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Breast Cancer-Related Cognitive Impairment Across the Cancer Continuum: Elucidating Clinical Drivers, Biological Mechanisms, and Trajectories

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A dissertation submitted in partial satisfaction of the

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in Psychology

by

Arielle Radin

2023

ABSTRACT OF THE DISSERTATION

Breast Cancer-Related Cognitive Impairment Across the Cancer Continuum: Elucidating Clinical Drivers, Biological Mechanisms, and Trajectories

by

Arielle Radin

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2023

Professor Julienne E. Bower, Chair

Cognitive impairment during and after treatments for breast cancer, referred to as cancer-related cognitive impairment (CRCI), is one of the most common and troublesome consequences of the cancer experience. Women report experiencing difficulties with memory, multi-tasking, and keeping up with the demands of what used to be cognitively manageable tasks. Over the last several decades, both pre-clinical and clinical research have provided empirical evidence supporting an association between the cancer experience and cognitive problems; however, several gaps in the literature remain. First, the study of CRCI has primarily focused on the influence of adjuvant therapies given that women often complain of cognitive disturbances following chemotherapy, referring to the experience as “chemo-brain.” However, longitudinal investigations into the onset and maintenance of CRCI have identified pre-chemotherapy cognitive impairment that cannot be explained by presumed cytotoxic effects. These pre-

systemic therapy cognitive problems could potentially be driven by breast cancer surgery, the primary treatment for solid tumor cancers. Although breast cancer surgery is included in almost every conceptual model of CRCI, few studies have examined the association between different surgery types and cognitive problems over time. Second, the prevailing biological mechanistic theory linking the cancer experience with cognitive problems is increases in peripheral inflammation resulting in neuroinflammation. However, a paucity of studies have examined associations between inflammation and CRCI, even fewer have investigated this relationship longitudinally, and only one study to our knowledge that has interrogated within-subject associations. Third, most studies have examined mean levels of cognitive problems over time, which masks heterogeneity. Therefore, investigations into distinct group-based trajectories of cognitive problems over time in breast cancer survivorship are required. This approach will also enable the identification of various clinical, psychological, and biological risk factors for elevated cognitive problems throughout survivorship.

Thus, this dissertation comprises three different studies of breast cancer-related cognitive impairment. Study 1, "Surgery-Chemo-Brain?" The role of surgery in cancer-related cognitive impairment in breast cancer survivors," assessed the associations between different surgery types and perceived and objective cognitive problems over time. Study 2, "The role of peripheral inflammation in cancer-related cognitive problems," assessed between- and within-subjects associations between inflammation and perceived and objective cognitive problems longitudinally. Study 3 "Trajectories of perceived and objective breast cancer-related cognitive problems," characterized group-based trajectories of perceived cognitive problems as well as identified clinical, psychological, and biological risk factors for group membership. We used rich biobehavioral data from one or both of two longitudinal observational cohort studies of breast

cancer survivors, the RISE and Mind-Body Studies, to conduct these studies. Together, these studies further our understanding of clinical drivers of, biological mechanisms of, and risk factors for trajectories of CRCI.

The dissertation of Arielle Radin is approved.

Patricia A. Ganz

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University of California, Los Angeles

2023

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Curriculum Vitae (abbreviated)

EDUCATION

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2017	Honorable Mention, NSF Graduate Research Fellowship Program
2017	UCLA Alumni Fellowship
2017	Stevan & Marilyn Simon Family Scholarship
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2010-2013	Columbia University Dean's List

PEER-REVIEWED PUBLICATIONS

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CONFERENCE PRESENTATIONS & POSTERS (ABBREVIATED)

Radin A, Ganz PA, Irwin M, Cole S, Bower JE (2023, June). Sensitivity to inflammation effects on cancer-related cognitive problems: moderation by age and chemotherapy. Poster to be presented at: Psychoneuroimmunology Research Society Annual Scientific Meeting; Boulder, Colorado.

Radin A, Ganz PA, Bower JE (2022, April). The physical toll of more extensive breast cancer surgery: associations with inflammation, depressive symptoms, and fatigue. Poster presentation at: Society for Behavioral Medicine; Baltimore, Maryland.

Radin A, Ganz PA, Crespi C, Bower JE (2022, March). Sleep, fatigue, depression, and pain following breast cancer surgery: lumpectomy versus mastectomy. Oral presentation at: American Psychosomatic Society Annual Scientific Meeting; Long Beach, California.

Radin A, Ganz PA, Bower JE (2021, May). Does extent of breast cancer surgery impact inflammation and fatigue? More is not better. Oral presentation at: Psychoneuroimmunology Research Society Annual Scientific Meeting; Virtual Conference

Radin A, Al-Akash L, Paine E, Gleason C, Gautam N, LeRaybaud N, Bower JE. (2020, December). Will life ever go back to normal? The effects of COVID-19 beliefs and behaviors on mental health in undergraduate students. Poster presented at: American Psychosomatic Society Virtual Conference

Chapter 1: General Introduction to the Dissertation

A. Breast Cancer: Incidence, Treatments, and Prognosis

Breast cancer is the most common cancer globally, accounting for 12% of all new annual cancer cases worldwide. Within the United States, breast cancer is the leading cancer among women with 1 in 8 developing breast cancer in their lifetime (American Cancer Society, 2019). Breast cancer can be diagnosed at various stages (0-IV), which are determined by the tumor's presentation in the breast(s) and in other organs. Breast cancer can be non-invasive (stage 0, ductal carcinoma in situ (DCIS)) or invasive in which abnormal cells have broken through the walls of the glands or ducts where they originated and grow into the surrounding breast tissue. Stage IV breast cancer describes "advanced" or "metastatic" cancer that has spread beyond the breast and nearby lymph nodes to other organs such as the lungs, distant lymph nodes, bones, brain, skin, and/or liver. In 2021, an estimated 281,550 new cases of invasive breast cancer and 49,290 new cases of non-invasive breast cancer are expected to be diagnosed in women in the United States (American Cancer Society, 2023).

Treatments for breast cancer include surgical excision of the primary tumor either through breast conserving approaches (lumpectomy) or removal of one or both breasts (unilateral and bilateral mastectomy, respectively) (Sakorafas, 2001). Patients may also have a sentinel lymph node biopsy in which the lymph node(s) under the arm is removed, or a less common axillary lymph node dissection in which several lymph nodes under the arm are removed, in order to examine whether the cancer has spread to these nearby sites (Veronesi et al., 1996). Women can receive chemotherapy either prior to surgery (neoadjuvant), in order to shrink the tumor before excision and evaluate whether the tumor is responsive to chemotherapy, or after surgery (adjuvant) in order to treat any residual cancer cells (Anampa, Makower, & Sparano,

2015; Smith et al., 2002). Chemotherapies include anthracyclines, such as doxorubicin (Adriamycin) and epirubicin (Ellence), taxanes, such as paclitaxel (Taxol) and docetaxel (Taxotere), 5-fluorouracil (5-FU) or capecitabine, cyclophosphamide (Cytoxan), and carboplatin (Paraplatin). For women who received unilateral or bilateral mastectomies, autologous breast reconstruction using the woman's own fat or implant-based breast reconstruction might also be performed either during the mastectomy operation (immediate reconstruction) or at another time (delayed reconstruction) (Cordeiro, 2008). Radiation therapy is also commonly used after breast conserving surgery and reduces the risk of local recurrence (Whelan et al., 2010). Following the initial treatment phase comprising surgery with or without chemotherapy and/or radiation, women whose tumors are estrogen receptor (ER) positive may also be prescribed endocrine therapy for 5-10 years. Endocrine therapies, most commonly including non-steroidal antiestrogens such as the first-line endocrine therapy for all breast cancer stages, tamoxifen, and aromatase inhibitors, work by blocking the production of estrogen or the action of estrogen at the cellular level (Buzdar & Hortobagyi, 1998). If a woman tests positive for human epidermal growth factor receptor 2 (HER2), which promotes the growth of breast cancer cells, she may also be prescribed trastuzumab (Herceptin) (Dean-Colomb & Esteva, 2008).

Due to advances in early detection and treatments, there has been a 40% reduction in overall breast cancer deaths from 1989 to 2007 (American Cancer Society, 2019). Additionally, genetic testing for germline mutations *BRCA1* and *BRCA2* in women with a family history of breast cancer allows for increased surveillance and earlier usage of risk-reduction strategies (Valencia et al., 2017). Further, gene-expression profiling (most commonly, the Mammaprint genomic test, which can be used for both ER-positive and ER-negative tumors) aids in guiding treatment selection by using genomic information from tumor biopsies (Slodkowska & Ross,

2014). In turn, breast cancer prognosis has become increasingly promising with 91% of women surviving 5 years after diagnosis, 84% surviving after 10 years, and 80% after 15 years. This has resulted in more than 3.8 million women living with breast cancer in the United States as of January 2022 (American Cancer Society, 2023).

Given the tremendous growth in the breast cancer survivor population, there has been an increasing emphasis on understanding how the cancer diagnosis and treatment experience impacts quality of life late into survivorship. The National Cancer Institute (NCI) considers a patient a cancer "survivor" from the time of diagnosis until end of life; for the purposes of this paper, we designate survivorship to start at the time of primary treatment completion. Life does not simply go "back to normal" when a woman completes her breast cancer treatment course. The "re-entry" phase brings unique challenges as women lose their safety net of active medical treatment and supportive care team (Stanton, 2012). Survivors are faced with resuming or altering their formal roles both at home and at work while managing the psychological side effects of the cancer experience including fear of recurrence, depressive symptoms, and anxiety. Below is a representative quote from a breast cancer survivor on her experience transitioning into the re-entry phase (Rowland, Hewitt, & Ganz, 2006).

> "After my very last radiation treatment for breast cancer, I lay on a cold steel table hairless, half-dressed and astonished by the tears streaming down my face. I thought I would feel happy about finally reaching the end of treatment, but instead I was sobbing. At the time, I wasn't sure what emotions I was feeling. Looking back, I think I cried because this body had so bravely made it through 18 months of surgery, chemotherapy, and radiation. Ironically, I also cried because I would not be coming back to that familiar

table where I had been comforted and encouraged. Instead of joyous, I felt lonely, abandoned and terrified. This was the rocky beginning of cancer survivorship for me."—Elizabeth D. McKinley, MD, MPH

Breast cancer survivors also experience long-term physical or behavioral side effects from cancer and its treatments (Ganz, 2006). Adverse effects that are present during treatment, such as cancer-related fatigue, can become chronic and persist for months or years into survivorship. Women might also exhibit late effects of treatment that are generally absent or subclinical at the end of treatment but manifest later (Aziz, 2002). Behavioral symptoms that are most common in breast cancer include fatigue, insomnia, depression, and cognitive problems and may endure for months or years following treatments (Bower, 2008). These behavioral symptoms can disrupt a survivor's quality of life and may impact treatment adherence, morbidity and mortality (Bower, 2008). Therefore, examinations into the etiology of these behavioral symptoms and mechanisms that explain their onset and maintenance will aid in identifying interventions that support the longevity and well-being of this growing population.

B. Cancer-Related Cognitive Impairment: Incidence, Presentation, and Assessment

Incidence: Cognitive impairment during and after treatments for breast cancer is one of the most common and troublesome consequences of the cancer experience. Referred to as cancer-related cognitive impairment (CRCI), women report experiencing difficulties with memory, multi-tasking, and keeping up with the demands of what used to be cognitively manageable tasks (Bolton & Isaacs, 2018; Myers, 2013). Traditionally, CRCI was thought to be driven by the cytotoxic effects of chemotherapy, with patients referring to the experience as

"chemo-brain" or "chemo-fog" (Wefel & Schagen, 2012). Indeed, initial studies of women who had received chemotherapy reported 1-year incidence ranges between 17-75%; however, most of these studies assessed women cross-sectionally using subjective measures (Cerulla Torrente, Navarro Pastor, & de la Osa Chaparro, 2020). When examining results of studies that employed objective assessments, the incidence is closer to 30-40% (Vardy, Bray, & Dhillon, 2017). Cross-sectional studies of women late into survivorship also report that cognitive problems can persist for 10-20 years following chemotherapy completion (Koppelmans et al., 2012; Stouten-Kemperman et al., 2015).

The first longitudinal study of chemotherapy and CRCI was published in 2004; Wefel and colleagues assessed 18 women with a neuropsychological battery before adjuvant chemotherapy, and 6 and 18 months later (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). They found that 33% of women exhibited cognitive impairment (defined as a z score less than or equal to −1.5 for more than 1 test or less than or equal to −2.0 for a single test) before the start of chemotherapy. Relative to baseline scores, 61% of women exhibited a decline in cognitive performance at 6 months post-chemotherapy, and 50% of those women continued to exhibit that impairment at 18 months. Subsequent longitudinal studies of women undergoing chemotherapy that included a pre-treatment assessment also found differences between patients and healthy controls in perceived and objective cognitive problems before the start of chemotherapy (Hermelink et al., 2007; Janelsins et al., 2018, 2016; Jansen, Cooper, Dodd, & Miaskowski, 2011). Most of these studies find evidence for impairment relative to healthy controls as well as changes from pre- to post-chemotherapy. However, a recent systematic review of 16 studies that assessed women before and after chemotherapy for brain changes that included healthy-matched or disease-specific controls did not find support for baseline differences in neuropsychological

testing (Sousa, Almeida, Bessa, & Pereira, 2020). Of note, because these studies used brain imaging methodologies, they had much smaller sample sizes than most of the longitudinal studies that focused on neuropsychological testing; therefore, it is likely that they were not powered to detect differences in performance. On the other hand, a recent systematic review of 17 longitudinal studies of objective CRCI in breast cancer patients found impairment prevalence estimates of 25% before chemotherapy, 24% after chemotherapy, and 21% at 1 year following chemotherapy (Dijkshoorn et al., 2021). As for decline from pre-treatment, 24% of women exhibited poorer performance following treatment and 24% exhibited decline at 1-year post-treatment. Across these studies, receipt of chemotherapy was associated with a greater risk of cognitive impairment and decline than women without chemotherapy and healthy controls. Therefore, depending on how CRCI is measured (objective vs. perceived), the study design (cross-sectional, longitudinal), and how CRCI is defined (decline, impairment), different results for the effects of chemotherapy emerge.

Importantly, women participating in studies examining the associations between chemotherapy and CRCI typically experience a host of other treatments in combination with their chemotherapy. Undergoing surgical excision of the primary tumor before the start of chemotherapy, receiving radiation after chemotherapy, as well as taking hormone therapy for years following primary treatments likely influence the results of these studies. Therefore, "chemo-brain" is too restrictive of a term and does not accurately describe this clinical phenomenon (Hurria, Somlo, & Ahles, 2007). Indeed, studies have shown that chemotherapy when combined with radiation is associated with greater perceived cognitive problems (Ganz, Kwan, et al., 2013). Further, radiation alone has been shown to be associated with impairments in verbal memory (Quesnel, Savard, & Ivers, 2009). Additionally, endocrine therapy has been

shown to be associated with greater language and communication cognitive complaints 6 months after therapy initiation (Ganz et al., 2014). Of note, when examining the effects of endocrine therapy on neuropsychological performance over 6 years following treatment completion, there were no effects of endocrine therapy on objective cognitive functioning or impairment (Van Dyk et al., 2019). Therefore, examining the influences of other common breast cancer treatments on both perceived and objective cognitive problems is critical.

Presentation and Assessment: Clinically, the presentation of cancer-related cognitive impairment varies from individual to individual but common themes emerge. Objective assessments of various cognitive functions show deficits in domains including memory, attention, executive functioning, and processing speed (Ahles, Root, & Ryan, 2012; Janelsins, Kesler, Ahles, & Morrow, 2014). Patient-reported subjective assessments also reflect deficits in these domains. A majority of women who experience CRCI report difficulties with memory as being their greatest concern, having trouble remembering important events like birthdays and scheduled appointments (Von Ah, Habermann, Carpenter, & Schneider, 2013). Women also exhibit objective problems with processing speed, corresponding with subjective reports that they feel less mentally sharp and noticing that tasks they used to complete regularly feel more difficult, and take longer, than before their cancer diagnosis (Padgett et al., 2020). Assessments of attention and concentration also reflect deficits, with women indicating that they find it more difficult to focus during meetings or keep their minds from wandering (Bolton & Isaacs, 2018). Language processes are also objectively compromised, corresponding with reports that survivors have trouble finding and producing words as quickly as they used to (Myers, 2013). Lastly, women commonly exhibit difficulties with higher-level cognitive processes (i.e., executive functioning), which results in difficulties with multi-tasking and critical thinking (Henderson,

Cross, & Baraniak, 2019). Disruptions in these cognitive processes are distressing and can impact quality of life (Von Ah et al., 2013). Indeed, survivors report that distress and reduced self-efficacy due to cognitive problems lead them to withdraw from work and avoid more demanding tasks (Boykoff, Moieni, & Subramanian, 2009).

To quantify the presence and magnitude of CRCI, researchers and clinicians use a variety of subjective and objective assessments. Subjective measures of perceived CRCI most commonly used in the literature include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), the Functional Assessment of Cancer Treatment–Cognitive Function (FACT-Cog), and the Cognitive Failures Questionnaire (CFQ) (Henneghan et al., 2021). The Patient's Assessment of Own Functioning Inventory (PAOFI) has also been validated in breast cancer patient samples (Bell, Terhorst, & Bender, 2013; Van Dyk, Ganz, Ercoli, Petersen, & Crespi, 2016). These measures differ greatly in terms of how many items assess cognitive functioning (e.g., the EORTC-QOL only has 2 items), the domains of cognitive functioning they tap, as well as the time frame to which questions refer. These differences result in heterogeneity across studies, hindering the progress of our understanding of CRCI etiology. In 2021, the Cancer Neuroscience Initiative Working Group put forth recommendations for assessments of patient-reported CRCI in order to promote standardization and suggested the use of the National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Scales (Henneghan et al., 2021). This measure is comprised of items from the FACT-Cog and has assessments of cognitive abilities as well as cognitive impairment.

The gold standard for assessing CRCI is the use of objective neuropsychological assessments. There are several validated neuropsychological batteries that assess cognitive

functions compromised in CRCI including learning and memory, executive functioning, processing speed, and working memory. In 2011, the International Cognition and Cancer Task Force put forth recommendations for which neuropsychological assessments to use to assess each domain of interest (Wefel, Vardy, Ahles, & Schagen, 2011). Recommended neuropsychological assessments include the Hopkins Verbal Learning Test-Revised (HVLT-R), the Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination. The task force also recommended including supplemental tasks that assess working memory performance, selecting from the Auditory Consonant Trigrams, the Paced Auditory Serial Addition Test (PASAT), Brief Test of Attention, and/or the WAIS-III Letter-Number Sequencing task.

One complicating factor in the study of CRCI is that the correlation between objective and subjective assessments of cognitive problems in the cancer population is weak (Henneghan et al., 2021; Vardy et al., 2006). This is likely driven by the fact that traditional neuropsychological assessments were developed in order to assess frank brain trauma; therefore, they may not be sensitive enough to detect subtle changes in cognitive function in neurologically healthy individuals (Benton, 1994). Other plausible explanations are that neuropsychological testing settings minimize distractions and allow for recruitment of compensatory mechanisms, and perceived memory difficulties might actually reflect deficits in information processing (Ahles & Hurria, 2018). It is also possible that traditional neuropsychological tests are not designed to capture the types of cognitive processes that are dysregulated in CRCI: in a recent review of neuroimaging studies that assessed breast cancer patients before and after chemotherapy, most studies reported perceived cognitive problems (71% of studies) immediately following chemotherapy, whereas only 17% of studies reported objective impairment following

chemotherapy (Sousa et al., 2020). The most frequent cognitive complaints were regarding problem-solving and distraction, which are more difficult to assess with traditional neuropsychological assessments. By no means does this negate the very real consequences that even minor declines in cognition have on a survivor's well-being (Van Dyk & Ganz, 2017). Therefore, it is recommended to include both objective and subjective assessments of cognitive functioning in the study of CRCI (Henneghan et al., 2021).

C. Models of Cancer-Related Cognitive Impairment

Since the first studies of objective CRCI in the 1990's, our understanding of the multifactorial nature of cognitive problems in breast cancer patients has evolved substantially. The initial focus of the study of CRCI was on chemotherapy with cross-sectional studies of objective and perceived cognitive impairment after chemotherapy completion. However, subsequent longitudinal studies demonstrating pre-treatment cognitive problems have highlighted how chemotherapy alone cannot explain these cognitive changes. Therefore, research into CRCI has broadened to include investigations into other demographic, clinical, psychosocial, and biological risk factors (Ahles & Hurria, 2018). Building on 30 years of empirical research, several complex and sophisticated models have been put forth to explain the onset and persistence of CRCI (see Appendix A for an integrative model). Some of these conceptual models take a broad approach to conceptualizing the manifestation of CRCI from a variety of clinical, psychological, and sociodemographic factors. There have also been models proposing biological mechanisms linking the cancer experience broadly with cognitive decline (neuroendocrine/immune pathways). Other models are tied specifically to chemotherapy

exposure. In this section, we detail each of these models and highlight shared features and key distinctions.

There are 3 models of CRCI that conceptualize the many clinical, biological, psychological, and sociodemographic factors that may lead to cognitive problems. Janelsins and colleagues posit that demographic and medical characteristics as well as biological and molecular factors may predispose a survivor to, and/or perpetuate, CRCI (Janelsins et al., 2014). Key demographic factors included in this model are age, race, ethnicity, and socioeconomic status. Medical characteristics listed in their model include stage of disease, menopause status, diet, body mass index (BMI), and "psychological symptoms." Biological and molecular factors are stratified across brain structure and function (metabolism, plasticity, neurogenesis, and oxidative stress), immune function (inflammation, neuroinflammation, and cellular responses), and genetics (APOE, COMT, and DNA damage genes). The authors recognize that not all these proposed factors are empirically based; although factors such as race, ethnicity, socioeconomic status, stage of disease, diet and BMI have not been rigorously tested in regard to CRCI, they have been linked with cognitive decline in the context of aging.

Ahles and Hurria put forth a model that includes similar sociodemographic factors (age, socioeconomic status, education, partner status) and genetic factors (APOE, COMT, and BDNF genes) but extends the scope to include tumor and treatment factors (stage, type, tumor markers, surgery, chemotherapy, endocrine therapy, and radiation), lifestyle factors (smoking, exercise, diet, and sleep hygiene), physiological factors (comorbidities and fatigue), and refines "psychological symptoms" to include stress, anxiety, depression, and cognitive reserve (Ahles & Hurria, 2018). One difference between these models is that Janelsins and colleagues focus on immune function as a biological mechanism whereas Ahles and Hurria include inflammation

underneath the umbrella of allostatic load, which functions broadly as a biological mechanism leading to CRCI. Their allostatic load factor includes cardiovascular factors (blood pressure and heart rate), glucose metabolism, lipid metabolism, HPA axis activity, and inflammation (e.g., pro-inflammatory cytokines, C-reactive protein). Ahles and Hurria also indicate that all predictors in their model potentially interact with one another.

In order to account for these interactions, Ahles and Root proposed a complimentary model that illustrates relationships between contributing factors (Ahles & Root, 2018). Like the previous models, this model includes individual difference factors like tumor characteristics, sociodemographic factors, and genetics. Treatment modality is depicted as having a direct effect on cognitive function, but also affects physiological, psychological, and lifestyle factors as well as allostatic load. These factors are shown to influence one another: physiological factors such as comorbidities, fatigue, and frailty interact with psychological factors like stress/trauma, anxiety, and depression. These psychological factors have bidirectional associations with allostatic load contributors (e.g., inflammation, HPA axis activity), which in turn interact with lifestyle factors. The Ahles and Root model provides a framework for understanding potential physiological, psychological, biological, and lifestyle pathways through which cancer treatments might influence cognitive functioning.

Lastly, Lange and colleagues proposed a model of cognitive functioning in cancer patient populations that includes sociodemographic variables (e.g., education, age, pre-morbid intelligence), clinical variables (e.g., surgery, chemotherapy, endocrine therapy, radiation), comorbidities (vascular risk, diabetes), genetic factors (APOE, COMT, BDNF, and IL-1R1 genes), and biological factors including pro-inflammatory cytokines, blood brain barrier alteration, and cell death (Lange et al., 2019). This model notably distinguishes between

subjective impairment/complaints and objective performance on cognitive tasks. The subjective cognitive problems they highlight include the domains of executive functioning and memory. Objective performance difficulties are noted for the domains of short-term and working memory, prospective memory, attention, and processing speed. They also parse "other altered functions" from cancer treatments that include fatigue, anxiety, depression, post-traumatic stress, motivation, sleep, and menopause.

Two models focus on more specific biological mechanisms linking the cancer experience with cognitive problems. First, Miller and colleagues put forth a neuroendocrine-immune pathway model through which cancer and its treatments result in a host of behavioral alterations, including cognitive dysfunction (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008). This model proposes that clinical factors such as tumor characteristics, metastases, chemotherapy, surgery, and radiation as well as the psychological stress associated with the cancer experience lead to an increase in pro-inflammatory cytokines which is further perpetuated by disrupted sleep and neuroendocrine dysregulation (e.g., reductions in glucocorticoid sensitivity through cytokine signaling pathways). These pro-inflammatory cytokines then impact the CNS leading to increases in corticotropin releasing hormone, reduced serotonin and dopamine, and decreased neuroprotective agents such as growth factors, ultimately leading to cognitive dysfunction.

Second, Andreotti and colleagues put forth a stress-reactivity model that implicates heightened allostatic load in the manifestation and maintenance of CRCI (Andreotti, Root, Ahles, McEwen, & Compas, 2015). They propose that a history of chronically stressful situations (e.g., adverse childhood experiences) combined with psychological distress resulting from cancer diagnosis and treatments serves as a double-hit on allostatic load leading to a similar neuroendocrine-immune cascade posited by Miller and colleagues. HPA axis dysregulation and

inflammation perpetuate one another resulting in changes in brain structure and function leading to neurocognitive changes and cognitive difficulties. Whereas Miller and colleagues emphasize the role of inflammation, Andreotti and colleagues place the emphasis on HPA axis dysregulation given that repeated and prolonged activation of the HPA axis is associated with neuronal atrophy in the prefrontal cortex and hippocampus, and that increases in glucocorticoid levels acutely suppress neuronal excitability and impair memory and attention (Wolf, 2003).

Other models have focused on the effects of chemotherapy on cognitive functioning specifically. Ahles and Saykin proposed four key candidate mechanisms linking chemotherapy exposure with changes in cognition, brain structure, and function: blood brain barrier integrity, accelerated biological aging via DNA damage and telomere shortening, cytokine deregulation, and estrogen or testosterone reduction (Ahles & Saykin, 2007). A core component of this model is shared genetic susceptibility for the development of cancer and cognitive problems. Three proposed genetic susceptibilities include 1) low-efficiency efflux pumps at the blood brain barrier that lead to exposure to toxins in the brain, 2) deficits in DNA-repair mechanisms that lead to greater DNA damage, and 3) dysregulation of the immune response. Patients who present with one or more of these genetic risk factors might exhibit cognitive problems at the time of diagnosis and would be more susceptible to the effects of chemotherapy on cognitive functioning.

In 2007, the Venice cognitive workshop published a model postulating mechanisms of chemotherapy-associated cognitive changes including direct neurotoxic effects (e.g., neuronal injury), oxidative stress and DNA damage, induced hormonal changes, immune dysregulation, and blood clotting in small CNS vessels (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008). Similar to Ahles and Saykin, the workshop attendees emphasized the role of host genetics.

Lastly, a recent paper from Nguyen and Ehrlich proposed molecular mechanisms linking chemotherapy and cognitive functioning (Nguyen & Ehrlich, 2020). Potential mechanisms include reduced neurogenesis, reductions in neuronal spines and dendrites, decreased neurotransmitter release, reduced gliogenesis, blood-brain barrier permeability, and neuroinflammation.

D. Knowledge Gaps in the Study of Cancer-Related Cognitive Impairment

Despite the accumulating evidence from studies over the last 30 years probing breast cancer-related cognitive impairment, its etiology and mechanisms that contribute to its initiation and maintenance into survivorship are still unclear. There are three key knowledge gaps that if explored would aid in clarifying how cognitive problems in this patient population manifest and persist. First, despite its inclusion in almost every conceptual model of CRCI, there has been a paucity of empirical research investigating the impact of surgery on cognitive problems in breast cancer patients and survivors. There is preclinical evidence that supports an effect of surgery on cognitive impairment as well as supporting evidence from cardiac and non-cardiac surgery patients (Fidalgo et al., 2011; Monk et al., 2008; Saczynski et al., 2012; Wan et al., 2007). The impact of surgery on CRCI in breast cancer patients in particular is of key interest given that the first line defense against breast cancer is surgical excision of the primary tumor, which requires a woman with her doctor to decide between various surgical options (breast conserving approaches (lumpectomy) or removal of the entire breast (unilateral or bilateral mastectomy)). Further, despite efforts to "deimplement" prophylactic contralateral mastectomy in women with early stage unilateral breast cancer, rates of elective bilateral mastectomies are rising (Lim, Metcalfe,

& Narod, 2020). Thus, understanding the role surgery has in the onset and maintenance of CRCI will aid in shared decision making regarding surgical options.

Second, the prevailing mechanistic theory linking cancer with cognitive problems is increases in circulating inflammation due to cancer and its treatments. All 3 multifactorial models of CRCI described above indicate a role of pro-inflammatory cytokines and immune mediators in the development of CRCI. However, there is a paucity of empirical evidence that examines the association between concentrations of pro-inflammatory cytokines and objective and subjective assessments of CRCI. Most studies that examine this relationship analyze associations between subjects at a single timepoint along the cancer continuum (Ahles & Root, 2018). Although these studies are helpful in assessing whether, on average, higher inflammation is associated with poorer cognitive functioning, this analytic approach is not conducive to examining how deviations in inflammation from a given patient's average correspond with deviations in perceived and objective cognitive problems. This within-subjects approach has illuminated our understanding of links between inflammation and other cancer-related behavioral symptoms, including fatigue (Bower et al., 2009). Only one recent study has applied this approach to CRCI, finding within subject associations between C-reactive protein (CRP) and perceived cognitive functioning; however, that study focused only on older breast cancer survivors (Carroll et al., 2023). Thus, more research employing longitudinal within-subjects analyses would help illuminate how subtle variations in inflammation and cognitive problems may relate to one another, and potentially interact with age, over time in a diverse samples.

Lastly, there is substantial heterogeneity in cognitive functioning across the breast cancer survivor population. The study of CRCI thus far has been one of averages, which masks considerable variability in the manifestation, maintenance, and resolution of cognitive problems

in this population. Indeed, some women may experience acute treatment effects on cognition that resolve shortly after treatment completion, whereas others might exhibit cognitive problems prior to treatment initiation that persist for years following re-entry. To our knowledge, there has yet to be a study of heterogeneous group-based trajectories using growth mixture models of both perceived and objective cognitive problems in the breast cancer patient and survivor population. Growth mixture modeling would not only illuminate the heterogeneity in the onset and duration of CRCI in this population, but also allow for investigating various predictors of trajectory group membership. Given the multifactorial nature of the existing models of CRCI, a trajectory approach will allow us to examine the influence of proposed sociodemographic, biological, and psychological predictors on group membership. This approach has been successfully used in the study of other behavioral symptoms of breast cancer including fatigue and depressive symptoms (Bower et al., 2021, 2018; Stanton et al., 2015).

This dissertation was designed to address these gaps in the literature and illuminate our understanding of CRCI. Study 1 examined the associations between surgery type and perceived cognitive problems in the RISE Study. We tested a "double hit" model and hypothesized that women who underwent a mastectomy in combination with chemotherapy would endorse more cognitive problems over time as compared to women who underwent a lumpectomy with or without chemotherapy. Study 2 examined between- and within-subjects associations between peripheral concentrations of inflammation and cognitive problems over time. We tested associations between inflammation and perceived cognitive problems over time in two cohorts of breast cancer survivors (RISE and MBS). We hypothesized that between subjects, greater increases in concentrations of circulating inflammatory markers would be associated with greater increases in cognitive problems over time. We also hypothesized that within a given participant,

increases in inflammation relative to that participant's average level of inflammation would be associated with increases in cognitive problems over time. We then examined whether receipt of chemotherapy and age moderated the associations between inflammation and perceived and objective cognitive problems.

Study 3 characterized trajectories of cognitive functioning over time. We identified heterogeneous group trajectories of perceived cognitive problems in the RISE study. We then examined risk factors of trajectory group membership based on prevailing models of CRCI (Ahles & Hurria, 2018; Ahles & Root, 2018; Lange et al., 2019; Miller et al., 2008). These included: demographic variables (age, income, education, employment, partner status); clinical variables (BMI, comorbidities, stage, surgery type (lumpectomy, unilateral mastectomy, bilateral mastectomy), total number of surgeries (1-3), adjuvant therapy type (chemotherapy, radiation), endocrine therapy (yes/no), chemotherapy with endocrine therapy); and psychosocial variables (history of depression (yes/no), baseline levels of fatigue, anxiety and depressive symptoms, sleep disturbance, and cancer-related distress, and childhood adversity).

E. Methods of the Mind-Body and RISE Studies

As described above, this dissertation includes three chapters employing data from one or both of two longitudinal observational studies of breast cancer survivors– the RISE Study and the Mind-Body Study (MBS), described below.

The Research on Inflammation, Stress, and Energy (RISE) Study

The RISE Study was conducted at the University of California, Los Angeles, Cedars-Sinai Medical Center, and other clinical sites in the Los Angeles area (Bower et al., 2019, 2021).

The study was a longitudinal observational study of breast cancer survivors aimed at identifying risk factors and mechanisms for breast cancer-related fatigue. Enrollment in this study began in January 2013 and data ended in July 2015. Inclusion criteria for the RISE Study were as follows: (1) had recently been diagnosed with stage 0 to stage IIIA breast cancer; (2) had not yet initiated adjuvant or neoadjuvant therapy with radiotherapy, chemotherapy, or endocrine therapy; and (3) were proficient in English. The primary recruitment sites for the RISE Study were the University of California, Los Angeles and Cedars-Sinai Medical Center. A total of 270 women enrolled in the study.

Procedures

Participants completed assessments at baseline (before the start of chemotherapy/ radiation); at the end of treatment (for women who received chemotherapy and/or radiation); and at 6-, 12-, and 18-month post-treatment follow-up study visits. A subset of women agreed to longer-term annual survey-based follow-up assessments for up to 5 years following treatment completion. The RISE Study CONSORT diagram is included in Appendix D.

Measures

The RISE Study includes several measures, and we will be focusing here on assessments included in the dissertation studies. Data for the RISE Study were collected through psychological and behavioral self-report questionnaires and interviews, medical chart review, and blood collection.

Demographic and Clinical Characteristics. Demographic and clinical characteristics were obtained from both self-report and medical records. These included: race/ethnicity, age, marital status, income, employment, cancer stage, surgery type, receipt of chemotherapy and/or radiation, and receipt of endocrine therapy.

Perceived cognitive problems. Perceived cognitive problems were assessed using the mental subscale of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) (Stein, Martin, Hann, & Jacobsen, 1998). The MFSI-SF assesses symptoms in the last 7 days on a Likert scale ranging from "Not at all" (0) to "Extremely" (4). The mental subscale includes 6 items including "I have trouble remembering things" and "I am unable to concentrate." Responses are summed resulting in a score ranging from 0 to 24, with higher scores indicating the presence of more symptomatology. The items of the MFSI-SF Mental subscale capture several key domains shown to be altered in breast cancer patients, including problems with attention, concentration, and memory (Ahles & Root, 2018). Further, the MFSI-SF mental subscale was highly correlated ($r = 0.85$) with a widely used measure of cancer-related cognitive complaints, the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-cog) in an earlier study of breast cancer survivors conducted by the committee members that included both measures, supporting the use of this scale to assess cognitive complaints (personal communication, unpublished data).

Fatigue. Fatigue was assessed using the MFSI-SF general fatigue subscale, which includes 6 items including "I feel fatigued" and "I am worn out." The MFSI-SF general fatigue subscale assesses symptoms in the last 7 days on a Likert scale ranging from "Not at all" (0) to "Extremely" (4). Responses from 6 items are summed resulting in a score ranging from 0-24.

Anxiety symptoms. Anxiety symptoms were assessed using 4 items from the MFSI-SF emotional fatigue subscale, which includes the items "I feel tense," "I feel nervous," "I feel relaxed," and "I feel calm (reverse scored)." Responses from these 4 items are summed resulting in a score ranging from 0-16.

Depressive symptoms. Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression scale (CES-D) (Hann, Winter, & Jacobsen, 1999; Schroevers, Sanderman, Van Sonderen, & Ranchor, 2000). The CES-D assesses symptoms in the last 7 days on a Likert scale ranging from "Rarely or none of the time (less than 1 day)" (0) to "Most or all of the time (5-7 days)" (3). Responses from 20 items are summed resulting in a score ranging from 0 to 60, with higher scores indicating the presence of more symptomatology.

Sleep. Subjective sleep disturbance was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Akman, Yavuzsen, Sevgen, Ellidokuz, & Yilmaz, 2015; Beck, Schwartz, Towsley, Dudley, & Barsevick, 2004). The PSQI assesses sleep over the last month using 19 individual items that form seven component scores, which combined into one overall sleep quality measure: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.

Childhood adversity. Adverse childhood events were assessed using the Childhood Trauma Questionnaire Short Form (CTQ), a 25-item valid and reliable measure of childhood adversity (Bernstein, Fink, Handelsman, & Foote, 1994). Items are grouped into subscales including

physical, emotional, and sexual abuse as well as physical and emotional neglect that occurred during childhood. Items for subscales are scored between 1 ("Never true") to 5 ("Very often true").

Inflammation.

At baseline, 6-, 12-, and 18-month study visits, blood samples were collected to assess circulating inflammatory markers. EDTA whole blood was collected, transported on wet ice, and plasma aliquots were prepared and frozen at -80°C until assayed for biomarkers. All plasma samples from a single subject were assayed together on the same 96-well plate to minimize effects of inter-assay variation; all samples were assayed in duplicate, and an internal quality control sample was included on every plate. We focus on three inflammatory markers: soluble tumor necrosis factor (TNF) receptor type II (sTNF-RII), interleukin (IL)-6, and C-reactive protein (CRP). These markers are reliable indicators of inflammation (Brockhaus, 1997; Germolec, Shipkowski, Frawley, & Evans, 2018), have been associated with behavioral symptoms in studies with breast cancer survivors (Bower et al., 2011; Cheung et al., 2015; Ganz, Bower, et al., 2013), and are also included in the Mind-Body Study. CRP and sTNF-RII were measured by Human Quantikine ELISA (R&D Systems, Minneapolis, MN) according to the manufacturer's protocols, with the following modifications. For sTNF-RII, samples were diluted 25-fold, to yield a standard curve range of 195-12,500 pg/mL, taking the dilution into account. For CRP, samples were diluted 500-fold, and the standard curve was extended to 0.39 ng/mL, to yield a lower limit of 0.2 mg/L, taking the dilution into account. Samples with CRP concentrations above the range of the standard curve (25 mg/L) were estimated using extrapolated values. IL6 was measured in a multiplex assay utilizing a V-PLEX Custom Human

Cytokine Proinflammatory Panel on the Meso Scale Discovery (MSD) electrochemiluminescence platform and Discovery Workbench software (MSD, Rockville, MD). Samples were assayed at a 2-fold dilution according to the manufacturer's protocol, with an eight-point standard curve with tripling dilutions. Analyte-specific lower limits were calculated for each assay plate, with typical lower limits of 0.2 pg/mL, taking the dilution into account. Values below the lower limit of detection (LLD) were replaced with values that were halfway between 0 and the LLD. For all plasma biomarkers, inter-assay coefficients of variation were less than or equal to 10% and mean intra-assay coefficients of variation were less than 5%.

The Mind-Body Study (MBS)

The MBS, conducted at the University of California, Los Angeles, was a longitudinal observational study of breast cancer survivors aimed at characterizing the effects of endocrine therapy on cognitive functioning (Ganz, Bower, et al., 2013; Ganz, Kwan, et al., 2013; Ganz, Petersen, Bower, & Crespi, 2016; Ganz et al., 2014). Enrollment in the study began in May 2007 and long-term follow-up ended in July 2014. Inclusion criteria for the MBS were as follows: (1) age 21–65 years; (2) diagnosed with stage 0, I, II, or IIIA breast cancer; (3) completed primary breast cancer treatments (surgery, radiation, and/or chemotherapy) within the past 3 months; (4) had not started endocrine therapy; and (5) proficient in the English language. Exclusion criteria were (1) evidence of current or past disorder/disease of the central nervous system or any medical condition that might be expected to impact cognitive functioning (e.g. multiple sclerosis, thyroid dysfunction); (2) history of head trauma with loss of consciousness greater than 30 min; (3) epilepsy, dementia, or severe learning disability; (4) current psychotic-spectrum disorder (e.g. schizophrenia), major affective disorder, or substance abuse or dependence; (5) history of whole

brain irradiation or surgery; (6) history of past cancer treatment with chemotherapy; (7) active diagnosis of autoimmune and/or inflammatory disorder or disorders that may influence inflammatory processes; (8) chronic use of oral steroid medication; and (9) hormone therapy (estrogen, progestin compounds) other than vaginal estrogen. Current major affective disorder was assessed by asking if women had depressed mood and/or anhedonia nearly every day for 2 weeks; women were considered ineligible if they said yes to this question and were not under the care of a physician. A total of 191 women were enrolled in this study.

Procedures

Initial (baseline) study assessments were conducted within three months after completion of primary treatment (surgery, radiation, and/or chemotherapy) and before onset of endocrine therapy, if indicated. In-person follow-up assessments were conducted at 6-months and 1-year post-treatment, with a final follow-up thereafter (3-6 years post-treatment). Subsets of women also completed surveys at additional time-points including 2, 3, and 4 years from baseline. Neuropsychological testing was conducted, and blood was drawn, at baseline, 6-month, 1-year and final follow-up (3-6 years post-treatment) assessments, and questionnaires were administered at each assessment. The Mind-Body Study CONSORT diagram is included in Appendix E.

Measures

Data for the MBS were collected at baseline and follow-up assessments through psychological and behavioral self-report questionnaires and interviews, neuropsychological testing, medical chart review, and blood collection.

Demographic and Clinical Characteristics. Demographic and clinical characteristics were obtained from both self-report and medical records. These included: race/ethnicity, age, marital status, income, employment, cancer stage, surgery type, receipt of chemotherapy and/or radiation, and receipt of endocrine therapy.

Objective cognitive problems. Participants completed a full neuropsychological test battery (Ganz et al., 2014; Van Dyk, Petersen, & Ganz, 2016). We focus on domains of cognitive functioning that are commonly disrupted in CRCI and that have the strongest evidence for links with inflammation in cancer and non-cancer samples: verbal memory and executive functioning (Janelsins et al., 2014). We conducted an expansive review of the literature on associations between inflammation and cognitive functioning (Radin et al., unpublished) and found the most consistent evidence for associations between inflammatory variables and the California Verbal Learning Test (CVLT)-II (verbal memory) and the Trail Making Test (TMT) Part B (executive functioning). For each cognitive domain of interest, neuropsychological test scores were transformed to z scores using published normative data. IQ was assessed at baseline using the Wechsler Test of Adult Reading (WTAR) (Ryan & Lopez, 2001).

Verbal Memory:

- California Verbal Learning Test (CVLT)-II List A Long Delay Free Recall (Delis, Kramer, Kaplan, & Ober, 2000)

Executive Functioning:

- Trail Making Test (TMT) Part B (Heaton, Miller, Taylor, & Grant, 2004; Reitan, 1958)

Perceived cognitive problems. We used the MFSI-SF mental subscale to streamline analyses and identify comparable trajectories of perceived CRCI in both the RISE and MBS samples.

Fatigue. Like the RISE Study, fatigue was assessed using the general fatigue subscale of the MFSI-SF.

Anxiety symptoms. Anxiety symptoms were assessed using the State Anxiety Inventory, which includes items such as "I feel tense" and "I feel nervous" (Spielberger, 1983). Items are anchored to how participants feel in "this moment" and are ranked on a 4-point scale (e.g., from "Almost Never" to "Almost Always"). Responses from 20 items are summed resulting in a score ranging from 20-80 with higher scores indicating greater anxiety.

Depressive symptoms. Depressive symptoms were assessed with the Beck Depression Inventory (BDI-II), a valid and reliable measure of depression (Beck, Steer, & Brown, 1996). The BDI-II assesses depressive symptoms over the past 2 weeks and comprises 21 questions assessing somatic, cognitive, and affective dimensions of depression. Clinical cutoffs for this version of the BDI are 0-13: minimal depression; 14-19: mild depression; 20-28: moderate depressions; and 29-63: severe depression.

Sleep. Consistent with the RISE Study, sleep disturbance was assessed using the Pittsburgh Sleep Quality Index (PSQI).

Inflammation.

At baseline, 6-month, 1-year and final follow-up (3-6 years post-treatment) blood samples were collected to assess circulating inflammatory markers. EDTA whole blood was collected, transported on wet ice, and plasma aliquots were prepared and frozen at -80°C until assayed for biomarkers. All plasma samples from a single subject were assayed together on the same 96-well plate to minimize effects of inter-assay variation; all samples were assayed in duplicate, and an internal quality control sample was included on every plate. We focus on three inflammatory markers: soluble tumor necrosis factor (TNF) receptor type II (sTNF-RII), interleukin (IL)-6, and C-reactive protein (CRP). These markers are reliable indicators of inflammation (Brockhaus, 1997; Germolec et al., 2018), have been associated with behavioral symptoms in studies with breast cancer survivors (Bower et al., 2011; Cheung et al., 2015; Ganz, Bower, et al., 2013), and are also included in the RISE Study. Plasma levels of sTNF-RII were determined by regular sensitivity enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN) according to the manufacturer's protocols, with a lower limit of detection of 234 pg/mL. Plasma levels of IL-6 was determined by high sensitivity ELISA (lower limit 0.2 pg/mL) (R&D Systems, Minneapolis, MN). CRP levels were determined by a high-sensitivity enzyme-linked immunosorbent assay (Immundiagnostik; ALPCO Immunoassays, Salem, NH) according to the manufacturer's protocol but with an extended standard curve to a lower limit of detection of 0.2 mg/L. All samples were run in duplicate, and assays were repeated on two separate assay days for sTNF-RII; inter- and intra-assay mean levels were used in all analyses. The inter- and intra-assay precision of all tests were less than or equal to 10%.

Chapter 2: "Surgery-Chemo-Brain?" The role of surgery in cancer-related cognitive impairment in breast cancer survivors [currently under review for publication]

A. Abstract

Purpose: Cancer-related cognitive impairment (CRCI) is a troublesome experience for breast cancer survivors often attributed to chemotherapy (CT). However, the role of other treatment exposures, particularly cancer surgeries, has rarely been examined in relation to CRCI.

Methods: Data were from a longitudinal, observational study of breast cancer survivors who completed assessments after surgery but before the start of adjuvant therapies and at post-treatment, 6-, 12-, and 18-month follow-ups. Perceived cognitive problems were assessed at each time point. Linear mixed models tested whether treatment type (lumpectomy or mastectomy with or without CT) was associated with perceived cognitive problems over time.

Results: Of the 214 participants, 112 (52%) had a lumpectomy without CT, 42 (19%) had a lumpectomy with CT, 38 (17%) had a mastectomy without CT, and 22 (10%) had a mastectomy with CT. The interaction between time and treatment type was significant only for the mastectomy with CT group ($p = .007$). This group on average experienced increases in cognitive problems that peaked at 18 months (linear effect: $b = .004$, $p < .001$). This linear effect was significantly steeper than mastectomy without CT ($p = .001$), lumpectomy without CT ($p < .001$), and lumpectomy with CT ($p = .047$).

Conclusions: Mastectomy in conjunction with chemotherapy is associated with greater cognitive problems over time as compared to mastectomy alone or lumpectomy with or without CT. Understanding how treatment options might impact cognitive functioning well into survivorship might guide women in decision making about more extensive surgery, especially when not clinically indicated.

B. Introduction

Cognitive problems that arise during and after cancer treatments are among the most troublesome consequences of the cancer experience (Bower, 2008; Myers, 2013). Formally referred to as cancer-related cognitive impairment (CRCI), patients often report experiencing difficulties with memory, multi-tasking, and keeping up with the demands of what used to be cognitively manageable tasks (Bolton & Isaacs, 2018; Myers, 2013). Historically, CRCI was primarily associated with the receipt of cytotoxic chemotherapy (CT), with patients referring to the experience as "chemo-brain" or "chemo-fog "(Wefel & Schagen, 2012). However, recent research finds that patients can experience CRCI even before the start of chemotherapy, suggesting a role for other factors (Dijkshoorn et al., 2021). In particular, little is known about the contribution of surgical treatment of breast cancer to CRCI, and whether such treatment in combination with CT might exacerbate CRCI.

Surgical excision of the primary tumor is an essential procedure that provides local control of breast cancer and involves either breast conservation (lumpectomy) or breast removal (unilateral or bilateral mastectomy) (Sakorafas, 2001). When possible, breast conserving approaches are recommended in lieu of breast removal given that they are equally efficacious for early stage disease and minimize physical and psychological impact from a more extensive

surgical procedure (Fisher et al., 2002). Bilateral mastectomies may be clinically indicated when a woman has breast cancer present in both breasts. Women may also elect to undergo a bilateral mastectomy for unilateral breast cancer as a risk-reducing strategy due to a high-risk genetic profile (e.g., *BRCA*1/2 carriers), in order to minimize fear of recurrence, or for cosmetic symmetry (Lim et al., 2020).

Previous research on psychosocial effects of surgery in women with breast cancer has focused primarily on body image, sexual health, and pain (Ganz, Coscarelli, Lee, Polinsky, & Tan, 1992; Pesce, Jaffe, Kuchta, Yao, & Sisco, 2021; Pozo et al., 1992; Rosenberg et al., 2020; Rowland et al., 2000). However, research in non-cancer populations (including cardiac and non-cardiac patients) has examined effects of surgery on cognitive function. These studies have shown that surgery with general anesthesia is associated with postoperative cognitive dysfunction, especially in older patients (Monk et al., 2008; Saczynski et al., 2012). The presentation of postoperative cognitive dysfunction mirrors that of CRCI: compromised cognitive domains include attention, memory, executive function and speed of information processing, with subjective complaints mainly concerning memory and reduced ability to handle intellectual challenges (Krenk, Rasmussen, & Kehlet, 2010).

Despite its inclusion in almost every conceptual model of CRCI (Ahles & Hurria, 2018; Ahles & Root, 2018; M. Lange et al., 2019), few empirical studies have examined the impact of surgery on cognitive problems in breast cancer patients and survivors (Appendix B). In a study of post-operative cancer survivors who had not yet started adjuvant therapies, 29.6% of patients exhibited CRCI as assessed by neuropsychological tests, though surgery type was not explicitly tested as a contributor to these effects (Lycke et al., 2017). In a cross-sectional study of breast cancer patients assessed 2 months after either tumor biopsy (50%) or breast surgical resection

(50%), women who had undergone lumpectomy or mastectomy were twice as likely to be cognitively impaired on neuropsychological assessments than women who had undergone a biopsy (Wefel, Lenzi, Theriault, Buzdar, et al., 2004). One longitudinal study evaluated 146 women who were presenting for mammography screening before diagnosis and approximately 2 months later (1 month after surgery for those diagnosed with breast cancer) (Hedayati, Schedin, Nyman, Alinaghizadeh, & Albertsson, 2011). Using a computerized neuropsychological battery, they found that women who were surgically treated for breast cancer did not exhibit expected practice effects on tasks of attention and processing speed from pre- to post-surgery that were evidenced in healthy controls. Further, regarding changes within the surgery group, women who received mastectomy exhibited decreases in attention and processing speed whereas those who underwent lumpectomy did not.

To our knowledge, there has yet to be an examination of cognitive problems among women who received different types of breast cancer surgeries (lumpectomy, mastectomy) beyond the acute post-surgical period. Further, in studies of CT associated CRCI, analyses often control for surgery type instead of examining its potential influence on the magnitude and trajectory of CRCI. Indeed, it is possible that more extensive surgery could prime patients for the effects of CT, resulting in a "double-hit" leading to greater cognitive problems. Understanding whether surgery type is associated with cognitive problems in survivorship will have relevance for helping prepare women for potential cognitive side effects following their surgery and adjuvant therapies. Therefore, the current study aimed to examine cognitive complaints in a longitudinal study of women with early-stage breast cancer undergoing either lumpectomy with or without CT or mastectomy with or without CT who completed assessments up to 24 months following surgery.

C. Materials and Methods

Participants and Procedures

This study was a secondary analysis employing data from a longitudinal, observational study of fatigue in women with breast cancer (RISE study) (Bower et al., 2019, 2021). Participants were recruited from oncology practices in Los Angeles to participate if they: 1) had been diagnosed with stage 0 to stage IIIA breast cancer; 2) had not yet started adjuvant or neoadjuvant therapy with radiotherapy, CT, or endocrine therapy; 3) and were proficient in English. Assessments were scheduled to capture acute and chronic effects of adjuvant therapies and so were conducted after surgery but prior to starting radiation and/or chemotherapy. Participants completed assessments at baseline (after surgery but before the start of adjuvant therapy) and at the end of treatment (for those who received radiation and/or CT). Additional follow-up assessments were conducted at 6, 12, and 18 months post-treatment (following surgery for those who did not receive adjuvant treatments and following radiation and/or chemotherapy for those who did). The institutional review boards at the University of California at Los Angeles and Cedars-Sinai Medical Center approved the study, and all participants provided written informed consent.

The RISE study enrolled 270 women and had excellent retention over the follow-up period (Bower et al., 2021). For the present study, we excluded women who did not have surgery as their initial treatment (i.e., women treated with neoadjuvant CT; n = 25) and women who completed the baseline assessment more than 60 days after surgical resection of their tumor (n = 30), resulting in a sample of 215 women. We chose to exclude these participants from the current analysis to capture acute effects of surgery prior to CT exposure. CT status was not available for

one participant resulting in a final analytic sample of 214. Figure 1 illustrates the number of participants who completed each assessment.

Measures

Data were collected through medical chart review and self-report questionnaires.

Perceived cognitive problems were assessed using the Mental subscale of the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) (Stein et al., 1998), which assesses how much respondents had trouble remembering things, felt confused, had trouble paying attention, were unable to concentrate, made mistakes, and were forgetful in the past week. Higher scores indicate more perceived cognitive problems. The items included in this measure are consistent with other measures of self-reported cognitive complaints, including the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-cog) (Van Dyk et al., 2017).

Demographic characteristics including age, race, ethnicity, marital status, educational level, income, and employment status were collected at baseline through self-report.

Clinical characteristics including stage, enrollment surgery type (lumpectomy, unilateral mastectomy, bilateral mastectomy) and date, receipt of reconstruction, adjuvant therapy type (CT, radiation and/or endocrine therapy), and additional breast cancer surgeries after enrollment were obtained from medical records. Cancer stage was determined using the 7th edition of the American Joint Committee on Cancer staging manual.

Psychosocial and behavioral covariates of interest included depressive symptoms, anxiety symptoms, general fatigue, and sleep disturbance given their potential influence on cognitive problems in this population (M. Lange et al., 2019). Depressive symptoms were assessed using

the Center for Epidemiologic Studies Depression scale (CES-D) and included items such as "I felt that I could not shake off the blues even with help from my family or friends" (Hann et al., 1999; Schroevers et al., 2000). Anxiety symptoms were assessed using four items from the MFSI-SF Emotional Fatigue subscale: "I feel tense," "I feel nervous," "I feel relaxed," and "I feel calm" (Stein et al., 1998). These items are consistent with those of other anxiety scales including the State Anxiety Inventory (Spielberger, 1983). General fatigue was assessed using the MFSI-SF General Fatigue subscale and included items such as "I feel fatigued" and "I am worn out" (Stein et al., 1998). Sleep disturbance was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Higher scores on each of these scales indicate higher levels of depressive and anxiety symptoms, fatigue, and sleep disturbance.

Statistical Analysis

Differences in demographic, clinical, and psychosocial variables between treatment groups were assessed at baseline. Chi-square tests were used to examine whether the associations between treatment groups and categorical variables were significant. We next examined differences between expected and observed counts to determine which levels of the categorical variables had the greatest impact on the observed association. Analysis of variance (ANOVA) was used for continuous variables.

A series of linear mixed models were fit to examine group differences over time. The MFSI-SF Mental subscale was the primary dependent variable and type of treatment (lumpectomy with or without CT, mastectomy with or without CT) were the primary independent variable. The model included key demographic (age, education, race) and clinical covariates, including stage, receipt of radiation prior to assessment (time varying), and receipt of

endocrine therapy at the time of assessment (time varying). Given the focus on surgery, the current study examined the effect of time anchored to the date of surgery. A continuous time variable was calculated based on the date of surgery and the date of assessment. We first tested whether the effect of time on cognitive problems depended on treatment type by including an interaction term between time and treatment type (modeled as both linear and quadratic). To evaluate within-group effects, we next tested whether linear effects for each treatment group differed from zero. For data visualization, we estimated mean perceived cognitive problems for each treatment group at baseline (1 day following treatment), 3, 6, 12, 18, and 24 months following surgery. To avoid multiple comparisons, we did not test differences between and within groups at these estimated time points.

Subsequent sensitivity analyses were conducted with the addition of additional breast cancer surgeries (e.g., delayed reconstruction; time varying) and other psychosocial variables (depressive symptoms, anxiety, general fatigue, and sleep disturbance; all time-varying) that might explain any group differences.

All analyses were conducted using Stata v. 16.1 for Mac.

Power Analysis

We conducted a post-hoc power analysis using G*Power 6 to determine the power at which we would be able to detect a small, medium, and large effect (Cohen's f) for both the RISE and MBS Study samples. Though analyses were conducted in a multilevel framework, the power analysis is based on the ability to detect a group-by-time interaction using a repeated measures analysis of variance (ANOVA), which represents a conservative estimate. Tables are presented below that indicate the power to detect different effect sizes at different repeated measures correlations derived from the RISE and MBS study datasets. For reference, a small

effect (Cohen's f = .10) translates to a Cohen's d of .2, a medium effect (Cohen's f = .25) translates to a Cohen's d of .5, and a large effect (Cohen's f = 0.40) translates to a Cohen's d of .80. Based on these power analyses, the study was strongly powered (power at least 0.98) to detect a small effect (Cohen's f = .10) for all proposed analyses.

	Repeated Measures Correlation		
	0.55	0.65	0.81
Effect Size (Cohen's f)			
Small = .10	0.99	0.99	0.99
Medium = .25	1.00	1.00	1.00
Large = .40	1.00	1.00	1.00

D. Results

Participant Characteristics: Descriptive statistics for demographics, clinical characteristics, and other study variables are presented in Table 1. Women were primarily White and on average 57 years old. Of the 214 women, 112 (52%) underwent a lumpectomy without CT, 42 (19%) underwent a lumpectomy with CT, 38 (17%) underwent a mastectomy without CT, and 22 (10%) underwent a mastectomy with CT. Women who received a mastectomy with CT were significantly younger than women who received lumpectomies without CT, but other groups did not differ significantly in age from those who received lumpectomies without CT. Treatment groups also differed in terms of cancer stage with women receiving lumpectomies without CT more likely to have stage 0 cancer and women receiving mastectomies with CT more likely to have stage III cancer, but other groups did not differ significantly in stage from each other. As expected, the lumpectomy groups were also more likely to receive radiation than the mastectomy groups. Although days elapsed from surgery to the enrollment visit was significantly associated with group membership, pairwise comparisons between groups did not reach statistical significance and all women completed the baseline assessment within 60 days of

surgery. In terms of psychosocial variables, treatment groups did not differ significantly on baseline anxiety. However, the mastectomy without CT group was more depressed than the lumpectomy with CT group, and both surgery groups without CT were more fatigued than the CT groups at the pre-treatment baseline assessment. Additionally, the mastectomy without CT group had greater baseline sleep disturbance than both lumpectomy groups. There were no other differences between groups.

Differences between treatment groups in cognitive problems over time: Linear mixed models were conducted predicting perceived cognitive problems over time based on surgery type and CT status while controlling for demographic and clinical covariates (age, education, race, stage, receipt of radiation, receipt of endocrine therapy). There were significant linear, and marginally significant quadratic, effects for time and its interaction with treatment type (Table 2). When comparing linear effects between treatment groups by changing the model reference group, women who received mastectomy with CT had greater increases in perceived cognitive problems than women who received lumpectomies with ($p = .047$) or without CT ($p < .001$) and women who received mastectomies without CT ($p = .001$). Through visual inspection, differences in average perceived cognitive problems between treatment groups appeared to emerge one-year post-surgery.

We next examined whether linear effects for each treatment group were significantly different from zero. Linear effects were only significant for the chemotherapy groups (lumpectomy $b = 0.002$, $p = .017$; mastectomy $b = 0.004$, $p < .001$, Table 3). In contrast, slopes for the lumpectomy and mastectomy groups that did not receive CT were not significantly different from zero. Upon visual inspection, both CT groups exhibited increases in perceived cognitive problems at each follow-up time point relative to baseline.

Finally, we examined the influence of potential clinical and psychological confounds (Supplementary Table 1). We first controlled for surgeries that may have occurred after study enrollment, which were more common in the mastectomy group and could potentially influence cognitive problems later in the follow-up period. These analyses showed the same pattern of results. We then controlled for psychological processes that are hypothesized contributors to CRCI that might explain differences in breast cancer surgery groups including depressive and anxiety symptoms, fatigue, and sleep disturbance (time-varying covariates). Although each psychological variable was significantly and positively associated with cognitive problems over time ($ps < .001$), analyses showed the same pattern of results after controlling for these covariates.

E. Discussion

Cognitive problems are a feared and troublesome consequence of cancer treatments and are often attributed to CT (i.e., "chemo-brain"). However, results from the current study demonstrate that surgery may also play a role in the manifestation and maintenance of perceived cognitive problems during breast cancer survivorship. In particular, the combination of mastectomy with adjuvant CT was associated with the greatest perceived cognitive complaints. Although women who received lumpectomies also exhibited increases in cognitive complaints following CT, these increases differed in magnitude from those in the mastectomy group. Mean scores on the MFSI-mental subscale reached an average of 7.5 in the mastectomy with chemotherapy group, which corresponds to experiencing cognitive problems at least a moderate amount over the last week. Importantly, accounting for demographic, clinical, and psychosocial covariates did not significantly diminish the associations between mastectomy coupled with CT

and cognitive problems over time. Overall, results suggest that surgery type combined with receipt of CT is a strong predictor of cancer-related cognitive impairment.

The results of the current study are consistent with the limited extant literature on breast cancer surgery and cognitive problems. In the acute context, we did not find differences between surgery groups, consistent with two cross-sectional studies that did not find differences between lumpectomy and mastectomy in neuropsychological testing prior to the onset of adjuvant therapy (Cimprich, 1992; Mandelblatt et al., 2014). Two months following surgery, one study found that women who received mastectomies did not exhibit expected practice effects on neuropsychological tests, suggesting neurocognitive impairment (Hedayati et al., 2011). Although we did not find differences between surgery groups at this time point, our study examined perceived cognitive problems and did not include neuropsychological testing. None of these studies examined differences in surgery type in the months following chemotherapy receipt, which was when differences between surgery groups appeared to emerge in the current study.

The current results suggest that mastectomy, when combined with CT, is associated with greater increases in perceived cognitive problems relative to lumpectomy with or without CT. Mastectomies, particularly when coupled with immediate reconstruction, result in more tissue manipulation and damage as well as longer times under anesthesia; therefore, one plausible biological mechanism to investigate further is peripheral inflammation resulting from greater surgery-induced physiological stress and tissue damage (Caza, Taha, Qi, & Blaise, 2008). This increase in peripheral inflammation might sensitize the nervous system to the effects of CT, resulting in greater morbidity (Radin et al., 2022). The observed results might also be driven by the fact that mastectomy is associated with more subsequent surgeries (e.g., delayed

reconstruction, corrections to the original surgery and reconstruction). However, mastectomy without CT was not associated with significant increases in cognitive problems over time. Further, accounting for additional surgeries in analyses did not significantly diminish the effects of mastectomy plus CT over time or the differences between treatment groups. It is possible that higher levels of anxiety might confound these results in that they might drive both choice of mastectomy due to fear of recurrence and more cognitive problems. However, baseline levels of anxiety did not differ between surgery groups in the present study and controlling for anxiety did not change the pattern of findings. Additional investigations into mechanisms linking mastectomy and CT with cognitive problems are warranted.

These findings highlight the critical role that breast cancer surgery type plays in the occurrence and maintenance of cognitive problems during subsequent treatment and throughout survivorship. However, limitations to the current study are worth noting. First, the RISE study was not designed to investigate the effects of surgery type on behavioral symptoms in survivorship; therefore, it did not include a pre-surgery assessment. Thus, causal effects cannot be determined. Although it is impossible that cognitive complaints caused mastectomy, third variables cannot be ruled out as causes of such complaints. Additionally, timepoints for RISE assessments were anchored to adjuvant therapies, making it challenging to capture shorter-term effects of surgery specifically, although they were sufficient for capturing longer-term effects. The current study did not include objective assessments of cognitive functioning (e.g., neuropsychological assessments), which might illuminate specific cognitive processes that are dysregulated following surgery. Lastly, the study sample consisted primarily of White, educated women, and results may not generalize to more diverse samples. The results of this study warrant future research with pre-surgery assessment timepoints and dedicated aims to investigate the

causal effects, and underlying mechanisms, of surgery type combined with adjuvant therapies on cognitive problems, both perceived and objective, over time.

F. Summary and Clinical Recommendations

Although adjuvant therapies are commonly blamed for the onset and maintenance of CRCI, findings from the current study suggest that surgery type might also play a part in the observed effects. These initial results require replication and further evaluation before influencing clinical care decisions. Nevertheless, these findings add to the limited but growing literature comparing contemporary breast cancer surgeries with respect to health-related quality of life. A recent longitudinal investigation of differences in women's quality of life outcomes between breast conservation with radiation therapy and mastectomy with reconstruction found that 10 years after surgery, patient-reported breast satisfaction was similar between groups and that breast conservation was associated with better psychosocial and sexual well-being (Hanson et al., 2022). Considering recent statistics that women are increasingly electing to undergo more extensive breast cancer surgery (Lim et al., 2020), clearly communicating the potential side effects associated with mastectomy will be important for informed decision making. Given that breast cancer survivors are living longer, understanding how treatment options might impact cognitive functioning well into survivorship might help women weigh the costs and benefits of choosing a more extensive surgery, especially when it is not clinically indicated.

Chapter 3: The role of peripheral inflammation in cancer-related cognitive problems

A. Introduction

Inflammation as a Driver of CRCI

One of the most common and troublesome behavioral symptoms cancer patients and survivors experience is problems with cognitive functioning, referred to as "cancer-related cognitive impairment" (CRCI). The prevailing biological mechanism linking the cancer experience with cognitive problems is hypothesized to be peripheral immune activation from cancer and its treatments leading to pro-inflammatory processes (Ahles & Saykin, 2007; Miller et al., 2008). Indeed, cancer treatments such as surgery (Shaashua et al., 2017), radiation (Bower et al., 2009), and chemotherapy (Janelsins et al., 2012), have been shown to result in increases in pro-inflammatory cytokines and other inflammatory markers. There is also considerable evidence that activation of peripheral inflammatory processes signals the brain and leads to behavioral changes that include cognitive disturbance among other symptoms (i.e., fatigue, sleep disturbance, depressed mood, social withdrawal, and appetite changes) (Dantzer, 2004). These behaviors play an adaptive role designed to enhance the immune response to infection and tissue injury as well as decrease community spread (Hart, 1988; Kent, Bluthé, Kelley, & Dantzer, 1992).

Although inflammation is a plausible biological mechanism linking cancer and its treatment with cognitive disturbance, the empirical basis for this association is still under-developed. Pre-clinical models of CRCI have provided the most compelling evidence for a role of peripheral immune activation in the development of cognitive problems following cancer diagnosis and treatments. The most well-studied preclinical models of CRCI involve

administering chemotherapy medications to rodents and then testing with various tasks that assess cognitive functions mediated by the hippocampus or frontal lobes. Examples of tasks include the hippocampal-dependent Morris water maze, novel location recognition, and context fear conditioning, as well as the frontal lobe-sensitive tasks of operant nose-poking and conditional associative learning (Winocur, Johnston, & Castel, 2018). Typically, these models administer common chemotherapeutic drugs (e.g., methotrexate, 5-fluorouracil (5-FU), and taxane docetaxel) at weekly intervals and employ healthy, young adult, male rodents (Fardell, Vardy, & Johnston, 2013; Winocur et al., 2012; Winocur, Vardy, Binns, Kerr, & Tannock, 2006). Taken together, these studies demonstrate causal effects of chemotherapy on hippocampal-dependent and frontal lobe mediated cognitive processes.

These studies provide evidence for a causal link between chemotherapy administration and compromised cognitive functioning. However, the use of healthy rodents lacks ecological validity given that healthy young people are never prescribed chemotherapies, only people who have been diagnosed with cancer or other medical conditions for which chemotherapies are indicated. Therefore, tumor-bearing rodent models are necessary for probing factors that might influence cancer-related cognitive functioning in a clinically relevant manor. Examples of such approaches include the FVB/N-Tg (MMTV-neu) 202 Mul/J mouse, a transgenic model of breast cancer that mimics tumorigenesis that occurs in humans (Winocur, Berman, et al., 2018). These models are also useful for probing the effects of cancer (without chemotherapy) on cognitive functioning given that a proportion of breast cancer patients exhibit cognitive impairment before adjuvant therapies (e.g., Casaril et al., 2020; Yang et al., 2014). Additionally, given that a proportion of breast cancer patients experience CRCI longer into survivorship, pre-clinical models that more closely resemble the survivorship experience are needed. Recently, a novel

animal model of breast cancer survivorship was developed by Pyter and colleagues that models the longer-term effects of breast cancer tumors on cognitive functioning following tumor resection (Pyter et al., 2017). In mice with a mammary tumor, excision of the tumor reversed tumor-induced circulating pro-inflammatory cytokines; however, anxiety-like behaviors and some peripheral immune markers persisted or progressed weeks following surgery. This model demonstrates how immune and behavioral alterations can persist following cancer treatment.

There are exciting new animal models emerging examining the impact of other cancer treatments such as radiation and immunotherapies on behavioral symptoms in cancer survivorship. For example, Renner and colleagues developed a murine model of peripheral irradiation-induced fatigue which could be adapted for the evaluation of irradiation-induced cognitive problems (Renner et al., 2016). Additionally, immunotherapies, which involve monoclonal antibodies directed against immune checkpoints that inhibit T-cell activation, have emerged as novel cancer therapies. Checkpoint inhibitors are known to cause inflammation (Champiat et al., 2016); therefore, there is interest in how immunotherapies might result in CRCI through their effects on the immune system (Joly, Castel, Tron, Lange, & Vardy, 2020). A novel animal model of the effects of immunotherapy on inflammation and cognitive problems has been developed in mice with colon or lung cancer (McGinnis et al., 2017).

Proposed Mechanisms Linking Cancer Treatments, Peripheral Immune Activation, and Cognitive Problems

How would peripheral inflammation lead to neurocognitive changes exhibited in CRCI? The key pathways through which the immune system can communicate with the brain are through binding of pro-inflammatory cytokines to receptors associated with afferent nerves (such

as the vagus), through humoral pathways such as pro-inflammatory cytokines including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 passing through leaky regions of the blood-brain-barrier (BBB), active transport across the BBB via saturable transport molecules, as well as activation of endothelial cells and other cell types lining the cerebral vasculature (Miller, Maletic, & Raison, 2009). Within the brain, glial cells such as oligodendrocytes, astrocytes, and the most commonly studied – microglia (the brain's resident immune cells) – play an active role in communicating immune signals from the periphery to the central nervous system. Additionally, there is now a recognized cellular pathway through which activated microglia recruit "inflammatory" monocytes from the periphery to the brain (Miller & Raison, 2015; Wohleb, McKim, Sheridan, & Godbout, 2015).

When microglia "hear" peripheral inflammatory signals to the brain, they become activated or "ramified," producing pro-inflammatory cytokines leading to neuroinflammation (Bilbo, Smith, & Schwarz, 2012). Chemotherapy has been shown to trigger this communication pathway, which results in increases in central cytokines inducing oxidative stress leading to neuronal damage (Joshi et al., 2005). Microglial activity has been shown to play a key role in neurological complications following common chemotherapeutic agents including methotrexate (Seigers et al., 2010), cyclophosphamide (Acharya et al., 2015), and doxorubicin (Allen et al., 2019) in preclinical studies. It has been proposed that neuronal damage might lead to white matter abnormalities through the effects of chemotherapy-induced neuroinflammation on myelin (Merriman, Von Ah, Miaskowski, & Aouizerat, 2013). Indeed, rats that were given chemotherapy exhibited increases in central IL-1β, TNF-α, and COX-2, myelin abnormalities, and cognitive deficits (Briones & Woods, 2014). Myelin abnormalities and cognitive problems were abolished when rats were given an anti-inflammatory medication (COX-2 inhibitor). Pre-

clinical work also supports a role of cancer-induced inflammation in the absence of chemotherapy or other treatments in CRCI: in a breast cancer mouse model, tumor-bearing mice had impaired memory relative to healthy mice which was induced by tumor-secreted pro-inflammatory cytokines (Walker et al., 2018). Oral administration of low-dose aspirin blocked the effects of the tumor on memory impairment. Interestingly, aspirin did not protect rats against chemotherapy-induced memory problems (Chang et al., 2020).

Novel paradigms are being developed to assess other potential mechanisms implicating peripheral immune activation with CRCI (Lomeli, Lepe, Gupta, & Bota, 2021). One of the most exciting possible explanations implicates chemotherapy as a moderator of the effect of inflammation on cognitive functioning through compromising blood-brain-barrier (BBB) integrity (Wardill et al., 2016). Although most chemotherapeutic agents are not able to cross the BBB, they are thought to indirectly induce neuroinflammation through direct effects on BBB integrity (via oxidative stress) or indirectly through an increase in pro-inflammatory cytokines in the periphery (Fernandez, Varma, Flowers, & Rebeck, 2020). In vitro as well as in vivo studies of chemotherapeutic agents effects on the immune system suggest that these agents are able to trigger the synthesis, processing, and release of IL-1β from macrophages, a key initiator of inflammatory responses (Wood & Weymann, 2013). It is plausible that these increases in peripheral inflammation might disrupt the integrity of the BBB resulting in greater sensitivity to systemic pro-inflammatory signaling (Saija et al., 1995; Varatharaj & Galea, 2017). Indeed, many of the pro-inflammatory cytokines that are upregulated during cancer progression and treatments, such as IL-6, TNF-α, and IL-1β, can cross or signal through the BBB (Banks, Ortiz, Plotkin, & Kastin, 1991; Banks, Kastin, & Gutierrez, 1994; Pan, Banks, Kennedy, Gutierrez, & Kastin, 1996).

Studies Assessing Inflammation and Cognitive Problems in Breast Cancer Patients

Most clinical research testing the associations between inflammation and cognitive problems has done so by examining cross-sectional associations between objective and/or subjective cognitive problems and one or more inflammatory markers at one or multiple time-points along the cancer-continuum. These studies typically quantify the molecular mediators through which peripheral immune cells are able to transmit messages to the brain: pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 and their downstream counterparts such as soluble TNF receptor type two (sTNF-RII), IL-1 receptor antagonist (IL-1ra), and C-reactive protein (CRP); and anti-inflammatory cytokines such as IL-4, IL-13, and IL-10. We identified only 8 studies that assessed associations between peripheral concentrations of inflammatory markers and objective and/or subjective assessments of cognitive functioning in breast cancer patients and survivors. It is possible that the disproportionately small number of studies published relative to the large emphasis on inflammation in models of CRCI is driven by null findings. Nevertheless, we summarize their results here and in Appendix C.

Three studies assessed cross-sectional associations between peripheral concentrations of inflammation and cognitive problems in women with breast cancer: one before the start of adjuvant therapies (objective assessments only), one during chemotherapy (objective assessments only), and one 5 years after treatment completion (subjective and objective assessments). Each study assessed for different domains of objective cognitive functioning: Patel et al. – executive functioning, verbal memory, and processing speed; Williams et al. – planning, visual memory, and verbal memory; and Kesler et al. – verbal memory. Before adjuvant therapies, Patel et al found that plasma IL-6, IL-1ra, and sTNF-RII were not associated with performance on tasks assessing executive functions; however, sTNF-RII was a significant

correlate of verbal memory performance (Patel et al., 2015). During chemotherapy, Williams et al found that sTNF-RII was associated with poorer visual, but not verbal, memory (Williams et al., 2018). Of note, these studies employed different tasks to assess verbal memory (Hopkins Verbal Learning Test (HVLT) vs. Verbal Recognition Memory), which could potentially have contributed to divergent results. In addition, Williams et al found that levels of monocyte chemoattractant protein-1 (MCP-1/CCL2, a chemokine that regulates macrophage migration and infiltration) was associated with better performance on a task of executive functioning. In post-treatment survivors, plasma concentrations of IL-6, IL-10, IL-12, IL-8, and TNF-α were not associated with performance on the HVLT or a subjective measure of memory problems (Multifactorial Memory Questionnaire Ability Scale) (Kesler et al., 2013).

Cross-sectional studies such as these are helpful for establishing an association between inflammation and CRCI; however, they are unable to support directionality. Thus, longitudinal studies with repeated measures are necessary to examine how inflammation is associated with cognitive problems over time. Six studies assessed peripheral inflammation and cognitive problems at multiple timepoints in women with breast cancer. When examining the effects of chemotherapy on inflammation and cognitive problems, Cheung and colleagues assessed both perceived and objective cognitive problems in relation to markers of peripheral inflammation before chemotherapy, 6 weeks later (1st day of 3rd cycle), and 6 weeks after that (treatment completion) (Cheung et al., 2015). They found that every unit increase in plasma IL-1β was associated with a 0.78 decrease in response speed but there were no associations between inflammation and changes in processing speed, memory, or attention. In terms of perceived cognitive problems, higher concentrations of IL-1β and IL-6 were associated with more self-perceived cognitive disturbances. IL-4 appeared to have a protective effect on both objective

(response speed) and subjective cognitive problems, such that increases in IL-4 resulted in an estimated 0.76 increase in response speed and a 0.95 increase in the FACT-Cog total score (less severe cognitive disturbances).

Lyon and colleagues also examined associations between inflammation (using a 17-cytokine panel) and objective cognitive problems (Computerized Neurocognitive Testing System) in the chemotherapy context: they assessed associations before chemotherapy, at the midpoint of chemotherapy, 6 months after treatment completion, 12 months and 24 months later (Lyon et al., 2016). At pre-treatment, they found that granulocyte colony-stimulating factor (G-CSF) was associated with executive functioning, whereas none of the inflammatory markers were associated with memory. During chemotherapy, IL-8 and IL-17 were associated with executive functioning and IL-17, IL-8, IL-13, IL-12, and IL-1β were associated with memory. After chemotherapy, IL-7 and IL-10 were associated with executive functioning and GM-CSF, IL-5, IL-7, G-CSF, IL-2, IFN-γ, IL-10 and IL-12 were associated with memory. Finally, 2 years after chemotherapy, IFN-γ, IL-8, and IL-4 were associated with executive functioning and IL-7 and IL-5 were associated with memory. This study highlights the differential associations between different inflammatory markers and various cognitive problems at different timepoints along the chemotherapy trajectory.

Belcher and colleagues similarly assessed the association between markers of inflammation (IL–4, IL-6, IL-8, IL-10, TNF-a, sTNF-RII) and objective cognitive problems (attention and processing speed) in women with breast cancer before and after chemotherapy (Belcher et al., 2022). Their study included a large cohort of breast cancer patients (n = 519). They did not find any significant associations between changes in inflammatory markers and changes in performance on Rapid Visual Processing; however they did find associations between

changes in IL-4 and performance on backward counting such that greater increases in IL-4 were associated with better performance at post-chemotherapy relative to pre-chemotherapy. The authors did not report on whether there were significant associations between changes in inflammatory markers and performance on the Trail Making Test Part A.

Two studies focused on associations between inflammatory markers and cognitive function after treatment completion (not restricted to chemotherapy) with 6- and 12-month follow-up assessments using data from the Mind-Body Study. The first study examined the association between IL-1ra, IL-6, CRP, and sTNF-RII and neuropsychological assessments of executive functioning, verbal, and visual memory, psychomotor function, visuo-spatial function, and motor speed and subjective memory complaints (the Squire Memory Questionnaire (SMQ)) (Ganz, Bower, et al., 2013). Although there were no associations between any of the inflammatory markers and any of the neuropsychological domains, the authors did find that at baseline (post-treatment), higher levels of sTNF-RII were associated with more memory complaints for survivors who had been treated with chemotherapy. In addition, in longitudinal analyses examining associations between change scores in sTNF-RII and change scores in the SMQ from baseline to 6-month follow-up, there was an association for chemotherapy treated women such that decreases in sTNF-RII were associated with fewer memory complaints. The second analysis of data from the MBS focused on a different measure of perceived cognitive problems: the PAOFI. Pomykala and colleagues found that at the baseline assessment, the total severity score on the PAOFI memory subscale was positively associated with IL-6 concentrations, suggesting a link between plasma IL-6 levels and memory problems (Pomykala et al., 2013). Although this study assessed inflammation, perceived cognitive problems, and cerebral metabolism (via positron emission tomography) at baseline and at the 12-month

assessment, the authors only reported on associations between inflammation and the PAOFI at the baseline assessment.

Lastly, Carroll and colleagues recently published a study employing between- and within-participant mixed linear effect modeling to test associations between C-reactive protein (CRP) and perceived and objective cognitive functioning over time in a cohort of older breast cancer survivors (ages 60-90) (Carroll et al., 2023). They found that higher levels of CRP predicted lower self-reported, but not objective, cognitive functioning in subsequent visits for older breast cancer survivors but not age matched controls. This study used random effect-lagged fluctuation models to test whether levels of CRP at one visit could predict cognitive functioning at subsequent visits (at least one year later).

The Current Study

Overall, these studies provide some evidence for an association between peripheral inflammation and perceived cognitive problems. However, only 6 assessed relations longitudinally (Belcher et al., 2022; Carroll et al., 2023; Cheung et al., 2015; Ganz, Bower, et al., 2013; Lyon et al., 2016; Pomykala et al., 2013). Of those, two studies employed mixed linear models with randomly varying intercepts to account for within-subject correlations (Cheung et al., 2015; Lyon et al., 2016) and only one study assessed how within a given participant, deviations from that individual's mean levels of inflammation over-time were associated with changes in perceived or objective cognitive problems (Carroll et al., 2023). Additionally, several studies focused specifically on women treated with chemotherapy (Cheung and Lyon) or older women (Carroll et al.); although these are potentially high-risk groups, evaluating associations in samples with a broader range of treatment exposures and ages is also important. Finally, no

studies to date have examined moderators of links between inflammation and CRCI. Chemotherapy might sensitize the brain to the effects of peripheral inflammation through its effects on the blood brain barrier. Age has been shown to moderate the association between inflammation and depressive symptoms in breast cancer survivors, another behavioral symptom with inflammation as a proposed biological mechanism. Specifically, younger women were more sensitive to the effects of inflammation on depressive symptoms (Kuhlman et al., 2022a). However, it is currently unknown whether younger age is a risk factor for the effects of inflammation on cognitive problems in breast cancer survivors.

Thus, the current study examined both between and within-participant associations between inflammation and cognitive problems over time in two rich longitudinal observational datasets of breast cancer survivors (the RISE and MBS studies). We employed both subjective and objective assessments of cognitive problems as well as tested receipt of chemotherapy and age as moderators of these relationships.

B. Specific Aims and Hypotheses

Specific Aim 1: Examine associations between inflammation and perceived cognitive problems over time in two cohorts of breast cancer survivors (MBS and RISE).

Hypothesis 1a: Between subjects, greater concentrations of circulating inflammatory markers will be associated with more perceived cognitive problems (as measured by the MFSI-mental subscale) across assessments.

Hypothesis 1b: Within a given participant, increases in inflammation relative to that participant's average level of inflammation will be associated with increases in perceived cognitive problems (as measured by the MFSI-mental subscale) across assessments.

Specific Aim 2: Examine associations between inflammation and objective cognitive problems over time in a cohort of breast cancer survivors (MBS).

Hypothesis 2a: Between subjects, greater concentrations of circulating inflammatory markers will be associated with more objective problems with verbal memory and executive functioning across assessments.

Hypothesis 2b: Within a given participant, increases in inflammation relative to that participant's average level of inflammation will be associated with more objective problems with verbal memory and executive functioning across assessments.

Specific Aim 3: Evaluate whether chemotherapy moderates the association between inflammation and cognitive problems over time in two cohorts of breast cancer survivors (RISE and MBS).

Hypothesis 3: Women who received chemotherapy will have a stronger relationship between inflammation and cognitive problems (both objective and subjective) over time than women who did not receive chemotherapy.

Specific Aim 4: Evaluate whether age moderates the association between inflammation and cognitive problems over time in two cohorts of breast cancer survivors (RISE and MBS).

Hypothesis 4: Younger women will have a stronger relationship between inflammation and cognitive problems (both objective and subjective) over time than older women.

C. Methods

To test Specific Aims 1-4, we used data from both the Mind-Body (MBS) and RISE Studies.

The RISE and MBS Study Timelines

Briefly, the MBS assessed women for both perceived and objective cognitive problems after the completion of adjuvant therapies but before the start of endocrine therapy (baseline n = 191) with 6- (n = 175) and 12- (n = 175) month follow-up assessments (see Consort Diagram in Appendix E) (Ganz, Kwan, et al., 2013). Therefore, the MBS data was used to examine longitudinal associations between peripheral inflammation and perceived and objective cognitive problems over the first year following adjuvant therapy treatment completion. The RISE study assessed women for perceived cognitive problems before the start of adjuvant therapies (n = 270), after treatment completion (n = 194), as well as at 6- (n = 254), 12- (n = 246), and 18- (n = 244) month follow-up assessments (see Consort Diagram in Appendix D). Therefore, the RISE Study data was used to examine longitudinal associations between peripheral inflammation and perceived cognitive problems from pre-treatment to 18 months following adjuvant therapies. Of note, across both studies, not all women provided blood samples for inflammatory markers, nor completed neuropsychological assessments for the MBS. Therefore, the sample sizes for these analyses were smaller (see Figures 1 and 2).

The RISE and MBS Study Assessments

RISE Study Assessments:

1. Demographic variables: Age, education, and race/ethnicity were collected at baseline

2. Clinical variables: Surgery type, adjuvant therapy type, and receipt of endocrine therapy were abstracted from medical charts

3. Perceived cognitive problems: MFSI-SF Mental subscale

4. Plasma concentrations of IL-6, CRP, and sTNFR-II

MBS Study Assessments:

1. Demographic variables: Age, education, and race/ethnicity were collected at baseline

2. Clinical variables: Surgery type, adjuvant therapy type, and receipt of endocrine therapy were abstracted from medical charts

3. Perceived cognitive problems: MFSI-SF Mental subscale

4. Objective cognitive problems: Neuropsychological assessments of executive functioning (Tail Making Test (TMT) Part B) and verbal memory (California Verbal Learning Test (CVLT)-II)

5. Plasma concentrations of IL-6, CRP, and sTNF-RII

D. Data Analysis

For Hypotheses 1 and 2, we employed multilevel models where repeated assessments of perceived and objective cognitive problems (level 1) are nested within individuals (level 2) using the mixed command in Stata. Time was modeled as a level 1 continuous predictor with both linear and quadratic effects. Including both linear and quadratic effects allowed for the possibility of modeling different patterns over time. The primary predictor of interest was concentrations of each inflammatory marker, and we included terms to represent within-participant markers and between-participant markers for each model. Post-hoc testing was

employed to examine between- and within-subject associations between inflammation and cognitive problems at each assessment time-point.

All analyses were conducted with covariates. We covaried for relevant demographic and clinical factors. We included age given its associations with neuropsychological testing and cognitive problems (Deary et al., 2009; Heaton, Ryan, Grant, & Matthews, 1996; Leckliter & Matarazzo, 1989) as well as inflammation (Franceschi & Campisi, 2014). We additionally covaried body mass index (BMI) given that BMI is a known driver of peripheral inflammation (O'Connor et al., 2009). We then added clinical covariates to the models including cancer stage, surgery type, adjuvant therapy type, and receipt of endocrine therapy.

To test moderating effects of chemotherapy, we examined whether chemotherapy moderated the association between inflammation and cognitive problems over time by entering receipt of chemotherapy as a level 2 predictor and allowing it to interact with the level 1 predictor inflammatory marker. Similarly, in separate models, we tested whether age moderated the association between inflammation and cognitive problems over time by entering continuous age as a level 2 predictor and allowing it to interact with the level 1 predictor inflammatory marker. Only models with significant effects are included as tables and figures.

Power Analysis

We conducted a post-hoc power analysis using G*Power 6 to determine the power at which we would be able to detect a small, medium, and large effect (Cohen's f) for both the RISE and MBS Study samples. Though analyses were conducted in a multilevel framework, the power analysis was based on the ability to detect associations between changes in inflammation and changes in cognitive problems using a repeated measures analysis of variance (ANOVA),

which represents a conservative estimate. Tables are presented below that indicate the power to detect different effect sizes at different repeated measures correlations derived from the RISE and MBS datasets. For reference, a small effect (Cohen's f = .10) translates for a Cohen's d of .2, a medium effect (Cohen's f = .25) translates to a Cohen's d of .5, and a large effect (Cohen's f = 0.40) translates to a Cohen's d of .80. Based on these power analyses, the study was strongly powered (power at least 0.98) to detect a small effect (Cohen's *f* = .10) for all analyses.

1. The RISE Study (n = 180 with immune markers and 2 assessment points)

	Repeated Measures Correlation		
	0.55	0.65	0.81
Effect Size (Cohen's f)			
Small = .10	0.96	0.99	0.99
Medium = .25	1.00	1.00	1.00
Large = .40	1.00	1.00	1.00

2. The Mind-Body Study (n = 161 with immune markers and 2 assessment points)

	Repeated Measures Correlation		
	0.69	0.75	0.88
Effect Size (Cohen's f)			
Small = .10	0.95	0.98	0.99
Medium = .25	1.00	1.00	1.00
Large = .40	1.00	1.00	1.00

E. Results

Participants

MBS

Of the 191 participants enrolled in the MBS, 173 had both perceived and/or objective cognitive data and inflammatory data for at least one assessment timepoint and comprised the

analytic sample. Figure 1 shows the sample size for each type of data at each assessment time point (baseline, 6 months, 12 months). The analytic sample had an average age of 52 years, was 79% White and 11% Hispanic, and 80% had at least a college degree (see Table 1). Participants had primarily stage I (46%) or II (31%) breast cancer and had undergone lumpectomy (67%). In terms of adjuvant therapies, 75% received radiation and 53% received chemotherapy. Most of the sample received endocrine therapy (68%).

RISE

Of the 270 participants enrolled in the RISE Study, 194 had both perceived cognitive problems data and inflammatory data for at least one assessment timepoint. Figure 2 shows the sample size for each type of data at each assessment time point (baseline, post-treatment, 6 months, 12 months, and 18 months). The analytic sample had an average age of 55 years, was 75% White and 7% Hispanic, and 70% had at least a college degree (see Table 1). Participants had primarily stage I (46%) or II (25%) breast cancer and had undergone lumpectomy (60%). In terms of adjuvant therapies, 70% received radiation and 39% received chemotherapy. Most of the sample received endocrine therapy (62%).

Between and within-subject associations between inflammation and perceived cognitive problems

MBS

We first examined bivariate associations between average levels of inflammatory markers (IL-6, CRP, sTNF-RII) and perceived cognitive problems (MFSI-mental subscale) across the assessment period as well as associations with covariates of interest (age, visit, BMI, stage,

surgery type, receipt of chemotherapy, receipt of radiation, and endocrine therapy) (Table 2). All three inflammatory markers were significantly positively correlated with one another (*p*s < .05). Perceived cognitive problems were associated with both IL-6 ($p < .01$) and sTNF-RII ($p < .05$) such higher levels of these markers were associated with more cognitive problems ($p < .01$). In terms of demographic and clinical variables, perceived cognitive problems were also associated with receipt of chemotherapy ($p < .01$).

We next examined associations utilizing multilevel models to 1) examine unique contributions of both participant-mean- and group-mean-centered inflammatory variables to perceived cognitive problems and 2) to test whether associations held over and above demographic and clinical covariates (age, visit, BMI, stage, surgery type, receipt of chemotherapy, receipt of radiation, and endocrine therapy). The first model included the participant mean- and group mean-centered inflammatory marker of interest, visit, age, and BMI. The second model added stage (low (0, I) or high (II, III)), surgery type (lumpectomy or mastectomy), receipt of chemotherapy (yes or no), receipt of radiation (yes or no), and endocrine therapy (yes or no, time varying).

For IL-6, the association between group mean-centered IL-6 and perceived cognitive problems was significant controlling for visit, age, and BMI ($b = 1.68$, $p = .032$) (model coefficients presented in Table 3). This association remained significant after additionally accounting for surgery type, receipt of chemotherapy, radiation, and endocrine therapy ($b = 1.64$, $p = .030$). In multivariable models, group and participant-mean centered CRP and sTNF-RII were not associated with perceived cognitive problems.

RISE

We first examined bivariate associations between mean levels of inflammatory markers (IL-6, CRP, sTNF-RII) and perceived cognitive problems (MFSI-mental subscale) across the assessment period as well as associations with covariates of interest (age, visit, BMI, stage, enrollment surgery type, additional surgeries, receipt of chemotherapy, receipt of radiation, and endocrine therapy) (Table 4). All three inflammatory markers were significantly positively correlated with one another (*p*s < .05). Perceived cognitive problems were associated with sTNF-RII such that higher levels of sTNF-RII were associated with fewer cognitive problems (*p* < .05). There were no significant associations between perceived cognitive problems and CRP or IL-6. In terms of demographic and clinical variables, perceived cognitive problems were also associated with younger age and mastectomy (*p*s < .05).

We next examined associations utilizing multilevel models to 1) examine unique contributions of both participant-mean- and group-mean-centered inflammatory variables to perceived cognitive problems and 2) to test whether associations held over and above demographic and clinical covariates as was done for the MBS Study (age, visit, BMI, stage, enrollment surgery type, additional surgeries, receipt of chemotherapy, receipt of radiation, and endocrine therapy). The first model included the participant mean- and group mean-centered inflammatory marker of interest, visit, age, and BMI. The second model added stage (low (0, I) or high (II, III)), surgery type (lumpectomy, unilateral or bilateral mastectomy, neoadjuvant chemotherapy), whether the participant had any additional surgeries, receipt of chemotherapy (yes or no), receipt of radiation (yes or no), and endocrine therapy (yes or no, time varying). In multivariable models, there were no associations between any of the inflammatory variables and perceived cognitive problems (all *p*s > .06).

Between and within-subject associations between inflammation and objective cognitive problems

MBS

We first examined bivariate associations between average levels of inflammatory markers (IL-6, CRP, sTNF-RII), executive functioning (Trails B completion time) and verbal memory (CVLT delayed free recall) across the assessment period as well as associations with covariates of interest (age, visit, BMI, IQ, stage, surgery type, receipt of chemotherapy, receipt of radiation, and endocrine therapy). Table 5 provides correlation coefficients for normed values of each neuropsychological test. Executive functioning was associated with both IL-6 and CRP such that higher average levels of inflammatory markers were associated with poorer performance ($p <$ .01). sTNF-RII was not associated with executive functioning performance. None of the three inflammatory markers were associated with verbal memory performance. In terms of demographic and clinical variables, younger age and time were associated with better performance on the Trails B, as expected, but not on the CVLT. Higher IQ was associated with better performance for both neuropsychological tasks. Receipt of mastectomy was associated with poorer performance on the CVLT, but not the Trails B.

We next examined associations utilizing multilevel models as before. These models additionally controlled for IQ. There were no significant associations between any of the inflammatory markers (participant or group mean centered) and performance on the neuropsychological tasks (all ps > .07). In multivariable models for IL-6 and sTNF-RII (which did show bivariate associations for executive functioning), visit, age and IQ were all significantly associated with performance.

Chemotherapy as a moderator of the associations between between and within-subject inflammation and perceived cognitive problems

MBS

To test whether receipt of chemotherapy sensitizes women to the effects of inflammation on perceived cognitive problems, we included an interaction term between chemotherapy status and both participant and group mean-centered inflammatory markers in the multivariable models. For IL-6, receipt of chemotherapy significantly moderated this association such that women who received chemotherapy had a stronger association between group mean-centered IL-6 and perceived cognitive problems (difference in slopes: $b = 3.56$, $p = .007$) (model coefficients presented in Table 6). Only women who received chemotherapy had a significant positive association between group mean-centered IL-6 and perceived cognitive problems ($b = 3.29$, $p = .001$) (Figure 3). Similarly, receipt of chemotherapy also moderated the association between sTNF-RII and perceived cognitive problems. However, moderation occurred at the level of within-participant differences: there was a significant difference in slopes between women who received chemotherapy and women who had not ($b = 5.46$, $p = .023$) (model coefficients presented in Table 7). Women who received chemotherapy had a marginally significant positive association between participant mean-centered sTNF-RII and perceived cognitive problems ($b = 2.63$, $p = .065$) (Figure 4). Chemotherapy status did not moderate the association between CRP and perceived cognitive problems.

RISE

To test whether receipt of chemotherapy sensitizes women to the effects of inflammation on perceived cognitive problems, we included an interaction term between chemotherapy status

and both participant and group mean-centered inflammatory markers in the multivariable models. For CRP, receipt of chemotherapy significantly moderated the association between participant mean-centered CRP and perceived cognitive problems (difference in slopes: b = -0.746, p = .013) (model coefficients presented in Table 8). Women who received chemotherapy reported lower cognitive problems when their levels of CRP were greater than their own average, whereas women who did not receive chemotherapy exhibited the opposite trend. However, neither simple slope for each treatment group was significantly different from zero (Figure 4).

Chemotherapy as a moderator of the associations between between and within-subject inflammation and objective cognitive problems

MBS

To test whether receipt of chemotherapy sensitizes women to the effects of inflammation on objective cognitive functioning, we included an interaction term between chemotherapy status and both participant and group mean-centered inflammatory markers in the multivariable models. We did not find any significant interactions between any of the inflammatory markers and chemotherapy status for predicting executive functioning or verbal memory.

Age as a moderator of the associations between between and within-subject inflammation and perceived cognitive problems

MBS

To test whether age moderates the association between inflammation and perceived cognitive problems, we included an interaction term between age and both participant and group mean-centered inflammatory markers in the multivariable models. Age significantly interacted

with participant mean-centered sTNF-RII (b = -0.33, p = .024) (model coefficients presented in Table 9). Only younger women exhibited a significant association between within-participant differences in sTNF-RII and perceived cognitive functioning (b = 3.55, p = .034) (Figure 5). Age did not moderate the associations between IL-6 or CRP and perceived cognitive problems.

RISE

To test whether age moderates the association between inflammation and perceived cognitive functioning, we included an interaction term between age and both participant and group mean-centered inflammatory markers in the multivariable models. We did not find any significant interactions between any of the inflammatory markers and age for predicting perceived cognitive problems over time.

Age as a moderator of the associations between between and within-subject inflammation and objective cognitive problem

MBS

To test whether age moderates the association between inflammation and objective cognitive functioning, we included an interaction term between age and both participant group mean-centered inflammatory markers in the multivariable models. We did not find any significant interactions between any of the inflammatory markers and age for predicting executive functioning or verbal memory.

F. Discussion

This study examined both between- and within-person associations between inflammation and cognitive problems in two samples of breast cancer survivors. Analyses using data from the MBS study revealed moderated effects for IL-6 such that higher levels of IL-6 relative to the group mean were associated with more perceived cognitive problems specifically for survivors who received chemotherapy. Moderated effects were also observed for sTNF-RII in the MBS sample, such that participants who received chemotherapy and who were younger had a stronger association between deviations in sTNF-RII relative to their average and perceived cognitive problems. Of note, similar results were not observed in the RISE study, where there were no significant main effects of any of the inflammatory variables, nor moderated effects for chemotherapy or age, on perceived cognitive problems. In addition, there were no main or moderated associations between inflammatory markers and performance on neuropsychological assessments of verbal memory and executive functioning controlling for critical covariates in MBS.

The current analyses for main effects of participant- and group-mean centered inflammation on cognitive problems are partially consistent with the limited extant literature testing associations between inflammation and cognitive problems over time. Results from MBS are consistent with Cheung et al., who also found significant between subject effects for IL-6 on perceived cognitive problems for women treated with chemotherapy (Cheung et al., 2015). However, we did not observe associations between CRP and perceived cognitive problems as reported by Carroll and colleagues (Carroll et al., 2023). It is possible that differences in sample age (only older breast cancer survivors) and analytic approach (CRP predicting cognitive problems at subsequent time points) contributed to these differences. Of the three previous longitudinal studies that assessed associations between inflammation and objective cognitive

problems, only one found associations between inflammation and performance on neuropsychological tests (Lyon et al., 2016). However, IL-6, CRP, and sTNF-RII were not among the inflammatory markers that were found to be significantly associated with any of the neuropsychological tests in that report. The previous study that reported on associations between inflammatory markers and neuropsychological testing in the MBS did not find any associations (Ganz, Bower, et al., 2013), consistent with the current results. To our knowledge, this is the first study to examine chemotherapy and age as moderators of the associations between inflammation and cognitive problems in cancer survivors. However, the present findings for age as a moderator are consistent with recent work demonstrating that younger breast cancer patients are more sensitive to the effects of inflammation on depressive symptoms (Kuhlman et al., 2022b).

The incongruence between the findings for the MBS and RISE studies are reflective of the inconsistent findings throughout the extant literature concerning inflammation and CRCI. A greater proportion of women in the MBS received chemotherapy and the mean age was younger than that of the RISE sample. Therefore, it is possible that discrepancies are driven by these differences. It is also possible that differences in assessment timing between the two studies might explain these incongruent findings. The MBS baseline assessment took place after adjuvant therapy completion but before the start of endocrine therapy whereas the RISE baseline assessment took place before the start of adjuvant therapy. To test whether these differences were due in part to timing of assessment, we conducted sensitivity analyses for the RISE data that excluded the baseline assessment and 18-month assessment. This left a dataset comprising data collected at the post-treatment assessment (including the baseline assessment for the surgery only group), with 6- and 12-month follow-up visits (as was done for the MBS protocol). Even after removing these assessment timepoints, the same pattern of results was observed, with no

main or moderated effects of inflammation and cognitive function in RISE. Therefore, it is unclear as to why different results emerged for the MBS and RISE studies. Given our inability to replicate the findings from MBS in the RISE sample, caution is warranted when interpreting these results.

Overall, these results highlight the analytic nuances and moderating factors that contribute to the complexity of associations between peripheral inflammation and cognitive functioning in breast cancer survivors. This is the first study to assess both within- and between-person associations between inflammation and cognitive problems in two treatment and age diverse samples of breast cancer survivors. Significant associations between inflammation and cognitive problems were moderated and were seen only for specific cytokines, at either the group (IL-6) or participant (sTNF-RII) level, and in only one of the two study samples assessed. Overall, these results do not provide strong evidence in support of inflammation as a biological mediator linking breast cancer and its treatment with perceived or objective cognitive problems, at least as measured by plasma concentrations of inflammatory markers. It is possible that other measures of inflammation (e.g., gene expression), or other biological processes might by more relevant for CRCI. In particular, examining processes that are upstream of peripheral inflammation and more proximal to neurocognitive functioning such as BBB integrity or microglial activation might yield more consistent and informative results. In addition, future research would benefit from using more sensitive measures of objective cognitive function, such as neurocognitive tasks that come from the cognitive neuroscience literature (Horowitz, Suls, & Treviño, 2018). By using more sensitive measures, employing demographically and clinically diverse samples, and assessing more proximal mediators, researchers will be better able to identify novel and precise biological targets for the prevention and treatment of CRCI.

Chapter 4: Trajectories of perceived breast cancer-related cognitive problems

A. Introduction

Cancer-related cognitive impairment (CRCI) is a common and troubling side effect of the breast cancer experience. Prevalence estimates can range between 17-75% depending on the timing of assessment, patient characteristics, treatments, and how CRCI is operationalized (Janelsins et al., 2014; Wefel, Lenzi, Theriault, Davis, et al., 2004). Although prevalence estimates are helpful for understanding the proportion of patients that experience CRCI at a given clinical timepoint, these estimates mask considerable variability in the onset, maintenance, and resolution of cognitive problems in this population. Indeed, some women might experience acute treatment effects on cognition that resolve shortly after treatment completion, whereas others might experience cognitive problems prior to treatment initiation, and others might have problems that persist for years following treatment completion. Without differentiating between these groups of patients, long-term CRCI might be attributed to treatments when in fact, cognitive problems might be present even before treatment onset.

By taking a group-based trajectory analysis approach using growth mixture modeling, we can instead identify subgroups of survivors who show similar changes in cognitive problems over time. The International Cognition and Cancer Task Force recommended such growth curve and growth mixture modeling approaches for analyzing longitudinal CRCI data (Wefel et al., 2011). Additionally, this approach allows for the profiling of these groups through the identification of differing clinical, biological, and psychosocial characteristics. Growth mixture modeling has been successful in the study of group-based trajectories of other behavioral symptoms in breast cancer survivorship (Bower et al., 2021, 2018; Stanton et al., 2015). In

particular, trajectory analyses of fatigue in the MBS and RISE Study samples have illuminated heterogeneous experiences, with the majority of women experiencing low or very low levels of fatigue throughout the study periods, but smaller groups of women exhibiting "reactive" fatigue (acute treatment effects) or higher levels of fatigue throughout (Bower et al., 2021, 2018). Trajectory analysis of depressive symptoms across the first year of breast cancer survivorship has also identified heterogeneous experiences of depression, with the majority of women exhibiting recovery or lower-level symptoms throughout but roughly 38% of women experiencing chronically elevated depressive symptoms (Stanton et al., 2015). Taken together, the findings for heterogeneous experiences of fatigue and depressive symptoms in breast cancer survivorship highlight the utility of such analytic approaches to uncovering trajectories for these behavioral symptoms.

Trajectories of cognitive function in cancer survivors and other groups

Despite the success of group-based growth-mixture modeling of fatigue and depression in breast cancer survivorship, to our knowledge, only one study has used this approach to examine profiles of CRCI in cancer populations. This study focused on objective cognitive problems in postmenopausal breast cancer survivors and healthy controls (Bender et al., 2018). Women completed a baseline assessment before the start of chemotherapy or aromatase inhibitor therapy and completed 6-, 12-, and 18-month follow-up assessments. At each visit, women were tested on neuropsychological tasks designed to tap executive functions, concentration, and visual working memory to identify specific subgroups of each cognitive domain. For executive functioning, three groups emerged: chronic low (lower than population norms at baseline that remained low), recovery (lower than population norms at baseline that improved linearly), and

delayed (higher than population norms at baseline with worsening at 18 months). Baseline predictors of group trajectories included older age and less education for the delayed group; lower IQ, receipt of aromatase inhibitor therapy with or without chemotherapy, and greater baseline fatigue for the chronic low group. Baseline neuropsychological performance also predicted group membership. The authors also tested whether polymorphisms in genes associated with DNA repair acted as risk factors for group trajectory membership and identified both risk and neuroprotective effects. For visual working memory, two groups emerged: low and improving and high and improving with similar risk and resilience profiles as the executive functioning groups. Group membership across the cognitive domains were also correlated such that being in the low executive functioning group was associated with being in the low memory group. Although women were assessed for anxiety and depressive symptoms, the authors did not report on their associations with group membership. This study provides initial support for the identification of, and risk factors for, heterogeneous subgroups of objective cognitive problems during breast cancer survivorship.

Growth mixture modeling approaches have also been applied to the characterization of objective cognitive functioning in non-cancer samples. For example, epidemiological studies of cognitive decline in healthy aging have used mixed-effects models to fit growth curves to repeated assessments of in-person and telephone-based cognitive performance testing to identify predictors of rates of cognitive decline in nationwide cohorts. Karlamangala and colleagues identified older age, female sex, widow-status, and never being married as risk factors for faster cognitive decline (Karlamangla et al., 2009). Studies such as this commonly find (and account for) a practice or learning effect from the first assessment to the second assessment that dissipates at subsequent visits (Unger, Van Belle, & Heyman, 1999).

To our knowledge, there has only been one study of trajectories of perceived cognitive impairment in breast cancer survivors; however, this study did not employ growth mixture modeling (Ng et al., 2018). A sample of 131 breast cancer survivors completed the FACT-Cog before chemotherapy (T1) and 6 weeks (T2), 12 weeks (T3), and 15 months (T4) following chemotherapy initiation. Patients were considered to have clinically significant cognitive impairment if their FACT-Cog score was at least 10.6 points lower than the previous time-point, which is the minimal clinically important difference score in breast cancer patients (Cheung et al., 2014). Five trajectory groups were defined *a priori* based on clinical observations: no decline (no clinically significant drops between any time-point), acute decline (clinically significant cognitive decline at either T2 or T3 but not T4), delayed decline (clinically significant cognitive decline at T4 only), persistent decline (clinically significant cognitive decline at T3 and T4 (with/without decline at T2)), and intermittent decline (clinically significant cognitive decline at T2 and T4 but not T3). They found that most patients did not report any clinically significant cognitive impairment, 16.0% reported acute cognitive changes during chemotherapy (T2 and/or T3) but not at T4, 30.5% reported clinically significant cognitive impairment at T4, 11.5% reported persistent cognitive impairment throughout all time points, and 5.3% reported intermittent cognitive impairment at T2 and T4 but not at T3. The authors also report that greater baseline cognitive problems and fatigue were risk factors for perceived impairment at 15 months following chemotherapy.

The Ng study adds to the existing literature in important ways in that it was the first to examine heterogeneous trajectories of perceived cognitive impairment in breast cancer survivors from before, during, and after chemotherapy. However, the authors did not examine group differences to characterize the profiles of women who made up each trajectory group. Further,

although using *a priori* defined trajectory group classifications has merit in that it allows for testing assumptions about the manifestations of CRCI based on clinical observations, employing a data-driven approach would allow for the experiences of the women in the study to speak for themselves and illuminate trajectories that might otherwise go undetected. Finally, restricting the sample to only women who received chemotherapy allows for the direct examination of chemotherapy-associated CRCI; however, given that CRCI can manifest in the absence of chemotherapy and might be driven by other treatments (surgery type, radiation, endocrine therapy), a study of trajectories from a more clinically diverse sample is needed. For example, in a study of postmenopausal breast cancer patients receiving either aromatase inhibitor therapy alone or chemotherapy followed by aromatase inhibitor therapy and healthy controls, women who received chemotherapy showed increases in perceived cognitive problems using the Patient's Assessment of Own Functioning Inventory (PAOFI) following chemotherapy whereas women who received aromatase inhibitors alone did not (Merriman et al., 2017). Growth mixture modeling approaches to analyzing clinically heterogeneous samples would allow for the characterization of natural trajectories as well as the examination of treatments as risk factors for group membership.

Predictors of group membership

There are several sociodemographic, clinical, treatment-specific, and psychological factors that might predict trajectory group membership. Potential demographic variables that might be associated with group membership include age, socioeconomic variables such as income, education, and employment, as well as partner status (Ahles & Hurria, 2018). With respect to potential clinical factors, higher cancer stage might be a risk factor for greater

cognitive problems. Prior to adjuvant therapies, women with stage 1-3 breast cancer have been shown to have poorer performance on neuropsychological assessments than women with stage 0 cancer (Ahles et al., 2008). Similarly, more advanced stage has been associated with poorer pre-adjuvant therapy executive functioning performance among older breast cancer patients (Mandelblatt et al., 2014). In addition, comorbidity status might be associated with CRCI such that more comorbidities would be associated with membership in higher cognitive problem groups.

There are also treatment-specific risk factors that would be of interest to explore as predictors of group membership. First, surgery type has been included in almost all models of CRCI (discussed extensively in Study 1); however, empirical evidence to support an association between surgery type and CRCI is scant. Therefore, evaluating surgery as a risk factor for CRCI trajectory group membership will be an important contribution to the literature. Notably, receipt of mastectomy has been identified as a clinical risk factor for high fatigue trajectory group membership in the RISE sample and fatigue is highly correlated with cognitive problems (Bower et al., 2018). Additionally, mastectomy has been shown to be associated with poorer physical functioning and worse pain and fatigue (Radin et al., 2022). Study 1 highlighted the synergistic role that mastectomy and chemotherapy can have in terms of impact on cognitive problems as well. Adjuvant therapies, and chemotherapy in particular, have been the most extensively studied risk factors for CRCI (Ahles & Saykin, 2002; Jim et al., 2012; Noal et al., 2011); however, it is currently unknown how patients differ in onset, maintenance, and resolution of CRCI in the context of chemotherapy and/or radiation. Endocrine therapy has also been shown to be associated with perceived cognitive problems including language and communication and attentional domains of cognition (Ganz et al., 2014; Kohler et al., 2020). However, there is less

support for associations between endocrine therapy and objective cognitive problems. When examining the effects of endocrine therapy on neuropsychological performance over 6 years following treatment completion, Van Dyk and colleagues found no effects of endocrine therapy on objective cognitive functioning or impairment (Van Dyk et al., 2019). Therefore, examining the role of endocrine therapy, particularly when preceded by chemotherapy, in perceived cognitive problems will help clarify its role in CRCI.

In addition to treatment-related risk factors, there are several psychological risk factors that might be associated with trajectory group membership. Previous studies of CRCI have identified psychological/behavioral variables that are associated with perceived and objective cognitive problems. In terms of perceived cognitive problems, sleep, anxiety, depressive symptoms and fatigue have been shown to be associated with greater complaints in cross-sectional studies (Henneghan et al., 2018). Similarly, in a longitudinal study of perceived attentional function assessed before and following breast cancer surgery, higher levels of trait anxiety, fatigue, and sleep disturbance were cross-sectionally associated with lower levels of attentional function before breast cancer surgery (Kohler et al., 2020). Another longitudinal study found that baseline levels of fatigue, depressive symptoms, and anxiety predicted more cognitive complaints over time (Merriman et al., 2017). Depressive and anxiety symptoms have also been found to be contemporaneously associated with perceived cognitive problems over time (Biglia et al., 2012; Hermelink et al., 2010). To our knowledge, no studies have examined the impact of lifetime depression on CRCI. A history of depression is associated with both dementia and self-reported cognitive problems outside of the cancer context (Jorm, 2001; Rapp et al., 2011; Sachs-Ericsson, Joiner, & Blazer, 2008); therefore, it is a possible culprit in the onset and maintenance of cognitive problems among women with breast cancer. Additionally,

although childhood adversity has been implicated as a risk factor for fatigue in breast cancer survivorship (Bower, Crosswell, & Slavich, 2014; Bower et al., 2018), and is associated with poorer cognitive functioning in patients with major depression (Dannehl, Rief, & Euteneuer, 2017), to our knowledge, there has yet to be a study of the association between childhood adversities and CRCI.

In terms of correlates of objective cognitive problems in breast cancer survivorship, fatigue has also been shown to be contemporaneously associated with neuropsychological performance at one and multiple time-points (Gullett et al., 2019; Van Dyk, Bower, Crespi, Petersen, & Ganz, 2018). Similarly, current sleep disturbance (Carroll et al., 2019; Van Dyk et al., 2018) has been associated with poorer neuropsychological performance following adjuvant therapies. Evidence for associations between anxiety and depressive symptoms and objective CRCI is more mixed: whereas some studies find that depressive symptoms are associated with neuropsychological testing performance following adjuvant therapies (Ganz, Kwan, et al., 2013), others have found associations between anxiety and depressive symptoms and perceived, but not objective, cognitive problems (Biglia et al., 2012; Hermelink et al., 2010; Schagen, Muller, Boogerd, & Van Dam, 2002). In studies of objective CRCI, psychological variables are often controlled for to examine treatment effects on cognitive functioning over and above the effects of anxiety and depression.

Current Study

The current study aimed to address gaps in the literature and advance understanding of the heterogeneity of CRCI by identifying and characterizing trajectories of perceived cognitive problems over time. We used data from a longitudinal observational study of breast cancer

survivors who were assessed before and after adjuvant therapies with 6-, 12-, and 18-month follow-up assessments (the RISE study). We also tested key sociodemographic, clinical, and psychological/behavioral risk factors for group membership, drawing from empirical literature as well as conceptual models of CRCI (described in detail in the General Introduction). In particular, we investigated sociodemographic factors (i.e., age, race/ethnicity, income, education, employment, partner status); clinical factors (i.e., stage, comorbidities, surgery, adjuvant therapy, endocrine therapy) and psychological/behavioral factors (i.e., baseline fatigue, anxiety and depressive symptoms, sleep disturbance, cancer-related distress, history of depression, and childhood adversity) in relation to group membership (Ahles & Hurria, 2018; Ahles & Root, 2018; Lange et al., 2019; Miller et al., 2008).

B. Specific Aims

Specific Aim 1: Identify trajectories of perceived cancer-related cognitive impairment in a longitudinal observational study of breast cancer survivors, the RISE study.

Hypothesis 1a: Based on previous studies of growth mixture models of fatigue and depressive symptoms, and one study of *a priori* defined perceived cognitive functioning trajectory groups in breast cancer survivors, we hypothesized that there would be stable low, chronically high, acute or treatment "reactive," and delayed or increasing groups.

Hypothesis 1b: We hypothesized that most women would be assigned to the stable low group, consistent with findings for fatigue and depressive symptoms.

Specific Aim 2: Identify clinical, psychological/behavioral, and biological risk factors of trajectory group membership for perceived cognitive problems over time.

Hypothesis 2: Risk factors for trajectories of higher perceived cognitive problems over time will include older age, lower income, less education, unemployment, being partnerless, undergoing a mastectomy, receipt of chemotherapy, receipt of mastectomy + chemotherapy, receipt of endocrine therapy, receipt of chemotherapy + endocrine therapy, greater fatigue, anxiety and depressive symptoms, sleep disturbance, and cancer-related distress at baseline, a history of depression, and greater exposure to childhood adversity.

C. Methods

The RISE Study Timeline

This study used previously collected data from a longitudinal observational study of breast cancer survivors: the RISE Study. Briefly, the RISE study assessed women for perceived cognitive problems before the start of adjuvant therapies (n = 270), after treatment completion (for those treated with adjuvant therapy; n = 194), as well as at 6- (n = 254), 12- (n = 246), and 18- (n = 244) month post-treatment follow-up assessments (see Consort Diagram in Appendix D). At each assessment, women completed surveys including the Multidimensional Fatigue Symptom Inventory short form (MFSI-SF) mental subscale, a measure of perceived cognitive problems.

The RISE Study Assessments

1. Perceived cognitive problems: MFSI-SF Mental subscale
2. Demographic variables: age, race/ethnicity, income, education, employment status, partnered status
3. BMI

4. Clinical variables: Stage, surgery type (lumpectomy, unilateral mastectomy, bilateral mastectomy, neoadjuvant therapy), number of surgeries, adjuvant therapy type (chemotherapy, radiation) and receipt of endocrine therapy were abstracted from medical charts.
5. Medical comorbidities: Charlson Comorbidity Scale
6. Baseline fatigue: MFSI-SF General subscale
7. Baseline anxiety symptoms: MFSI-SF Emotional Fatigue Subscale items that have construct validity for anxiety
8. Baseline depressive symptoms: Center for Epidemiologic Studies-Depression (CES-D)
9. Baseline sleep disturbance: Pittsburgh Sleep Quality Index (PSQI) sleep disturbance score
10. Cancer-related distress: Impact of Events Scale (IES)
11. History of depression: SCID (Structured Clinical Interview for DSM-IV-TR Axis I Disorders)
12. Childhood adversity: Childhood Trauma Questionnaire (CTQ). We used the Walker et al, 1999 scoring criteria (Walker et al., 1999): women who scored 8 or above on the sexual abuse scale were placed in the "sexual maltreatment" group (including women who met criteria for non-sexual maltreatment); women who scored at or above the threshold for one or more of the nonsexual scales (physical abuse (8), physical neglect (8), emotional neglect (15), or emotional abuse (10) were placed in the "nonsexual maltreatment" group. All other women were categorized as "neither form of maltreatment." Because we did not have specific hypotheses about sexual vs.

nonsexual maltreatment, women were collapsed into a binary variable of history of childhood adversity (yes or no).

D. Data Analytic Plan

Group-based trajectory modeling, a specialized form of finite mixture modeling, was employed using the *lcmm* package from R Stats. The MFSI-SF mental subscale was used as the dependent variable to model trajectories of perceived cognitive problems. For each trajectory of interest, we fit a series of models specifying varying numbers of latent classes (potential trajectory groups) and varying linear mixed model complexity and compared model fit indices. Following the approach of Bower and colleagues who modeled trajectories of fatigue in the RISE sample, we fit models specifying 1 to 5 latent classes (trajectory groups) and linear mixed model complexity ranging from intercept and slope parameters varying within class to intercept, slope, quadratic, and cubic parameters varying within class (Bower et al., 2021). We modeled time as discrete given that assessments were anchored to specific events. To avoid small class sizes, we considered models for which the smallest group had at least 10 participants. Model fit was compared using Akaike information criterion (AIC), Bayesian information criterion (BIC), sample size–adjusted BIC, and entropy (Tofighi & Enders, 2008). Once the final model was selected, each participant was assigned to the trajectory group for which they had the highest membership probability.

To test the proposed biobehavioral risk factors for trajectory group membership, we tested for differences in risk factors between groups using Fisher exact tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Significant associations for categorical variables were further probed by examining the adjusted residuals, which are

statistically significant when more extreme than what would be expected if the null hypothesis of independence was true. Significant associations for continuous variables were further probed using post-hoc pairwise comparisons adjusted for multiple comparisons (Tukey adjustments). Categorical variables included income, education, employment, partner status, comorbidities, stage, surgery type at the enrollment visit (lumpectomy or mastectomy), total number of surgeries over the assessment period (1-3+), adjuvant therapy type (chemotherapy, radiation, chemotherapy and radiation, none), endocrine therapy (yes/no), surgery type with or without chemotherapy, chemotherapy with or without endocrine therapy, history of depression (yes/no), and childhood adversity (yes/no). Continuous variables included age, BMI, baseline levels of fatigue, anxiety and depressive symptoms, sleep disturbance, and cancer-related distress.

Power Considerations:

We assessed whether the RISE dataset had enough observations to perform growth mixture modeling as described above. Growth mixture models have few strict data requirements; however, there are general characteristics that are favorable (Curran, Obeidat, & Losardo, 2010). Samples that approach at least 100 participants are preferable. At least 100 women participated in each timepoint for the RISE study. Therefore, the RISE dataset was adequately powered for performing trajectory analyses.

E. Results

Participants

The full analytic sample for the RISE study included 270 women at baseline. Figure 1 illustrates the number of women who completed each assessment timepoint. Only women who

had chemotherapy and/or radiation were assessed at the "post-treatment" assessment timepoint (n = 194). Retention throughout the study period was high with 254 women completing the 6-month follow-up, 246 completing the 12-month follow-up, and 244 completing the 18-month follow-up.

Identifying Fatigue Trajectories

Model comparison revealed a 5-class solution as the best fitting model in terms of AIC and sample size-adjusted BIC (see Table 1 for all models and their model fit indices). The chosen model had the 3rd best BIC rank and an entropy value of 0.91 (entropy values greater than 0.80 are valid). This model was selected over the 5-class solution with the best BIC rank because its smallest class size was 4.07% as compared to 2.96%. The mean MFSI-SF Mental trajectories for the 5 latent classes are depicted in Figure 2. The five classes were categorized as follows: Stable Low (79% of the sample), Reactive (6% of the sample), Delayed Reactive (5.5% of the sample), Decreasing (5.5% of the sample), and Increasing (4% of the sample). The baseline values on the MFSI-SF Mental subscale were as follows: Stable Low, 3.3 (SD: 2.7); Reactive, 5.3 (SD: 2.0); Delayed Reactive, 9.8 (SD: 4.2); Decreasing, 15.1 (SD: 2.9); and Increasing, 8.2 (SD: 3.7). For reference, in the validation study for the MFSI, the mean score on the MFSI-SF Mental subscale was 3.37 in noncancer controls and 3.96 in a group of breast cancer patients (both undergoing treatment and survivors who had completed treatment) (Stein et al., 1998).

To ensure that individuals assigned to each trajectory group fit within their assigned groups, we plotted participant-level raw mean scores on the MFSI-SF Mental subscale. Spaghetti plots of raw mean scores for each trajectory group are presented in Figure 5. Upon visual inspection, the majority of women assigned to each group fit within their respective trajectory

group.

Characterizing Fatigue Trajectories

Descriptive statistics for all demographic, clinical, psychosocial, and inflammatory potential predictors of group membership along with tests of significance can be found in Table 2. There were significant or marginally significant associations between trajectory group and age ($p = .06$), cancer stage ($p = .006$), receipt of chemotherapy ($p = .07$), receipt of endocrine therapy ($p = .006$), receipt of chemotherapy + endocrine therapy ($p = .009$), childhood maltreatment ($p < .001$), history of major depressive disorder ($p = .06$), baseline depressive symptoms ($p < .001$), baseline sleep disturbance ($p < .001$), baseline general fatigue ($p < .001$), baseline anxiety symptoms ($p < .001$), and baseline cancer-related distress ($p < .001$). Proportions and mean values for significant predictors are presented in Figure 3 (categorical predictors, percentage) and Figure 4 (continuous predictors, mean ratings).

Women in the Stable Low group had the lowest baseline levels of cognitive complaints as well as the lowest baseline depressive and anxiety symptoms, sleep disturbance, fatigue, and cancer-related distress. Women in this group also reported the lowest level of childhood adversity and the lowest prevalence of history of major depressive disorder. In contrast, women in the Decreasing group had the highest levels of cognitive complaints at baseline as well as the highest baseline depressive and anxiety symptoms, sleep disturbance, fatigue, and cancer-related distress. The Decreasing group also reported the highest level of childhood adversity. Interestingly, all the women in the Decreasing group had stage 0 or I cancer.

The Increasing group had the highest percentage of women treated with chemotherapy and endocrine therapy, either on their own or in combination with one another. Surprisingly,

none of the clinical variables predicted membership to the Reactive group. The Reactive group only differed from the Increasing group in terms of having lower baseline depressive symptoms, sleep disturbance, and fatigue. Lastly, the Delayed Reactive group was less likely to have received endocrine therapy but report higher levels of childhood adversity than the Stable Low group. This group also exhibited higher baseline depressive symptoms, fatigue, and anxiety symptoms than the Stable Low group, and *lower* baseline levels of sleep disturbance and fatigue than the Decreasing group. Baseline levels of inflammatory markers were not associated with any of the trajectory groups.

Given that depression may underlie cognitive problems, it is possible that the trajectory groups identified here reflect longitudinal patterns of depressive symptoms rather than cognitive problems. We examined this possibility by plotting the mean CESD scores at each study visit for each cognitive trajectory group (Figure 6). Although there are similarities between patterns of CESD scores and those of the MFSI-SF Mental subscale scores for each trajectory group, there are also clear differences. The Stable Low group has similarly stable low depressive symptoms over the 18-month study period. However, the Decreasing group shows a slight increase in depressive symptoms at the post-treatment visit. Additionally, the treatment Reactive group does not show an increase in depressive symptoms until the 6-month follow-up visit. Lastly, the Increasing group exhibits a slight decrease in depressive symptoms at the post-treatment visit.

F. Discussion

Cognitive problems are a commonly reported behavioral symptom during and after breast cancer treatments. The current results highlight the heterogeneity in cognitive problem onset, severity, and persistence in women with early-stage breast cancer. Data-driven trajectory

analyses revealed 5 different latent classes reflecting different experiences of cognitive problems from diagnosis through 18-months post-treatment: a Stable Low group that remained low throughout the study period (79%), a Reactive group that exhibited increases at the post-treatment assessment that declined by 6 months (6%), an Increasing group that steadily rose throughout the study period (4%), a Decreasing group that steadily decreased throughout the study period (5.5%), and a Delayed Reactive group that did not exhibit increases following treatment until 6 months that declined by 18 months (5.5%). The MFSI-SF Mental subscale does not have reference scores for minimal clinically significant differences; however, the Stable Low group had an average baseline score of 3.3 (comparable to reported score of 3.4 in noncancer controls; (Stein et al., 1998)) whereas the trajectory groups that exhibited elevated cognitive problems at any timepoint had maximum scores 5 times higher than that (15-16). Consistent with a priori hypotheses, most of the sample was categorized by the Stable Low trajectory, and there were also Reactive and Increasing groups. However, we did not identify a chronically high group; instead, the selected model included Decreasing and Delayed Reactive groups which were not included in our hypotheses.

These results are partially consistent with the one *a priori* defined trajectory group analysis for cognitive problems in breast cancer survivors that used the FACT-Cog (Ng et al., 2018). Like Ng et al., we observed a stable low or "no decline" group; however, more of the women in the RISE sample were assigned to the stable low group than the Ng sample (79% vs. 53%). We also detected a reactive or "acute" group; however, more participants were assigned this group in the Ng study (16% vs. 6%). What Ng and colleagues called "delayed decline" we also observed by categorized as "Increasing." Unlike the Ng study, our findings also included a Delayed Reactive group that exhibited greatest increases in cognitive problems at 6 months post-

treatment. The Ng study did not assess women at 6 months so it is possible that their sample also exhibited this pattern but it went undetected. Lastly, they categorized a group of women as "persistent decline" which was characterized by treatment reactivity that never declined to baseline levels. We did not observe a similar pattern in the current data. However, important methodological differences might explain these discrepancies. Besides not using data-driven trajectory analyses, that study also employed the minimal clinically important difference for the FACT-Cog to characterize participants into groups. They also only studied women who were undergoing chemotherapy and were assessed at different time points (before chemotherapy, 6 weeks, 12 weeks, and 15 months following chemotherapy initiation).

There are similarities and notable differences between these cognitive trajectory groups and trajectories for other common behavioral symptoms in breast cancer survivors including fatigue, depressive symptoms, and insomnia (Bean et al., 2021; Bower et al., 2021, 2018; Stanton et al., 2015). For example, fatigue trajectory groups in the same sample of RISE participants also included Stable Low, Increasing, and Decreasing trajectory groups (Bower et al., 2021). However, fatigue reactivity to treatments peaked at 6 months, whereas women's cognitive problems following treatments either peaked at the post-treatment assessment (Reactive) or at the 6- and 12-month assessments (Delayed Reactive). To our surprise, we did not identify a stable high group like what has been observed for fatigue, insomnia, and depressive symptoms. Instead, women with the greatest cognitive problems at baseline all were categorized by a declining (or "recovery") trajectory group. Although highly correlated, there are distinct differences between experiences with cognitive problems, fatigue, depressive symptoms, and insomnia, and the trajectories identified here reflect that.

Several of the hypothesized demographic, clinical, and psychosocial predictors of group

membership were found to be significant across the identified trajectory groups. The Stable Low group was categorized by having the lowest baseline levels of all behavioral symptoms (depressive symptoms, sleep disturbance, fatigue, anxiety symptoms, and cancer-related distress), an absence of childhood adversity and no history of major depressive disorder. The Decreasing group, on the other hand, had the highest levels of baseline behavioral symptoms, were more likely to have stage 0 or 1 disease, less likely to receive chemotherapy, and had the highest proportions of childhood maltreatment and history of major depressive disorder. The Increasing group was the one group that was associated with a particular treatment exposure – this group had the higher proportion of women who received endocrine therapy as well as women who received both chemotherapy and endocrine therapy.

Surprisingly, none of the clinical or treatment-related variables predicted assignment to the Reactive group. In large cohort studies with healthy controls, average levels of perceived cognitive problems are typically higher than healthy controls at baseline, increase at post-chemotherapy, and decline (although not to baseline levels) by 6 months post-treatment, most consistent with the Reactive trajectory group (e.g., Janelsins et al., 2016). However, we found no evidence that women were more likely to be in the Reactive group if they received chemotherapy. Additionally, none of the demographic variables predicted group membership which was surprising given the role they place in trajectories of depression in breast cancer patients (Stanton et al., 2015). Of course, this does not mean that these variables are not important or relevant for CRCI, just that they do not cluster within the identified trajectory groups.

Neither surgery type on its own or surgery type in combination with chemotherapy status predicted group membership. Receipt of mastectomy has been shown to predict group

membership for fatigue in the RISE sample but not the MBS sample (Bower et al., 2021, 2018). This is likely due to differences in assessment timing (the RISE Study baseline assessment took place after surgery whereas the MBS baseline took place after adjuvant therapies). Receipt of mastectomy has also been shown to be associated with more fatigue, physical functioning, and pain as compared to lumpectomy (Radin et al., 2022). However, surgery type does not appear to play a predictive role in data-driven cognitive trajectories. Similarly, surgery type in combination with chemotherapy status was not predictive of group membership. This is surprising in light of findings from Study 1 which found that mastectomy in combination with chemotherapy was associated with higher levels of cognitive problems over time in the RISE sample. The pattern of mean levels of the MFSI-Mental subscale in that group resembled the Delayed Reactive group in the current study. However, based on the present results, it does not appear that that group had an over-representation of women with that treatment profile.

There are important contextual factors and limitations to consider while interpreting these results. First, RISE Study participants were predominantly White and well educated and therefore are not representative of the broader population of women with breast cancer. Second, the RISE Study used the MFSI-SF Mental subscale to assess perceived cognitive problems rather than the FACT-Cog, the gold standard assessment in cancer survivors (Van Dyk et al., 2017). However, the items on the MFSI-SF Mental subscale overlap considerably with the FACT-Cog and other validated measures of cognitive problems, supporting the construct validity of this measure. In addition, assessment of objective measures of cognitive functioning would be informative given that mean patterns of objective and subjective cognitive problems over time do not always mirror one another (e.g., Janelsins et al., 2018 vs. 2016). Third, although we followed patients for 18 months after treatment completion, different trajectory groups might arise for data

collected further out from adjuvant therapy. This is particularly important given that the Increasing group was more likely to receive endocrine therapy and that women are prescribed to take endocrine therapy for 5 or more years after adjuvant therapy. Future analyses of longer-term datasets will aid in understanding the role of endocrine therapy in cognitive functioning over time.

In conclusion, the trajectory groups identified and characterized here aid in our understanding of the heterogeneity in breast cancer survivors' experiences with cognitive problems from initial treatment through the initial phase of survivorship. Importantly, most women were assigned to the Stable Low trajectory, and we did not identify a stable high trajectory. Additionally, most women who experienced high levels of cognitive problems at one or more timepoints eventually declined. However, 4% of women did increase in cognitive problems over the study period and this group had the highest proportion of women who received chemotherapy with endocrine therapy. Informing clinicians of these risk factors will aid in identifying, preparing, and supporting patients who are most vulnerable to cancer-related cognitive impairment.

Chapter 5: General Discussion

The three studies included in this dissertation contribute to the growing understanding of the clinical drivers, biological mechanisms, and trajectories of breast cancer-related cognitive impairment. Study 1 tested the role of surgery type in the onset and maintenance of CRCI, a novel contribution given the primary focus on chemotherapy as a clinical driver of cognitive problems. The results of Study 1 demonstrate how mastectomy can prime patients for the effects of chemotherapy on cognitive functioning, leading to more pronounced and persistent cognitive problems over time. Study 2 extended these findings by investigating inflammation as a biological mediator linking cancer and its treatments with both perceived and objective cognitive problems in two different cohorts of breast cancer survivors (the RISE and MBS studies). The inconsistent findings from Study 2 highlight how nuanced the relationship between peripheral inflammation and cognitive problems is. Significant associations between inflammatory markers and perceived cognitive problems were only evidenced in the MBS study, and these relationships were only present for women who were younger or received chemotherapy. Lastly, Study 3 provided an alternative analytic lens through which we can study CRCI across the cancer continuum. Using growth mixture modeling, we identified 5 heterogenous trajectories of perceived cognitive problems: a Stable Low group, a Reactive group, an Increasing group, a Decreasing group, and a Delayed Reactive. Characterization of these trajectory groups in terms of clinical and psychosocial risk factors illuminated chemotherapy in combination with endocrine therapy as a risk factor for membership to the Increasing group.

Taken together, the findings from all three studies reveal particularly impactful and synergistic roles of mastectomy, chemotherapy, and endocrine therapy in driving elevations of perceived cognitive problems through two years following breast cancer surgery. This is critical

given that studies of CRCI typically evaluate the influence of a particular therapy (e.g., chemotherapy, radiation, endocrine therapy) in isolation or while statistically covarying for the effects of the others. Although investigating the unique influences and contributions of each cancer therapy is important both scientifically and clinically, breast cancer treatment regimens often involve a series of treatments. Indeed, in their conceptual model of sociodemographic, clinical, behavioral, psychological, and biological processes that influence cognitive functioning in the cancer context, Ahles and Hurria indicated "all predictors of cognitive function/cognitive aging potentially interact with each other" (p. 4; Ahles & Hurria, 2018). Therefore, further investigations into how these treatments interact to precipitate cognitive problems throughout breast cancer survivorship will have high clinical validity and more accurately capture the CRCI experience for a large proportion of patients.

One example of such an approach comes from analyses using data from the TAILORx Study which longitudinally assessed cognitive functioning in women who either received chemotherapy plus endocrine therapy (CT+ET) or endocrine therapy (ET) alone (Wagner et al., 2020). The researchers found that perceived cognitive functioning (FACT-Cog perceived cognitive impairment (PCI) scale) was significantly worse for the CT+ET group than the ET group at 3 and 6 months. However, given that there was considerable variability in PCI scores, a trajectory analysis as was conducted in Study 3 could aid in capturing the heterogeneity in cognitive functioning across the study period and within these two treatment groups.

Additionally, the findings from Study 2 challenge the characterization of peripheral inflammation as the leading biological mechanism linking the breast cancer experience with cognitive problems. While the inflammatory markers IL-6 and sTNF-RII might be biological mechanisms of perceived cognitive problems in younger women and women undergoing

chemotherapy, further research is needed to investigate other potential biological mediators linking cancer and its treatments with both perceived and objective cognitive dysfunction. There are biological processes further upstream of peripheral inflammation that might be more closely linked with cognitive functioning including compromised blood-brain barrier (BBB) integrity (Lange et al., 2019), and impaired glucose metabolism (Ahles & Hurria, 2018; Ahles & Root, 2018; Janelsins et al., 2014), both of which are included in the conceptual models that guided these studies.

A more recent conceptual model put forth by Fleming, Edison, and Kenny includes neuroestrogen levels as a putative mechanism linking endocrine therapy with CRCI (Fleming, Edison, & Kenny, 2023). Neuroestrogens increase brain-derived neurotrophic factor (BDNF) in the hippocampus and prefrontal cortex, which increases dendritic spines and induces spine plasticity leading to enhanced cognition (Luine & Frankfurt, 2013). There is exciting new pre-clinical work examining the associations between circulating estrogen (estradiol) and peripheral inflammation in mammary tumor-bearing mice that have been ovariectomized. Grant and colleagues found that mammary tumors are associated with higher levels of peripheral and central inflammation and alter estrogen signaling in the hypothalamus, hippocampus, and frontal cortex (Grant, Russart, & Pyter, 2022). Given that neuroestrogens decline with age especially during menopause, and that chemotherapy can induce early-onset menopause, it is possible that the combination of chemotherapy plus endocrine therapy acts as a "double hit" through synergistic effects on neuroestrogens. Future work should test the associations between peripheral inflammation, circulating estrogens (i.e., estradiol), and cognitive functioning in clinical samples undergoing chemotherapy and endocrine therapy.

Another potential biological mediator that is more proximal to cognitive functioning than

peripheral inflammation is excess extracellular glutamate (Haroon, Miller, & Sanacora, 2016). Central inflammation triggered by peripheral inflammation can lead to failed clearance and exaggerated release of glutamate. Excess extracellular glutamate can have deleterious effects on cognition through excitotoxicity, leading to synaptic dysfunction and death (Haroon et al., 2016). Nutraceuticals that act as "scavengers" by clearing excess extracellular glutamate are currently being investigated as novel therapeutics for CRCI. For example, a Phase 2 clinical trial of oxaloacetate is currently underway at UCLA (clinicaltrials.gov identifier: NCT04290897). While this study is not designed to directly test whether clearance of excess extracellular glutamate is the biological mechanism linking oxaloacetate treatment with improved cognitive functioning, findings from this study will add to the understanding of whether this biological process is a potential treatment target worthy of further investigation.

Findings from these studies have implications for theory, research, and the treatment of CRCI. Whereas the leading conceptual models of CRCI are helpful for identifying sociodemographic, clinical, psychological, and biological factors of interest for the study of CRCI, they are not designed to reflect how these processes interact with one another to precipitate and maintain cognitive problems over time (Ahles & Hurria, 2018; Ahles & Root, 2018; Janelsins et al., 2014; Lange et al., 2019). Conceptualization of CRCI may benefit from considering how common treatment sequences (e.g., mastectomy + chemotherapy and chemotherapy + endocrine therapy) interact with sociodemographic, psychological, and biological processes to precipitate and maintain cognitive problems throughout survivorship. In terms of implications for future research, Studies 2 and 3 highlighted analytic approaches that might be better equipped to reflect the nuanced and heterogeneous nature of CRCI. First, Study 2 highlighted how peripheral inflammatory markers might be associated with perceived cognitive

problems when analyzed in terms of differences from the sample mean (IL-6) or fluctuations around a given participant's own mean levels (sTNF-RII). Further, these associations were moderated by both receipt of chemotherapy and younger age. Therefore, future research examining associations between inflammation (and other potential biological mediators) and cognitive problems should be adequately powered with diverse samples to test for moderation. Second, Study 3 illustrated the large variability in patterns of cognitive problems over time and provides compelling support for the use of data-driven approaches to identifying and characterizing trajectories of cognitive problems throughout survivorship.

Lastly, the results of these studies have clinical implications for the prevention and treatment of cognitive problems during breast cancer survivorship. Providers should counsel their patients on the association between mastectomy with chemotherapy and CRCI, especially when more extensive surgery is not clinically indicated but chemotherapy is. Further, providers should be aware that women who will be receiving chemotherapy + endocrine therapy might be at risk for increasing cognitive complaints that persist at least 18 months following treatment. Given that these studies do not provide strong support for peripheral inflammation as a biological mediator linking cancer and its treatments with CRCI, other biological targets such as BBB integrity, glucose metabolism, neuroestrogens, and excess glutamate should be further investigated as potential treatment targets. In the meantime, these results identify several modifiable psychological targets that appear to be associated with more favorable trajectories of cognitive problems over time including sleep, anxiety, depressive symptoms, distress, and fatigue.

Study 1 Tables and Figures

Table 1. Participant characteristics for each treatment group and the total sample

	Lump no CT (n = 112)	Lump + CT (n = 42)	Mast no CT (n = 38)	Mast + CT (n = 22)	Total (n = 214)	Differences between groups
Demographics						
Age, mean (SD), years	58 (11)	57 (11)	55 (10)	50 (9)	57 (11)	p < .01 • Mast + CT < Lump no CT
Race & Ethnicity, N (%)						p = .06
Asian	9 (8)	6 (14)	5 (13)	5 (23)	25 (12)	
Black	3 (3)	5 (12)	0 (0)	3 (14)	11 (5)	
Hispanic	12 (11)	4 (10)	2 (5)	2 (9)	20 (9)	
Other	2 (1)	1 (2)	1 (3)	1 (4)	5 (2)	
White (Non-Hispanic)	86 (77)	26 (62)	30 (79)	11 (50)	153 (71)	
Education, N (%)						p = .89
Less than college degree	34 (30)	12 (29)	8 (21)	8 (36)	62 (29)	
College graduate	43 (38)	17 (40)	16 (42)	9 (41)	85 (40)	
Post-graduate degree	35 (31)	13 (31)	14 (37)	5 (23)	67 (31)	
Annual Household Income ≥ $100,000, N (%)	60 (54)	22 (52)	18 (47)	13 (59)	113 (53)	p = .87
Employed, N (%)	62 (55)	27 (64)	20 (53)	16 (73)	125 (58)	p = .75
Partnered, N (%)	72 (64)	26 (62)	26 (68)	16 (73)	140 (65)	p = .81
Clinical Characteristics						
Days from surgery to enrollment visit, mean (SD)	26 (13)	32 (12)	29 (15)	33 (12)	28 (13)	p = .036 • No significant pairwise comparisons
Days from surgery to start of chemotherapy	N/A	43 (20)	N/A	44 (14)	43 (18)	p = .87
Days from surgery to end of chemotherapy	N/A	133 (30)	N/A	138 (25)	135 (28)	p = .50
Stage						p < .001
0	22 (20)	0 (0)	4 (11)	0 (0)	26 (12)	• Lump no CT > Mast no CT
I	66 (59)	16 (38)	25 (66)	7 (32)	114 (53)	• No CT > CT
II	18 (16)	20 (48)	7 (18)	11 (50)	56 (26)	• CT > no CT
III	0 (0)	4 (10)	0 (0)	4 (18)	8 (4)	• Mast + CT > Lump + CT
Receipt of radiation	104 (93)	36 (86)	6 (16)	11 (50)	157	p < .001 • Lump > Mast • Mast + CT > Mast no CT

Endocrine therapy, N (%)	80 (71)	24 (57)	27 (71)	17 (77)	148 (69)	p = .28
Bilateral mastectomy, N (%)	N/A	N/A	25 (66)	16 (73)	41 (68)	p = .58
Immediate reconstruction, N (%)	N/A	N/A	11 (28)	18 (81)	29 (48)	p = .57
Additional surgeries, N (%)	3 (2)	7 (16)	15 (39)	10 (45)	35 (16)	p < .001 • Mast > Lump
Psychosocial and Behavioral Variables						
MFSI-SF Mental, baseline, mean (SD)	4.6 (4.5)	3.5 (3.2)	5.6 (3.8)	4.2 (3.6)	4.5 (4.1)	p = .18
CES-D, baseline, mean (SD)	11.9 (10.2)	10.1 (9.4)	16.6 (9.9)	14.1 (10.3)	12.6 (10.1)	p = .02 • Mast no CT > Lump + CT
MFSI-SF Anxiety Items, baseline, mean (SD)	7.0 (3.5)	6.7 (3.6)	7.3 (3.5)	7.6 (3.7)	7.0 (3.7)	p = .78
MFSI-SF General fatigue, baseline, mean (SD)	7.6 (5.6)	4.9 (4.6)	9.9 (5.4)	7.9 (5.3)	7.5 (5.5)	p < .001 • Lump no CT > Lump + CT • Mast no CT > Lump + CT
PSQI, baseline, mean (SD)	7.2 (4.1)	6.3 (3.7)	9.18 (4.1)	7.5 (3.5)	7.4 (4.0)	p = .01 • Mast no CT > Lump no CT • Mast no CT > Lump + CT

Note: ANOVA tests were used for continuous variables and Chi-square tests were used for categorical variables. Lump: Lumpectomy, Mast: Mastectomy, CT: chemotherapy, MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form, CES-D: Center for Epidemiologic Studies-Depression, PSQI: Pittsburgh Sleep Quality Index

Table 2. Coefficient estimates from linear mixed models predicting perceived cognitive problems over time based on treatment type.

	b (SE)	*p*
Intercept	5.629 (0.943)	<.001
Treatment group (Lumpectomy no CT ref)		
Lumpectomy + CT	-0.909 (0.942)	.33
Mastectomy no CT	0.878 (0.935)	.35
Mastectomy + CT	-0.860 (1.217)	.48
Days since surgery	0.003 (0.002)	.10
Days since surgery x Days since surgery	<.001 (<.001)	.18
Treatment group x Days since surgery (Lumpectomy no CT ref)		
Lumpectomy + CT	0.003 (0.003)	.37
Mastectomy no CT	0.003 (0.004)	.42
Mastectomy + CT	0.012 (0.004)	.007*
Surgery type x Days since surgery x Days since surgery (Lumpectomy no CT ref)		
Lumpectomy + CT	<.001 (<.001)	.64
Mastectomy no CT	<.001 (<.001)	.33
Mastectomy + CT	<.001 (<.001)	.056^{+}
Age	-0.06 (0.03)	.043*
Education (high school ref)		
College degree	-0.982 (0.702)	.16
Graduate degree	-0.837 (0.726)	.25
Race (White ref)	0.989 (0.663)	.14
Stage (0 ref)		
I	-0.745 (0.886)	.40
II	-1.423 (1.033)	.17
III	-1.424 (1.769)	.42
Radiation	0.002 (0.274)	.99
Endocrine therapy	-0.131 (0.289)	.65

Table 3. Linear effects of time for each treatment group.

	dy/dx	*SE*	*p*
Treatment group			
Lumpectomy no CT	0.001	0.001	.067
Lumpectomy + CT	0.002	0.001	.017
Mastectomy no CT	0.001	0.001	.479
Mastectomy + CT	0.004	0.001	< .001

Figure 1 The number of participants who completed each assessment and were included in analyses

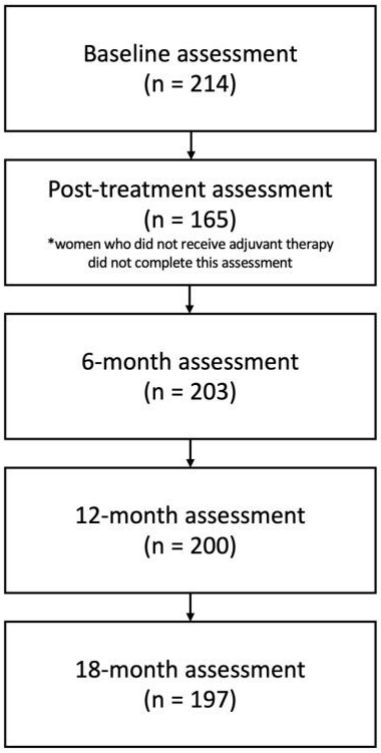
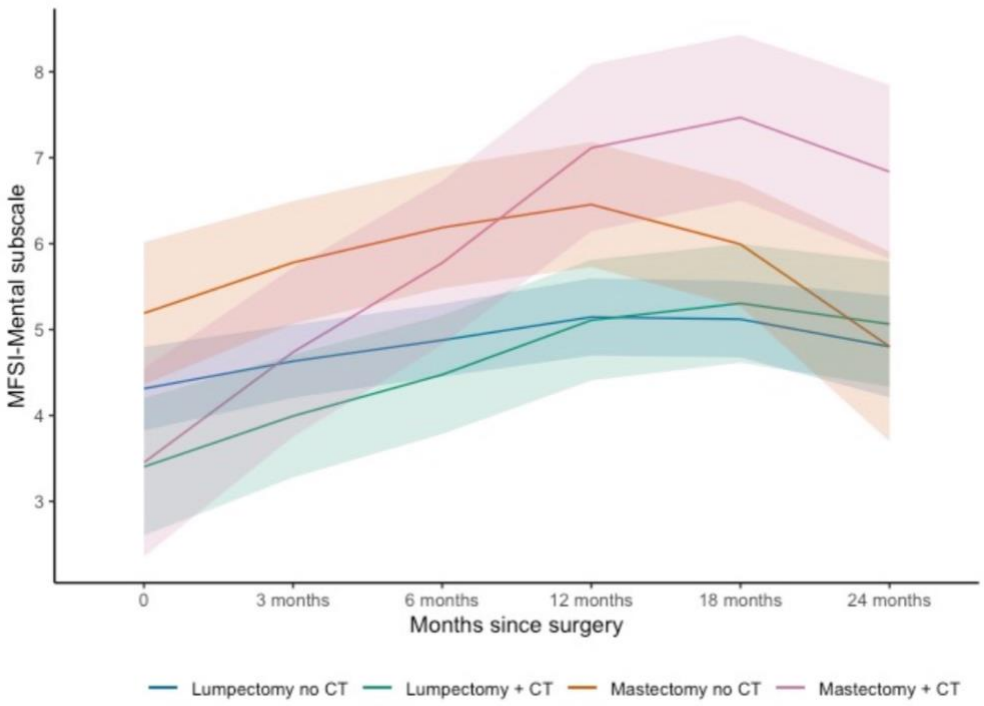


Figure 2 Estimated mean scores on the MFSI-SF Mental subscale are shown for the 4 different treatment groups (lumpectomy with or without chemotherapy, mastectomy with or without chemotherapy) estimated timepoints since surgery: 0- (1 day after surgery), 3-, 6-, 12-, 18-, and 24-months



Study 2 Tables and Figures

Table 1: Demographics, clinical characteristics, and baseline values of study variables

	MBS (n = 173)	RISE (n = 194)
Age, mean (SD), years	52 (8)	55.3 (11.2)
Race, N (%)		
Asian	8 (4)	21 (11)
Black	5 (3)	8 (4)
Hispanic	19 (11)	14 (7)
Other	5 (3)	6 (3)
White, non-Hispanic	136 (79)	147 (75)
Education, N (%)		
Less than college degree	35 (20)	57 (29)
College graduate	52 (30)	76 (39)
Post-graduate degree	86 (50)	61 (31)
Annual Household Income ≥ $100,000, N (%)	103 (60)	104 (53)
Employed (full or part-time), N (%)	109 (63)	125 (63)
Partnered, N (%)	113 (65)	126 (65)
Stage		
0	21 (12)	25 (13)
I	81 (46)	91 (46)
II	55 (31)	49 (25)
III	16 (9)	8 (4)
Initial Surgery		
Lumpectomy	116 (67)	116 (60)
Mastectomy	57 (33)	59 (30)
Neoadjuvant Chemotherapy	N/A	19 (9)
Adjuvant therapy		
Chemotherapy	92 (53)	76 (39)
Radiation	130 (75)	137 (70)
Endocrine therapy	118 (68)	121 (62)
IL-6, baseline, mean (SD) pg/mL	1.66 (1.06)	0.86 (0.83)
CRP, baseline, mean (SD) pg/mL	2.17 (2.89)	3.46 (5.21)
sTNF-RII, baseline, mean (SD) pg/mL	2,288.19 (615.50)	2,105.45 (750)
BMI, baseline, mean (SD)	25.53 (5.17)	25.436 (5.715)
IQ, baseline, mean (SD)	113.70 (9.27)	N/A
MFSI-SF Mental, baseline, mean (SD)	5.56 (4.68)	4.773 (4.141)

Table 2: Bivariate associations between all study variables across all assessments for the MBS

	MFSI-Mental	IL-6	CRP	sTNF-RII
IL-6	0.12**			
CRP	0.00	0.46**		
sTNF-RII	0.10*	0.25**	0.23**	
Age	-0.04	0.05	0.10*	0.25**
Visit (continuous)	-0.00	-0.11*	-0.07	-0.20**
BMI	0.05	0.41**	0.52**	0.20**
Stage	0.04	0.07	0.11*	0.12*
Surgery type	0.05	-0.03	-0.08	0.02
Chemotherapy	0.22*	-0.02	-0.03	0.13*
Radiation	0.01	0.09	0.13*	0.08
Endocrine therapy	0.02	-0.14*	-0.15*	-0.14*

Note: Pearson's correlations were run for all continuous variables, point-biserial correlations were used for all binary categorical variables. Log transformations were applied to all inflammatory variables. Chemotherapy and Radiation were entered as individual difference factors given that the baseline assessment took place after adjuvant therapy. Endocrine therapy was entered as time varying given that the baseline visit took place before endocrine therapy initiation.

Table 3. Coefficient estimates from the full linear mixed model predicting perceived cognitive problems from participant and group mean-centered IL-6 for the MBS

	b (SE)	*p*
Participant mean-centered IL-6	-0.14 (0.43)	.751
Group mean-centered IL-6	1.64 (0.76)	.030
Visit	0.01 (0.21)	.979
Age	0.01 (0.04)	.859
BMI	0.02 (0.07)	.753
Stage (low reference group)	-1.63 (0.04)	.044
Surgery type (lumpectomy reference group)	-0.39 (0.99)	.692
Chemotherapy	3.20 (0.84)	< .001
Radiation	-0.58 (1.05)	.583
Endocrine therapy	-0.06 (0.40)	.877

Table 4: Bivariate associations between all study variables across all assessments for the RISE Study

	MFSI-Mental	IL-6	CRP	sTNF-RII
IL-6	-0.04			
CRP	0.03	0.54**		
sTNF-RII	-0.12**	0.39**	0.27**	
Age	-0.17**	0.29**	0.27**	0.31**
Visit	0.05	-0.01	-0.08*	-0.02
BMI	0.02	0.44**	0.51**	0.31**
Stage	-0.05	-0.02	0.03	0.01
Surgery type at enrollment	0.11*	-0.08*	-0.04	-0.04
Additional surgeries	0.06	0.05	0.04	0.05
Chemotherapy	0.01	0.07*	0.03	0.15*
Radiation	-0.01	0.08*	0.01	0.11*
Endocrine	-0.02	0.02	-0.09*	0.02

Note: Pearson's correlations were run for all continuous variables, point-biserial correlations were used for all binary categorical variables. Stage was categorized as low (0 or I) or high (II or III). Surgery type was coded as lumpectomy or mastectomy at enrollment. Chemotherapy, radiation, and endocrine therapy were all coded as time varying.

Table 5: Bivariate associations between all study variables and neuropsychological assessments across all assessments for the MBS

	Trails B (normed)	CVLT (normed)
IL-6	-0.13**	-0.05
CRP	-0.17**	0.00
sTNF-RII	0.01	-0.07
Age	-0.18**	0.00
IQ	0.35**	0.23**
Visit	0.14**	0.07
BMI	-0.08	0.00
Stage (low reference group)	0.01	0.07
Surgery type (lumpectomy reference group)	-0.05	-0.10*
Chemotherapy	-0.03	-0.05
Radiation	0.04	0.02
Endocrine (time varying)	0.11*	0.00

Note: Pearson's correlations were run for all continuous variables, point-biserial correlations were used for all binary categorical variables. Log transformations were applied to all inflammatory variables. Chemotherapy and Radiation were entered as individual difference factors.

Table 6. Coefficient estimates from the full linear mixed model predicting perceived cognitive problems from participant and group mean-centered IL-6 interacting with receipt of chemotherapy for the MBS

	b (SE)	*p*
Participant mean-centered IL-6	0.05 (0.63)	.933
Group mean-centered IL-6	-0.27 (1.02)	.790
Chemotherapy	3.33 (0.79)	< .001
Participant mean-centered IL-6 x Chemotherapy	-0.36 (0.86)	.674
Group mean-centered IL-6 x Chemotherapy	3.56 (1.32)	.007
Visit	-0.03 (0.21)	.907
Age	0.01 (0.04)	.743
BMI	0.03 (0.07)	.653
Stage (low reference group)	-1.73	.028
Surgery type (lumpectomy reference group)	-0.53 (0.97)	.587
Radiation	-0.62 (1.03)	.548
Endocrine therapy	-0.01 (0.40)	.986

Table 7. Coefficient estimates from the full linear mixed model predicting perceived cognitive problems from participant and group mean-centered sTNF-RII interacting with receipt of chemotherapy for the MBS

	b (SE)	*p*
Participant mean-centered sTNF-RII	-2.83 (2.04)	.166
Group mean-centered sTNF-RII	-0.07 (2.07)	.974
Chemotherapy	3.09 (0.82)	< .001
Participant mean-centered sTNF-RII x Chemotherapy	5.46 (2.40)	.023
Group mean-centered sTNF-RII x Chemotherapy	-0.07 (2.07)	.974
Visit	0.12 (0.21)	.583
Age	-0.00 (0.04)	.910
BMI	0.06 (0.06)	.299
Stage (low reference group)	-1.65 (0.82)	.044
Surgery type (lumpectomy reference group)	-0.33 (1.00)	.741
Radiation	-0.38 (1.06)	.722
Endocrine therapy	-0.00 (0.40)	.992

Table 8. Coefficient estimates from the full linear mixed model predicting perceived cognitive problems from participant and group mean-centered CRP interacting with receipt of chemotherapy for the RISE Study.

	b (SE)	*p*
Participant mean-centered CRP	0.40 (.23)	.089
Group mean-centered CRP	0.38 (0.39)	.328
Chemotherapy	0.12 (0.83)	.886
Participant mean-centered CRP x Chemotherapy	-0.70 (0.35)	.045
Group mean-centered CRP x Chemotherapy	-0.51 (0.56)	.365
Visit	-0.19 (0.14)	.176
Age	-0.08 (0.03)	.025
BMI	0.02 (0.07)	.814
Stage (low reference group)	-0.47 (0.83)	.575
Surgery type (lumpectomy reference group)		
Unilateral mastectomy	-0.12 (1.16)	.917
Bilateral mastectomy	1.53 (0.87)	.080
Neoadjuvant chemotherapy	0.17 (1.31)	.898
Interim surgery (none reference group)	0.58 (0.43)	.174
Radiation	-0.74 (0.39)	.058
Endocrine therapy	-0.35 (0.34)	.307

Table 9. Coefficient estimates from the full linear mixed model predicting perceived cognitive problems from participant and group mean-centered sTNF-RII interacting with age for the MBS

	b (SE)	*p*
Participant mean-centered sTNF-RII	18.09 (7.73)	.019
Group mean-centered sTNF-RII	11.16 (9.74)	.252
Age	-0.01 (0.04)	.861
Participant mean-centered sTNF-RII x Age	-0.33 (0.15)	.024
Group mean-centered sTNF-RII x Age	-0.19 (0.18)	.309
Visit	0.11 (0.21)	.607
BMI	0.06 (0.06)	.298
Stage (low reference group)	-1.76 (0.83)	.034
Surgery type (lumpectomy reference group)	-0.28 (1.00)	.782
Chemotherapy	3.11 (0.82)	< .001
Radiation	-0.38 (1.06)	.721
Endocrine therapy	-0.03 (0.40)	.947

Figure 1 Data availability for each assessment timepoint of the MBS

	MFSI-Mental	Neuropsych Testing	Inflammatory Markers
Baseline	172	173	IL-6: 167
			CRP: 166
			sTNF-RII: 169
6 Months	160	160	IL-6: 156
			CRP: 157
			sTNF-RII: 158
12 Months	159	157	IL-6: 152
			CRP: 152
			sTNF-RII: 153

Figure 2. Data availability for each assessment time point of the RISE Study

	MFSI-Mental	Inflammatory Markers
Baseline	194	IL-6: 194
		CRP: 194
		sTNF-RII: 194
Post-Treatment	140	IL-6: 140
		CRP: 140
		sTNF-RII: 140
6 Months	167	IL-6: 167
		CRP: 167
		sTNF-RII: 167
12 Months	158	IL-6: 158
		CRP: 158
		sTNF-RII: 158
18 months	158	IL-6: 158
		CRP: 158
		sTNF-RII: 158

Figure 3 Group mean-centered IL-6 interacting with chemotherapy for the MBS

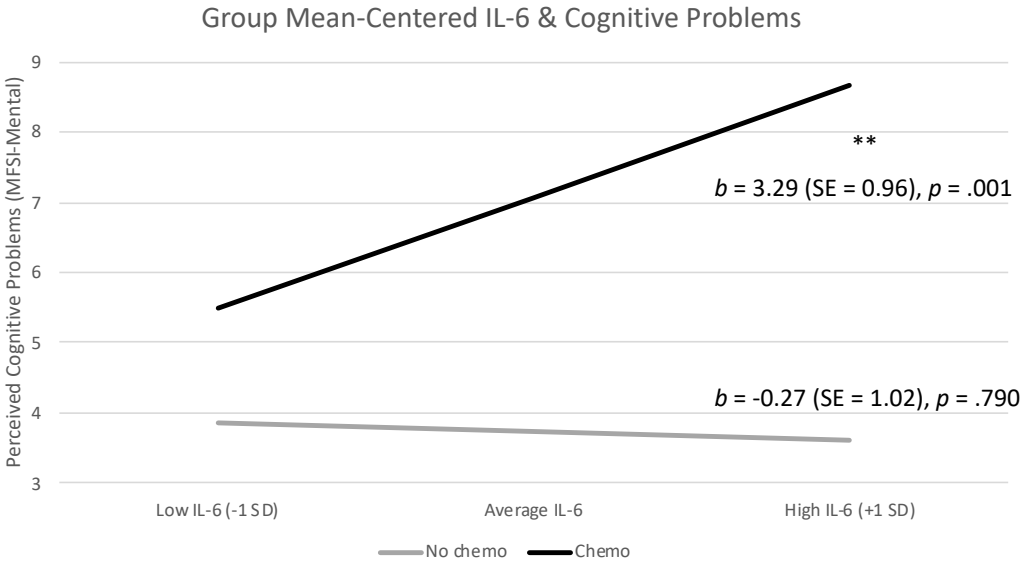


Figure 4 Participant mean-centered sTNF-RII interacting with chemotherapy for the MBS

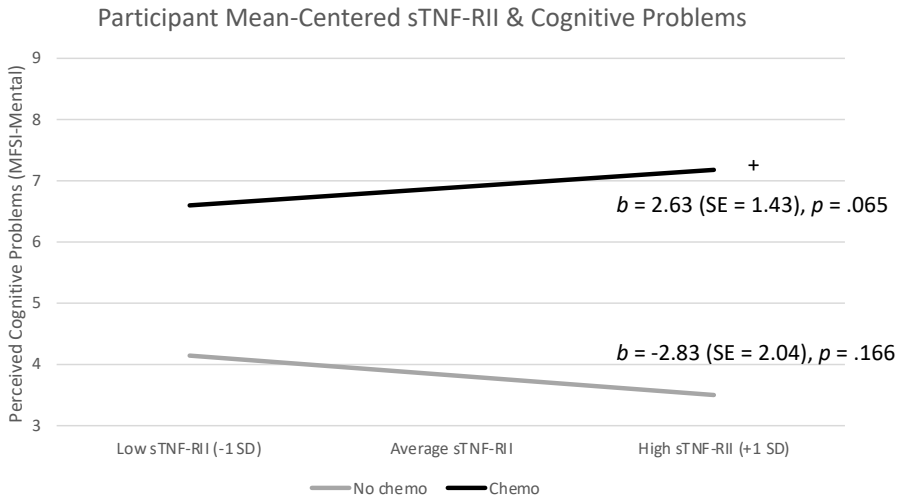


Figure 5 Participant mean-centered CRP interacting with chemotherapy for the RISE Study.

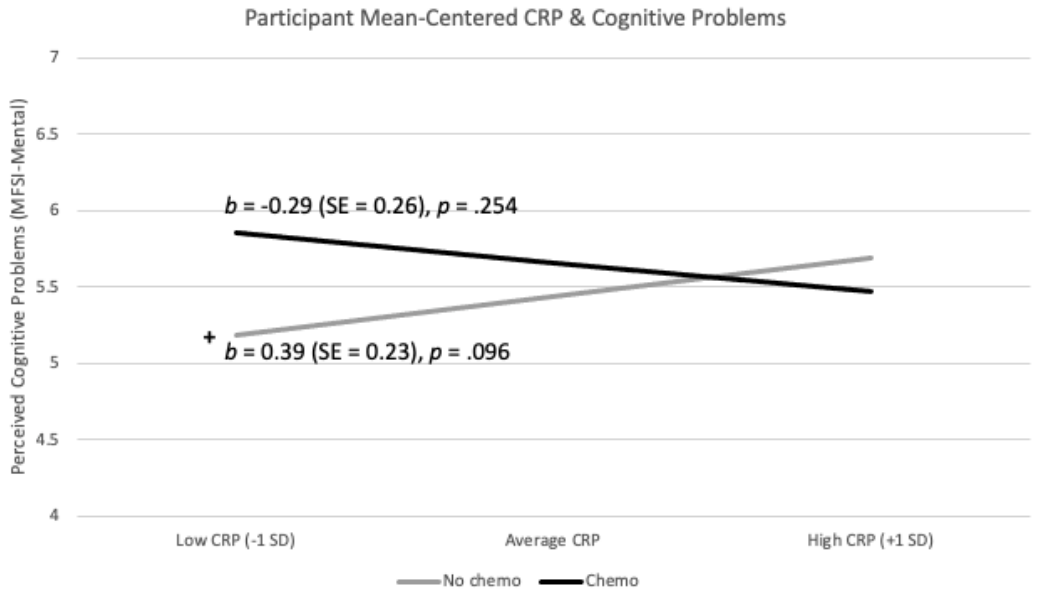
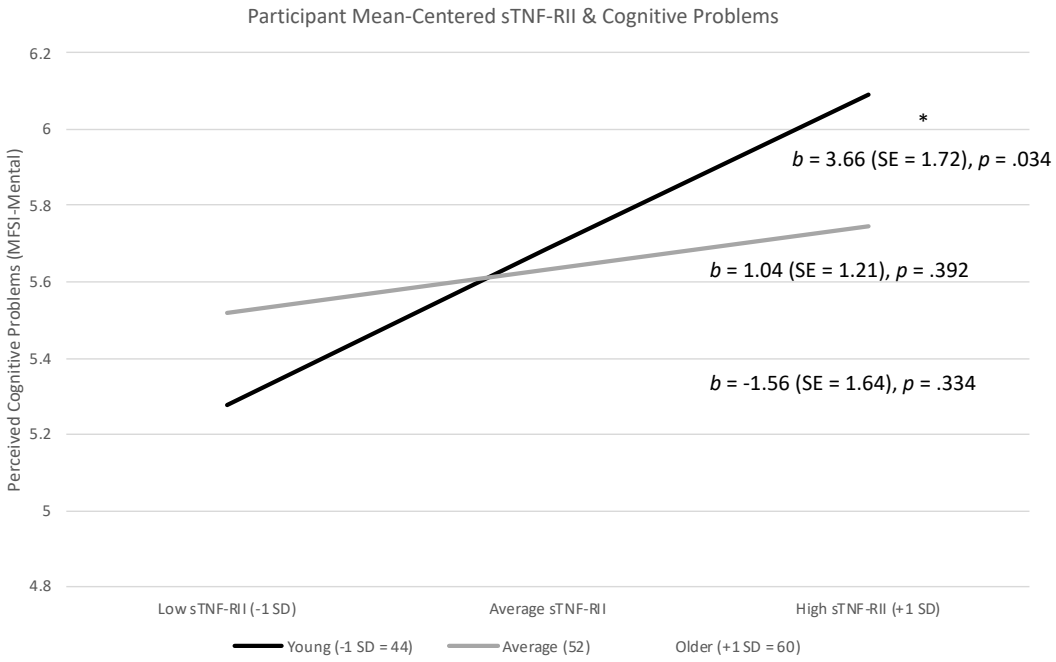


Figure 6 Participant mean-centered sTNF-RII interacting with age for the MBS



Study 3 Tables and Figures

Table 1: Model fit statistics for each growth mixture model

Model	No. of classes	fixed	random	fixed vary by class	AIC	SABIC	BIC	Entropy	smallest class size (%)	AIC rank	SABIC rank	BIC rank	Entropy rank
48	2	ISQC	ISQC	ISQC	6303.323	6311.878	6375.291	0.923	8.89%	24	24	30	1
60	2	ISQC	ISQ	ISQC	6313.683	6320.527	6371.257	0.922	8.52%	33	32	28	2
20	2	ISQ	ISQ	ISQ	6311.379	6317.368	6361.757	0.920	8.15%	28	28	17	3
35	2	ISQC	ISQ	ISQ	6313.376	6319.793	6367.353	0.920	8.15%	31	30	24	4
16	2	ISQ	ISQ	IS	6311.47	6317.031	6358.25	0.920	7.78%	29	27	15	5
30	2	ISQC	ISQ	IS	6313.468	6319.457	6363.846	0.920	7.78%	32	29	19	6
57	3	ISQC	IS	ISQC	6242.678	6250.377	6307.449	0.919	6.67%	8	7	4	7
44	2	ISQC	ISQC	ISQ	6302.578	6310.705	6370.948	0.919	8.89%	23	22	27	8
40	2	ISQC	ISQC	IS	6302.359	6310.059	6367.131	0.918	7.78%	22	21	23	9
58	4	ISQC	IS	ISQC	6197.102	6206.94	6279.866	0.917	4.81%	3	3	2	10
59	5	ISQC	IS	ISQC	6175.353	6187.33	6276.109	0.915	2.96%	2	2	1	11
63	5	ISQC	ISQ	ISQC	6173.419	6186.68	6284.971	0.909	4.07%	1	1	3	12
53	3	ISQC	IS	ISQ	6264.052	6270.896	6321.627	0.901	6.30%	12	11	8	13
12	3	ISQ	IS	ISQ	6262.093	6268.509	6316.069	0.901	6.30%	11	10	7	14
7	2	ISQ	IS	IS	6358.217	6362.494	6394.201	0.885	10.74%	53	52	42	15
25	2	ISQC	IS	IS	6360.203	6364.908	6399.785	0.885	10.74%	54	54	45	16
51	5	ISQC	ISQC	ISQC	6211.47	6226.441	6337.415	0.866	4.07%	4	4	10	17
23	5	ISQ	ISQ	ISQ	6220.224	6231.345	6313.783	0.863	3.70%	5	5	6	18
52	2	ISQC	IS	ISQ	6322.492	6327.625	6365.673	0.858	14.81%	39	37	21	19
11	2	ISQ	IS	ISQ	6320.505	6325.21	6360.088	0.858	14.81%	37	34	16	20

56	2	ISQC	IS	ISQC	6323.595	6329.156	6370.374	0.855	14.81%	40	38	26	21
50	4	ISQC	ISQC	ISQC	6260.873	6273.705	6368.825	0.848	3.33%	10	12	25	22
61	3	ISQC	ISQ	ISQC	6289.944	6298.927	6365.511	0.845	6.30%	18	18	20	23
33	5	ISQC	ISQ	IS	6241.358	6251.196	6324.122	0.833	3.70%	7	8	9	24
62	4	ISQC	ISQ	ISQC	6245.019	6256.141	6338.578	0.826	5.56%	9	9	12	25
8	3	ISQ	IS	IS	6333.35	6338.911	6380.13	0.805	7.78%	43	42	34	26
26	3	ISQC	IS	IS	6335.341	6341.33	6385.719	0.805	7.78%	44	44	37	27
3	3	IS	IS	IS	6342.952	6348.085	6386.133	0.803	7.78%	48	46	38	28
41	3	ISQC	ISQC	IS	6287.587	6296.57	6363.154	0.773	7.78%	17	17	18	29
17	3	ISQ	ISQ	IS	6299.929	6306.773	6357.504	0.759	7.78%	21	20	14	30
54	4	ISQC	IS	ISQ	6272.052	6280.607	6344.02	0.693	0.00%	15	15	13	31
42	4	ISQC	ISQC	IS	6293.587	6303.853	6379.95	0.617	0.00%	19	19	33	32
47	5	ISQC	ISQC	ISQ	6264.62	6277.88	6376.171	0.615	0.00%	13	13	31	33
14	5	ISQ	IS	ISQ	6227.449	6237.287	6310.212	0.588	0.00%	6	6	5	34
32	4	ISQC	ISQ	IS	6307.926	6316.481	6379.894	0.532	0.00%	26	26	32	35
27	4	ISQC	IS	IS	6341.34	6348.612	6402.514	0.517	0.00%	47	47	46	36
13	4	ISQ	IS	ISQ	6270.093	6278.22	6338.463	0.517	0.00%	14	14	11	37
9	4	ISQ	IS	IS	6339.35	6346.194	6396.925	0.516	0.00%	46	45	44	38
4	4	IS	IS	IS	6348.952	6355.368	6402.928	0.514	0.00%	51	50	47	39
18	4	ISQ	ISQ	IS	6305.929	6314.056	6374.299	0.512	0.00%	25	25	29	40
55	5	ISQC	IS	ISQ	6280.052	6290.318	6366.414	0.487	0.00%	16	16	22	41
43	5	ISQC	ISQC	IS	6299.587	6311.137	6396.745	0.450	0.00%	20	23	43	42
28	5	ISQC	IS	IS	6347.341	6355.896	6419.309	0.438	0.00%	50	51	56	43
19	5	ISQ	ISQ	IS	6311.929	6321.34	6391.094	0.433	0.00%	30	33	40	44
10	5	ISQ	IS	IS	6345.35	6353.478	6413.72	0.418	0.00%	49	49	51	45
5	5	IS	IS	IS	6354.952	6362.651	6419.723	0.418	0.00%	52	53	57	46
36	3	ISQC	ISQ	ISQ	6321.378	6329.505	6389.748	0.413	0.00%	38	39	39	47

21	3	ISQ	ISQ	ISQ	6319.379	6327.079	6384.151	0.413	0.00%	35	36	36	48
45	3	ISQC	ISQC	ISQ	6310.578	6320.416	6393.342	0.378	0.00%	27	31	41	49
31	3	ISQC	ISQ	IS	6319.468	6326.74	6380.642	0.376	0.00%	36	35	35	50
46	4	ISQC	ISQC	ISQ	6318.578	6330.127	6415.735	0.356	0.00%	34	40	54	51
38	5	ISQC	ISQ	ISQ	6337.376	6348.926	6434.534	0.271	0.00%	45	48	58	52
37	4	ISQC	ISQ	ISQ	6329.376	6339.215	6412.14	0.267	0.00%	42	43	50	53
22	4	ISQ	ISQ	ISQ	6327.379	6336.79	6406.545	0.241	0.00%	41	41	48	54
2	2	IS	IS	IS	6428.478	6432.327	6460.863	0.002	40.00%	62	62	62	55
15	1	ISQ	ISQ	IS	6372.667	6376.945	6408.651	NA	NA	56	56	49	NA
29	1	ISQC	ISQ	IS	6374.664	6379.369	6414.246	NA	NA	57	57	52	NA
34	1	ISQC	ISQ	ISQ	6374.664	6379.369	6414.246	NA	NA	58	58	53	NA
39	1	ISQC	ISQC	IS	6362.172	6368.588	6416.148	NA	NA	55	55	55	NA
6	1	ISQ	IS	IS	6413.283	6416.278	6438.472	NA	NA	59	59	59	NA
24	1	ISQC	IS	IS	6415.27	6418.692	6444.057	NA	NA	60	60	60	NA
1	1	IS	IS	IS	6422.477	6425.044	6444.068	NA	NA	61	61	61	NA
49	3	ISQC	ISQC	ISQC	2.00E+09	2.00E+09	2.00E+09	2.00E+09	0.00%	NA	NA	NA	NA

Table 2: Sociodemographic and clinical characteristics of the total sample and each trajectory group

	Overall	Class 1 Decreasing N = 15 (6%)	Class 2 Stable Low N = 213 (79%)	Class 3 Delayed Reactive N = 15 (6%)	Class 4 Increasing N = 11 (4%)	Class 5 Reactive 16 (6%)	Omnibus *p*	Group comparisons w/ $p < .05$
Demographic and General Health Characteristics								
Mean age (SD), y	56 (11)	56 (8)	56 (11)	55 (10)	48 (11)	51 (9)	.06^{+}	
Mean BMI (SD), kg/m^2	25 (6)	26 (6)	25 (6)	23 (3)	28 (7)	24 (6)	.30	
Race/ethnicity n (%)							.62	
Asian	30 (11)	1 (7)	24 (11)	1 (7)	1 (9)	3 (19)		
Black	12 (4)	1 (7)	9 (4)	1 (7)	1 (9)	0 (0)		
Other	25 (9)	2 (13)	17 (8)	1 (7)	2 (18)	3 (19)		
White	203 (75)	11 (73)	163 (77)	12 (80)	7 (64)	10 (63)		
Income n (%)							.17	
< 100,000	120 (45)	10 (66)	89 (43)	10 (67)	4 (36)	7 (44)		
≥ 100,000	146 (55)	5 (33)	120 (57)	5 (33)	7 (64)	9 (56)		
Education n (%)							.18	
≤ College	186 (69)	12 (80)	146 (69)	8 (53)	6 (55)	14 (88)		
Post-graduate degree	84 (31)	3 (20)	67 (31)	7 (47)	5 (45)	2 (13)		
Employed n (%)							.86	
Employed full-time	123 (46)	7 (47)	100 (47)	5 (33)	6 (55)	5 (31)		
Employed part-time	38 (14)	1 (7)	31 (15)	2 (13)	1 (9)	3 (19)		
Not employed	109 (40)	7 (47)	82 (39)	8 (53)	4 (36)	8 (50)		
Partnered n (%)	174 (64)	12 (80)	135 (63)	8 (53)	8 (73)	11 (69)	.60	
Charlson Comorbidity Scale (any	70 (26)	5 (33)	54 (25)	4 (27)	3 (27)	4 (25)	.95	

comorbidities) n (%)								
Disease and Treatment Related Characteristics								
Stage n (%)							.006	Class 1 over representation of stage 0 or 1 ($p < .01$)
0 or 1	160 (62)	15 (100)	123 (60)	10 (67)	5 (45)	7 (50)		
2 or 3	99 (38)	0 (0)	81 (40)	5 (33)	6 (55)	7 (50)		
Enrollment Surgery n (%)							.50	
Lumpectomy	159 (64)	9 (60)	128 (66)	8 (53)	4 (44)	10 (71)		
Mastectomy	86 (35)	6 (40)	64 (33)	7 (46)	5 (55)	4 (28)		
Number of Surgeries n (%)							.31	
1	209 (77)	14 (93)	163 (76)	14 (93)	6 (54)	12 (75)		
2	49 (18)	1 (6)	38 (17)	1 (6)	5 (45)	4 (25)		
3	11 (4)	0 (0)	11 (5)	0 (0)	0 (0)	0 (0)		
Receipt of chemotherapy n (%)	97 (36)	1 (7)	78 (37)	5 (33)	6 (55)	7 (44)	$.07^{+}$	Class 1 under representation of chemotherapy ($p < .05$)
Combinations of Surgery Type and Chemotherapy							0.359	
Lumpectomy no chemo	114 (46)	8 (53)	90 (46)	7 (46)	2 (22)	7 (50)		
Lumpectomy + chemo	45 (18)	1 (6)	38 (19)	1 (6)	2 (22)	3 (21)		
Mastectomy no chemo	58 (23)	6 (40)	44 (22)	3 (20)	3 (33)	2 (14)		
Mastectomy + chemo	28 (11)	0 (0)	20 (10)	4 (26)	2 (22)	2 (14)		
Receipt of radiation n (%)	183 (68)	9 (60)	147 (69)	8 (57)	8 (73)	11 (69)	.80	
Receipt of endocrine	169 (63)	10 (67)	132 (62)	4 (27)	10 (91)	13 (81)	.006	Class 3 under

therapy n (%)								representation of endocrine therapy ($p < .01$) Class 4 over representation of endocrine therapy ($p < .05$)
Receipt of chemotherapy + endocrine therapy n (%)	55 (20)	0 (0)	42 (19)	2 (13)	6 (54)	5 (31)	.009	Class 1 under representation of chemotherapy + endocrine therapy ($p < .01$) Class 4 over representation of chemotherapy + endocrine therapy ($p < .001$)
Psychosocial Characteristics								
Childhood Adversity n (%)	107 (40)	12 (80)	70 (33)	11 (73)	6 (55)	8 (50)	< .001	Class 1 over representation of maltreatment ($p < .001$) Class 2 under representation of maltreatment ($p < .001$) Class 3 over representation of maltreatment ($p < .001$)
History of Major Depressive Disorder n (%)	60 (23)	6 (40)	40 (19)	6 (43)	4 (36)	4 (25)	$.060^{+}$	Class 2 under representation of MDD history ($p < .001$)

Mean baseline CES-D (SD)	12.7 (10.4)	27.1 (11.0)	10.6 (8.7)	22.2 (13.4)	18.5 (11.5)	14.1 (10.5)	$p < .001$	2 vs 1 ($p < .001$) 5 vs 1 ($p = .001$) 3 vs 2 ($p < .001$)
Mean baseline PSQI (SD)	7.4 (4.0)	12.6 (3.8)	6.8 (3.8)	8.6 (2.6)	9.0 (2.9)	8.6 (4.7)	$p < .001$	2 vs 1 ($p < .001$) 3 vs 1 ($p = .030$) 5 vs 1 ($p = .028$)
Mean baseline MFSI-General (SD)	7.7 (5.8)	16.9 (6.0)	6.5 (4.9)	11.3 (5.9)	12.6 (5.7)	8.1 (6.2)	$p < .001$	2 vs 1 ($p < .001$) 3 vs 1 ($p = .026$) 5 vs 1 ($p < .001$) 3 vs 2 ($p = .005$) 4 vs 2 ($p = .001$)
Mean baseline anxiety (SD)	7.1 (3.6)	10.6 (4.5)	6.5 (3.2)	9 (3.8)	8.4 (3.7)	8.4 (3.8)	$p < .001$	2 vs 1 ($p < .001$) 3 vs 2 ($p = .049$)
Mean baseline IES (SD)	1.7 (1.3)	2.9 (1.2)	1.6 (1.2)	1.9 (1.3)	2.8 (1.4)	1.8 (1.4)	$p < .001$	2 vs 1 ($p < .001$) 4 vs 2 ($p = .014$)

Note: For all categorical variables, group comparisons reflect significant adjusted residuals, which are more extreme than what would be expected if the null hypothesis of independence was true.

Figure 1: The number of participants who contributed data for each study visit

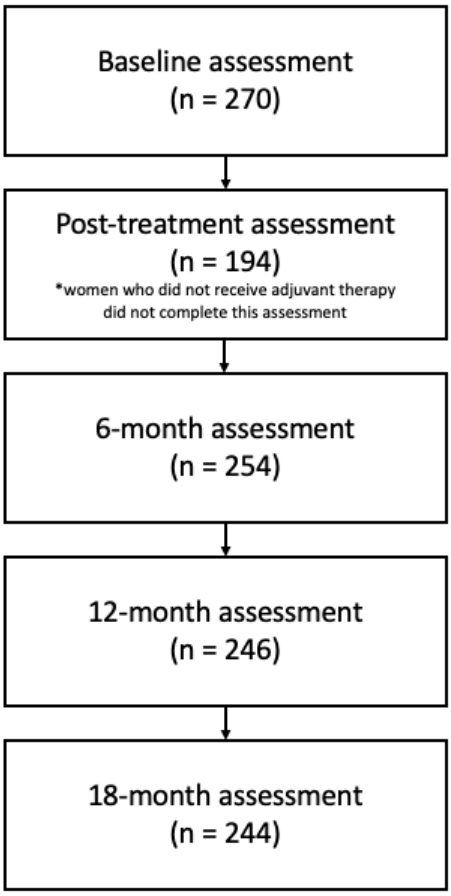


Figure 2: Mean levels of the MFSI-Mental subscale at each timepoint for each trajectory group

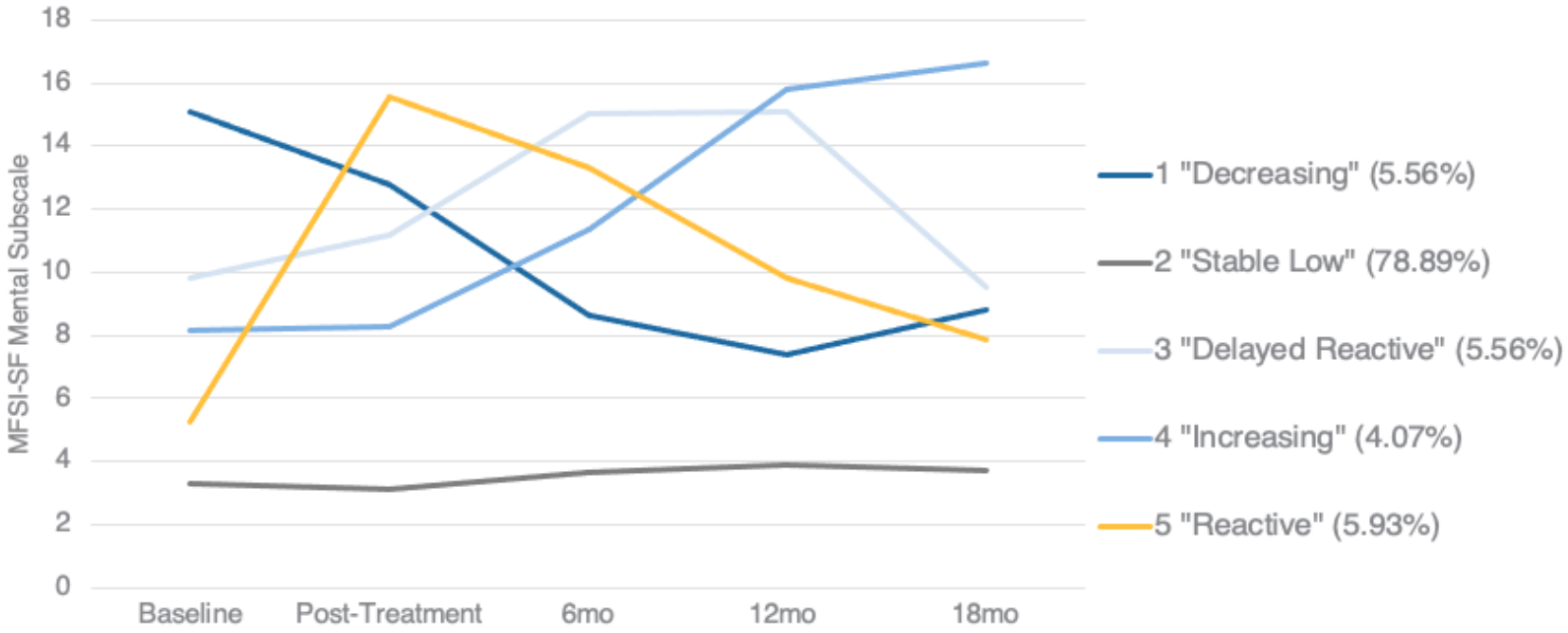


Figure 3: Categorical predictors of group membership

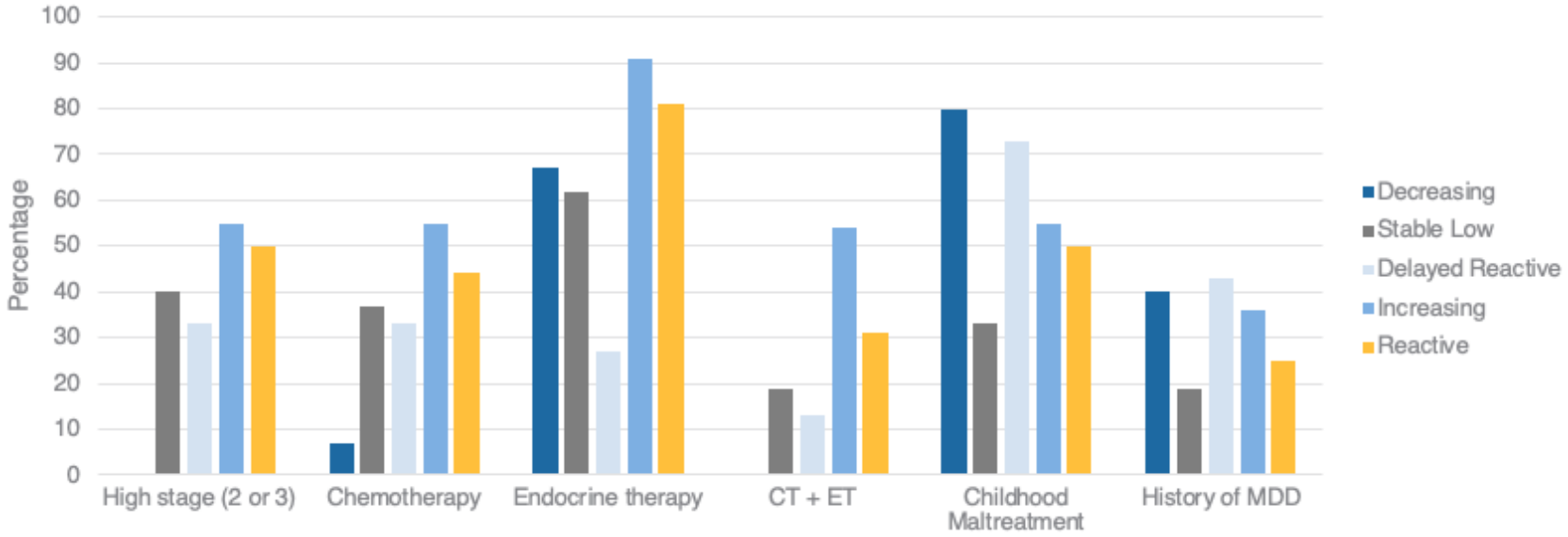


Figure 4: Continuous predictors of group membership

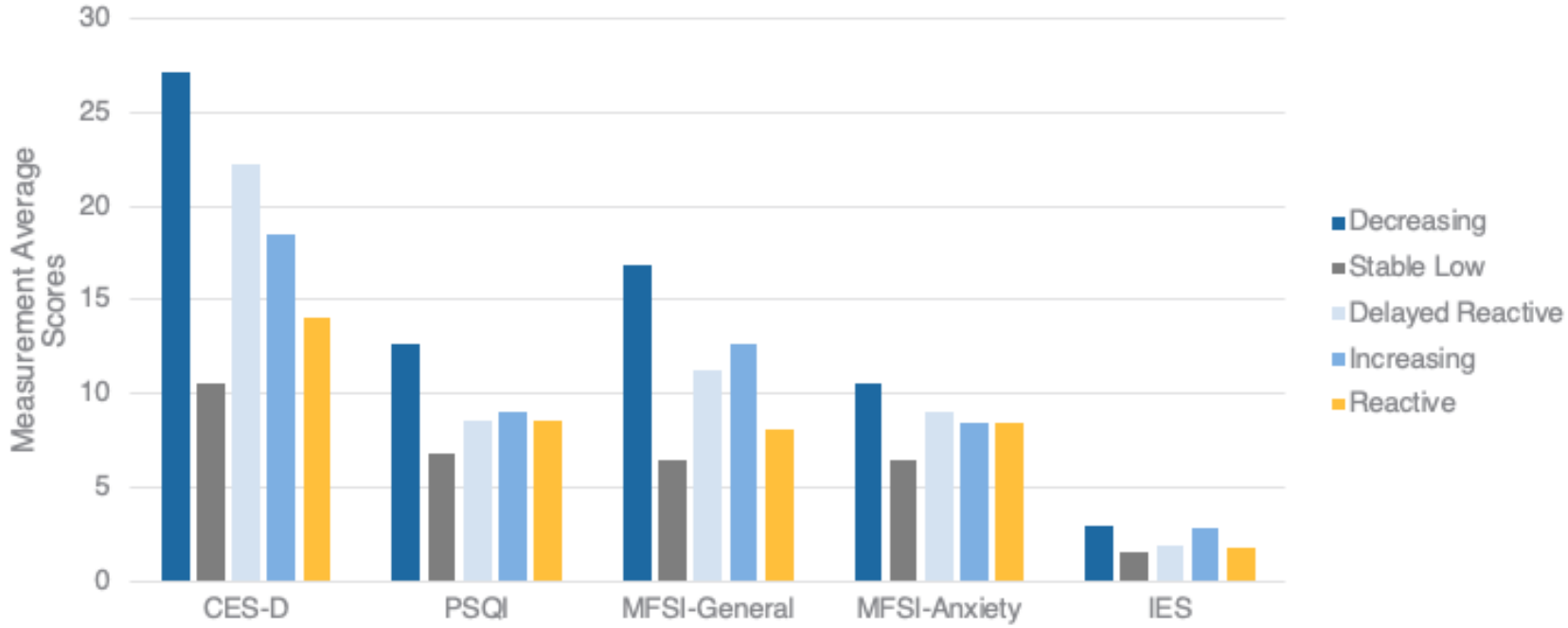


Figure 5: Spaghetti plots of participant level MFSI-SF Mental Subscale values for each trajectory group

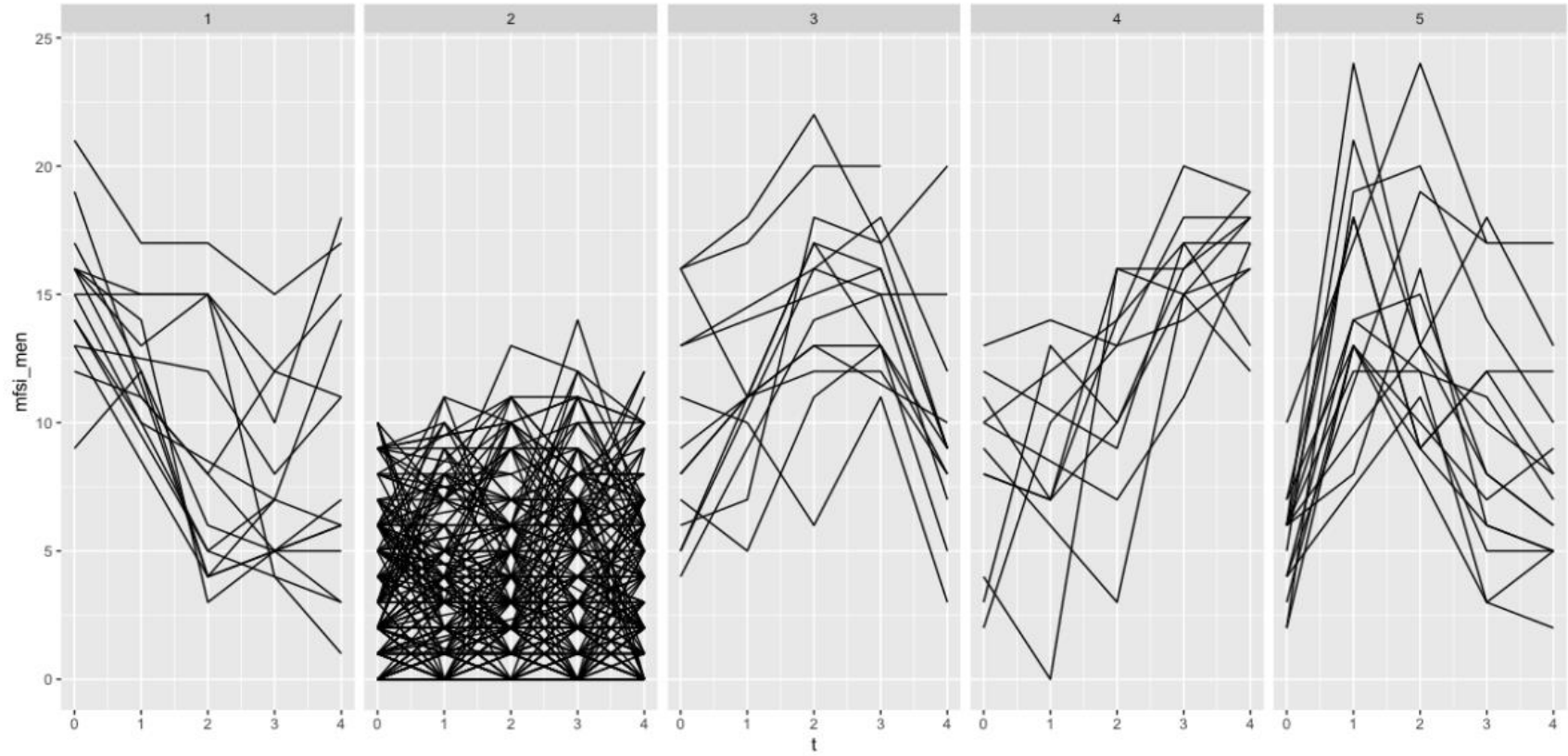
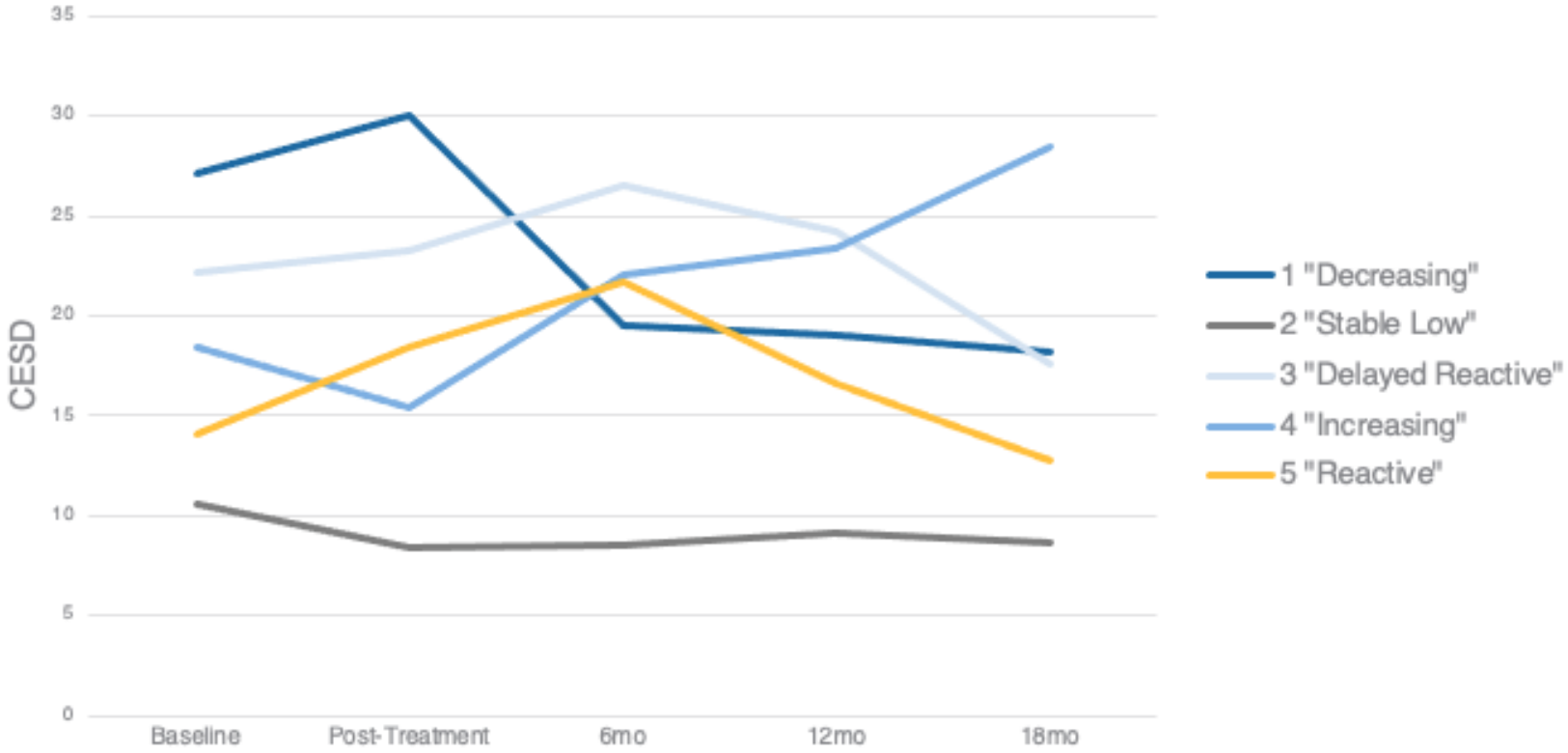
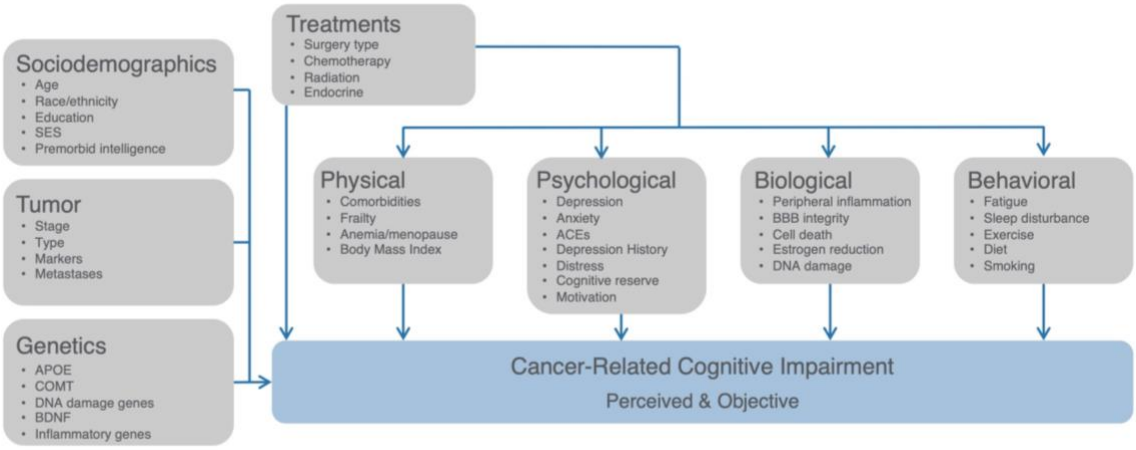


Figure 6: Mean depressive symptoms over time based on trajectory group



Appendices

Appendix A: Integrative Model of Cancer-Related Cognitive Impairment



Appendix B: Breast Cancer Surgery and Cognitive Problems

Citation	Participants	Design	Assessments	Results	Notes
(Hedayati et al., 2011)	146 women undergoing mammography screening → 77 breast cancer patients, 69 healthy controls (71% lumpectomy, 29% mastectomy)	Longitudinal, acute effects: Baseline assessment prior to diagnosis, follow-up assessment 2 months later (~1 month after surgery)	Headminder Cognitive Stability Index: response speed, processing speed, memory, attention	Breast Cancer (Surgery) vs. Healthy: Women surgically treated for breast cancer did not exhibit changes from pre- to post- surgery, whereas healthy women improved in attention and in processing speed. Surgery type analyses: Compared with women who did not receive a diagnosis and those who received a lumpectomy after diagnosis, women who received a mastectomy did not exhibit practice effects on attention and processing speed tasks.	1. This study was not powered to detect subgroup differences, should be interpreted as trend. 2. Did not include measures of perceived cognitive problems.

(Reid-Arndt & Cox, 2012)	36 post-operative breast cancer patients who had not yet initiated adjuvant therapy (6% biopsy, 11% lumpectomy, 81% mastectomy, 2% unknown) compared with age- and education matched population means	Cross-sectional, acute effects: Assessed once 1-2 weeks following surgery	RAVLT: immediate and delayed memory COWA: verbal fluency WAIS Digit Span Task: attention Subtle deficits were defined as 1–1.49 SD below the normative mean, moderate impairments were defined as -1.5 to -1.99 SD below, and severe impairment was defined -2.0 and below.	Verbal fluency: moderate or severe deficits were noted in 11-27% of women. Memory: moderate or severe deficits were noted in 14-17% of women.	1. Cross-sectional analyses. 2. Did not assess differences between surgery types. 3. Did not include measures of perceived cognitive problems.
(Chen et al., 2014)	53 women who had undergone surgery, 58 women who had undergone surgery + chemotherapy, 55 healthy controls	Cross-sectional, late effects: ~5 months after diagnosis	Attention Network Test: alerting, orienting, executive control Attention/concentration: WAIS Digit Span forward and backward, Stroop Color Test, TMT A Memory: RAVLT immediate, delayed, recognition tests	Across all measures, there were no differences between surgery only group and healthy controls	1. Designed to examine effects of chemotherapy. 2. Surgery type not noted 3. Cross-sectional analyses 4. Did not include measures of perceived cognitive problems.

			Executive functioning: TMT B, Stroop Word and Interference, Verbal fluency (task not specified)		
(Debess, Riis, Pedersen, & Ewertz, 2009)	124 post-operative breast cancer patients who had not yet initiated adjuvant therapy (32% lumpectomy, 68% mastectomy), 24 healthy controls	Cross-sectional, acute-late effects: mean of 34 days after surgery, range: 19-75 days	Objective Assessments: Visual Verbal Learning Test, total and a delayed score Concept Shifting Test Stroop Color Word Test Letter-Digit Coding Test Subjective Assessment: EORTC QLQ Cognitive subscale	Raw scores and Z scores of all tests were comparable across cancer and control groups. Delayed verbal memory trended towards being better for controls (p = .07) Rates of "lower than expected" cognitive function were higher in the breast cancer group than the control group (3.8% vs. 7.3%) Breast cancer patients endorsed more cognitive problems than controls for memory, concentration, mental fatigue, and vigor	1. Did not assess differences between surgery types. 2. Cross-sectional analyses
(Cimprich, 1992)	32 post-operative breast cancer patients who had not yet initiated adjuvant therapy (41%	Cross-sectional, acute effects: mean of 3	Objective Assessments: Attention: Digit Span forward and backward, Alphabet Backward,	Breast Cancer (Surgery) vs. Age Norms: Digit Span Forward: 56% of patients on the lower end	1. This study cannot isolate effects of surgery alone (cannot

	lumpectomy, 59% mastectomy)	days after surgery, in-patient	Symbol Digit Modalities Test, Letter Cancellation Used published clinical cutoffs to detect impairment relative to age norms Subjective Assessment: Attentional Function Index (developed for this study)	of the range; 25% in the impaired range Digit Span Backward: 50% of patients on the lower end of the range; 19% in the impaired range Alphabet backward: 34% scored zero, 75% scored 4 or less Symbol Digit Modalities Test: 25% scored below the age norm, 50% of those were at least one SD below the norm (severe dysfunction) AFI: 78% rated themselves at or below the midpoint on the scales Surgery type analyses: No differences between mastectomy and lumpectomy on objective or subjective assessments	control for diagnosis effects). 2. Cross-sectional analyses 3. Subjective assessment was study-specific

(Wefel, Lenzi, Theriault, Buzdar, et al., 2004)	84 post-operative breast cancer patients who had not yet initiated adjuvant therapy (50% lumpectomy/mastectomy, 50% core-needle biopsy). 12% of patients received adjuvant radiation before neuropsych evaluation.	Cross-sectional, late effects: mean of 7.5 weeks after surgery	Attention: WAIS Digit Span, Digit Symbol, Arithmetic, Letter-Number Sequencing, Mental Control, TMT A Memory: HVLT, VSRT, NVSRT, ROCFT Language: COWA, Boston Naming, Sequential commands Executive Functioning: TMT B, Category Test, WAIS Similarities Visuospatial: WAIS Block Design, ROCFT Copy, Judgment of Line Orientation Used published clinical cutoffs to detect impairment relative to age norms → Overall Cognitive Function Index (OCFI)	35% of patients were classified as impaired before adjuvant chemotherapy Women who had undergone lumpectomy/mastectomy were nearly twice as likely to be cognitively impaired compared with women who had undergone biopsy (p = .03).	1. Study lumped surgery type together and compared with needle biopsy 2. Cross-sectional analyses 3. Did not include measures of perceived cognitive problems. 4. 12% of patients received radiation before the assessment.
(Marie Lange et al., 2014)	123 post-operative elderly breast cancer patients who had not yet initiated adjuvant therapy	Cross-sectional, acute-late effects: mean	Objective Assessments: Verbal episodic memory: Grober & Buschke procedure	41% of patients had impaired overall cognitive function.	1. Cross-sectional analyses

	(72% lumpectomy, 28% mastectomy), 71 healthy age matched controls for subjective cognitive complaints	of 36 days after surgery, range: 19-141 days	Visual episodic memory: Rey Complex Figure Working memory: WAIS arithmetic, digit span, letter number sequencing Information processing speed: TMT A Executive functioning: TMT B, Verbal fluency (animal and letter) Subjective Assessments: FACT-Cog Used published clinical cutoffs to detect impairment relative to age norms	Impairment was mainly exhibited on tests of visual episodic memory and executive functions Healthy subjects had significantly more complaints on Perceived Cognitive Impairments and Perceived Cognitive Abilities FACT-Cog subscales than patients. Patients had more complaints on the Impact on Quality of Life scale. No association between surgery type and cognitive problems.	
(Mandelblatt et al., 2014)	164 post-operative elderly breast cancer patients who had not yet initiated adjuvant therapy (58% lumpectomy, 42% mastectomy), 182 healthy age matched controls	Cross-sectional, late effects: mean of 51 days after surgery, SD: 20 days	Objective Assessments: Attention, Working Memory, and Processing Speed: digit span, TMT A, digit symbol test, driving scenes	There were no differences between patients and controls on objective measures of cognitive functioning. Patients who had high comorbidity levels had	1. Cross-sectional analyses

			Language: Boston naming test, verbal fluency (category) Executive Functioning: TMT B, COWA, Figure drawing Learning and Memory: WAIS Logical, Word list immediate and delayed recall Visuo-spatial: figure drawing copy Subjective Assessments: FACT-Cog Used published clinical cutoffs to detect impairment relative to age norms	higher rates of impairment, whereas comorbidity did not matter for controls. There were no differences between patients and controls on subjective assessment of cognitive functioning. Surgery type did not influence objective cognitive problems.	
(M. L. Chen, Miaskowski, Liu, & Chen, 2012)	200 preoperative breast cancer patients (40% lumpectomy, 60% unilateral mastectomy)	Longitudinal, acute and late effects: Baseline assessment prior to surgery, follow-up assessment	Subjective Assessment: Attentional Function Index A difference greater than 1.09 from baseline was defined as a reliable decline or improvement	1. 54% of women were found to have a decline in perceived attentional function at 1 month after surgery. At 1 and 2 years after surgery, 41% and 30%, respectively, continued to have	1. Excluded for women who received a bilateral mastectomy 2. Did not examine the effect of surgery type

		1, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 months after surgery		declines in perceived attentional function.	

COWA: Controlled Oral Word Association Test
WAIS: Wechsler Adult Intelligence Scale
RAVLT: Rey Auditory Verbal Learning Test
TMT: Trail Making Test
EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
HVLT: Hopkins Verbal Learning Test
VSRT: Verbal Selective Reminding Test
NVSRT: Nonverbal Selective Reminding Test
ROCFT: Rey–Osterreith Complex Figure Test

Appendix C: Inflammation and Cognitive Problems in Breast Cancer Patients

Study	Sample (n, type, age)	Inflammatory Measure(s) and Levels	Cognitive Outcome(s)	Assessment Time Points	Main Findings
(Lyon et al., 2016)	75 breast cancer survivors, age ranges from 23-71	Basal plasma cytokine 17-panel (raw averages not provided)	Executive functioning and Memory subscales of the CNSVS	Longitudinal: T1: before chemotherapy, T2: midpoint of chemotherapy, T3: 6 months after chemotherapy, T4: one year after chemotherapy, T5: 2 years after chemotherapy	Executive Functioning: 1. G-CSF was associated with executive functioning at baseline 2. IL-8 and IL-17 were associated with executive functioning during chemotherapy 3. IL-7 and IL-10 were associated with executive functioning after chemotherapy 4. IFN-γ, IL-8, and IL-4 were associated with executive functioning 2 years following chemotherapy Memory: 1. Inflammation was not associated with memory at baseline assessment. 2. IL-17, IL-8, IL-13, IL-12, and IL-1b were associated with memory during chemotherapy 3. GM-CSF, IL-5, IL-7, G-CSF, IL-2, IFN-γ, IL-10 and IL-12 were associated with memory after chemotherapy 4. IL-7 and IL-5 were associated with memory 2 years after chemotherapy

(Patel et al., 2015)	174 breast cancer patients before treatment, mean age of 60	Basal plasma IL-6 (Mean = 2.43 pg/mL, range = 0.40-33.70 pg/mL), IL-1ra (Mean = 375 pg/mL, range = 98-1606 pg/mL), sTNF-RII (Mean = 2361 pg/mL, range = 1213-9784)	Executive functioning composite made up of the Trails 4, color-word inhibition, and switching from the DKEF Memory: HVLT Processing speed: PSI from the WAIS	Cross-sectional: Assessed before the start of radiation or chemotherapy	Executive Functioning: 1. Inflammatory markers were not associated with cognitive control composite controlling for the other inflammatory variables and other covariates Memory: 1. Inflammatory variables as a block were associated with verbal memory 2. sTNF-RII was a significant independent predictor of memory No associations for processing speed
(Williams et al., 2018)	22 breast cancer patients undergoing chemotherapy, mean age = 54	Basal serum MCP-1 (Median = 123.47), TNF-a (Median = 6.43), sTNF-RI (Median = 1721.89), and sTNF-RII (Median = 6815.29)	Planning: SOC Visual memory: Delayed Matching to Sample Verbal memory: Verbal recognition memory	Cross-sectional: Assessment during chemotherapy treatment (cycle 2 or after), before chemotherapy administration	Executive Functioning: 1. Higher levels of MCP-1 were associated with better performance on the SOC Memory: 1. Higher levels of both sTNF-RI and -RII were associated with poorer visual memory performance 2. No associations for verbal memory

(Ganz, Bower, et al., 2013)	93 breast cancer survivors from the Mind-Body Study, mean age = 51	Basal plasma IL-1ra (Mean = 261-331 pg/mL), IL-6 (Mean = 1.6-1.6 pg/mL), CRP (Mean = 1.99-2.30 mg/L), sTNF-RII (Mean = 2580-2113 pg.mL) Means reported as chemo-no chemo groups	Executive Functioning composite made up of TMT-B, Stroop, Letter-Number Sequencing Verbal memory: CVLT-2, WMS-3 Visual memory: BVMT-R Visuospatial Function: Complex Figure Copy, Block Design Psychomotor Speed: Digit Symbol, Trails A, Stroop Color Naming Motor Speed: Grooved Pegboard	Longitudinal: Baseline: after primary treatment completion, 6 and 12 months later	1. There were no associations between any markers of inflammation and performance on any of the neuropsychological assessments 2. Higher baseline sTNF-RII in chemotherapy patients was significantly associated with increased memory complaints 3. In chemotherapy exposed patients, decline in sTNF-RII over time was correlated with fewer memory complaints over 12 months

			Subjective Memory: SMQ		
(Kesler et al., 2013)	20 Chemotherapy treated breast cancer patients, age on average 55	Basal serum IL-6 (Mean = 1.1 pg/mL, SD = 1.1 pg/mL), IL-10 (Mean = 7.9 pg/mL, SD = 16.7 pg/mL), IL-12 (Mean = 10.8 pg/mL, SD = 32.5 pg/mL), IL-8 (Mean = 9 pg/mL, SD = 4.5 pg/mL), TNF-a (Mean = 6.7 pg/mL, SD = 7.5 pg/mL)	Subjective Memory: MMQ Objective Verbal memory: HVLT	Cross-sectional: Assessment after 5 years after chemotherapy	1. The interaction between TNF-a and IL-6 was associated with poorer performance on the HVLT 2. The other cytokines were not associated with HVLT performance 3. MMQ was not associated with inflammation
(Pomykala et al., 2013)	33 breast cancer patients (23 chemo and 10 no	Basal plasma IL-1ra (Mean = 283 pg/mL, SD = 146 pg/mL), sTNF-	Perceived cognitive impairment: PAOFI	Longitudinal: Baseline: after primary treatment completion and 12 months later	1. Baseline total severity scores on the PAOFI memory subscale positively correlated with baseline IL-6 values, suggesting a link between cognitive complaints and plasma IL-6 levels.

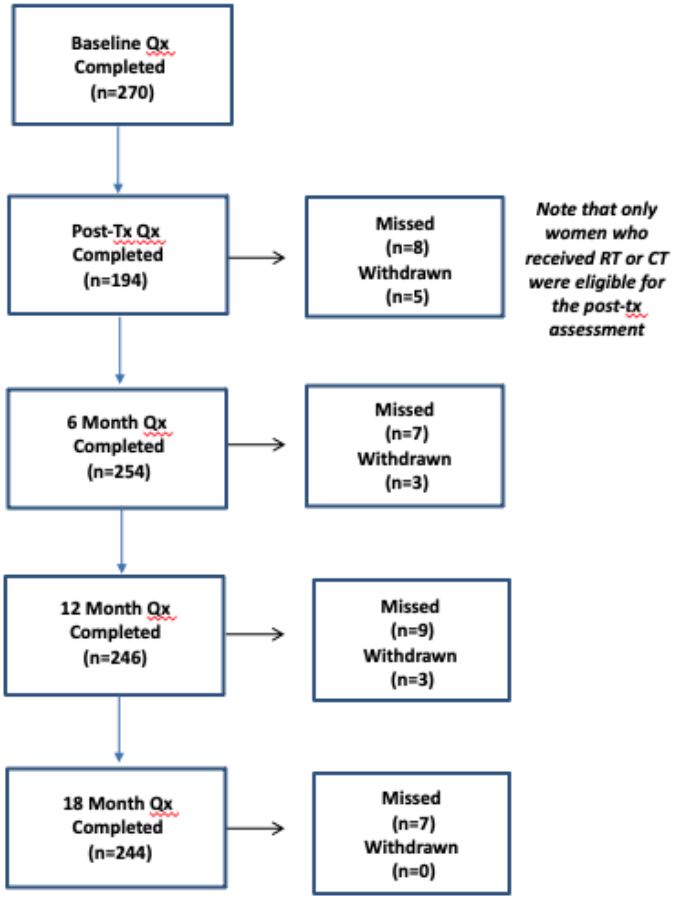
	chemo) from the Mind-Body Study, mean age = 52	RII (Mean = 2,480 pg/mL, SD = 669 pg/mL) , CRP (Mean = 4.1 mg/L, SD = 7.4 mg/L), and IL-6 (Mean = 1.7 pg/mL, SD = 1.3 pg/mL) *Means at baseline for the chemo group (post-treatment)			
(Y. T. Cheung et al., 2015)	99 breast cancer patients, mean age = 50	Basal plasma TNF-α (Mean = 1.39 pg/mL), IL-1β (Mean = .71 pg/mL), IL-2 (Mean = 0 pg/mL), IL-4 (Mean = 0 pg/mL), IL-6 (Mean = 1.14 pg/mL), IL-8 (Mean = 4.53 pg/mL), IL-10 (Mean = 0 pg/mL), GM-CSF (Mean =	Perceived CRCI: FACT-Cog Objective CRCI: Headminder Employed reliable change index (RCI) to examine cognitive changes within subjects: an RCI > −1.5 = no change; an	Longitudinal: T1: Pre-chemo, T2: 6 weeks later, 1st day of 3rd cycle, T3: 12 weeks after T1, chemo completed	1. Every unit increase in plasma IL-1β was associated with a 0.78 decrease in the response speed performance 2. A higher concentration of IL-4 was associated with better response speed performance 3. No association with inflammation for changes in processing speed, memory and attention 4. Higher concentrations of IL-1β and IL-6 were associated with more severe self-perceived cognitive disturbances

		.28 pg/mL), IFN-γ (Mean = 0 pg/mL) *Means at T1	RCI −1.5 to −2.5 = mild impairment; an RCI < −2.5 = 'severe impairment' A drop of 10.6 points in the total FACT-Cog score = perceived CRCI		5. Every unit increase in IL-4 concentration was associated with an estimated 0.95 increase of the FACT-Cog total score (less cognitive problems)
(Belcher et al., 2022)	519 breast cancer patients, mean age = 53	IL–4, IL-6, IL-8, IL-10, TNF-a, sTNF-RII (raw averages not provided)	Objective CRCI: Rapid Visual Processing Task (RVP) Backward Counting Task TMT-A	Longitudinal – before and after chemotherapy	Greater increases in IL-4 were associated with better performance at post-chemotherapy relative to pre-chemotherapy. No associations between changes in inflammatory markers and changes in performance on the Trail Making Test Part A & Rapid Visual Processing.
(Carroll et al., 2023)	400 breast cancer survivors, mean age = 67	CRP (5.9 mg/L for patients)	Objective CRCI: NP tests of Attention, Processing speed, and Executive function [APE] & and Learning and Memory [LM]	Longitudinal – before adjuvant therapies within 1, 2, 3, 4, and 5 year follow-ups	Higher levels of CRP predicted lower self-reported, but not objective, cognitive functioning in subsequent visits (at least 1 year later) for older breast cancer survivors and not age matched controls.

			Subjective CRCI: FACT-Cog		

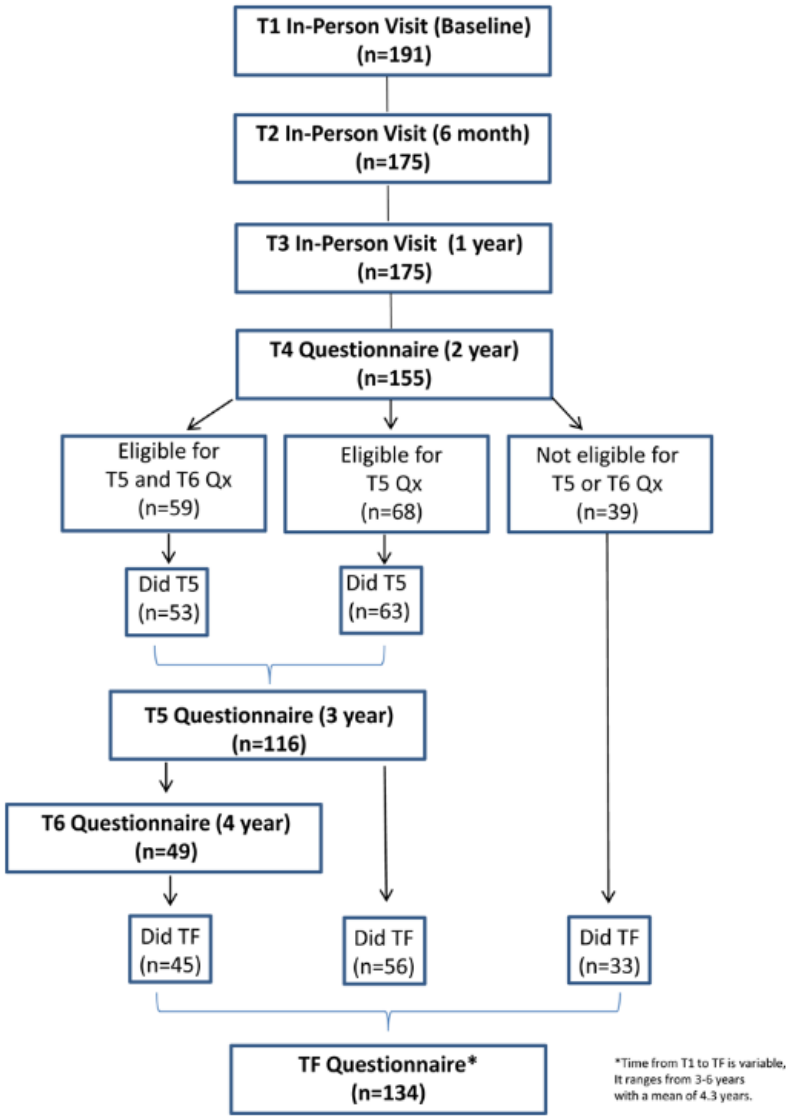
MMQ: Multifactorial Memory Questionnaire Ability Scale
SMQ: Squire Memory Questionnaire
WAIS: Wechsler Adult Intelligence Scale
PSI: Processing Speed Index
DKEF: Delis Kaplan Executive Function neuropsychological battery
CNSVS: Computerized Neurocognitive Testing System
TMT: Trail Making Test
SOC: Stockings of Cambridge
HVLT: Hopkins Verbal Learning Test
Functional Assessment of Cancer Therapy - Cognitive Function
PAOFI: Patient's Assessment of Own Functioning Inventory

Appendix D: RISE Study CONSORT Diagram



*Missed=no response from participant after multiple outreach attempts. Considered missed 8 weeks after target due date.
**Withdrawn=participant asked to be removed from study

Appendix E: The Mind-Body Study CONSORT Diagram



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