Evaluating the Relationship between Objective and Perceived Cognitive Impairment Induced by Adjuvant Chemotherapy among Breast Cancer Survivors By

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Abstract

A wide-range of breast cancer survivors (BCS) report cognitive-related concerns (e.g., changes in memory) after receiving adjuvant chemotherapy, a standardized treatment protocol for breast cancer. With adjuvant chemotherapy induced cognitive impairment linked to psychological distress and reduced quality of life among BCS, it is imperative that researchers and clinicians evaluate and address this phenomenon. However, researchers and clinicians alike have encountered difficulty in evaluating cognitive impairment among BCS due to the discrepancy found between objective cognitive impairment (OCI), characterized by neuropsychological testing, and perceived cognitive impairment (PCI), characterized by self –report, in the literature. Thus, the purpose of the present study was to explore the relationship between OCI and PCI, including a HC comparison group, CR, and examining whether MC, mood, and SoP explained the discrepancy between OCI and PCI. Twenty-seven BCS, 25 collateral reporters, and 32 healthy controls were recruited. A mixed- method approach was used. T-test and ordinary least squares regressions were conducted to compare group differences and examine the predictive value of PCI, SoP, mood, and MC, respectively. Thematic analysis was used to understand BCS's current cognitive experience. Although BCS reported more cognitive complaints than HC, our findings indicate that there is little difference between BCS and HCs on any dimension of cognitive function, including discordance in the OCI-PCI relationship, but that for BCS mood played key role in perceptions of cognitive functioning.

Keywords: Breast cancer, survivorship, adjuvant chemotherapy, cognitive impairment, working memory, speed of processing, medical comorbidities, & collateral reporter.

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Introduction

Breast cancer survivors (BCS) face numerous issues that negatively affect their quality of life as well as their overall health. A prominent issue within the literature is the "late effects of treatment," which refers to the delayed side effects that occur after treatment. Late effects of treatment can range from body image concerns to fatigue. One particular late effect of treatment is cognitive impairment induced by adjuvant chemotherapy. Researchers have explored this topic since the 90's (Ozyilkan, Baltali, Tekuzman, Firat, 1998; van Dam, et al., 1998), reporting worsening health outcomes and poor quality of life for BCS (Ahles et al., 2010; Vincent Koppelmans, Breteler, Boogerd, Seynaeve, & Schagen, 2013; Seliktar, Polek, Brooks, & Hardie, 2015; Wefel & Schagen, 2012; Zheng et al., 2014). With an estimated range of 17-75% of BCS reporting cognitive impairment, it is imperative that we examine this particular phenomenon to better assess the impact on survivorship for BCS (Ahles, Root, & Ryan, 2012; Correa & Ahles, 2008; Wefel & Schagen, 2012).

Extant literature identifies two subdomains of cognitive impairment: objective and perceived. The objective cognitive impairment (OCI) domain refers to the use of objective measures (i.e., neuropsychological testing/assessment) to detect the presence of cognitive impairment. Conversely, perceived cognitive impairment (PCI) relies on subjective measures (i.e., self-report) to identify the experience of cognitive impairment within BCS. Both OCI and PCI are vital in not only examining existing cognitive impairment among BCS, but also in addressing quality of life and other psychosocial concerns. While BCS show evidence of impairment in both subdomains, there is a significant discordancy between OCI and PCI (Ganz et al., 2013; Hermelink et al., 2010; Mehnert et al., 2007; Mihuta, Green, Man, & Shum, 2016). Such a discordance negatively affects researchers and health care professionals' ability to

predict, identify, and address accurately the occurrence of cognitive impairment in BCS. Hence, understanding of the discordancy between OCI and PCI is vital in accurately assessing the impact of cognitive impairment on BCS.

Background

Breast cancer is the leading cancer among females, with an incidence of 124.9 cases per 100,000 in the United States and an estimate of over 250,000 new diagnoses in 2017 (Howlader et al., 2016; U.S. Cancer Statistics Working Group, 2017). Despite being the fourth leading cause of death compared to all cancers and the second leading cause of death among women of all races, breast cancer has an 89.7% five-year survival rate. Survival rate has increased approximately 20% among those diagnosed with breast cancer due to early detection and the availability of effective treatments (American Cancer Society, 2016). Consequently, BCS are the largest female cancer survivor group representing about 23% of cancer survivor populations (American Cancer Society, 2016; Boykoff, Moieni, & Subramanian, 2009). As a significant proportion of all cancers and cancer survivors, BCS report increased difficulties navigating and managing survivorship concerns, particularly cognitive impairment induced by adjuvant chemotherapy, making them an important population to examine.

Adjuvant chemotherapy is a component of a standard cancer treatment protocol that impacts quality of life among BCS. Adjuvant chemotherapy is a systemic therapy that eliminates remaining cancerous cells in the body after surgery. Adjuvant chemotherapy increases survival rates among BCS and reduces the likelihood of cancer reoccurrence (Marin, Sanchez, Arranz, Aunon, & Baron, 2009; Wefel, Saleeba, Buzdar, & Meyers, 2010). Despite being a lifesaving and life prolonging treatment, researchers have documented that adjuvant chemotherapy leads to negative late effects and adversely affects survivorship. Recently,

Sparano et al. questioned the need for adjuvant chemotherapy for BCS (2018). In particular, they suggested that adjuvant chemotherapy may not be necessary for patients diagnosed with early-stage breast cancer with the following characteristics: no infected lymph nodes, human epidermal growth factor receptor 2 (HER2) negative, tumor size measuring between one to five centimeters, estrogen sensitivity, and recurrence score that is ranges between 11-25 based on the Oncotype DX Breast Cancer Assay. This is in contrast with extant research suggesting that BCS below the age of 50 may still benefit from adjuvant chemotherapy because adjuvant chemotherapy decreases the risk of recurrence for this age-population. However, more research is needed to support the study's findings and the utility of the genetic assay. Despite the potential for new guidelines, adjuvant chemotherapy remains a common component in treatment protocols for breast cancer. Thus, further research into late effects of adjuvant chemotherapy is vital in addressing survivorship concerns amongst BCS.

Adjuvant Chemotherapy Induced Cognitive Impairment

Cognitive impairment is a late effect of adjuvant chemotherapy that has been studied extensively and seen to negatively affect overall survivorship within the BCS population. (Boykoff et al., 2009; Marin et al., 2009). Researchers and clinicians have coined adjuvant chemotherapy induced cognitive impairment as "chemo fog" or "chemo brain" (American Cancer Society, 2016; Ando-Tanabe et al., 2014; Mihuta et al., 2016). BCS have described chemo brain as an inability to retain and recall information along with a diminished ability to think (i.e., word finding) and concentrate on tasks (Mehnert et al., 2007; Mihuta et al., 2016; Myers, 2012; Myers, Jo A. Wick, & Klemp, 2015; Paquet et al., 2017). Multiple cognitive domains (e.g., memory, executive function) have been implicated as being adversely affected. Along with a wide range of BCS endorsing chemo brain, researchers have documented cognitive

impairment ranging from mild to severe (Correa & Ahles, 2008; Jim et al., 2012; Marin et al., 2009) and temporary to permanent (Michelle C. Janelsins et al., 2017; McDougall, Oliver, & Scogin, 2014). Overall, researchers have characterized cognitive impairment as being subtle and mild (Hermelink, 2015; Von Ah et al., 2009). Regardless of the presence of variability (i.e., endorsement, severity, and temporality) that exists in the literature, cognitive impairment as a late effect of treatment negatively affects both physical health (e.g., medical adherence) and psychological health (e.g., quality of life), resulting in an increased number of survivorship concerns among BCS (Buchanan et al., 2015; McDougall et al., 2014; Wefel et al., 2010; Wefel & Schagen, 2012). As such, healthcare providers and researchers should focus on cognitive impairment and the subsequent consequences that affect BCS.

Underlining Mechanism of Adjuvant Chemotherapy Induced Cognitive Impairment

To understand adjuvant chemotherapy induced cognitive impairment, it is imperative to briefly review a few of the putative theoretical mechanisms driving cognitive impairment within the BCS population. One popular theoretical explanation, the primary mediational model (MM1), suggests that the cognitive effects of adjuvant chemotherapy are really due to the effects of cancer and adjuvant chemotherapy on inflammation (Ahles et al., 2012; Ahles & Saykin, 2007; Burstein, 2007; M. C. Janelsins et al., 2011; Wefel & Schagen, 2012; Zheng et al., 2014). Specifically, researchers have hypothesized that cancer induces peripheral inflammation, which then results in the body releasing neurotoxic cytokines. The released neurotoxic cytokines then damage healthy functioning neurons through oxidative stress (Ahles et al., 2012; Merriman, Von Ah, Maskowski, & Aouizerat, 2013). Adjuvant chemotherapy then creates an additive effect by initiating oxidative stress, thus increasing inflammation that impairs mitochondrial and neuronal functioning systemically (Ahles & Saykin, 2007; M. C. Janelsins et al., 2011; Merriman et al.,

2013). Moreover, adjuvant chemotherapy (e.g., methotrexate and cisplatin) can cross over the blood brain barrier and introduce neurotoxicity, causing further neuronal damage in the brain. The combined effects of cancer, cytokines, and adjuvant chemotherapy produce cascading and damaging chain events that result in impaired cognitive functioning.

Similarly, a stress-diathesis model with genetic markers (gene x adjuvant chemotherapy) have been implicated in the relationship between cognitive impairment and adjuvant chemotherapy (Ahles et al., 2012; M. C. Janelsins et al., 2011). Researchers have explored two specific genes of interest within the literature, catechol-o-methyltransferase (*COMT*) and apolipoprotein E (*APOE*). *COMT* has been associated with cognitive dysfunction and linked to decreased ability in the neurocognitive domains of executive function and complex attention among BCS (Ahles et al., 2012; Bower & Ganz, 2015; M. C. Janelsins et al., 2011; Merriman et al., 2013). In fact, BCS, who had a Val+ variation of the *COMT* gene, experienced reduced attention after treatment with adjuvant chemotherapy compared to other BCS, who did not have the *COMT* gene variation. Researchers have associated *APOE* gene with cognitive impairment in individuals with Alzheimer (Ahles et al., 2012; Bower & Ganz, 2015; M. C. Janelsins et al., 2011; Lange, Rigal, et al., 2014; Mandelblatt et al., 2014). With BCS, those with *APOE* gene variant have demonstrated specific impairment in visual memory when treated with adjuvant chemotherapy compared to BCS, who lack the variant of the *APOE* gene. Evidence regarding the influence of these genes is preliminary with ongoing research, so findings regarding the influence of these genes along with adjuvant chemotherapy in a BCS population are limited. Yet, preliminary findings suggest that adjuvant chemotherapy, again, plays an additive role in activating genetic markers, increasing the likelihood of cognitive dysfunction. Genetic markers, like *COMT* and *APOE* may further compound the experience of cognitive impairment amongst BCS and add to the inconsistency in the literature.

Finally, researchers have hypothesized a secondary mediational model (MM2) with a pathway between cancer, adjuvant chemotherapy, and hormones, like estrogen. Researchers have linked estrogen and the body's natural shift into menopause to a reduction in cognitive functioning in healthy aging women (Ahles & Saykin, 2007; Ahles et al., 2010; Amidi et al., 2015; M. C. Janelsins et al., 2011; Seliktar et al., 2015; Tager et al., 2010). Adjuvant chemotherapy, as a systemic therapy, stops ovaries and fat tissues from producing estrogen. As such, BCS undergoing adjuvant chemotherapy experience a sudden and dramatic decrease in estrogen, triggering a rapid shift into menopause (Ahles & Saykin, 2007; M. C. Janelsins et al., 2011). Since estrogen is a neuroprotective hormone linked objectively to "verbal memory and learning" functioning, a rapid decrease in estrogen versus a natural and slower progression may increase the probability of cognitive impairment among BCS (Buchanan et al., 2015; Hermelink et al., 2010; Merriman et al., 2013). Janelsins, et al. postulated that differences in report of cognitive impairment amongst BCS receiving adjuvant chemotherapy could be due to the hormonal induced menopausal state of the survivors (2011). Extant literature has demonstrated mixed support for this theory (Amidi et al., 2015; Buchanan et al., 2015; Klemp et al., 2017; Myers et al., 2015), indicating that adjuvant chemotherapy may cause cognitive impairment by damaging the production of neuroprotective hormones in BCS.

Adjuvant chemotherapy may drive cognitive impairment through its neurotoxic effect on cytokines, neurons, genetic markers, and hormones associated with cognitive functioning. Despite multiple theories and supporting evidence, a clear underlying mechanism between adjuvant chemotherapy and cognitive impairment does not exist. Indeed, the underlying mechanisms—mediational models with interactions between chemotherapy and cancer with cytokines (MM1), and hormones (MM2) and the gene X chemotherapy interaction— reviewed

above are insufficient alone to explain the wide-ranging occurrence of cognitive impairment among BCS treated with adjuvant chemotherapy. The absence of a clear underlying mechanism between adjuvant chemotherapy and cognitive impairment suggests a multifactorial etiology. A multifactorial etiology may contribute to BCS' experience of not only OCI, but also PCI with contributing factors, such as mood disorders and medical comorbidities, augmenting the relationship between adjuvant chemotherapy and cognitive impairment. As such, these potential contributing factors may provide a more comprehensive understanding of the causal linkage between adjuvant chemotherapy and cognitive impairment would be especially useful when evaluating the relationship between OCI and PCI. In summary, adjuvant chemotherapy and its related effects may act as a precipitating factor along with cancer and other contributing variables to increase the likelihood of cognitive impairment among BCS.

Relationship between OCI and PCI

Current research on adjuvant chemotherapy induced cognitive impairment has trended in the last decade towards examining both OCI and PCI among BCS. Historically, studies on adjuvant chemotherapy induced cognitive impairment have focused on examining solely OCI, disregarding PCI as a substandard measure of cognitive impairment (Ando-Tanabe et al., 2014; Andryszak, Wiłkość, Żurawski, & Izdebski, 2017; Jansen, Cooper, Dodd, & Miaskowski, 2011; Kesler & Blayney, 2016). Touted as the gold standard, OCI seems to provide a clear understanding of the effects of adjuvant chemotherapy on cognitive functioning and its affected neurocognitive domains. However, PCI is equally important since it assesses BCS' beliefs about their abilities to manage day-to-day cognitive tasks (Jung & Cimprich, 2014; Myers, Koleck, Sereika, Conley, & Bender, 2017; Pullens, De Vries, Van Warmerdam, Van De Wal, &

Roukema, 2013). Both OCI and PCI can lead BCS to feel inadequate and incompetent about their ability to cope as a survivor, resulting in symptom distress (i.e., anxiety, depression, or social isolation) that can ultimately affect physical functioning. As such, OCI and PCI are important in gaining a comprehensive understanding of adjuvant chemotherapy induced cognitive impairment, resulting in researchers beginning to examine the relationship between these two subdomains of cognitive impairment.

Consequently, examining both OCI and PCI have advanced clinical science; however, the discordancy found between these subdomains has negative clinical implications. The prevailing clinical opinion regarding the source of the discordancy between OCI and PCI is that BCS overestimate their deficits. BCS typically endorse chemobrain, noting current difficulties in performing cognitive tasks (e.g., remembering instructions or losing items), despite the absence of cognitive impairment when assessed by objective measures. Such discordancy suggests that BCS are either experiencing cognitive distortion, believing that they are experiencing cognitive impairment due to their treatment, or rather overestimating cognitive impairment (Collins, Paquet, Dominelli, White, & MacKenzie, 2017; Mehnert et al., 2007). In fact, it is commonly thought that informing BCS patients that cognitive impairment may be a side effect of adjuvant chemotherapy, may serve as a cognitive "prime", increasing attention to normal errors in memory and attention (Hermelink et al., 2010; Schagen, Das, & Vermeulen, 2012; Schagen, Das, & van Dam, 2009).

Although it is possible that BCS are overestimating their cognitive deficits and reporting higher PCI scores, it is still of the utmost importance that PCI be accounted for and understood. PCI is an indicator of BCS' quality of life as well as their current distress. If quality of life is poor and distress high among BCS, then how they engage in healthy behaviors (i.e., proper

nutrition and sleep hygiene) may be affected. PCI may affect not only their mental and physical health, but also their social health, resulting in an increase negative outcome, such as anxiety, medical non-adherence, potential isolation, and loss of employment. Hence, examining PCI along with OCI neurocognitive domains is vital to have a comprehensive and accurate assessment in understanding cognitive impairment among BCS.

Discordancy between OCI and PCI

BCS have described chemo brain as troubling problems with memory, attention, concentration and executive functioning (Mehnert et al., 2007; Mihuta et al., 2016; Myers, 2012; Myers, Jo A. Wick, & Klemp, 2015; Paquet et al., 2017). However, researchers have characterized cognitive impairment as being subtle and mild (Hermelink, 2015; Von Ah et al., 2009). The discordancy between OCI and PCI is not well understood and has been inconsistently operationalized.

Evidence regarding the relationship between OCI and PCI is inconclusive. The majority of studies have shown that OCI and PCI are uncorrelated (Ahles et al., 2010; Collins, Paquet, Dominelli, White, & MacKenzie, 2017; Debess et al., 2010; Hermelink et al., 2010; Myers et al., 2015; Paquet et al., 2017; Shilling & Jenkins, 2007). Yet, studies exist that report a small to moderate positive correlation, ranging from $R = 0.32$ to 0.50 between OCI and PCI (Bender et al., 2008; Berman et al., 2014; Ganz et al., 2013; Lange, Giffard, et al., 2014; Mehnert et al., 2007; Mihuta et al., 2016; Oh, 2017; Von Ah & Tallman, 2015; Weis, Poppelreuter, & Bartsch, 2009). The discordancy between OCI and PCI causes confusion and affects researchers and clinicians' ability to provide comprehensive information about how to identify, predict, and treat cognitive impairment effectively. This discordance also causes researchers and clinicians to underestimate and disregard the importance of PCI, the felt experience of the person, in measuring cognitive

functioning amongst BCS. Instead, PCI is seen as BCS overestimating their experience of cognitive impairment. In the section below the author identifies possible sources causing the discordance between OCI and PCI.

Definition of OCI. First of all, when examining the relationship between OCI and PCI, operationalizing OCI among BCS is vital because differing definitions can affect how researchers classify and identify cognitive impairment. For instance, some studies lack a clear definition of OCI among BCS. Instead, these studies appear to define OCI based on the individual assessment measures' published definitions of impairment (i.e., cut-off scores) (Askren et al., 2014; Bender et al., 2008; Berman et al., 2014; Hermelink et al., 2010; Shilling & Jenkins, 2007). Researchers in other studies have defined OCI as one or two standard deviation lower than the published "normative mean" on a domain, like memory (Lange, Giffard, et al., 2014; Mandelblatt et al., 2014; Mihuta et al., 2016; Prokasheva, Faran, Cwikel, & Geffen, 2011). Researchers also have created alternative definitions (i.e., calculating an objective cognitive summary scores and creating an average z score for each individual measure and time point) to avoid inflating cognitive impairment by using multiple assessment (Ahles et al., 2008; Collins, Mackenzie, Tasca, Scherling, & Smith, 2013; Debess, Riis, Engebjerg, & Ewertz, 2010; Ganz et al., 2013; V. Koppelmans et al., 2012; Mehnert et al., 2007; O'Farrell, Smith, & Collins, 2016). Alternatively, researchers have incorporated control groups to provide a better estimation of the effect of chemotherapy on BCS' cognition (Ando-Tanabe et al., 2014; Askren et al., 2014; Cheung, Shwe, et al., 2012; Myers et al., 2015; Paquet et al., 2017; Schilder et al., 2010; Von Ah et al., 2009). Control groups, particularly age-matched healthy controls (HC), provide a better comparison group in which researchers can study a specific condition and make an accurate inference regarding the condition (Schilder et al., 2010). Although published norm-referenced

data, particularly for OCI, are available, these data are gathered from multiple sources (e.g., different populations; different testing time points) and may not be applicable to the current BCS sample's experience of OCI. Indeed, published norm-referenced data may lead to inaccurate inferences regarding the existence of OCI among BCS, skewing our understanding of the relationship between OCI and PCI. Conversely, using HC allows researchers to establish the presence of both OCI and PCI among BCS and operationalize impairment more consistently. This is of particular importance in the present study since our understanding of the occurrence of OCI and PCI among BCS is unclear given the differing definitions within the literature.

Assessment measures. Another probable cause for the discordance between OCI and PCI is the use of different assessment measures. Not all neuropsychological assessments or self report measurements are created equally or capture the same aspects of cognitive functioning. Differences between the types of OCI measures (e.g., cognitive screen measures versus more comprehensive neuropsychological measures) differ in their ability to detect cognitive impairment amongst BCS. Cognitive screening tests lack sensitivity and are less robust, particularly when examining changes in cognitive status across time (Klemp et al., 2017; Lezak, Howieson, Loring, Hannay, & Fischer, 2004; Oh, 2017; Paquet et al., 2017). Neuropsychological batteries lack the limitations of cognitive screening tests. However, more comprehensive neuropsychological measures lack ecological validity, which could contribute to the mixed findings reported in studies examining the discordancy between OCI and PCI (Chaytor & Schmitter-Edgecombe, 2003; Collins et al., 2017; Hermelink et al., 2010; Lezak et al., 2004; Mihuta et al., 2016; O'Farrell et al., 2016). PCI measures are quite variable. They are designed to capture a wide range of domains of cognitive functioning (e.g., attention versus memory complaints), and have inherent drawbacks (i.e., self-report bias) that may contribute to the

discordance between OCI and PCI. Thus, limitations (i.e., defining cognitive impairment), affecting how OCI and PCI are assessed and classified. When examining assessment measures, a wide array of measures and factors exist that influence the relationship between OCI and PCI, resulting in the discordant findings among researchers.

Collateral information. Collection of collateral information is considered to be an important neuropsychological assessment tool when assessing cognitive functioning (Lezak et al., 2004). Absence of collateral information is a key limitation in the extant literature evaluating the relationship between OCI and PCI. Collateral information provides more information regarding BCS' lived experience of cognitive limitations and would give a more externally valid, clear and accurate view of perceived cognitive functioning. Using collateral information within the BCS population may lead to gaining a more comprehensive view of OCI and perhaps a more concordant relationship with PCI. The lack of collateral information as an integral assessment measure is a noticeable gap in the literature, particularly when examining the relationship between OCI and PCI.

Neurocognitive domains. The discordancy between OCI and PCI may be because of differential sensitivity across differing neurocognitive domains. Extant research has focused heavily on examining learning and memory (Jim et al., 2009; Jim et al., 2012; McDougall et al., 2014; Myers, 2012; Von Ah et al., 2009; Wefel & Schagen, 2012), executive functioning (Askren et al., 2014; Menning et al., 2017; Von Ah & Tallman, 2015), and complex attention (Berman et al., 2014; Jaremka et al., 2014; Mihuta et al., 2016) with BCS treated with adjuvant chemotherapy. As such, the extant literature is rich with supporting evidence of adjuvant chemotherapy induced OCI as well as the presence (or lack thereof) of a relationship between OCI and PCI in BCS among these particular neurocognitive domains (Refer to Table 1). OCI is

evident in executive function, complex attention; however, OCI is limited within the language neurocognitive domains. This is in contrast with PCI, which has been reported in language domains (Jansen et al., 2011; Jim et al., 2012) but there are few studies assessing executive functioning and complex attention (Askren et al., 2014; Berman et al., 2014; Jansen et al., 2011; Myers et al., 2015), leading to discordant results between OCI and PCI. In fact, the lack of concordance between OCI and PCI on these neurocognitive domains suggests that PCI measures may not be sensitive enough to identify deficits in executive function and complex attention and OCI measures may not be effective in identifying language deficits. Identifying neurocognitive domains in which OCI and PCI share sensitivity in detecting deficits may be key to understanding the discordant relationship between these two cognitive subdomains.

Learning and memory are neurocognitive domains in which OCI and PCI measures may have similar sensitivity to deficits among BCS. Indeed, researchers have identified various aspects of memory, particularly working memory, to be objectively impaired among BCS (i.e., stages 0-III) treated with chemotherapy compared to healthy controls (Andryszamk et al., 2017; Collins et al., 2017; Von Ah et al., 2015) and in BCS treated with radiation (Berman et al., 2014). Researchers have also found that BCS endorse a high number of working memory complaints (Bender et al., 2008; Ganz et al., 2013; Lange, Giffard et al., 2014; Mihuta et al., 2016). Consequently, some researchers who have examined working memory have found OCI and PCI to be concordant in this particular cognitive domain. However, other studies have reported discordance among OCI and PCI among working memory (Ahles et al., 2008; Jim et al., 2009; Weis et al., 2009). The nature of the observed relationship between OCI and PCI measures of working memory suggests that BCS overestimate their experience of cognitive impairment, perhaps because of the presence of another variable (e.g., interference of another cognitive

function or mood) that affects the relationship between OCI and PCI. Thus, working memory presents an area in which to examine the discordant relationship between OCI and PCI by exploring both the claim that BCS overestimate cognitive impairment as well as the existence of an unknown secondary variable affecting the relationship between OCI and PCI.

Speed of processing. Speed of processing (SoP) is a cognitive function that may provide a less discordant relationship between OCI and PCI. SoP refers to the rate in which a person can absorb, comprehend, and react to incoming information. As such, SoP is a global cognitive function that intersects with multiple major neurocognitive domains, such as learning and memory, complex attention, and executive function (Lezak et al., 2004). Evidence exists that BCS treated with adjuvant chemotherapy experience a noticeable reduction in their SoP ability (Ahles et al., 2012; M. C. Janelsins et al., 2011; Jim et al., 2012; Merriman et al., 2013; Wefel & Schagen, 2012), leading to BCS endorsing PCI (Shilling & Jenkins, 2007). Thus, BCS may report PCI because they experience slowing of SoP, which they may attribute to other cognitive complaints, like difficulties with word finding, and concentrating/completing an assigned task (Shilling & Jenkins, 2007). The hypothesis that OCI and PCI may be correlated and be less discordant on SoP measures among BCS has been tested by several research studies with mixed results (Ahles et al., 2008; Ando-Tanabe et al., 2014; Bender et al., 2008; Collins et al., 2013; Ganz et al., 2013; Lange, Rigal, et al., 2014; Mihuta et al., 2016; Von Ah & Tallman, 2015), perhaps because some SoP measures capture attention and/or memory complaints versus true SoP. This is unsurprising, given that SoP is a cognitive ability underlining multiple neurocognitive domains and thus can be tricky to isolate. In light of the mixed results, it is imperative to examine SoP to see if the experience of this cognitive ability indirect affects the

relationship between OCI and PCI, resulting in a less discordant relationship between OCI and PCI.

Contributing factors. Contributing factors (e.g., age, medical comorbidities, and mood disorders) may underlie the relationship between OCI and PCI, resulting in the discordance between these subdomains. Age and age-related cognitive changes, like medical comorbidities, have been identified as risk factors or rather confounding variables in the relationship between adjuvant chemotherapy and overall cognitive impairment. Mood disorders also are potential factor that contribute to the discordancy between OCI and PCI. Researchers have used mood disorders to explain PCI in the literature with BCS. However, the extant literature lacks sufficient research to make a definitive determination regarding what role that these factors may play in the relationship between OCI and PCI.

Age. Age and age-related cognitive changes are factors that impact overall cognition in both the absence and presence of a disease. In the absence of disease researchers have shown a relationship between age, age-related changes and cognitive abilities in multiple neurocognitive domains (Harada, Love, & Triebel, 2014; Salthouse, 2017; Salthouse, 2018). Neurocognitive domains, such as learning and memory, executive function along with cognitive abilities (i.e., memory and SoP) have been reported to be significantly impacted by the aging process (Harada et al., 2014). Meaning, as an individual age, a slow and subtle deterioration of current cognitive abilities in these areas begin. Noteworthy, the trajectory of cognitive decline in these abilities, particularly SoP, typically begin in the 30-age range, peaking and then slowly declining until the age of 65, when a sharper, faster, and more noticeable cognitive decline begins to occur. Given that age and age-related cognitive changes occur regardless, it is important to account for such

how such a typical trajectory and its formidable influences can affect our understanding of cognitive abilities in the presence of disease.

In the presence of a disease like cancer, age and age-related cognitive changes add further complications to other cognitive and physical processes co-occurring throughout the disease trajectory. The disease trajectory in turn may accelerate the aging processing impacting the normal aging trajectory by causing a noticeable sharp decline in cognitive abilities faster. In fact, researchers have posited that older BCS (> 65 years old) versus younger BCS (<65 years old) have increased susceptibility to the toxicity of adjuvant chemotherapy along with neuronal damage, resulting in speeding up cognitive decline among BCS (Ahles et al., 2010; Buchanan et al., 2015; Lange, Giffard et al., 2014; Mandelblatt et al., 2014). Thus, the discordant relationship between OCI and PCI may be due to the combined impact of age and age-related cognitive changes and the effect of their cancer trajectory. As such, the present study attempts to account for age, as an influential factor, by providing age-matched HC group.

Medical comorbidity. Medical comorbidity (MC) may affect the relationship between adjuvant chemotherapy and cognitive impairment, particularly the relationship between OCI and PCI (Klepin et al., 2014; Lange, Rigal, et al., 2014). Researchers have posited and demonstrated that having other medical diagnoses affect cognition along with overall life expectancy for BCS (Freedman et al., 2013; Klepin et al., 2014; Mandelblatt et al., 2014; Prokasheva et al., 2011; Wefel & Schagen, 2012). For instance, neuropathy, a common MC, may become severe and intensely painful with the addition of adjuvant chemotherapy increasing peripheral nerve damage, and interfering with overall cognition and motor abilities (Jansen et al., 2011; Tager et al., 2010). Hence, the cancer process may have an additive effect by increasing pain, which is known to impair cognitive functioning. Thus, MC may affect the relationship between OCI and PCI as a moderating factor between adjuvant chemotherapy and overall cognitive impairment.

The majority of extant studies do not explore the role of MC within the relationship between OCI and PCI, but rather exclude BCS with MC, which biases estimates of PCI to the most healthy of patients (Ahles et al., 2008; Bender et al., 2008; Berman et al., 2014; Collins et al., 2017; Debess et al., 2010; Ganz et al., 2013; Hermelink et al., 2010; Klemp et al., 2017; Mehnert et al., 2007; Oh, 2017).

Researchers, who have examined the relationship between MC and OCI and PCI, have found complex relationships with MC. For instance, neuropathy and obesity are correlated with higher PCI (Klemp et al., 2017; Myers et al., 2015; Zhezhou et al., 2017) and anemia covaries with OCI in a positive direction (Bower & Ganz, 2015; Vearncombe et al., 2009). Other researchers have found no association of MC with either PCI or OCI among an older BCS population (Lange, Giffard, et al., 2014; Lange, Rigal, et al., 2014). Such contradictory evidence is likely because there are so few studies that assess for MC, since studies commonly exclude BCS who endorse any MC. MC are linked with aging in older BCS; and, as with the literature regarding aging, there is a gap in the research focusing on the role that MC plays in the relationship between OCI and PCI. Thus, the influence of MC on cognitive impairment, particularly the relationship between OCI and PCI is unclear. Although MC either may play a role in overall cognitive impairment apart from adjuvant chemotherapy or compound the negative effects of adjuvant chemotherapy, there is a lack of consistent literature to delineate how MC affects the relationship between OCI and PCI.

Mood disorders. Researchers have identified mood disorders (e.g., depression and anxiety) as a late effect of treatment, particularly adjuvant chemotherapy (American Cancer Society, 2016). Mood disorders have been linked to impaired cognitive functioning (Merriman et al., 2013). In fact, one of the symptoms of depression is the inability to think or make decisions (American Psychiatric Association, 2013). Moreover, anxiety symptoms which are a

common symptom of depression are also known to interfere with cognitive processes. Mood disorders may play a large part in how BCS may experience cognitive impairment. It seems likely that depressed or highly anxious BCS may incorrectly attribute their cognitive impairment to adjuvant chemotherapy rather than their mood or mood-disorder. This hypothesis is supported by research showing a correlation between PCI and depression (Ahles et al., 2008; Bender et al., 2008; Collins et al., 2017; Ganz et al., 2013; Hermelink et al., 2010; Michelle C. Janelsins et al., 2017; Jansen et al., 2011; Klemp et al., 2017; Lange, Giffard, et al., 2014; O'Farrell et al., 2016; Oh, 2017; Pullens et al., 2013; Shilling & Jenkins, 2007) and anxiety (Bender et al., 2008; Collins et al., 2017; Michelle C. Janelsins et al., 2017; Jansen et al., 2011; Lange, Giffard, et al., 2014; O'Farrell et al., 2016; Paquet et al., 2017; Pullens et al., 2013), but not OCI. Consequently, researchers in general have posited that the discordancy between OCI and PCI is due to the mood disorder (i.e., anxiety and depression) versus "true" cognitive impairment. As such, evidence supports the relationship between PCI and mood disorders, reinforcing the assumption that PCI is not an accurate or adequate measure of cognitive impairment. Conversely, it may be that a mood disorder compounds the cognitive dysfunction attributed to the adjuvant chemotherapy. BCS may experience emotional distress due to their experience of OCI, which may go undetected because cognitive reserve may mask more subtle and mild cognitive impairment. Although mood disorders affect the experience of PCI, researchers may be overlooking the directionality and the influence of the mood disorder and the relationship between OCI and PCI.

Normative Discordance. A common explanation for the discordancy between OCI and PCI is that BCS overestimate their cognitive dysfunction perhaps due to cognitive priming or deficits in metamemory (Collins, Paquet, Dominelli, White, & MacKenzie, 2017; Mehnert et al., 2007; Hermelink et al., 2010; Schagen, Das, & Vermeulen, 2012; Schagen, Das, & van Dam,

2009). Yet, another explanation exists. The discordancy between OCI and PCI may be a normative phenomenon given that the majority of OCI measures used to assess cognitive functioning are not ecologically valid and cannot accurately detect mild and subtle cognitive impairment in everyday situations. Indeed, OCI and PCI may be measuring different constructs. Extant literature examining "fibro fog" along with the discordancy between OCI and PCI among patients with fibromyalgia supports this explanation (Ambrose, Gracely, & Glass, 2012; Kravitz & Katz, 2015; Walitt et al., 2016). As such, it would be useful to examine whether this discordancy exists within the HC sample as well.

Summary

BCS are the largest female cancer survivorship group and thus are a population of interest among researchers and clinicians alike. Adjuvant chemotherapy induced cognitive impairment is a distressing late effect of treatment endorsed by BCS. Researchers have utilized both OCI and PCI measures to explore and evaluate cognitive impairment. Although OCI is still seen as the gold standard in identifying cognitive impairment among BCS, PCI is of equal importance as perception shapes how people interact with their world and relates to a sense of efficacy. BCS, who report experiencing cognitive impairment, are more likely to have difficulty engaging in day-to-day activities, like social and occupational obligations (Oh, 2017; Pullens et al., 2013). In turn, PCI along with OCI increases the risk for overall negative health outcomes, such as medical non-adherence and poor quality of life. Unfortunately, mixed findings regarding the relationship between OCI and PCI have been reported, suggesting that BCS may not be consistent in their reports. A commonly held belief is that BCS overestimate cognitive impairment, furthering the difficulty in exploring the relationship between OCI and PCI. On the other hand, OCI measures may lack ecological validity, resulting in OCI measures inability to capture more subtle cognitive impairment affecting everyday activities. This discordancy causes

confusion and impairs researchers and clinicians' ability to provide comprehensive information about how to identify, predict, and treat cognitive impairment effectively. Perhaps more importantly, this discordancy also causes researchers and clinicians to underestimate and disregard the importance of PCI, the felt experience of the person, in measuring cognitive functioning amongst BCS.

Remaining Questions

Little is known about the nature of the discordancy between OCI and PCI, nor how best to minimize or at least understand the discordancy, creating gaps within the literature that are ripe for exploration. First of all, it would be important to select a cognitive domain in which there are comparable OCI and PCI assessment tools. Memory and working memory are common complaints among BCS. Measures associated with memory and working memory for both OCI and PCI exist and have been identified as being comparable in the literature, particularly with regards to OCI and PCI being related (Bender et al., 2006; Collins et al 2017; Mihuta et al., 2016; Tager et al., 2010). It also would be useful to gather data from age-matched, HC. HC as a study-specific norm comparison group would be a better alternative to referencing published norms since a study specific norm-reference group would lead to a more accurate picture of OCI. In addition to creating a current norm referenced group, examining the discordancy between OCI and PCI in HCs would establish a norm reference baseline for the discordancy between OCI and PCI. Second, the use of a collateral reporter (CR) may lead to a better understand the OCI-PCI discordancy. CRs are an integral part of a thorough neuropsychological assessment; however, they are almost never included in studies examining the relationship between OCI and PCI. Gaining information from an informant may provide an ecologically valid independent assessment of BCS cognitive impairment, leading to a less discordant relationship between OCI and PCI. Conversely, collateral reports from an informant

also may provide further evidence that current OCI measures lack ecological validity or that discordancy may in fact be normative. Collecting information from a CR will allow us to examine the potential for biased processing in BCS and examining the discordancy between OCI and PCI in HC will allow us to establish a normative baseline for the discordancy. It is possible that the discordancy between OCI and PCI is a normative phenomenon and not indicative of biased processing that is particular to BCS. To the extent that the OCI-PCI discordancy reflects biased processing, it would be useful to identify factors that lead to overestimation of cognitive impairment. BCS patients may mistake reduced SoP for deficits in other cognitive domains, like working memory. Furthermore, other factors, like MC and mood, may also color BCS PCI. The extant literature has not consistently examined measures of SoP, mood or MC, so it is not possible to determine definitively whether they are related to the discordance between OCI and PCI. Thus, the present study addresses these remaining questions to clarify both the occurrence of OCI and PCI and the discordant relationship between OCI and PCI among BCS in an effort to provide tools that screen and appropriately address this late effect of treatment for BCS.

The Present Study

The discordance between OCI and PCI is problematic because it hinders researchers and clinicians' ability to evaluate cognitive impairment among BCS treated with adjuvant chemotherapy. Since the extant literature continues to report discordant findings regarding the relationship between OCI and PCI and the discordancy has interpreted by medical professionals as a cognitive distortion, further exploration in understanding the relationship between OCI and PCI is warranted. The purpose of the present study was to examine and further understand the relationship between OCI and PCI, while exploring the impact of collateral information, SoP, mood, and MC— probable causes of the discordancy —on the relationship between these two

subdomains. The present study defined OCI as impairment in verbal working memory because working memory is a common complaint amongst BCS. Additionally, in an effort to explore the relationship between OCI and PCI among BCS, a HC group was included within the present study to act as a reference group and a CR group were included to provide an objective perspective on BCS' cognitive functioning. Hypotheses and aims of the present study are specified below.

Aims & Hypotheses

Aim 1 and hypothesis. The overarching aim of this study was to better characterize the relationship between OCI and PCI in BCS. To that end, **Aim 1a**) was to characterize differences as well as to assess the relationship between OCI and PCI in BCS and HC; and **Aim 1b**) was to assess the relationship between OCI and PCI in BCS CRs. We hypothesized that BCS would score significantly lower on OCI measure compared to HC, signifying cognitive impairment. Although it is possible that OCI-PCI differences are normative, we hypothesized that the HC's PCI would predict their own OCI and that CR's PCI would predict OCI, whereas BCS' PCI would not predict their own OCI.

Aim 2 and hypothesis. The purpose of Aim 2 was to identify the source of the discordance between OCI and PCI among BCS by examining whether MC, mood, and SoP indirectly affected the relationship between OCI and PCI (please see Figure 1). We hypothesized that MC and SoP would predict both PCI and OCI; whereas, mood only would predict PCI.

Aim 3 and hypothesis. To understand the BCS' narrative regarding the effects of chemotherapy on their overall cognition, memory, and concentration/attention by identifying prevalent themes related to BCS' PCI. We hypothesized that BCS' would report cognitive complaints associated with their cognitive functioning.

Methods

The present study's protocol along with subsequent modifications were reviewed and approved by the Institutional Review Board at the University of Kansas Medical Center.

Participants

Seventy BCS were identified and invited to participate in the present study. Medical oncology team (e.g., nurses) at KUMC identified BCS participants and collected contact information from those interested in participating in the present study. BCS participants were eligible to participate if they met the following criteria: 1) females aged between 20 to 60 years of age; 2) diagnosed with Stage I to IIIA breast cancer; 3) fluent in English, 4) completed chemotherapy for breast cancer within the last ten years; and 5) had a contact who could serve as a collateral reporter (CR).

A total of 16 BCS were ineligible due to the exclusion criteria (e.g., developed a concurrent cancer, did not have chemotherapy, were male, or over the age of 60), 16 BCS declined to participate, and 11 withdrew from the study before giving informed consent. BCS, who declined, reported that they did not want to participate in the present study. BCS who were deemed ineligible were over the age of 60 (75%), male (6.25%), had a concurrent cancer and/or chemotherapy (6.25%), or did not receive chemotherapy (12.5%; M=44.50; SD=7.78). BCS who withdrew reported scheduling conflicts due to either family events (81.8%) or travel (18.2%). There did not appear to be any significant differences between those participated in the study and those who either declined (M=49.75 years old; SD=8.04) or withdrew (M=49.70; SD= 6.93) with regards to age. Please see Figure 2.

BCS nominated their own CR. A CR was defined as an individual, who interacted with the BCS for at least five days a week for a significant part of the day (i.e., four hours). Exclusion criteria included the following: 1) previous history of a concurrent cancer and/ or chemotherapy;

2) a diagnosis of a neurological disorder (i.e., thought disorder or dementia) as identified by the severe mental illness, defined as diagnosable mental illness (e.g., mental, emotional, behavioral) from the DSM-5.

HCs were recruited through snowball sampling, so that BCS nominated her own control. For BCS participants who were unable to nominate their own control, HCs were recruited through the KU SONA system and through word of mouth. Twenty-seven HC were identified by BCS with 21 HC declining to participate. No information was collected from the HC who declined. A total of six of 27 HC were recruited via the snowball method (age M= 45.50, SD=10.77). A total of 15 were recruited via KU SONA (age M=20.93, SD=1.83) and 11 via word of mouth (age M=31.4SD=7.67). The inclusion and exclusion criteria for HC were the same as those for BCS, with the exception that HC were excluded if they had ever received cancer diagnosis or received adjuvant chemotherapy.

Measures

Demographic Questionnaire. Participants completed a demographic questionnaire that collected information about age, menopausal status, education level, and race. Data on breast cancer stage and survivorship years were also collected as part of the questionnaire.

SoP Measures. Following established procedures for measuring SoP (Ahles et al., 2008, 2010; Ganz et al., 2013; Jansen et al., 2011; Jung & Cimprich, 2014; Middleton, Denney, Lynch, & Parmenter, 2006; Von Ah et al., 2009), each individual's raw scores from a set of SoP assessment tools were transformed to z scores using the HC's group mean and standard deviation then averaged to create a SoP Composite Standard Score (SoP-CSS). The individual tests used to create this composite score were the Finger Tapping Test, Stroop Test, and Symbol Digit Modality Test and are described below.

Finger Tapping Test (FTT). Introduced in the Halstead-Reitan Neuropsychological

Test Battery, the Finger Tapping Test (FTT) was utilized to measure motor speed and control (Christianson, Leathem, 20014; Hubel, Reed, Yund, Herron, and Woods, 2013; Lezak et al., 2004; Reitan & Wolfson, 1993). Using the computerized version of the FTT, participants were asked to simply press the space bar repeatedly as fast as they could, using the index finger of their dominant hand for 45 seconds. The computerized FTT is reported to have a specificity rate of 90% and a sensitivity rate of 40% in diagnosing traumatic brain injuries when compared to health sample (Axelrod, Davis, & Myers, 2014). Overall, the computerized FTT has demonstrated to be an effective measure of motor speed in healthy community controls (Hubel et al., 2013) as well as those with cancer (Kurita et al., 2018).

Stroop test. The Stroop Test was used in the present study as a measure of SoP, as it relates to the ability to inhibit incorrect responses to a color-word interference task (i.e., naming the color the word is printed in). A computerized component of the Stroop test was administered in the present study. Respondents were asked to read the color/word out loud and press the space bar to proceed to the next item until 45 seconds have expired. As recommended by Scarpina and Tagini (2017), data were collected on both the accuracy of the oral response as well as the number of items completed (number of times the space bar is pressed) within 45 seconds. The Stroop test has been reported to have good test-retest reliability (0.83-0.91) and be an acceptable measure for processing speed (Morrow, 2013; Spreen & Strauss, 1998).

Symbol digit modality test (SDMT). SDMT is a common measure for processing speed among healthy community sample (Sheridan et al, 2006) and patients with multiple sclerosis (Benedict et al., 2017; Zarif et al., 2015). In the oral response format of SDMT, a legend of nine geometric shapes were paired with associated numbers and remained visible throughout the trial. Participants were then presented with a geometric shape and a blank box and tasked to name the paired number out loud for 90 seconds. The SDMT in the oral format has shown acceptable

construct validity (Benedict et al., 2017; Berrigan, Fisk, Walker, et al., 2014) and test-retest reliability (r=0.76) (Lezak et al., 2004). Additionally, the SDMT has been shown to be an adequate measure of SoP within the BCS population (Verancombe, Wright, Rolfe, & Pachana, 2009; Von, Harvison, Monahan, et al., 2009; Von & Tallman, 2015).

OCI-Working Memory Objective Cognitive Measure.

Digit Span (DS). The DS is a subtest from the *Wechsler Adult Intelligence Scale-IV* (WAIS-IV) designed to measure working memory (Wechsler, Coalson, Raiford, 2008). DS is composed of three tasks: DS Forward, DS Backward, and DS Sequencing. Participants were given a string of two to eight-digits and asked to either recall the digits in the order that they heard them (DS Forward), recall the digits in the reverse order of what they heard (DS Backward), or recall the digits in ascending order (DS Sequencing). A score was generated for each task then combined to a total score for the DS subtest, which was used in the present study. DS has shown evidence of reliability with an internal consistency, ranging from .89 to .94 across age groups (i.e., 16-90) and good test-retest reliability. In addition, DS has demonstrated acceptable validity with an intercorrelation score of .60 on the Working Memory Index of the WAIS-IV and moderately correlated (r=0.57) with the Working Memory Index on the Wechsler Memory Scale-IV (WMS-IV).

PCI-Patient-Reported Outcomes Measures Information System (PROMIS) Applied Cognition-Scale. The PROMIS Applied Cognition- Scale version 2, hereafter referred to the PROMIS, is a 32-item questionnaire that assesses subjective cognitive concerns as reported by the patient. The PROMIS evaluates participants perceived cognitive function related to memory, attention, language, and SoP within the last seven days by asking participants to rate from 1(Very Often) to 5 (Never) on questions, like "m*y reactions in everyday situations have been slow."* The PROMIS has shown acceptable validity and great internal consistency reliability (r=0.982)

and an item total correlation that ranges from 0.64 to 0.86 (Cella et al., Lai, Wagner, Jacobsen, Cella, 2014). Although not a disease specific measure, the PROMIS has been demonstrated to be applicable to the cancer population (Minisimi et al., 2008). In the present study, the PROMIS was used as a measure of perceived cognitive functioning among BCS, and also as collateral report for informants to rate BCS' perceived cognitive functioning. Having the PROMIS act as both a participant and informant report allowed the authors to compare reports across reporters

Profile of Mood States (POMS)-Abbreviated Version. POMS-AV is a 40-item questionnaire that evaluates for six dimensions of mood — anger-hostility, depression-dejection, tension-anxiety, vigor-activity, confusion-bewilderment, and fatigue-inertia. Respondents were given a list of 40 mood-based adjectives and instructed to rate how each adjective described their mood for the past week on a 5-point Likert scale from 0 (not at all) to 4 (extreme). The POMSAV provided a score for each index and a Total Mood Disturbance (TMD)score. The TMD score was calculated by combining the index scores for each negative subscale and subtracting the index scores from each positive subscale (Grove & Prapavessis, 2016). An additional 100 points were added to the total to avoid a negative TMD scores. The original long-form POMS has been documented to have excellent internal consistency, ranging from 0.62 (confusion) to 0.96 (depression), and acceptable concurrent and discriminant validity (Curran, Andrykowski, & Studts, 1995). The POMS-AV has comparable psychometric properties to the long-form POMS (Baker et al., 2002; Curran, Andrykowski, & Studts, 1995; Shacham, 1983). The POMS-AV along with the POMS-SF has been validated within the cancer population (Curran, Andrykowski, & Studts, 1995; DiLorenzo et al., 1999; Shacham, 1983).

Self-Administered Comorbidity Questionnaire (SACQ). The SACQ is an15 item-questionnaire that asked respondents to note the presence of a MC, its severity, and the impact of the MC on their functionality (Sangha et al., 2003). The SACQ results in a score that ranges from 0 to 45 points in total with each item worth three points. SACQ has been shown to have great test-retest reliability (0.94), which is comparable to the Charlson Index and other comorbidities measures, an evidence for predictive validity (Sangha et al., 2003; Stolwijk et al., 2014). The SACQ is an appropriate measure to use within the present study since it not only identifies the presence of a MC, but also the limitations that MC may place on the functionality of the respondent. The SACQ also allows for respondents to report MC in outpatient population without relying on abstracting information from medical records.

Qualitative questions. Qualitative questions were abstracted from Shillings & Jenkins's study (2007). BCS were asked to briefly to describe their overall cognition has been impacted. Afterwards, BCS were asked the following questions: "How has your memory been affected" and "How has your attention/concentration been affected." Follow-up question, "Has anyone commented on those particular area" was asked for each section. The final question, "Anything I have not asked you that you would like to let me know," was asked before the conclusion of the session. Interviews were recorded and transcribed verbatim.

Procedure

BCS participants were recruited through KUMC. Interested BCS participants and nominated HCs were contacted by a member of a research team, who explained the present study and answered study related questions, and then scheduled a mutually agreed upon meeting time

at a quiet and convenient location (e.g., private residences). Data were collected in the patients' homes in order to minimize transportation related barriers to participation. HCs collected via the KU Sona System were assessed on campus in a laboratory setting.

The data collection protocol began with BCS and HC participants completing a battery of questionnaires (i.e., POMS-SF, SACQ, and PROMIS) and a brief neuropsychological battery. BCS and their CR often completed the study protocol during the same visit. While BCS participants took the neuropsychological and psychological battery, BCS's CRs completed the PROMIS in a separate location (e.g., in either another room in the patient's home). Each of these assessment appointments took between approximately 30 to 40 minutes. After completing the required assessments, BCS participants and nominated HCs received a $20 gift card for participation.

Data Analysis Plan

Statistical analyses were conducted using the Statistical Package for Social Sciences25(SPSS-25) software packages.

Prior to testing group differences or assessing other relationships, we consulted a correlation table in order to identify variables that could act as confounds and thus should be included as covariates for hypothesis testing. Identifying potential covariates provided an opportunity to account for any variation from other variables of interest that may have obscured the relationship between PCI and OCI. The correlation tables are presented in Tables 2, 3, & 4, demonstrating no significant correlations between demographic variables, such as age and education, with the outcome variable, digit span. Because there were no identified confounds, Independent Sample t-tests were used to test group differences between OCI and PCI in Table 6; OLS regression equations were used to assess the relationship between OCI and PCI (AIM

1); and OLS regression equations were used to examine whether the SoP, MC, and mood predicted either OCI and PCI (Aim 2). OLS regression equations used to assess the relationship between OCI and PCI in BCS, HCs, and CRs are presented in Tables 7, 8, & 9. Additionally, the OLS regression equations used to examine the predictive value of SoP, MC, and mood are presented in Tables 10 and 11. Our third hypothesis focused on qualitative exploration of BCS' cognitive complaints, interviews were recorded and then transcribed verbatim. Additionally, the principal investigator and the research assistant examined each transcribed interview using a thematic analysis approach with deducting coding. This approach was utilized to assess latent content (i.e., more interpretive coding) of the major themes from the transcribed interviews.

Results

Participant Characteristics

Twenty-seven BCS between the ages of 29-60 (M= 48.56; SD=9.46) were enrolled in the present study. As shown in Table 5, the majority of the BCS were Caucasian (88.9%), non-Hispanic or Latinx (92.6%), and married (74.1%) with a college degree (29.6%). BCS had typically been diagnosed with Stage II (37.0%) breast cancer, had a mastectomy (70.4%), and were currently in menopause (66.7%). It is important to note that our BCS sample is an overwhelming homogenous (Caucasian) with limited diversity in race and ethnicity. Nationally, non-Hispanic Caucasian women have the highest incident rates of breast cancer (125.6 per 100,000 persons) followed by African American women (123.3 per 100,000 persons), Asian/Pacific Islander (94.3 per 100,000 persons), Caucasian Hispanic (93.6 per 100,000 persons), and American Indian/Alaska Native (71.2 per 100,000 persons) women having lower rates of breast cancer in the population (CDC, 2017). Given these rates of breast cancer among race/ethnicity in the United States, our BCS sample is not representative of the US national BCS population, which limits our ability to generalize findings.

Twenty-five CRs between the ages of 25-71 (M=46.32, SD=13.45) were included in the study. CRs were typically male (68%), Caucasian (88%), non-Hispanic or Latinx (96%), and married (68%) with a college degree (40%). BCS typical chose their (male) spouses (68%) as CRs although female adult children (16%), close female family friends (12%), and mothers (8%) were also chosen to act as a BCS's CR.

Thirty-two HC between the ages of 20-60 (M=29.13; SD=11.20) were enrolled in the present study. HC were also mostly Caucasian (65.6%), non-Hispanic or Latinx (90.6%), single (71.9%) and had some college (50.0%). Of note, the 50% of participants who endorsed "some college" were recruited through the KU SONA system. Please refer to Table 5 for further information regarding participants' characteristics. It should be noted that although the goal of this study was to create an age and SES matched sample using a snowballing-friend technique, the HC group was supplemented with college students, creating an HC group who were younger, with a lower educational attainment and household income than BCS patients. However, it should again be noted (i.e., Tables 2, 3, & 4) that neither age nor education correlated with the measure of OCI. Because the sample sizes in this study were small, we will contextualize results in terms of effect size, power, and when appropriate clinical significance.

Furthermore, a comparison between BCS and HC on age, mood, MC, SoP are reported in Table 6. BCS were older than HC, t (57) = 7.12, $p<.05$, reported more negative affect (M=105.92, SD=26.31), and medical comorbidities (M=4.48, SD=4.41) compared to HC's negative affect [(M= 91.25, SD=14.51), t (57) =2.694, $p<.05$], and medical comorbidities [(M=1.88, SD=2.81), t (57) = 2.65, $p<.05$]. With regards to SoP as measured by SoP-CSS, BCS demonstrated equivalent abilities on SoP (M=-.06, SD=.40) compared to HC's SoP [(M=.00, SD=.32), t (57) = -.640, p =.525].

Aim 1: Characterizing the Relationship between OCI and PCI in BCS

Aim 1a. Consistent with AIM 1a, we first used t-tests to determine whether there were differences between BCS and HC in OCI and PCI. The results of those tests can be found in Table 6 along with their accompanying effect sizes. Contrary to study hypotheses, the difference between BCS and HC in OCI as measured by the Digit Span Test was not significantly different. Consistent with study hypotheses BCS reported more cognitive complaints (M=105.52, SD=27.22) as measured by the PROMIS compared to HC [(M=130.91, SD= 18.08), *t* (56) =-4.28, p<.05].

It should be noted here that the sample size limited our ability to detect differences between groups. We had 9.2% power to detect a small effect, such as what we observed here for the Digit Span test (Cohen's d=-.16: 95% CI=-.63-.34), 46% power to detect a moderate effect size (Cohen's d=.50-.80), and 85% power to detect a large effect (Cohen's D=.8-1.0), similar to what we found for the PROMIS. A clinical meaningful difference in the literature has been reported as 1.5 standard deviation within the subtest, particularly when using comparison groups (von Ah et al). Clinically, although we were underpowered to see a small or medium effect, we were adequately powered to able to detect large effects, supporting the finding that there were no discernable differences in OCI, as measured by the Digit Span, between BCS and HC.

To assess whether PCI predicted OCI an OLS regression equation was used to examine the relationship between PCI and OCI in both BCS and HC groups. In the BCS group, results indicated that PCI did not account for any variance in OCI [R^2=.000, F (1,25) =.012, p =.913] (please see Table 7). Thus, BCS' PCI did not predict OCI. Similarly, an OLS equation was used to assess the relationship between PCI and OCI in the HC group. The outcome was similar to BCS patients in that PCI did not account for a significant amount of variance in OCI, [R^2=.111,

F (1, 30) =3.74, p =.062] in the HC group (see Table 8). Thus, PCI did not predict OCI for either the BCS or the HC group. Although our findings were consistent with the study hypothesis with regards to BCS, our findings about the relationship between HC's PCI and OCI were contradictory to our hypothesis. It should also be noted that our current sample size provided us with 12% power to detect a small effect size, 49% for a medium effect size, and 84% for a large effect size among BCS; whereas, 12% power to detect a small effect size, 56% for medium effect size, and 89% for a large effect size among HC, indicating that our present study was sufficient enough to detect a large effect.

Aim 1b. To assess whether CR'PCI predicted BCS' OCI, an OLS equation was used to assess the relationship between CR-PCI and BCS-OCI. The results indicated that the overall model did not account for a significant amount of variance [R^2=.022, F (1,23) =.527, p =.475] (see Table 6), demonstrating that there was no significant relationship between PCI-CR and OCIBCS, which was also contrary to the study hypothesis. Again, it should be noted that our current sample size provided us with 11% power to detect a small effect size, 49% for a medium effect size, and 84% for a large effect size among CR, indicating that our sample size was sufficient to detect a large effect.

Aim 2: Assessing Principal Predictors on the Relationship between OCI and PCI.

BCS: Using two OLS equations, we explored whether SoP, MC, and mood predicted PCI and OCI and thus could have an indirect effect on the relationship between PCI and OCI (Refer to Figure 1). The first OLS regression equation examined the relationship between PCI and the predictors— SoP, MC, and mood (see Table 10). This set of predictors accounted for 61% of the variance [R^2=.610, F (3,23) =12.01, p <.01]. However, only mood (β=-.700, p<.01) significantly predicted PCI. A second OLS regression model was used to determine whether OCI

was predicted by SoP, MC, and mood. The model as a whole, was not significant [R^2=.146, F (3, 23) =1.313, p =.294], nor did any of the principle variables predict OCI (see Table 11). Consistent with extant literature, mood predicted PCI, but contrary to the study hypothesis, SoP and MC did not predict either PCI or OCI.

HC: Parallel analyses examined whether SoP, MC, and mood predicted either PCI or OCI within the HC group. Examining the relationship between the principal predictor variables and PCI, the principal predictor variables were found to explain 55% of the variance in the model [R^2=.550, F (3, 28) =11.43, p <.01]. Both MC (β=-2.40, p<.05) and mood (β=-4.25, p<.01) significantly predicted PCI (see Table 10). OCI, results were similar to the BCS group. The OLS regression model as a whole was not significant [R^2=.061, F (3, 28) =.607, p =.616], nor were any of the individual predictors (see Table 11). Given the sample sizes, and with three predictors in the model, we had 7.8% power to detect a small effect, 31% a medium, and 65% a large effect.

Aim 3: Qualitative Analysis of BCS' Cognitive Experience

To understand the BCS' narrative regarding the effects of chemotherapy on their cognition, interviews were conducted with BCS to discuss their experience and impressions. Utilizing thematic analysis (Shilling & Jenkins, 2007), two coders read through transcribed interviews, discussed and established a coding criterion. Disagreements regarding coding were resolved after a discussion and the appropriate coding was applied. Major themes abstracted from the interview can be seen in Table 9. Consistent with the study hypothesis, majority of BCS reported cognitive complaints.

Current cognitive experience and memory. One major theme that was found was current cognitive experience. BCS either reported improvement in their overall cognitive status since treatment or endorsed a more negative view of their current cognitive status. BCS, who

endorsed a negative view of their cognitive status, reported that they were *"worse with things… everyday things*." Going further, they expressed "*frustration and embarrassment*" as well as "*anger*" with their current functioning and ability to function on everyday activities (e.g., grocery shopping, taking medication, and job duties). Moreover, when further examining current cognitive impairment, BCS endorsed memory concerns, identifying concerns with both long and short-term memory, as the main culprit. Often, BCS expressed their memory concern by recounting an experience of losing/misplacing items or forgetting important events. For instance, one BCS reported a recent experience where she lost her health journal, stating "*I am crying because I can't find it, and I am beating myself up because I can't remember*." Another BCS reported being unsure whether she took her medication at times and forgetting doing activities, requested by her spouse. With regards to family and friends commenting on such lapses in memory, BCS have pointed out spouses and children are common commenters. Interestingly, when BCS reported that a peer noticed their memory lapse, they typically described the peer as being patient and helpful. For example, peers will assist in providing the details that the BSC is missing versus family members, who may come off as criticizing. Current cognition and memory were common complaints among BCS during the interview.

Concentration/attention. Concentration/attention was also reported as a significant concern, emerging as a secondary theme. Although reported less frequently than memory complaints, BCS noted that their ability to "focus" as being affected by treatment. Common complaints were similar to the following statement: "*I have the hardest time like staying focused on that and that's my biggest problem*." It should be noted that when BCS noted a lack of concentration and attention, they rarely identified it as a problem that was commented on by family and friends. Indeed, the majority of the time BCS noted that only their partners noticed or commented on their lack of ability to concentrate.

Compensatory/coping strategies. A noteworthy theme that was found was the compensatory and coping strategies used by BCS to cope with their current cognitive impairment. BCS reported commonly suggested compensatory strategies, such as making lists, seeking out a quiet environment, and double-checking themselves. BCS noted quite a few effective coping strategies, like exercise, acceptance, and meditation. Commonly, BCS also stated that "*we [family] make a joke out of it*," indicating their use of humor being another effective coping strategy. One BCS even noted her desire to "*learn new things*" to increase her cognitive abilities. Conversely, other BCS noted that they lacked effective strategies, relying on themselves to "*push through*" or try to gain more "*control*" of their cognitive ability. When asked in a follow-up question about their other coping strategies, BCS, who lacked effected compensatory strategies, demonstrated an awareness of their skill-deficits and self-reported a lack of coping strategies. Indeed, when asked if they would like to share anything else, BCS would inquire about cognitive rehabilitation and other compensatory and coping strategies.

Contributing cognitive impairment to other sources. Interestingly, some BCS questioned whether their current experience of cognitive impairment was due to their treatment rather than another causal factor. Common causal factors expressed by BCS that contributed to their cognitive impairment were aging, another disease (i.e., Alzheimer or Dementia), or psychological factors, such anxiety and post-traumatic stress disorder (PTSD). A majority of BCS thought age was a likely culprit, making comments, like "*I don't know if it is my normal age or [treatment].*" Others noted current relatives, who were diagnosed with Alzheimer and Dementia, and expressed concern that deficits in their currently cognitive ability, particularly their memory, were due to these disease processes beginning earlier. Such concerns were followed by a desire to seek out further neurological and neuropsychological testing. On the

other hand, one BCS expressed her belief that PTSD was the culprit to her inability to concentrate and focus, stating "*Yeah, I think that I a lot of stuff had to come from PTSD effects of cancer and the anxiety effects.*" She noted that her ability to cope with her psychological symptoms assisted her concentration. Acknowledging the existence of other causal factors with regards to their cognitive functioning appeared to provide both relief and anxiety as BCS attempted to explain their current experience.

Discussion

BCS are the largest female cancer survivorship group and thus are a population of interest for understanding, evaluating, and addressing late effects of treatment and the consequent survivorship concerns. Despite lacking evidence of OCI, BCS often report significant distress related to cognitive impairment induced by adjuvant chemotherapy. Such distress contributes to reduced quality of life as BCS struggle to understand their cognitive experience. Additionally, such distress is difficult to manage and presents a serious challenge to physicians, who typically disregard and invalidate BCS' experience, which in turn negatively affects the provider-patient relationship. Thus, the purpose of the present study was to explore the relationship between OCI and PCI, including a HC comparison group, CR, and also examining whether MC, mood, and SoP explained the discrepancy between OCI and PCI. Although PCI were elevated over that of HC, the results reported here suggest that there was little difference between BCS and HCs on any dimension of cognitive function, including discordance in the OCI-PCI relationship, but that for BCS mood played key role in perceptions of cognitive functioning.

The discordant relationship between OCI-PCI has negative clinical implications, particularly for the patient and provider relationship. The OCI-PCI discordancy has been interpreted as the result of cognitive priming, or reflecting cognitive distortion (Collins, Paquet,

Dominelli, White, & MacKenzie, 2017; Mehnert et al., 2007; Hermelink et al., 2010; Schagen, Das, & Vermeulen, 2012; Schagen, Das, & van Dam, 2009). Given the overall findings of the present study, two of these potential explanations are viable. In the present study, BCS overestimated their cognitive dysfunction. Additionally, our finding that mood playing a key role supports the explanation of cognitive distortion with BCS engaging in emotional reasoning (i.e., how we feel about situation affects how we interpret a situation) when assessing their cognitive experience. These quantitative findings are supported by our qualitative data that showed that 61% of BCS indicated that their cancer experience negatively impacted their perception of their current cognitive experience. However, it is important to note that a subset of BCS identified alternative explanations for their cognitive problems. This subset of BCS said that their cognitive functioning had not been negatively impacted by their cancer experience; yet, they too overestimate their cognitive dysfunction. This qualitative finding along with data showing that HC demonstrate a similar OCI-PCI discordancy that is also mood related, suggests that overestimating cognitive dysfunction is normal and that mood has a robust effect on perception across patient and demographic groups.

The first aim of the study was to characterize the relationship between OCI and PCI in BCS. HC were used in the present study to provide a specific-norm comparison group that allowed us to gain a more accurate picture of OCI in BCS as well as provide an objective reference point for the OCI-PCI discordancy. We hypothesized that HC's PCI would predict their OCI, whereas BCS' PCI would not predict their OCI, as measured by a verbal working memory task. As hypothesized, BCS' PCI did not predict their OCI, providing further support for the discordant relationship between OCI and PCI. Interestingly, HC's PCI did not predict OCI. Given that PCI did not predict OCI among either group, our findings suggested that OCIPCI discordancy is not unique to BCS. Rather than discordance reflecting a phenomena that

is unique to the BCS, it appears normative for subjective cognitive complaints not to map onto objective cognitive measures.

We also wanted to examine whether CR's PCI was predictive BCS' OCI. To our knowledge, the present study is the first to introduce the use of CR to gain an objective perspective on BCS' OCI. CRs were included as a part of this study as another way to capture a report that was both objective and ecologically valid without using objective cognitive measures. Similarly, to HC and BCS, CR's perceptions of their target's cognitive functioning (PCI) did not predict OCI, although BCS' PCI and CR's PCI were significantly correlated (r= .648, p <.01). Given the amount of shared variance between BCS and CRs, it seems likely that our CRs perceptions were influenced by BCS's perceptions of their own OCI. Another possibility is that the CR may be a witness to day-to-day cognitive impairment that is not captured by our current measure (please see limitations). Given the discordance between PCI and OCI in both BCS and HCs as well as the concordance between BCS and their CR, our finding suggests that PCI and OCI may be different constructs rather than capturing a true discordant relationship between OCI and PCI.

The second aim of the study was to examine whether SoP, mood, and MC indirectly impacted the relationship between OCI and PCI. We predicted that MC and SoP would predict both PCI and OCI; whereas, mood would only predict PCI in BCS. SoP is a ubiquitous cognitive function, underlying multiple neurocognitive domains (i.e., memory), and has been shown to be affected in BCS treated with adjuvant chemotherapy. We also posited that if BCS were experiencing reduced SoP, it might be mistaken for problems with memory and attention, leading to inflated levels of PCI. Mood and medical comorbidities (MC) may also impact the

relationship between OCI and PCI. As seen in the literature, mood has been shown to be correlated with PCI (Ahles et al., 2008; Bender et al., 2008; Collins et al., 2017; Ganz et al., 2013; Hermelink et al., 2010). MC also has also been shown to correlate with both OCI and PCI (Freedman et al., 2013; Klepin et al., 2014; Mandelblatt et al., 2014). Therefore, we hypothesized that mood would only predict PCI; and MC and SoP would predict both OCI and PCI. Although mood was predictive of PCI in BCS as hypothesized, MC and SoP did not predict BCS' PCI or OCI.

The findings regarding MC and SoP should be added to a small and sometimes contradictory literature base. Although a few studies have found MC to have a predictive relationship with OCI and PCI among BCS, these studies examined an older BCS population (i.e., an average of 68 years old), who endorsed on average about 2.4 MCs before chemotherapy (Mandelblatt et al., 2014) or endorsed either the presence of diabetes (37%) or high blood pressure (11%) (Schilder et al., 2010). In the present study, BCS reported an average number of MC = 4.4, with 14% endorsing diabetes and 22%, high blood pressure. The present study assessed a broader range of MC rather than summing the amount of times a MC was present and also examined a younger BCS sample. Incorporating these data into the broader literature, the effects of MC may be restricted to older BCS, who are experiencing more functional limiting MC.

SoP has been identified in literature as being objectively impaired among BCS treated with chemotherapy (Collins et al., 2013; Mihuta et al, 2016; Poppeulter &, 2009; Tannock et al., 2004). Researchers also have found that SoP was significantly correlated with PCI—using the Functional Assessment of Cancer Therapy- Cognition version 3, Patient's Assessment of Own Functioning Inventory, and Multiple Ability Self-Report Questionnaire measures— among BCS (Ahles et al., 2010; Ganz et al., 2013; Mihuta et al, 2016). Unfortunately, our findings did not

align with these studies or the present study hypothesis. A potential explanation for our contradictory finding is that the SoP measures used in the present study did not map onto the current OCI and PCI constructs as measured by the DS and PROMIS measures.

Although SoP and MC did not predict PCI or OCI, mood was predictive of PCI in BCS and HC, although the effect size was larger in the BCS. Consistent with a wealth of literature, mood has been shown to tap into the PCI domain (Collins et al., 2017; Hermelink et al., 2010; Lange et al, 2014; O'Farrell et al., 2016; Oh, 2017; Paquet et al., 2017). Although negative affect has been shown to bias attention toward negative stimuli (Clasen, Wells, Ellis, & Beevers, 2013), there may be another simpler explanation, mood, particularly negative affect, may be related to BCS experience of their cognition. Meaning, BCS, who reported cognitive complaints, might be experiencing a negative affect related to their cognitive concerns. The present study provides further support for the relationship between mood and PCI.

Noteworthy, a parallel analysis examining the impact of SoP, mood, and MC on PCI and OCI in the HC group, mood and MC were predictive of PCI; whereas, neither SoP, mood, and MC were predictive of OCI. Such findings support that cognitive complaints may be paired with emotional well-being and that our SoP measures may not be sensitive enough to tap into other cognitive domains. Despite not predicting PCI within BCS, MC may still influence PCI, considering the relationship between MC and PCI in HC. The reason for this relationship is unclear and warrants further study.

The third aim of the present study was to understand the BCS' narrative regarding the effects of chemotherapy on their overall cognition, memory, and concentration/attention. The genesis of this project was clinical observations, supported by empirical literature, that BCS were troubled by problems with attention and memory and were also bothered that those complaints

were not taken seriously that providers typically disregard or did not adequately address BCS' cognitive complaints. Consequently, we predicted that BCS would report complaints associated with their cognitive functioning. A majority of BCS, indeed, reported cognitive complaints and significant distress regarding their current cognitive experience. BCS reported memory complaints noting concerns with word finding and memory. Although their cognitive complaints aligned with the current literature, our current findings do not support any evidence of objectively impaired working memory. Noteworthy, BCS did not typically express any concern about any co-occurring illnesses, which may explain why we saw a lack of a relationship between MC and OCI and PCI in our findings. Indeed, BCS may not be experiencing functional limiting MC in conjunction with their cancer experience that warrants significant concern.

Furthermore, BCS noted that family and friends were more likely to comment on memory concerns than attention and concentration, which was consistent with an earlier study (Shillings & Jenkins, 2007). Interestingly, BCS typically used multiple effective compensatory/coping strategies (i.e., writing things down and humor) to manage their cognitive complaints. However, a few BCS endorsed an absence of effective strategies (i.e., not having any coping/compensatory strategies at all). Another interesting finding was that BCS were unsure about the cause of their cognitive complaints. Although a majority BCS reported chemotherapy as being the main culprit, some BCS expressed concerns that their cognitive impairment was due to other co-occurring disease processes (i.e., Dementia, Alzheimer) or to the natural aging trajectory.

Integrating the qualitative data with the quantitative data, it appears that many BCS experience heightened awareness of normative memory lapses, with their cancer status coloring their perceptions and casting subtle cognitive changes in a more sinister and frightening light. For instance, 61% of BCS reported cognitive impairment, contextualizing their current cognitive

concerns through cancer experience. Such reports were typically accompanied by fear and confusion regarding the impact of cancer on their cognitive experience and re-occurrence of cancer. Conversely, 39% of BCS identified alternative hypotheses, such as aging or another disease process, and appeared to be less agitated and fearful when describing their cognitive experience. These BCS provided a stark comparison to BCS whose cancer experience appeared more salient, bleeding into their understanding of their cognitive experience and influencing their emotional lives.

Clinical Implications

Based on the results from the qualitative analysis, BCS experience of PCI is real and negatively affected day-to- day functioning, resulting in the endorsement of significant ongoing distress. The present study's results suggest that no relationship exists between PCI and OCI in both BCS and HC along with evidence of increased negative affect among BCS. Given our findings, the present study provides clear clinical implications for both BCS and healthcare professionals.

BCS should be provided psychoeducation that focuses on the potential cognitive experience after chemotherapy and the effects of aging on cognition. Specifically, BCS should be provided the tools to distinguish chemotherapy related cognitive changes from the typical age-related cognitive trajectory with regards to such cognitive functions, like memory, attention, and SoP. Such information would provide context to the BCS' experience and provide reassurance to those BCS who express heighten sensitivity regarding their current cognitive status. BCS along with physicians and nurses should also be informed that poor correspondence between OCI and PCI are normative and do not reflect a distortion in thinking. Indeed, the lack of the relationship between OCI and PCI should be emphasized with PCI being noted as equally important to be addressed for beneficial health outcomes. Such knowledge should help alleviate

some concerns and distress while providing validating information regarding their experience. As such, healthcare providers should be proactive in delivering accurate and accessible information as a preventative measure.

Addressing BCS' cognitive complaints can be difficult, especially given the present study's lack of a relationship between PCI and OCI. Healthcare providers should not invalidate or disregard BCS' complaints as mood-related concerns or evidence of priming just because PCI is not related to OCI. Rather, healthcare providers should focus on educating themselves about the discordant OCI-PCI relationship and ways to address and manage such cognitive complaints within a limited time setting. Providing a supportive environment (i.e., validating BCS' experience, giving appropriate information) is the first step in addressing and managing BCS' cognitive complaints. Secondly, healthcare providers can de-mystify BCS' cancer experience with regards to their cognition early and continue to do so as they progress further out from treatment. Healthcare providers also should share results from OCI measures when used to provide reassurance of non-cognitive impairment along with further validation, reassurance that BCS' are not "crazy" by normalizing their experience. Throughout each of these steps, healthcare providers should provide further information regarding the discordant OCI and PCI relationship, reinforcing BCS' understanding that such a poor correspondence between these two cognitive subdomains is normal and happens to everyone. For BCS who continuously endorse PCI and are negatively impacted by their cancer experience, healthcare professionals can assist by providing resources, such as effective active coping strategies (i.e., making notes/lists, using organizational tools like calendars, Pomodoro technique, exercise, and meditation) or cognitive rehabilitation. Resources again validate BCS' experiences and provide opportunities to engage

in cognitive exercises and in more positive experiences to alleviate BCS' distress and helplessness, thus, improving their overall quality of life.

Limitations

There are a number of critical limitations within the present study. One significant limitation is the small sample size. The present study included 27 BCS, 25 CR, and 32 HC. Although the sample size was equivalent to previous studies (Ando-Tanabe et al., 2014; Klemp et al., 2017; Mehnert et al., 2007; Mihuta et al 2016), our sample size limited the power to detect medium and small effects. As such, conclusions derived regarding the predictive ability of our variables were limited. Additionally, our BCS sample was not a truly representative of the breast cancer survivor population in the US, given the oversampling of Caucasian and highly educated patients. Such a homogeneous sample compounds the difficultly for generalizable conclusions from the present study. Thus, future studies should incorporate larger and diverse sample sizes to detect smaller effects and to provide more generalizable results. The present study also was unable to provide an age-matched HC comparison group, which potentially affected our results, even though age was not correlated with either the outcome or predictor variables. Of note, BCS, on average, did not look objectively different on cognitive measures despite using a younger and potential more cognitively healthier HC comparison group. With a figuratively high cognitive bar set, BCS rose to the occasion and provided further support to the supposition that their cognitive experience is a normative experience.

A more significant concern is that OCI measure lacked ecological validity. The OCI tasks required the engagement of effortful memory processes in order to encode and recall a list of digits in a controlled, quiet environment, without distractions. Digit span tasks assess a single function of memory, working memory and thus the Digit Span task, may not be an effective analogue for memory problems that emerge as part of everyday activities. For instance, BCS

(and adults in general) are expected to manage and multi-task responsibilities (i.e., grocery shopping, occupational obligations, or childcare). Memory problems in daily life ("where are my car keys?") are not dependent on working memory. Memory tasks that tap other memory processes, like incidental memory (i.e., memory of information that was not effortfully encoded) may provide more ecologically valid results since it would be a closer analogue for everyday memory problems experienced by BCS.

Likewise, the PROMIS may not be a sensitive measure to map unto OCI measures despite being developed for the cancer population. The PROMIS is a self-report questionnaire that includes multiple cognitive functions. Additionally, the PROMIS does not offer subscales to partition out these cognitive functions. Consequently, the PROMIS may not map on to OCI measures due to the variety cognitive functions that underlie differing neurocognitive domain, like language, learning and memory, and executive function. In turn, the variety of cognitive functions and neurocognitive domain may drown out the potential relationship between PCI and OCI as measured by DS, a verbal working memory task.

The qualitative section provided a more well-round view of BCS understanding of their cognitive impairment. Given the utility of this qualitative data, it would have been useful to have collected qualitative data from HCs and CRs. Gaining HC's views of their cognitive experience would have allowed for a richer understanding of the relationship between PCI and OCI as well as provide another point of comparison to BCS' experience, especially with the HC being younger and potentially cognitively healthier. Additionally, gaining CR's view could have provided information regarding the objectivity of their observation of BCS' cognition (i.e., do they describe events where they witnessed cognitive concerns versus repeating complaints as told to them by BCS), allowing us to provide more context around CR's ratings of BCS' PCI.

Finally, the present study failed to take in account the time post chemotherapy for BCS and the use of prescribed medications to address medical comorbidities. Time post chemotherapy is an important factor to consider given that the presence of OCI is more readily seen in BCS who recently completed chemotherapy versus those who been out of treatment longer (Hutchinson et al., 2012; Janelsins et al., 2017; Jim et al., 2009). The majority of BCS see cognitive improvement after six months; and those who do not typically are characterized as experiencing late effect of treatment and chronic cognitive impairment. Although BCS in the present study had to be six months post-chemotherapy, knowing the exact time post chemotherapy could have provided context for our findings, allowing us to examine whether time post chemotherapy influenced BCS' PCI and OCI. Having time post chemotherapy for each BCS also could have facilitated our understanding of BCS' PCI with regards to some BCS expressing concerns that another source (i.e., disease process or healthy aging) was responsible for their experience of cognitive impairment. Furthermore, BCS, who experience medical comorbidities, are often prescribed medication to treat their underlying condition. Evidence exists that such medication negatively impacts cognition, especially in the elderly (Campbell et al., 2009; Marvanova, 2016). Unfortunately, the present study only accounts for medical comorbidities and does not collect information regarding the potential effects of medications utilized to treat underlying medical conditions on overall cognition.

Conclusion

Identifying screening tools and assessments that could be used as preventative measures to detect and monitor overall cognitive impairment is of the utmost importance, especially considering that cognitive impairment is a distressing late effect of treatment for BCS. Ongoing investigation into PCI is also warranted and should not be dismissed or disregarded given the cognitive complaints and subsequent associated distress being reported and

negatively affecting and shaping BCS' day-to-day existence. Therefore, future studies should continue examining the relationship between OCI and PCI to further understand these two constructs in an effort to create and provide screening tools that can assist healthcare professionals in detecting, monitoring, and addressing both cognitive impairment and subsequent distress associated with the experience of cognitive impairment.

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Figures

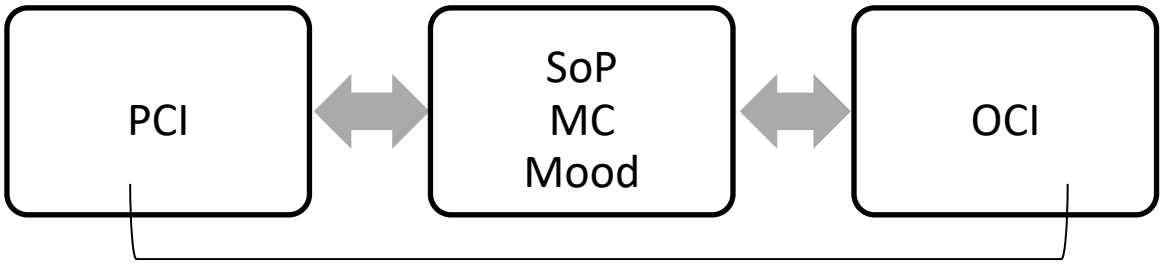

Figure 1 Relationship between PCI and OCI

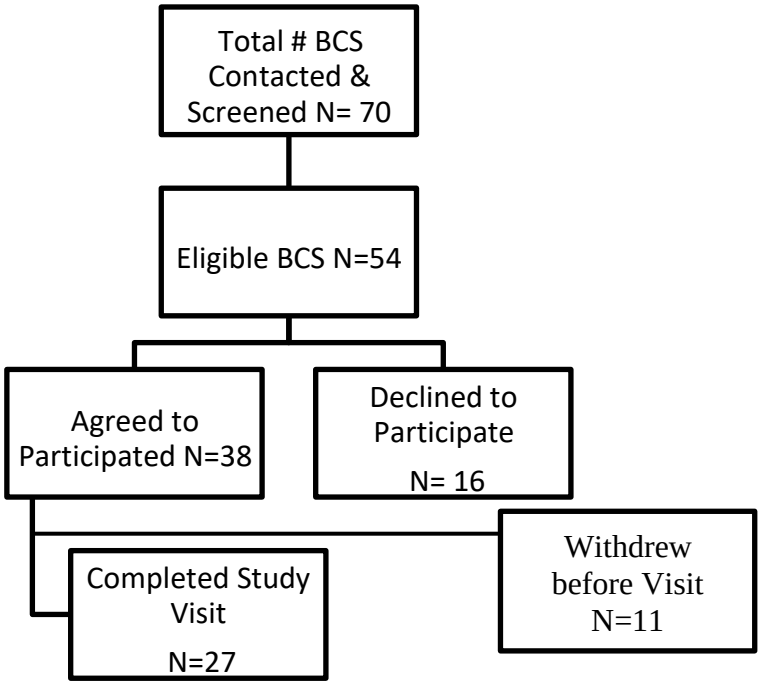

Figure 2. ChemoBrain Recruitment Flow Chart

Tables

Table 1

OCI and PCI Associated Neurocognitive Domains

Study Reference	**Mehnert, et al. (2007)**	**Bender et al. (2008)**	**Jim et al. (2009)**
Number of Subjects (Mean Age)	23 Standard-dose Chemotherapy group (M=51.8); 24 High-dose Chemotherapy group (M=53.3); 29 HC (M=54.6)	31 BCS (M=52.68)	187 BCS (M=50)
PCI and OCI relationship (PCI Measure)	Relationship b/w OCI and PCI on Verbal Working Memory and Visuospatial Working Memory among Standard-dose Chemotherapy Group (EORTC Quality of Life Questionnaire)	Relationship between OCI and PCI: Increase report of PCI related to poorer OCI related to verbal learning and memory (Patient's Assessment of Own Functioning-22)	No relationship between OCI/PCI(Mental Abilities Questionnaire-25
Attention	Trails Making Test A/B; Test Battery for Attentional Performance;		
Executive Function	Regensburg Word Fluency; Achievement Measure System; Achievement Measure System; WAIS-R	Trail Making Test-B; National Adult Reading Test-Revised; Rey Osterrieth Complex Figure Copy	National Adult Reading Test; Digit Symbol; Trail Making B; Controlled Oral Word Association Test;
Perceptual-Motor	N/A	Grooved Pegboard Test; Digit Substitution Test	
Language Measures	N/A		
Learning & Memory Measures	WMS-R; Auditory Verbal Learning Test; Rey-Osterrieth Complex Figure Test;	Rey Auditory Verbal Learning Test; Rey Osterrieth Complex Figure Recall; Rivermead Behavioral Memory Test Story Recall; Four-Word Short-Term	California Verbal Learning Test-2; WMS-III
Conclusion	Compared BCS across Standard Chemotherapy-dose group against High-dose and HC.	Verbal Learning and Memory; Mental Flexibility;	Episodic Memory

Study Reference	**Weis, Poppelreuter, & Bartsch HH. (2009)**	**Von Ah, et al.(2009)**	**Ahles, et al. (2010)**	**Debess, et al (2010)**
Number of Subjects (Mean Age)	90 BCS (M=49.7)	52 BCS (M=58.2); 52 HC (M=59.0)	60 BCS Chemotherapy (M= 51.7); 72 BCS No Chemotherapy (M=56.6); 45 HC (M=52.9)	75% patients received CFE chemo; 21%- in tamoxifen grp; 13% no medical tx (120 BC patients and 208 controls)
PCI and OCI relationship (PCI Measure)	Relationship between OCI and PCI: Increased reports of PCI related to poor performance on TAP: Alertness (Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire C30)	Squire Self-Report Scale (Squire Self-Report Scale)	No significant relationship observed (Multiple Ability Self-Report Questionnaire)	Squire Self-Report Scale (Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire)
Attention				
Executive Function		Controlled Oral Word Associations	D-KEFS;	ISPOCD: Stroop Colour Word Interference Test
Perceptual-Motor	Test Battery for Assessment of Attention	Symbol Digit Modalities Test	Digit-Symbol Coding; Trail Making Test; Color- Word Interference Test; Grooved	ISPOCD: Letter-Digit Coding
Language Measures			Vocabulary (WASI); Verbal Fluency Test(D-KEFS)	
Learning & Memory Measures	Rivermead Behavioral Memory; WMS-R;Lern- und Gedächtnistest -3	Rey Auditory Verbal Learning; WAIS-III	California Verbal Learning Test-II; WMS-III; Paced Auditory Serial Addition Test	Revised neuropsychological test battery from International Study of Postoperative Cognitive Dysfunction (ISPOCD): Visual Verbal Learning Test
Conclusion	Verbal Semantic Memory; Sustained Attention; Speed	Verbal Learning; Executive	Processing Speed and Verbal Ability	No Cognitive Impairment

Study Reference	**Hermelink, et al. (2010)**	**Jansen, et al. (2010)**	**Tager et al. (2010)**	**Biglia, et al. (2012)**
Number of Subjects (Mean Age)	48 BCS w/Standard Chemo (M=49.9) and 53 BCS w/Intensified Chemo (M=47.1)	71 BCS (M=50.3)	30 BCS w/Chemo (M=61.1); 31 BCS No Chemo (M=61.1);	40 BCS(M=51)
PCI and OCI relationship (PCI Measure)	No relationship b/w PCI or OCI found. (Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire C30)	No relationship between PCI and OCI observed (Attentional Function Index)	No relationship between PCI and OCI observed (5-point Likert Scale on Perceived Memory Abilities)	No relationship between PCI and OCI observed (Functional Assessment of Cancer Therapy-Cognition-2)
Attention		RBANS	Trail Making Test	
Executive Function	Trail Making Test B MWT-B	Stroop Test; RBANS	Trail Making Test; WAIS-III Digit Span; WAIS-III Number/Letter; WAIS-III Arithmetic; Rey Complex Figure Test Copy;	Brief Intelligence Test; Mini Mental Status Exam; Trail Making Test ;Raven's Progressive Matrices.
Perceptual-Motor	Trail Making Test A	Grooved Pegboard	WAIS-III Digit Symbol; Trail Making Test;Grooved Pegboard; Finger Tapper	Trail Making Test
Language Measures	Regensburg Word Fluency Test: letter fluency; category fluency; letter fluency with Switch;	RBANS	Controlled Oral Word Association Test; Boston Naming	Phonemic Word Fluency
Learning & Memory Measures	Logical Memory I & II	Repeatable Battery of Adult Neuropsychological Status(RBANS)	WAIS-III Digit Span; WAIS-III Number/Letter; Buscke Selective Reminding Test; Benton Visual Retention Test	Digit Span Forward; Rey Auditory Verbal Learning Test-Immediate Recall; Rey Auditory Verbal Learning Test-Delayed Recall; Short Story-Immediate recall; Short Story-delayed
Conclusion	None Reported	Published Normative Data	Cognitive Domain-Specific Score created	Global cognitive functioning and Visual Selective Attention

Study Reference	**Ganz, et al. (2013)**	**Askren, et al. (2014)**	**Berman, et al. (2014)**	**Lange, et al. (2014)**	**Von Ah & Tallman, 2015**
Number of Subjects (Mean Age)	189 (M=51.8) BCS	28 BCS chemo (M=50) and 37 non-chemo (M=53); 32 HC(M=50)	25 BCS Pre-chemotherapy (M=48.76) 25 BCS Pre-Radiation (52.96)	123 BCS (M= 70.4)	88 BCS(M=56.7)
PCI and OCI relationship (PCI Measure)	Increase Report PCI on memory had lower verbal memory performance vs normal grp; BCS with higher-level cognition complaints demonstrated worse performance on psychomotor speed and executive functioning	No relationship between PCI and OCI observed (Attentional Function Index)	Did not compare OCI and PCI (Attentional Function Index)	Relationship b/w Verbal episodic memory and higher reports of PCI (Functional Assessment of Cancer Therapy-Cognition-3)	Relationship b/w OCI and PCI: Higher scores on Immediate & Delayed Verbal Memory and Executive Function related to increase reports of PCI (Functional Assessment of Cancer Therapy-Cognition-3)
Attention					
Executive Function	Wechsler Test of Adult Reading; Stroop; Trails Making Test; Halstead-Reitan	FMRI	fMRI acquisition parameter	Trails Making Test B	Controlled Oral Word Associations
Perceptual-Motor	Grooved Pegboard			Trails Making Test A	Symbol Digit Modalities Test
Language Measures				Verbal Fluency: Category (animal) and Letter P	
Learning & Memory Measures	California Verbal Learning Test; WMS-3; Brief Visuospatial Memory Test- Revised; Rey-Ostettieth Complex Figure lWAIS-3;	Verbal Working Memory Tasks	Verbal Working Memory Task	Grober and Buschke Procedure; Rey Complex Figure; WAIS-III: Arithmetic, Digit Span, & Letter-Number Sequencing	Rey Auditory Verbal Learning Test; Rivermead Behavioral Memory Test
Conclusion	Verbal Memory	Spatial variance in executive network activation	Verbal Working Memory	Overall Cognitive Impairment: Visual Episodic Memory and Executive Functions	Memory

Study Reference	**Mihuta, Green, Man, & Shum (2016)**	**O' Farrel, Smith, & Collins (2016)**	**Andryszak, et al. (2017)**
Number of Subjects (Mean Age)	26 BCS (M=53.0); 25 HC (M=50.4)	60 BCS (M=52.35); 60 HC (M=51.97)	31 BCS (M=52.4); 30 HC (M=51.8)
PCI and OCI relationship (PCI Measure)	Relationship b/w OCI and PCI: Increased VR-time based activity showed a decreased in reported PCI; Faster Trails A scores related to less reports in PCI (Functional Assessment of Cancer Therapy-Cognition-2)	No relationship between OCI and PCI observed (Functional Assessment of Cancer Therapy-Cognition)	No Comparison Made
Attention			
Executive Function	Trail Making Test Part B.		
Perceptual-Motor	Trail Making Test Part A	Digit Symbol Coding; Symbol Search-WAIS_III; Trail A/B;CNS-VS processing speed index; CNS-VS reaction time index	
Language Measures	Controlled Oral Word Association Test		
Learning & Memory Measures	Virtual Reality shopping; Event-based Prospective Memory Quiz; Activity-based Prospective Memory; Hopkins Verbal Learning Test-Revised)	Digit Span, Letter-Number Sequencing; Paced Auditory Serial Addition Task; Auditory Consonant Trigrams Test; Controlled Oral Word Association Test; CNS-VS Flexibility Index; CNS-VS Working Memory; Hopkins Verbal	Rey Auditory Verbal Learning Test
Conclusion	Processing Speed and Verbal Memory	Not Indicated	Verbal Memory

Study Reference	**Collins, et al. (2017)**
Number of Subjects (Mean Age)	54 BCS (M=52.78); 54 HC (M=52.30).
PCI and OCI relationship (PCI Measure)	No relationship b/w OCI and PCI observed (Functional Assessment of Cancer Therapy-Cognitive Function scale-3)
Attention	
Executive Function	
Perceptual-Motor	
Language Measures	
Learning & Memory Measures	CNS- Vital Signs assessment; *Metamemory*
Conclusion	Memory Recall ; Working Memory

Table 2

Correlation between Demographic Variables and Outcome and Predictor Variables in Breast Cancer Survivors

Variables	1	2	3	4	5	6	7	8	9	10
1.Age	1	.073	.169	.101	-.085	.075	.343	.054	.008	-.033
2.Education	.	1	.421*	.111	.296	.313	.010	.047	-.099	-.243
3.Income	.	.	1	.049	-.152	-.135	-.331	-.030	.117	-.170
4. Breast Cancer Stage	.	.	.	1	-.123	-.062	-.026	-.096	.208	-.248*
5.Menopause	.	.	.	.	1	.310	-.164	.127	-.205	-.087
6.Digit Span [a]	.	.	.	.	.	1	-.112	-.022	.056	-.302
7.SoP-CSS[b]	.	.	.	.	.	.	1	.060	-.303	.108
8. PROMIS [c]	.	.	.	.	.	.	.	1	-.732**	-.431*
9.Mood [d]	.	.	.	.	.	.	.	.	1	.224
10. Medical Comorbidity [e]	.	.	.	.	.	.	.	.	.	1

*p <.05; **p < .01; [a] Digit Span measures OCI: Objective Cognitive Impairment; [b] SoP-CSS= SoP Composite Standard Score; [c] PROMIS measures PCI: Perceived Cognitive Impairment; [d] Mood is measured by POMS-TMD: Profile of Mood States Total Mood Disturbance; [e] Medical Comorbidity is measured by Self-Administered Comorbidity Questionnaire**.**

Table 3

Correlation between Demographic Variables and Outcome and Predictor Variables in Healthy Controls

Variables	1	2	3	4	5	6	7	8	9
1.Age	1	.674**	.168	.311	-.115	-.348	.074	-.280	.183
2.Education	.	1	-.034	.232	.303	-.142	.304	-.208	.171
3.Income	.	.	1	.207	-.244	-.256	-.198	-.027	.291
4.Menopause Status	.	.	.	1	-.277	-.286	-.143	-.266	.239
5.Digit Span [a]	.	.	.	.	1	.219	.333	-.038	-.156
6.SoP-CSS [b]	.	.	.	.	.	1	.361*	-.152	-.200
7.PROMIS [c]	.	.	.	.	.	.	1	-.621**	-.427*
8.Mood [d]	.	.	.	.	.	.	.	1	-.191
9.Medical Comorbidity [e]		.	.	.	.	.	.		1

*p <.05; **p < .01; [a] Digit Span measures OCI: Objective Cognitive Impairment; [b] SoP-CSS= SoP Composite Standard Score; [c] PROMIS measures PCI: Perceived Cognitive Impairment; [d]Mood is measured by POMS-TMD: Profile of Mood States Total Mood Disturbance; [e] Medical Comorbidity is measured by Self-Administered Comorbidity Questionnaire**.**

Table 4

Correlation between Demographic Variables and Outcome and Predictor Variables in Collateral Reporters

Variables	1	2	3	4
1.Age	1	.-.020	.213	-.342
2.Education	.	1	.332	-.040
3.Income	.	.	1	-.093
4.PROMIS-CR[a]	.	.	.	1

*p <.05; **p < .01; [a] PROMIS- CR measures PCI: Perceived Cognitive Impairment among Collateral Reporters**.**

Table 5

Participant Characteristics

	Breast Cancer Survivors (n=27)		**Collateral Reporters (n=25)**		**Healthy Controls (n=32)**	
	n %	M (SD)	%	M (SD)	%	M (SD)
Age, Current		48.56(9.46)		46.32 (13.45)		29.13 (11.20)
Gender						
Male			17 (68%)			
Female	27 (100%)		8 (32%)		32 (100%)	
Race						
Caucasian	24 (88.9%)		22 (88%)		21(65.6%)	
African American	2 (7.4%)		3 (12%)		5 (15.6%)	
Asian/ Pacific Islander	1 (3.7%)				3 (9.4%)	
Native American or American Indian	1 (3.7%)					
Hispanic/Latinx	2 (7.4%)		1 (4%)		3 (9.4%)	
Biracial					1 (3.1%)	
Annual Household Income						
<10,000-10,000	1 (3.7%)				5 (15.6%)	
10,000-29,000	1 (3.7%)		3 (12%)		11(34.4%)	
30,000-49,000	3 (11.1%)		2 (8%)		4 (12.5%)	
50,000-69,000	2 (7.4%)		3 (12%)		3 (9.4%)	
70,000-99,000	4 (14.8%)		8 (32%)		2 (6.3%)	
Over 100,000	12 (44.4%)		8 (32%)		3 (9.4%)	

Prefer Not to Answer	4 (14.8%)	1 (4%)	4 (12.5%)
Education Level			
High School Degree/GED		3 (12%)	
Post-Secondary Education**	3 (11.1%)	4 (16%)	2 (6.3%)
Some College	5 (18.5%)	2 (8%)	16 (50.0)
College Degree (BA, BS)	8 (29.6%)	10 (40%)	4 (12.5%)
Post-Graduate Degree (MA, MS, PhD.)	8 (29.6%)	5 (20%)	10(31.3%)
Other	3 (11.1%)	1 (4%)	
Relationship Status			
Single	2 (7.4%)	5 (20%)	23(71.9%)
Partnered	1 (3.7%)	1 (4%)	3 (9.4%)
Married	20 (74.1%)	17 (68%)	3 (9.4%)
Divorced/ Separated	3 (11.1%)	1 (4%)	3 (9.4%)
Widowed	1 (3.7%)	1 (4%)	3 (9.4%)
Employment			
Full-Time	19 (70.4%)	20 (80%)	10(31.3%)
Part-Time	2 (7.4%)	1 (4%)	21(65.6%)
Retired	2 (7.4%)	3 (12%)	
Disability	1 (3.7%)		
Other*	3 (11.1%)	1 (4%)	1 (3.1%)
Stage of Cancer			
Stage I	9 (33.3%)		
Stage II	10 (37.0%)		
Stage IIIA	8 (29.7%)		

Surgery		
Mastectomy	19 (70.4%)	
Breast Conserving Surgery	8 (29.6%)	
Menopause (current)		
Yes	18 (66.7%)	30(93.8%)
No	5 (18.5%)	2 (6.2)
Unsure	4 (14.8)	

Note. *Employment-Other refers to Full-Time Students & Caregivers; ** Post-Secondary education includes the following: Post-High School, Business, Associate Degree, or Trade School.

Table 6

Comparisons between BCS and Healthy Controls

	Breast Cancer Survivors (n=27)	Healthy Controls (n=32)				
	M (SD)	M (SD)	T	p	d	95% CI
Age	48.56(9.46)	29.13 (11.20)	7.12**	.000	1.86	[13.97, 24.89]
Perceived Cognitive Impairment						
PROMIS	105.52 (27.22)	130.91 (18.08)	-4.28**	.000	-1.12	[-37.27, -13.51]
Mood [a]	105.92 (26.31)	91.25 (14.51)	2.55*	.015	0.67	[3.00, 26.35]
Medical Comorbidity [b]	4.48 (4.41)	1.88 (2.81)	2.65*	.011	0.69	[.62, 4.59]
Speed of Processing						
Finger Tapping Test	236.33 (31.02)	251.59 (32.02)	-1.86	.069	-0.49	[-.99, .04]
Stroop Interference	34.04 (7.62)	36.75 (9.25)	-1.22	.229	-0.32	[-.78,.19]
Symbol Digit Modality Test	1.60 (.36)	1.44 (.27)	1.93	.059	0.50	[-.02,1.20]
SoP-CSS [c]	-.06 (.40)	.00 (.32)	-.640	.525	-0.17	[-.25, -.13]
Objective Cognitive Impairment						
Digit Span	27.52 (4.42)	28.31 (5.33)	-.616	.540	-0.16	[-.63,.34]

*p<.05, ** p<.01; [a] Mood is measured by the Profile of Mood States; [b] Medical Comorbidity measured by the Self-Administered Comorbidity Questionnaire; [c]SoP-CSS= Speed of Process Composite Standard Score

Table 7

BCS: Does PCI Predict OCI?

Variable	**β**	**t**	**p**	**95% CI**
Constant		-.117	.908	[1.44, 1.29]
PROMIS [a]	-.022	-.111	.913	[-0.013, 0.012]

*p <.05; **p < .01; [a] PROMIS measures PCI: Perceived Cognitive Impairment.

Table 8

HC: Does PCI Predict OCI?

	β	**t**	**p**	**95% CI**
Constant		-1.92	.065	[-4.98, .158]
PROMIS [a]	.333	1.94	.062	[-0.001, 0.038]

*p <.05; **p < .01; [a] PROMIS measures PCI: Perceived Cognitive Impairment.

Table 9

CR: Do others' perceptions of BCS cognitive impairment (PCI) Predict BCS' OCI

Variable	**β**	**t**	**p**	**95% CI**
Constant		.437	.666	[-1.289, 1.979]
PROMIS-CR[a]	-.150	-.726	.475	[-.016, .008]

*p <.05; **p < .01; [a] PROMIS-CR measures PCI: Perceived Cognitive Impairment of Collateral Reporters.

Table 10

Do the Principal Predictor Variables—SoP, Mood, and MC—Predict PCI?

Breast Cancer Survivors				
Variable	β	t	p	95% CI
Constant		22.86	.000	[158.43-222.57]
SoP-CSS[a]	-.123	-.89	.385	[-27.69, 11.08
Medical Comorbidity [b]	-.261	-1.92	.067	[-3.35, -0.13]
Mood [c]	-.700**	-4.94	.000	[-1.05, -0.430]
Healthy Controls				
Variable	β	t	p	95% CI
Constant		13.35	.000	[166.66, 227.07]
SoP-CSS[a]	.215	1.65	.111	[-2.96,27.22]
Medical Comorbidity [b]	-.312*	-2.40	.023	[-3.72, -0.29]
Mood [c]	-.547 **	-4.25	.000	[-1.01, -0.35]

*p<.05, ** p<.01; [a] SoP-CSS= SoP Composite Standard Score; [b] Medical Comorbidity measured by the Self-Administered Comorbidity Questionnaire; [c] Mood measured by the Profile of Mood-Abbreviated Form.

Table 11

Do the Principal Predictor Variables—SoP, Mood, and MC—Predict OCI?

Breast Cancer Survivors				
Variable	β	t	P	95% CI
Constant		-.704	.488	[-1.94, 0.953]
SoP-CSS[a]	.213	1.03	.312	[-0.437, 1.309]
Medical Comorbidity [b]	-.370	-1.84	.079	[-0.148, 0.009]
Mood [c]	.200	.954	.350	[-0.008, 0.020]
Healthy Control				
Variable				
Constant		.026	.979	[-2.38, 2.45]
SoP-CSS[a]	.196	1.04	.307	[-0.594, 1.82]
Medical Comorbidity [b]	-.118	-.629	.535	[-0.179, 0.095]
Mood [c]	.008	.041	.968	[-0.026, 0.270]

*p<.05, ** p<.01; [a] SoP-CSS= SoP Composite Standard Score; [b] Medical Comorbidity measured by the Self-Administered Comorbidity Questionnaire; [c] Mood measured by the Profile of Mood-Abbreviated Form.

Table 12

Selected Quotes from the Qualitative Analysis

Themes	Subthemes	Quotes
Overall Cognitive Experience	Positive	"[Overall cognitive experience is] slowly improving. I'm getting back into things that I used to do. everything." "I think it has improved." "Pretty good! I make great connections at work and I'm able to articulate myself."
	Negative	"I am worse with things…everyday things." "…the main thing is definitely cognitive dullness." "…it has made it it's more difficult to do everyday tasks that seemed simple before."
Memory Concerns		"I am crying because it is almost like two years' worth of notes and...and reflections and journaling. I am crying because I can't find it and I am beating myself up because I can't remember." "And I will get mad at [my partner] because I will be like '… you know come on the..the..the.' I use my hands a lot. I am like come on 'you know.' I want some telepathic communication." " I think that I took or second guess that I took my medication in the morning. I do it all the time and I can't ...I can't remember if I actually took it."
	Family/Friends Noted Concerns	"I like my family will remember. And they'll be like " what do you mean you don't remember."
Concentration/Attention Concerns		"I have the hardest time like staying focused on that and that's my biggest problem." " [I] start all completely focused and then can't remember what I just read then I will get it."
	Family/Friends Noted Concerns	"My husband doesn't think I probably can stay focus on one thing for very long." "He [husband] really has comment on how I don't listen maybe it is that I'm not listening ."
Compensatory/Coping Strategies	Positive	"Constantly…constantly, I am writing things down, putting it on my phone, or texting it to myself."

		"I'm trying to learn new things because that what's I am reading and hearing that it's not just retrieving information and knowing it[information]. It's learning something new."
		"I have to make it a joke or otherwise it won't be fun."
	Negative	"I get really frustrated and angry."
		"You know basically [I] try to hide my problems."
		" I don't have any strategies. I just get frustrated."
Contributing Negative Cognitive Experience to Sources Other Than Chemotherapy		"Yeah, I think that alot of stuff had to come from PTSD effects of cancer and the anxiety effects cause a lot of attention deficits issue."
		"You're getting older now and you start forgetting things when you get older."
		"I don't know if it has anything to do with that or just like a family thing. My Grandma had Alzheimer's or dementia."