1, TP2), 5 ml of blood will be drawn using two PaxGene RNA tubes (Qiagen) and 10 ml of blood will be drawn using one or a combination of smaller EDTA tubes, totaling 15 ml (approximately 1 tablespoon) of blood drawn at each assessment time point. If a participant completes the study, 30 ml (approximately 3 tablespoons) of blood will be drawn in total. Blood banked at each time point will be processed in the Aouizerat lab in bulk after data collection. PaxGene RNA tubes are stored at -80°C before RNA processing. EDTA tubes will be subjected to ultra-centrifugation to separate plasma (stored at -80°C) and to collect buffy coats. Cell pellets, which are re-suspended in freezing solution, are isolated from buffy coats prior to storage at -20°C for future use. Biobanked samples will be stored with bar-coded identification labels associated with only each participant's study ID number.

Individual results of study-specific procedures will not be provided to study participants because these procedures are completed for research purposes and are not conducted in CLIA-certified labs. The MRI scans in this study are done to answer research questions and are not the type that are used to reveal medical conditions. However, it is possible that a clinically significant, unexpected disease or condition could be identified during the conduct of the study as an incidental finding. In particular, the MRI technologist, study personnel, and other researchers will be able to view images of participants' brains collected during scanning sessions, and the investigators could detect something unusual. In the unlikely event that the investigators detect an abnormality in a scan, the technologist will refer the scan without the participant's name to a radiologist for further examination as soon as possible. The participant will be contacted should the consulting radiologist recommend further examination. Then the participant and the participant's oncologist or primary care provider will decide if the participant should undergo further examination. The consulting radiologist will be available to this clinician to answer any questions about the findings of the scan.

It is unlikely that study participants will require counseling due to study procedures. However, should a participant express distress indicating the need for counseling, even if that distress is unrelated to study participation, the participant will be referred to a psychologist for further evaluation. If a participant asks for counseling resources but is not expressing distress, local counseling resources will be provided.

Study intervention adherence will be assessed as detailed in section 6.1.3.

7.1.2 Standard of Care Study Procedures

Not applicable

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Not applicable

7.2.2 Other Assays or Procedures

See section 7.1.1 for MRI procedures.

7.2.3 Specimen Preparation, Handling, and Storage

All procedures will be performed in the Aouizerat lab with biosafety level 2+ procedures in a chemical fume hood. Personal protective equipment including goggles, safety glasses, and lab coat will be worn while working with the samples. Empty pipettes and tubes will be placed in biohazardous waste disposal containers after processing. Any materials derived from the blood samples will be treated with the appropriate level of precaution. Waste materials from processing will be stored securely in watertight, sealed, biohazard-labeled containers until disposal by the University's department of environmental health and safety.

See section 7.1.1 for other specimen handling and storage procedures.

7.2.4 Specimen Shipment

The BCCR Biospecimen Bank (B3) is a secure facility in the Bluestone Center at the College of Dentistry that features three -80°C freezers with integrated freezer failure alert that are powered by circuits with emergency back-up power. Sample location and linking information are managed by a commercial specimen tracking system. Dr. Aouizerat, a study team member, is Director of B3. Biospecimens collected as part of the study will be stored in B3 on the date of collection or, if collected on a weekend, on the next business day. If biospecimens are drawn outside the Bluestone Center, blood tubes will be placed in a sealed plastic bag inside a sealed, watertight, biohazard-labeled, hard-sided container and sealed, biohazard-labeled secondary container with absorptive material between the two containers for transport to B3.

7.3 Study Schedule

7.3.1 Screening

Recruitment (within three months of enrollment)

- Review self-reported medical history to determine eligibility based on inclusion/exclusion criteria.
- Conduct preliminary MRI safety screen.
- If potential participant meets eligibility criteria by self-report and wishes to enroll, notify that we will schedule enrollment visit (TP0) once a potential group of participants is formed. The potential participant will have the opportunity to decline participation again at that point.

7.3.2 Enrollment/Baseline

Visit 1. Enrollment/Baseline Visit (TP0 assessment, Day 1*, within three weeks of beginning intervention)

- Verify inclusion/exclusion criteria, confirming that eligibility criteria have not changed since the screening visit.
- Review informed consent form and, if desired by potential participant, obtain written informed consent. Provide copy of signed form to participant.
- Collect 15 ml (1 tablespoon) of blood for biobanking.
- Obtain demographic information, medical history, medication history, and alcohol and tobacco use history.
- Complete patient-reported outcome measures**
- Complete neuropsychological testing.

Visit 2. Enrollment/Baseline Visit (TP0 assessment, Day 2*)

- Study personnel or MRI technologist to conduct final MRI safety screen.
- Conduct urine and saliva toxicology screen.
- Practice fMRI task.
- Complete Behavioral Handedness Index.
- Confirm completion of patient-reported outcome measures.
- Complete MRI scan.
- Complete study assessment questionnaire.

Note: Randomization will occur after TP0 procedures are completed.
*If preferred the participant may schedule procedures for Day 1 (enrollment, neuropsychological testing) and Day 2 (MRI scan) on the same day or within three days of each other.
**If preferred, the participant may complete patient-reported outcome measures at home before Day 2 of the enrollment visit.

7.3.3 Intermediate Visits

7.3.3.1 Visit 3

Week 1 of intervention

- Administer the study intervention in accordance with the MBSR or HEP manual, as appropriate to randomization. Both interventions will include the weekly in-person group meeting and homework completed on all other days, with the same time requirements.
- Record participant's adherence to intervention program using REDCap diary, which can be completed during the study visit or at home.

7.3.3.2 Visit 4

Week 2 of intervention

- Administer the study intervention in accordance with the MBSR or HEP manual, as appropriate to randomization. Both interventions will include the weekly in-person group meeting and homework completed on all other days, with the same time requirements.
- Record participant's adherence to intervention program using REDCap diary, which can be completed during the study visit or at home.

7.3.3.3 Visit 5

Week 3 of intervention

- Administer the study intervention in accordance with the MBSR or HEP manual, as appropriate to randomization. Both interventions will include the weekly in-person group meeting and homework completed on all other days, with the same time requirements.
- Record participant's adherence to intervention program using REDCap diary, which can be completed during the study visit or at home.

7.3.3.4 Visit 6

Week 4 of intervention

- Administer the study intervention in accordance with the MBSR or HEP manual, as appropriate to randomization. Both interventions will include the weekly in-person group meeting and homework completed on all other days, with the same time requirements.
- Record participant's adherence to intervention program using REDCap diary, which can be completed during the study visit or at home.

7.3.3.5 Visit 7

Week 5 of intervention

- Administer the study intervention in accordance with the MBSR or HEP manual, as appropriate to randomization. Both interventions will include the weekly in-person group meeting and homework completed on all other days, with the same time requirements.
- Record participant's adherence to intervention program using REDCap diary, which can be completed during the study visit or at home.

7.3.3.6 Visit 8

Week 6 of intervention

- Administer the study intervention in accordance with the MBSR or HEP manual, as appropriate to randomization. Both interventions will include the weekly in-person group meeting and homework completed on all other days, with the same time requirements.
- Record participant's adherence to intervention program using REDCap diary, which can be completed during the study visit or at home.

7.3.3.7 Visit 9

Week 7 of intervention

- Administer the study intervention in accordance with the MBSR or HEP manual, as appropriate to randomization. Both interventions will include the weekly in-person group meeting and homework completed on all other days, with the same time requirements.
- Record participant's adherence to intervention program using REDCap diary, which can be completed during the study visit or at home.

7.3.3.8 Visit 10

Week 7 of intervention

- One-day weekend retreat in accordance with MBSR or HEP manual (may be completed in week 6 or week 7)

7.3.3.9 Visit 11

Week 8 of intervention

- Administer the study intervention in accordance with the MBSR or HEP manual, as appropriate to randomization. Both interventions will include the weekly in-person group meeting and homework completed on all other days, with the same time requirements.
- Record participant's adherence to intervention program using REDCap diary, which can be completed during the study visit or at home.

7.3.4 Visit 12

TP1 (short-term follow-up assessment within three weeks of completion of intervention)

- Confirm that eligibility criteria have not changed since TP0 assessment.
- Collect 15 ml (1 tablespoon) of blood for biobanking.
- Obtain any changes in demographic information, medical history, medication history, and alcohol and tobacco use history.
- Assess for any adverse events, serious adverse events, or unexpected problems.
- Complete patient-reported outcome measures.
- Study personnel or MRI technologist to confirm MRI safety screen.
- Conduct urine and saliva toxicology screen.
- Practice fMRI task.
- Complete MRI scan.
- Complete study assessment questionnaire.

Note: Between visit 10 and the final study visit, all participants will continue to complete weekly REDCap diaries of mindfulness activities to evaluate whether findings at three months post intervention (i.e., TP2) vary by level of continued mindfulness activities in the MBSR group or contamination of new mindfulness activities in the HEP group.

7.3.5 Final Study Visit (Visit 13)

TP2 (long-term follow-up assessment within three months [+/- 1.5 weeks] of completion of intervention)

- Confirming that eligibility criteria have not changed since TP1 assessment.
- Collect 15 ml (1 tablespoon) of blood for biobanking.
- Obtain any changes in demographic information, medical history, medication history, and alcohol and tobacco use history.
- Assess for any adverse events, serious adverse events, or unexpected problems.
- Complete patient-reported outcome measures.
- Complete neuropsychological testing.
- Complete study assessment questionnaire.

- Complete final REDCapdiary.
- Notify participant that aggregate-level results will be available after dissemination of study findings begins.
- Instruct participant to report any subsequent event(s) that the participant, or the participant's physician, believes might reasonably be related to participation in this study.

7.3.6 Withdrawal Visit

If a participant withdraws or is withdrawn from the study, no further study visits or procedures will be completed.

7.3.7 Unscheduled Visit

Not applicable.

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5 Justification for Sensitive Procedures

Not applicable

7.6 Precautionary Medications, Treatments, and Procedures

Not applicable

7.7 Prohibited Medications, Treatments, and Procedures

Not applicable

7.8 Prophylactic Medications, Treatments, and Procedures

Not applicable

7.9 Participant Access to Study Intervention at Study Closure

If a participant in the HEP active control group wishes to participate in MBSR after she is no longer enrolled in the study, study staff will provide information on local MBSR groups.

8 Assessment of Safety

8.1 Specification of Safety Parameters

The study will involve no more than minimal risk to research participants. The probability and magnitude of harm or discomfort anticipated for this research are not greater than what this same population encounters in daily life or during the performance of physical or psychological examinations or tests. The only alternative to study participation is non-participation.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Intervention

A clinician's assessment of an AE's relationship to study intervention is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study intervention assessed. In a clinical trial, the study intervention must always be suspect. The following guidelines are used for determination of relationship of any AE to the intervention or study procedures:

- **Related** – The AE is known to occur with the study intervention or study procedure, there is a reasonable possibility that the study intervention or procedure caused the AE, or there is a

temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention or procedure caused the event, there is no temporal relationship between the study intervention or procedure and event onset, or an alternate etiology has been established.

8.2.3 Expectedness

As this study is minimal risk, no adverse events are expected.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

AEs are not expected due to participation in this minimal risk study. However, AE forms will be completed at each of the three study assessments, and study participants will be encouraged to contact study staff immediately should any AEs occur during study participation. Periodic adverse event reporting will include any AE that occurs while a participant is on the research protocol, regardless of whether it is considered related to study participation.

The PI will submit as part of annual progress reports to the IRB and NINR a summary of monitoring that took place; cumulative adverse event data; assessments that were performed to evaluate external factors or relevant information that may have an impact on the safety of study participants or ethics of the research study; outcomes of procedural reviews conducted to ensure participant privacy and confidentiality; and final conclusions regarding changes to the anticipated risk-to-benefit ratio of study participants and recommendations related to continuing, changing, or terminating the study.

8.4.2 Serious Adverse Event Reporting

SAEs are not expected due to participation in this minimal risk study. The procedure for AE reporting will be followed for SAEs. In addition, if a serious adverse event occurs, it will be reported in a timely fashion after adjudication: All SAE reports will be made to the IRB within 5 working days; any participant deaths will be reported to the NINR Program Officer within 24 hours of realization, and all other serious adverse events will be reported to NINR within 72 hours of realization.

8.4.3 Unanticipated Problem Reporting

UPs are not mentioned in the consent form or final study protocol; however, should UPs that are related to the intervention occur, the informed consent will be modified accordingly. The procedure for AE reporting will be followed for SAEs. In addition, if changes to the risk-to-benefit ratio of the study are determined based on occurrence of UPs, the IRB and NINR Program Officer will be notified.

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the PI's responsibility to report UPs to the IRB and to the NINR. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to NINR within the timeframe described in 8.4.2 for SAEs.
- Any other UP will be reported to the IRB and to NINR within the timeframe described in 8.4.1 for AEs.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within the timeframe described for AEs or SAEs, as appropriate, after the IRB's receipt of the report of the UP from the investigator.

8.4.4 Reporting of Pregnancy

As all participants will be postmenopausal per the medical record, pregnancy is not an anticipated event. However, should a participant become pregnant during the study, she will be allowed to continue in all study activities except MRI assessment.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the data and safety monitoring team/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the data and safety monitoring team /study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the data and safety monitoring team/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in

the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Reporting Procedures – Participating Investigators

As the study intervention and data collection will be conducted only at NYU, procedures for monitoring and reporting across sites are not provided.

8.7 Study Halting Rules

As this study is minimal risk, it is not anticipated that the study may be halted. However, if there is a determination of unexpected, significant, or unacceptable risk to participants, the study may be temporarily suspended or prematurely terminated as described in section 5.7.3

8.8 Safety Oversight

Following are plans for data and safety monitoring during the R00 study.

Monitoring entity. Data and safety monitoring will be overseen primarily by the PI, who will complete all monitoring procedures except those for which he will be blinded (i.e., any procedures involving group assignment). The project's biostatistician will be designated to oversee any aspects of the study for which the PI is blinded. The PI will submit any necessary reports to the IRB and NINR.

Monitoring procedures. The PI, biostatistician, and study personnel will meet quarterly to review the study protocol, participant recruitment, intervention attendance rates, achievement of intervention goals, retention rates, minimizing risk of adverse events, and data quality control. Because the PI and study personnel collecting data will be blinded to group assignment, any metrics by group assignment will be monitored by the biostatistician. **Multi-site procedures.** As the study intervention and data collection will be conducted only at NYU, procedures for monitoring across sites are not provided.

Minimizing risk. It is possible that a breach of confidentiality may occur during screening or study participation. However, every effort will be made to ensure that participant confidentiality is maintained. All investigators and key personnel will have trained in HIPAA policies and procedures and signed confidentiality agreements. Each participant will be assigned a unique ID number for data collected during the study; all study data will be de-identified so that only the ID number is associated with it. Paper linkage records for these ID numbers will be stored in the PI's office in a separate locked file cabinet, and an associated password-protected file containing the linkage records will be kept on an encrypted, password-protected server.

Each participant's blood sample will be associated with only the study ID number and stored in the Bluestone Center Biospecimen Bank (i.e., B3). De-identified data collected from study measures and blood samples will be stored on encrypted, password-protected servers indefinitely. Paper-based records will be stored in a locked file cabinet. Access to de-identified data will be restricted to the PI, co-investigators, and other study personnel, as well as approved secondary investigators. These procedures will be reviewed at quarterly meetings to ensure that data are collected in a manner to protect confidentiality of participants.

After the data retention period, de-identified data will be retained in an electronic format indefinitely for future analyses. Paper records of data obtained during the study, such as subjective measures, will be scanned or retained in secured long-term retention. Blood samples and materials derived from them will be retained until they are used completely. All protected health information, including the PI's linkage record, will be destroyed at that time to protect confidentiality.

Personnel who draw blood will apply universal precautions to reduce the risk of infection and will take steps to minimize discomfort, including application of pressure on the site following withdrawal of the needle. Participants will be observed after blood draws for any ill effects. To minimize fatigue, frustration, and anxiety that might occur during task performance, participants will be asked how they are feeling and will be offered breaks between tasks. During the MRI scan, participants will be able to squeeze a panic

ball if they become claustrophobic; doing so will stop the scan so that the participant can exit the scanner.

External factors. The PI will monitor developments in the literature as the study progresses. Should it become clear that the intervention would be in any way harmful to participants, would increase risk, or would be unethical to continue, the IRB and NINR Program Officer will be notified and the study will be stopped.

Futility analysis. As this pilot randomized controlled trial is designed to provide preliminary data (e.g., effect sizes) for a future well-powered R01 application, it will not be possible to determine whether the intervention is futile for this population during the proposed study.

9 Clinical Monitoring

Clinical site monitoring may be conducted to ensure that the rights and well-being of human subjects are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Authorized representatives of the IRB and the NINR may review de-identified information, as well as participants' identifiable information, for the purposes of assuring proper conduct of the research, addressing a specific reported incident, or verifying appropriate use of funds. The Quality Assurance and Quality Improvement Division of NYU's Research and Regulatory Services may audit the study to confirm compliance. Access of any protected health information will be done in the offices of the PI in his presence. No identifiable information may be copied or taken off-site.
- The project manager (or clinical research coordinator) will audit one case per quarter, selected at random, to confirm compliance with IRB requirements, including conformance with informed consent requirements, verification of source documents, and investigator compliance.

10 Statistical Considerations

10.1 Statistical and Analytical Plans

A formal SAP will be developed for this study in consultation with the study biostatistician. Only a general overview of study statistics is included in this protocol.

10.2 Statistical Hypotheses

The sample size is too small to make inferences about relationships evaluated in the R00 study to the larger population of postmenopausal women with breast cancer. For the primary aim, effect sizes for neural markers of changes in cognitive function will be obtained. For the exploratory aims, effect sizes for correlations of exploratory outcomes to neural markers of changes in cognitive function will be calculated. The effect sizes for these relationships will be determined in the R00 study, which will inform the sample size for a well-powered study planned for future R01 applications.

10.3 Analysis Datasets

The analysis dataset will include all randomized participants (i.e., intention-to-treat).

10.4 Description of Statistical Methods

10.4.1 General Approach

See study schematic for the design of this pilot, single-center randomized controlled trial of the preliminary efficacy of an eight-week, group-based MBSR intervention versus HEP active control to improve neural markers of changes in cognitive function in postmenopausal women receiving aromatase inhibitor therapy for breast cancer. Using exploratory and descriptive analyses, the investigators will first evaluate whether any data anomalies (e.g., nonrandom missing data, erroneous outliers, multicollinearity,

possible confounding) may invalidate planned analyses and then summarize data in terms of location and variability using appropriate descriptive statistics, given the variable's level of measurement and observed data distribution. As needed, appropriate remedial approaches (e.g., data transformations, imputation, nonparametric analysis methods) will be applied.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

See SAP.

10.4.3 Analysis of the Secondary Endpoint(s)

There are no secondary endpoints.

10.4.4 Safety Analyses

As this study is minimal risk, no adverse events are expected, and no formal plan for safety analyses will be developed. The procedures in section 8 will be followed for any AEs, SAEs, or UPs that occur during this study.

10.4.5 Adherence and Retention Analyses

Adherence to the intervention will be assessed using data collected in attendance records and weekly REDCap diaries of completion of homework and other mindfulness activities. These data will be described as percentage homework completed and number of minutes of mindfulness activities. Retention will be assessed as number of study assessment time points (i.e., TP0, TP1, TP2) completed.

10.4.6 Baseline Descriptive Statistics

Intervention groups will be compared on baseline characteristics, including demographic and clinical characteristics of the sample, using descriptive statistics. Inferential statistics will not be used.

10.4.7 Planned Interim Analysis

Not applicable.

10.4.8 Safety Review

As this study is minimal risk, it is not anticipated that the study may be halted. However, if there is a determination of unexpected, significant, or unacceptable risk to participants, the study may be temporarily suspended or prematurely terminated as described in section 5.7.3.

10.4.9 Efficacy Review

This study will not evaluate efficacy.

10.4.10 Additional Sub-Group Analyses

Primary or secondary endpoints may be analyzed for descriptive purposes by age, race/ethnicity, or any other participant characteristic as described in detail in the SAP.

10.4.11 Multiple Comparison/Multiplicity

For these analyses, the investigators will generally not control for multiple comparisons. Any specific controls for multiple comparisons for the neuroimaging or gene expression data may be considered as part of the SAP.

10.4.12 Tabulation of Individual Response Data

Individual participant data will not be listed.

10.4.13 Exploratory Analyses

See SAP.

10.5 Sample Size

The R00 study will recruit up to 32 participants (i.e. 16 participants per group) with analyzable data. Up to 40 participants will be recruited to reach this goal. The projected sample size is sufficient to meet the specific aims of the R00 study and falls within the range of pilot neuroimaging studies.[53,54] It is unknown what effect sizes for the intervention versus active control will be uncovered for neural markers in this population. However, based on the investigators' finding of large effect sizes for neural markers of cognitive changes in the K99 study, group sample sizes of 16 will achieve 78.1% power to reject the null hypothesis of no effect size when the population effect size is 1 and the significance level (alpha) is 0.05 using a two-sided, two-sample equal variance t-test.

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

After written informed consent at the enrollment visit, participants will complete the baseline assessment (TP0) and be randomly assigned to the MBSR intervention group or HEP active control group in a permuted block design stratified by receipt of chemotherapy (i.e., two strata). It will not be possible to blind study participants or interventionists to group assignment. However, to reduce bias, research staff who conduct participant assessments (TP0, TP1, TP2), including the PI, will be blinded to group assignment (i.e., single blind). Participants will be reminded not to reveal their group assignment to study staff conducting assessments. The study biostatistician will have no direct contact with study participants and will not be blinded to group assignment. The biostatistician will produce and maintain the randomization codes for the permuted blocks. Randomization may only be unmasked by the biostatistician at the completion of analysis of the primary outcome, or for reporting of SAEs or UPs for which it will be essential to provide information to the PI on group assignment.

As described in section 5.7.2, participants who withdraw or are withdrawn from the study may be replaced with additional participants in the next cycle of the intervention with the intent of obtain at least 32 analyzable participants. For this study of preliminary efficacy, which is determining effect sizes, as large an analyzable sample size as possible will refine the estimates of these effect sizes.

10.6.2 Evaluation of Success of Blinding

Blinding will be considered successful if, with the exception of SAE and UP reporting, the PI and study staff conducting assessments remain unaware of group assignment until after data collection is complete.

10.6.3 Breaking the Study Blind/Participant Code

Single blinding will be broken before completion of data collection only for reporting of SAEs or UPs for which it will be essential to provide information to the PI on group assignment. For SAEs or UPs that could affect other participants, the entire group will be unblinded so that the PI and study staff can discuss with these participants whether it is safe for them to continue in the study.

While every effort will be made to remind participants not to unblind themselves, it is possible that a participant may unintentionally unblind themselves to study staff conducting assessments or to the PI. If a blind is unintentionally broken, it will be reported to the study biostatician and discussed by the data and safety monitoring team. Any unintentional unblindings will be reported to the IRB as a deviation from protocol. As this is a pilot study, the participant will be allowed to continue in the study and data will be analyzed.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm

or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. Bluestone Center for Clinical Research, Center for Brain Imaging, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system, and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs in the MOP, the PI will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

The informed consent form describing in detail the study intervention, study procedures, and risks are given to the participant, and written documentation of informed consent is required prior to starting any

study procedures.

13.3.2 Consent Procedures and Documentation

Information will be obtained during screening for the study by study staff or the MRI technologist to determine eligibility. Obtaining this information before written informed consent for the study will save time for potential participants by avoiding unnecessary trips to the study sites at which enrollment will be completed. During screening, study staff will review the purpose, nature, risks, and benefits of the study; determine eligibility; and, if desired, schedule an enrollment appointment at NYU to obtain written informed consent from the candidate. The period of time between screening and enrollment will vary, depending on the availability of the potential participant and recruitment of a sufficient number of potential participants to begin an intervention cycle.

This process will give the potential participant time between screening and enrollment to consider whether she wants to participate in the study. Participants will be reminded when the study is introduced, during screening, and during written informed consent that participation is voluntary and that choosing not to participate in no way affects the quality or quantity of medical or nursing care provided to them. During this time between screening and the enrollment visit, the candidate will have a copy of the consent form. If at any point the candidate prefers not to proceed, the enrollment visit will be canceled. The candidate will be offered time after the in-person review of the consent form during the enrollment visit to think about her potential participation and to ask any questions before choosing to sign the study consent. In addition, subjects are told that they may choose to withdraw from the study at any time.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to potential participants. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. The participant will sign the informed consent document prior to any procedures being done for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. A copy of the signed informed consent document will be stored in the participant's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process and the justification for such alteration will likewise be documented.

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor or

the PI.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored in the PI's office in the NYU Meyers College of Nursing for internal use during the study. Only the PI and study staff authorized by the PI will be allowed access to the document linking ID numbers to study participant's personally identifiable information. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by IRB and institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the research offices of the PI at the NYU Meyers College of Nursing. These data will be shared with study investigators and may be shared with non-study investigators for secondary analyses at the discretion of the PI. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Meyers College of Nursing research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Meyers College of Nursing. Blood samples will be identified only by a study ID number and stored in the B3 biobank in the College of Dentistry until genomic data collection. Data generated in genomic data collection will be transferred to the research offices of the PI and shared as described herein. MRI scans will be stored on secure servers at the Center for Brain Imaging. Scans will be transferred when ready for pre-processing and analysis to the research offices of the PI and shared as described herein.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

Genomic Data Sharing Plan. The R00 study will not produce large-scale human genomic data (i.e., at least 100 samples for RNA-seq). Therefore, the NIH Genomic Data Sharing Policy does not require submission of the data to an NIH-designated repository. Currently, the maximum number of samples that will be submitted for RNA-seq using samples collected during the R00 study will be 96. However, it is unlikely that the investigators will successfully collect RNA-seq data from all samples.

If the maximum number of samples from which RNA-seq data is successfully collected were to exceed the threshold for data sharing (due to, for example, securing additional funds to increase sample size), the appropriate program official at the NINR will be notified, and a detailed plan for sharing of generated data will be developed. In that case, it is anticipated that the study will be registered in dbGaP and that gene expression data and associated phenotypic data will be submitted to an NIH-designated data repository (e.g., Gene Expression Omnibus [GEO]) so that it can be released no later than six months after initial data submission begins, or at the time of acceptance of the first publication, whichever occurs first. To allow for this possibility, the consent form for the R00 study will be worded to allow broad data sharing, should it become necessary.

Even though the R00 study is not anticipated to reach the threshold for required genomic data sharing, the study will have in place plans for sharing de-identified data for secondary analyses with qualified investigators. The consent language for the R00 study will be worded for possible broad data sharing, as described above. The investigators also plan to submit genomic data and relevant phenotypic data (e.g., clinical characteristics of the sample) generated in the R00 study to an NIH-designated data

repository in a timely manner. In this case, the timeline for submission to an NIH-designated data repository will allow first for publication of findings related to the aims of the R00 study, as well as submission as preliminary data for anticipated R01 grant application(s). The submission process will likely include registration in dbGaP and submission to GEO for controlled access to the data.

13.5 Research Use of Stored Human Samples, Specimens, and Data

- Intended Use: Samples and genomic data collected under this protocol may be used to study relationships between genes or gene products and neural markers of changes in cognitive function, for exploratory analyses consistent with the SAP, and for any purpose described in the Genomic Data Sharing Plan. To accomplish these aims, study samples may be shipped to locations outside NYU for processing and data collection. Any samples so shipped will be returned to the B3 after data collection for future storage. Any data generated in said process will be returned to the PI at the NYU Meyers College of Nursing and shared as described herein.
- Storage: Access to stored samples in the B3 will be limited to study investigators and their approved staff. Samples and genomic data will be stored using codes assigned by the investigators. Genomic data generated from the samples will be kept in University-approved encrypted, password-protected servers. Only investigators and their approved staff will have access to the samples and data.
- Tracking: Sample location and linking information are managed by a commercial specimen tracking system. Dr. Aouizerat, a study team member, is Director of B3.
    - Disposition at the completion of the study: All stored samples remain in B3 until used completely. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.6 Future Use of Stored Human Samples, Specimens, and Data

Participants may provide optional permission for future broad use of their stored samples, specimens, and data after the study is completed. We do not yet know the purpose of such future research, which could be related to any of the samples, specimens, or data collected as part of the study.

After the study is completed, the de-identified, archived data will remain at NYU, under the supervision of the PI, for use by other researchers including those outside the study. These other researchers may include the PI's students, other researchers at NYU, or researchers at other institutions. The PI will monitor the research activities of students and other researchers at NYU to ensure that data generated in this study are used appropriately. Data shared with researchers at other institutions via NIH databases will be covered under the NINR-approved Genomic Data Sharing Plan. The PI will enter into Data Use Agreements with researchers at other institutions not covered under this plan. The optional permission for future use includes future uses that are unknown at this time, so the PI will ensure that any such future uses are appropriate.

These biological samples will be stored indefinitely at the B3 until used up. The samples could be used for research consistent with this protocol, for research consistent with the genomic data sharing plan, or for broad use with any data collected as part of the study. True genetic testing is not planned for these samples or specimens. Samples, specimens, and data will be labeled using codes assigned by study investigators. Data will be stored in University-approved, encrypted, cloud-based storage (e.g., Box), which is password protected. With the exception of NIH databases, any data shared with secondary investigators will be accessed by them using shared Box folders. Study investigators and their approved staff will have access to the samples and data. Secondary investigators will be granted access to the data with time, as consistent with the Genomic Data Sharing Plan.

Sample location and linking information will be managed in B3 by a commercial specimen tracking system. The PI will maintain a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant. This code link will be shared with approval by the PI. Some data collected as part of the study may constitute a Limited Data Set, which will be shared with researchers at other institutions only as approved by the University in Data Use Agreements.

During the conduct of the study, an individual participant can choose to withdraw consent to have samples, specimens, and data stored for future research by contacting the PI in writing. However, withdrawal of consent for storage will not be possible after the study is completed.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents, or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record. Data obtained from paper source documents (e.g., patient-reported outcomes) will be entered twice and compared to reduce potential for data entry error.

Data generated in the study and clinical data entered directly from source documents (e.g., AEs, concomitant medications) will be entered into the SPSS dataset maintained by the PI and approved study staff. The dataset will be password protected and will be examined for data that appear inconsistent, incomplete, or inaccurate.

14.2 Study Records Retention

Study documents will be retained for at least the longest of 3 years after closeout, 3 years after the date of Federal Financial Report (FFR) submission, or 5 years after final reporting/publication. These documents may be retained for a longer period, however, if required by local regulations or if data analysis remains ongoing (e.g., secondary analyses). No records will be destroyed without the written consent of the PI.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, an investigator, or the study staff. As a result of deviations, corrective actions are to be developed and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NINR Program Official and the data and safety monitoring team. Protocol deviations must be reported to the local IRB per their guidelines. The site PI and study staff are responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

Data will be shared with study investigators, with secondary investigators as approved by the PI, and as described in the genomic data sharing plan for the purpose of disseminating findings to the scientific community and to the public. This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials." NIH grantees, such as the R00 study PI, will take specific steps to ensure compliance with NIH implementation of FDAAA, including registering the trial with clinicaltrials.gov.

15 Study Finances

15.1 Funding Source

This study is funded through a grant from the National Institute of Nursing Research (R00NR015473).

15.2 Costs to the Participant

Participants will not be charged for any procedures of this study.

15.3 Participant Reimbursements or Payments

Participants will receive a modest compensation of $100 for the two-part pre-intervention assessment, which includes MRI and neuropsychological testing; $75 for the post-intervention assessment, which does not include neuropsychological testing; and $75 for the three-month follow-up visit, which does not include MRI (total compensation of $250 if all three study visits are completed). Participants will receive reimbursement for public transit or parking at NYU for each of the study assessment visits. Parking fines will not be reimbursed. Reimbursements for public transit or parking at NYU may be provided for the MBSR or HEP visits.

16 Study Administration

16.1 Study Leadership

The study team will govern the conduct of the study. The study team will be composed of the PI, study investigators, and representatives of NINR, as listed in section 1. With the exception of NINR personnel, who will meet with the study team when required, the PI will schedule monthly study team meetings. In addition, the PI will meet individually with study team members as needed.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NINR has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYU Langone Health investigators will follow the applicable conflict of interest policies.

18 References

1. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: Update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol.* 2010;28(23):3784-3796.
2. Bender CM, Sereika SM, Brufsky AM, et al. Memory impairments with adjuvant anastrozole versus tamoxifen in women with early-stage breast cancer. *Menopause.* 2007;14(6):995-998.
3. Zhou L, Fester L, von Blittersdorff B, et al. Aromatase inhibitors induce spine synapse loss in the hippocampus of ovariectomized mice. *Endocrinology.* 2010;151(3):1153-1160.
4. Cimprich B, So H, Ronis DL, Trask C. Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer. *Psychooncology.* 2005;14(1):70-78.
5. Lehto RH, Cimprich B. Anxiety and directed attention in women awaiting breast cancer surgery. *Oncol Nurs Forum.* 1999;26(4):767-772.
6. Jansen CE, Cooper BA, Dodd MJ, Miaskowski CA. A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients. *Support Care Cancer.* 2011;19(10):1647-1656.
7. Bender CM, Sereika SM, Berga SL, et al. Cognitive impairment associated with adjuvant therapy in breast cancer.*Psychooncology.* 2006;15(5):422-430.
8. Collins B, Mackenzie J, Stewart A, Bielajew C, Verma S. Cognitive effects of hormonal therapy in early stage breast cancer patients: a prospective study. *Psychooncology.* 2009;18(8):811-821.
9. Bender CM, Merriman JD, Gentry AL, et al. Patterns of change in cognitivefunction with anastrozole therapy. *Cancer.* 2015;121(15):2627-2636.
10. Berman MG, Askren MK, Jung M, et al. Pretreatment worry and neurocognitive responses in women with breast cancer. *Health Psychol.* 2014;33(3):222-231.
11. Merriman JD, Dodd M, Lee K, et al. Differences in self-reported attentional fatigue between patients with breast and prostate cancer at the initiation of radiation therapy. *Cancer Nurs.* 2011;34(5):345-353.
12. Creswell JD, Lindsay EK. How does mindfulness training affect health? A mindfulness stress buffering account. *Curr Dir Psychol Sci.* 2014;23(6):401-407.
13. Bower JE, Crosswell AD, Stanton AL, et al. Mindfulness meditation for younger breast cancer survivors: A randomized controlled trial. *Cancer.* 2015;121(8):1231-1240.
14. Boyle CC, Stanton AL, Ganz PA, Crespi CM, Bower JE. Improvements in emotion regulation following mindfulness meditation: Effects on depressive symptoms and perceived stress in younger breast cancer survivors. *J Consul Clin Psychol.* 2017;85(4):397-402.
15. Henderson VP, Massion AO, Clemow L, Hurley TG, Druker S, Hebert JR. A randomized controlled trial of mindfulness-based stress reduction for women with early-stage breast cancer receiving radiotherapy. *Integr Cancer Ther.* 2013;12(5):404-413.
16. Hoffman CJ, Ersser SJ, Hopkinson JB, Nicholls PG, Harrington JE, Thomas PW. Effectiveness of mindfulness-based stress reduction in mood, breast- and endocrine-related quality of life, and well-being in stage 0 to III breast cancer: A randomized, controlled trial. *J Clin Oncol.* 2012;30(12):1335-1342.
17. Lengacher CA, Shelton MM, Reich RR, et al. Mindfulness based stress reduction (MBSR(BC)) in breast cancer: Evaluating fear of recurrence (FOR) as a mediator of psychological and physical symptoms in a randomized control trial (RCT). *J Behav Med.* 2014;37(2):185-195.
18. Monti DA, Kash KM, Kunkel EJ, et al. Changes in cerebral blood flow and anxiety associated with an 8-week mindfulness programme in women with breast cancer. *Stress Health.* 2012;28(5):397-407.
19. Reich RR, Lengacher CA, Alinat CB, et al. Mindfulness-based stress reduction in post-treatment breast cancer patients: Immediate and sustained effects across multiple symptom clusters. *J Pain Symptom Manage.*2017;53(1):85-95.
20. Kenne Sarenmalm E, Martensson LB, Andersson BA, Karlsson P, Bergh I. Mindfulness and its efficacy for psychological and biological responses in women with breast cancer. *Cancer Med.* 2017;6(5):1108-1122.
21. Johns SA, Von Ah D, Brown LF, et al. Randomized controlled pilot trial of mindfulness-based stress reduction for breast and colorectal cancer survivors: Effects on cancer-related cognitive impairment. *J Cancer Surviv*. 2016;10(3):437-448.

22. Milbury K, Chaoul A, Biegler K, et al. Tibetan sound meditation for cognitive dysfunction: Results of a randomized controlled pilot trial. *Psychooncology.* 2013;22(10):2354-2363.
23. Vardy JL, Stouten-Kemperman MM, Pond G, et al. A mechanistic cohort study evaluating cognitive impairment in women treated for breast cancer. *Brain Imaging Behav.* 2017.
24. Reich RR, Lengacher CA, Klein TW, et al. A randomized controlled trial of the effects of mindfulness-based stress reduction (MBSR[BC]) on levels of inflammatory biomarkers among recovering breast cancer survivors. *Biol Res Nurs.* 2017:1099800417707268.
25. Creswell JD, Taren AA, Lindsay EK, et al. Alterations in resting-state functional connectivity link mindfulness meditation with reduced interleukin-6: A randomized controlled trial. *Biol Psychiatry.* 2016;80(1):53-61.
26. Carlson LE, Doll R, Stephen J, et al. Randomized controlled trial of mindfulness-based cancer recovery versus supportive expressive group therapy for distressed survivors of breast cancer. *J Clin Oncol.* 2013;31(25):3119-3126.
27. Black DS, Peng C, Sleight AG, Nguyen N, Lenz HJ, Figueiredo JC. Mindfulness practice reduces cortisol blunting during chemotherapy: A randomized controlled study of colorectal cancer patients. *Cancer.* 2017.
28. Taren AA, Gianaros PJ, Greco CM, et al. Mindfulness meditation training and executive control network resting state functional connectivity: A randomized controlled trial. *Psychosom Med.* 2017.
29. Lengacher CA, Reich RR, Kip KE, et al. Moderating effects of genetic polymorphisms on improvements in cognitive impairment in breast cancer survivors participating in a 6-week mindfulness-based stress reduction program. *Biol Res Nurs.* 2015;17(4):393-404.
30. American Cancer Society. Breast Cancer Facts & Figures 2015-2016. http://www.cancer.org/research/cancerfactsstatistics/breast-cancer-facts-figures. Accessed May 15, 2017.
31. Stilley CS, Bender CM, Dunbar-Jacob J, Sereika S, Ryan CM. The impact of cognitive function on medication management: Three studies. *Health Psychol.* 2010;29(1):50-55.
32. Bender CM, Gentry AL, Brufsky AM, et al. Influence of patient and treatment factors on adherence to adjuvant endocrine therapy in breast cancer. *Oncol Nurs Forum.* 2014;41(3):274-285.
33. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index—A self-report cognitive measure. *Psychooncology.* 2011;20(2):194-202.
34. Myers JS. Chemotherapy-related cognitive impairment: The breast cancer experience. *Oncol Nurs Forum.* 2012;39(1):E31-40.
35. Boykoff N, Moieni M, Subramanian SK. Confronting chemobrain: An in-depth look at survivors' reports of impact on work, social networks, and health care response. *J Cancer Surviv.* 2009;3(4):223-232.
36. Liu F, Day M, Muniz LC, et al. Activation of estrogen receptor-beta regulates hippocampal synaptic plasticity and improves memory. *Nat Neurosci.* 2008;11(3):334-343.
37. Turgeon JL, Carr MC, Maki PM, Mendelsohn ME, Wise PM. Complex actions of sex steroids in adipose tissue, the cardiovascular system, and brain: Insights from basic science and clinical studies. *Endocr Rev.* 2006;27(6):575-605.
38. Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: An update on the state of the science. *J Clin Oncol.* 2012;30(30):3675-3686.
39. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer.* 2007;7(3):192-201.
40. Merriman JD, Von Ah D, Miaskowski C, Aouizerat BE. Proposed mechanisms for cancer- and treatment-related cognitive changes. *Semin Oncol Nurs.* 2013;29(4):260-269.
41. De Raedt R, Koster EH. Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework. *Cogn Affect Behav Neurosci.* 2010;10(1):50-70.
42. de Ruiter MB, Reneman L, Boogerd W, et al. Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. *Hum Brain Mapp.* 2011;32(8):1206-1219.
43. Kesler SR, Bennett FC, Mahaffey ML, Spiegel D. Regional brain activation during verbal declarative memory in metastatic breast cancer. *Clin Cancer Res.* 2009;15(21):6665-6673.

44. Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition—The case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc.* 2002;50(12):2041-2056.
45. Capuron L, Miller AH. Immune system to brain signaling: Neuropsychopharmacological implications. *Pharmacology & Therapeutics.* 2011;130(2):226-238.
46. Watkins LR, Goehler LE, Relton JK, et al. Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune-brain communication. *Neurosci Lett.* 1995;183(1-2):27-31.
47. Joshi G, Sultana R, Tangpong J, et al. Free radical mediated oxidative stress and toxic side effects in brain induced by the anti cancer drug adriamycin: Insight into chemobrain. *Free Radic Res.* 2005;39(11):1147-1154.
48. Creswell JD. Mindfulness interventions. *Annu Rev Psychol.* 2017;68:491-516.
49. Muehsam D, Lutgendorf S, Mills PJ, et al. The embodied mind: A review on functional genomic and neurological correlates of mind-body therapies. *Neurosci Biobehav Rev.* 2017;73:165-181.
50. Merriman JD, Aouizerat BE, Cataldo JK, et al. Association between an interleukin 1 receptor, type I promoter polymorphism and self-reported attentional function in women with breast cancer. *Cytokine.* 2014;65(2):192-201.
51. Merriman JD, Aouizerat BE, Langford DJ, et al. Preliminary evidence of an association between an interleukin 6 promoter polymorphism and self-reported attentional function in oncology patients and their family caregivers. *Biol Res Nurs.* 2014;16(2):152-159.
52. Merriman JD, Bertocci M, Phillips ML, Ryan C, Sereika S, Bender C. Preliminary evidence of pre- therapy relationships between cognitive and emotion processing and cognitive difficulties in postmenopausal women with breast cancer. Oncology Nursing Society 42nd Annual Congress; 2017; Denver, CO.
53. de Ruiter MB, Schagen SB. Functional MRI studies in non-CNS cancers. *Brain Imaging Behav.* 2013;7(4):388-408.
54. Cimprich B, Reuter-Lorenz P, Nelson J, et al. Prechemotherapy alterations in brain function in women with breast cancer. *J Clin Exp Neuropsychol.* 2010;32(3):324-331.
55. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983;24(4):385-396.
56. MacCoon DG, Imel ZE, Rosenkranz MA, et al. The validation of an active control intervention for mindfulness based stress reduction (MBSR). *Behav Res Ther.* 2012;50(1):3-12.
57. Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinski CJ. NIH Toolbox for assessment of neurological and behavioral function. *Neurology.* 2013;80(11 Suppl 3):S2-6.
58. Chelune GJ, Heaton RK, Lehman RAW. Neuropsychological and personality correlates of patients' complaints of disability. In: Goldstein G, Tarter RE, eds. *Advances in Clinical Neuropsychology.* Vol 3. New York: Plenum Press; 1986:95-126.
59. Roth RM, Isquith PK, Gioia GA. *Behavior Rating Inventory of Executive Function-Adult Version: Professional Manual.* Lutz, FL: PAR; 2005.
60. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol.* 2010;63(11):1179-1194.
61. Kelly THE INVESTIGATORS. A brief measure of general worry: The Three Item Worry Index. *N Am J Psychol.* 2004;6:219-226.
62. Bertocci MA, Bebko GM, Mullin BC, et al. Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. *Psychol Med.* 2012;42(7):1417-1428.
63. Schooler JW, Smallwood J, Christoff K, Handy TC, Reichle ED, Sayette MA. Meta-awareness, perceptual decoupling and the wandering mind. *Trends Cogn Sci.* 2011;15(7):319-326.
64. Kangelaris KN, Prakash A, Liu KD, et al. Increased expression of neutrophil-related genes in patients with early sepsis-induced ARDS. *Am J Physiol Lung Cell Mol Physiol.* 2015;308(11):L1102-1113.
65. Kober KM, Dunn L, Mastick J, et al. Gene expression profiling of evening fatigue in women undergoing chemotherapy for breast cancer. *Biol Res Nurs.* 2016:*In press*.
66. Kim D, Langmead B, Salzberg SL. HISAT: a fast spliced aligner with low memory requirements.

Nat Methods. 2015;12(4):357-360.
67. Pertea M, Pertea GM, Antonescu CM, Chang TC, Mendell JT, Salzberg SL. StringTie enables improved reconstruction of a transcriptome from RNA-seq reads. *Nat Biotechnol*. 2015;33(3):290-295.
68. Andrews S. FASTQC. A quality control tool for high throughput sequence data. 2014; http://www.bioinfomratics.babraham.ac.uk/projects/fastqc.
69. Hannon G. FASTX-Toolkit. 2016; http://hannonlab.cshl.edu/fastx_toolkit/.
70. Wang L, Wang S, Li W. RSeQC: quality control of RNA-seq experiments. *Bioinformatics.* 2012;28(16):2184-2185.
71. Tarazona S, Furio-Tari P, Turra D, et al. Data quality aware analysis of differential expression in RNA-seq with NOISeq R/Bioc package. *Nucleic Acids Res.* 2015;43(21):e140.
72. Leek JT, Scharpf RB, Bravo HC, et al. Tackling the widespread and critical impact of batch effects in high-throughput data. *Nat Rev Genet.* 2010;11(10):733-739.
73. Leek JT, Storey JD. Capturing heterogeneity in gene expression studies by surrogate variable analysis. *PLoS Genet.* 2007;3(9):1724-1735.
74. Smyth GK. Linear models and empirical Bayes methods for assessing differential expression in microarray experiments. *Stat Appl Genet Mol Biol.* 2004;3:Article3.
75. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol.* 1995;57(1):289-300.
76. Satterthwaite TD, Elliott MA, Gerraty RT, et al. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage.* 2013;64:240-256.
77. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 2000;97(20):11050-11055.
78. Brown KW, Ryan RM. The benefits of being present: Mindfulness and its role in psychological well-being. J Pers Soc Psychol. 2003;84(4):822-848.

19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Data and safety monitoring plan (approved by NINR 07-07-2017)
- Informed consent form
- Lab protocol, including specimen preparation and handling
- Manual of procedures, including intervention manuals
- Screening script (including screening form)
- Statistical analysis plan

Table A

Schedule of Events

Activity	**Recruitment** ≤ 3 months before enrollment	**Enrollment TP0 -** Day 1	**Enrollment TP0 -** Day 2	**Intervention** ≤ 3 weeks after	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Follow-up TP1** ≤ 3 weeks after	**Final study visit (TP2)** 3 months after +/- 1.5 weeks
Study team procedures													
Screen for eligibility	X												
Preliminary MRI safety screen	X												
Schedule enrollment	X												
Verify eligibility has not changed		X										X	X
Study consent		X											
Blood samples		X										X	X
Demographic and clinical data		X											
Update demos and clinicals												X	X
Assess for AEs, SAEs, UPs												X	X
Patient-reported outcomes (PROs)		X										X	X
Neuropsychological testing		X											X
Verbal IQ (NART-R)		X											
Confirm MRI safety			X									X	
Toxicology screen			X									X	
Practice MRI task			X									X	
Behavioral Handedness Index			X										
Confirm completion of PROs			X										
MRI scan			X									X	
Study assessment questionnaire			X									X	X

Weekly REDCap diary				X	X	X	X	X	X	X	X	X	X
Remind about aggregate findings													X
AE instruction													X
Interventionist procedures													
Weekly MBSR or HEP meeting				X	X	X	X	X	X	X	X		
Daily homework				X	X	X	X	X	X	X	X		
One-day retreat										X*			

*The one-day retreat may be scheduled in week 6 or 7 of the intervention.