RELATIONSHIP BETWEEN EXERCISE AND COGNITIVE FUNCTIONING IN BREAST CANCER SURVIVORS FOLLOWING CHEMOTHERAPY

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DEDICATION

With gratitude towards the members of my graduate committee, without whom this work would not have been possible. And to my parents, Melissa, Jaison, Jerin, Sylvia and countless others who have been a constant source of love, support, and encouragement along the way.

A.M.D.G.

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THESIS

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Abstract

BACKGROUND: A growing body of research suggests that individuals who undergo chemotherapy for treatment of cancer experience adverse changes in cognitive functioning as a side effect of treatment. While there is not yet a known remedy for such effects, exercise has shown to improve cognitive functioning in individuals within other clinical populations. Therefore, the purpose of this current study is to examine whether any relationships exist between self-reported post-chemotherapy exercise and cognitive functioning.

SUBJECTS: The sample consisted of sixty female breast cancer survivors between the ages of 38-71. All participants had been diagnosed with stage I, II, or III breast cancer and had completed chemotherapy between three months to two years prior to their study visit.

METHOD: Participants completed a self-report measure of post-chemotherapy exercise behavior and were administered a battery of neurocognitive tests to measure cognitive functioning. Subjects were categorized into one of three exercise groups based on their total exercise score (LSI): sedentary (LSI < 14), moderately active (LSI = 14-23), or active (LSI $\geq$ 24). Mean scores on cognitive tests between exercise groups were compared to determine whether significant differences existed between groups both before and after controlling for IQ. Additionally, a hierarchical multiple regression was performed to determine how much of the variance in cognitive test scores could be explained by the following predictors: age, education, IQ, anxiety, depression, and exercise.

RESULTS: Only three test scores (CVLT, Digit Span Backward, and Digit Symbol Coding) showed significant differences between exercise groups. Before controlling for IQ, CVLT (F=7.40, p=.001) and Digit Span Backward (F=3.01, p=.057) displayed significant differences between groups. After controlling for IQ, CVLT (F=4.19, p=.012), Digit Span Backward (F=5.98, p=.004), and Coding

(*F*=3.05, *p*=.055) displayed significant differences. Predictors explained a small portion of the variance in cognitive test scores.

DISCUSSION: Only three out of seven cognitive test scores demonstrated differences between exercise groups. Even among those tests that showed differences, higher levels of exercise were not consistently associated with better performance. In some cases, a moderate level of exercise seemed to have an optimal effect with regard to cognitive performance, suggesting the possibility of a dosing effect of exercise. Overall these findings suggest that a possible relationship may exist, but additional research is warranted.

Keywords: cognitive function, chemo brain, breast cancer, exercise, physical activity, chemotherapy

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LIST OF ABBREVIATIONS

5FU	Fluorouracil
ADAS-Cog	Alzheimer's Disease Assessment Scale- Cognitive Subscale
AMNART	American National Adult Reading Test
BDNF	Brain-derived Neurotrophic Factor
BrdUrd	Bromodeoxyuridine
CEF	Cyclophosphamide, Epirubicin, and Fluorouracil
CICI	Chemotherapy-induced Cognitive Impairment
CMF	Cyclophosphamide, Methotrexate, and Fluorouracil
CVLT-II	California Verbal Learning Test- Second Edition
DKEFS	Delis-Kaplan Executive Function System
DNA	Deoxyribonucleic Acid
FACT- Cog	Functional Assessment of Cancer Therapy- Cognitive Function
FACT-B	Functional Assessment of Cancer Therapy- Breast
FACT-F	Functional Assessment of Chronic Therapy- Fatigue
FACT-G	Functional Assessment of Cancer Therapy- General
FEC	Fluorouracil, Cyclophosphamide, and Epirubicin
GED	General Equivalency Diploma
GLTEQ	Godin Leisure-Time Exercise Questionnaire
Gy	Gray (Units of Irradiation)
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus

ICD-10	International Statistical Classification of Diseases-10th Revision
IGF-1	Insulin-like Growth Factor -1
IRB	Institutional Review Board
LSI	Leisure Score Index
MET	Metabolic Equivalents for Tasks
MMSE	Mini-Mental State Examination
mRNA	Messenger Ribonucleic Acid
MS	Multiple Sclerosis
NeuN	Neuron-specific Nuclear Antigen
OX	Oxaliplatin
PASAT	Paced Auditory Serial Addition Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SPSS	Statistical Package for the Social Sciences
TMT	Trail Making Test
UTSW	University of Texas at Southwestern Medical Center
WAIS-IV	Wechsler Adult Intelligence Scale- Fourth Edition
WBI	Whole Brain Irradiation
WMS-III	Wechsler Memory Scale- Third Edition
WMS-R	Wechsler Memory Scale- Revised
WRATR	Wide Range Achievement Test- Revised
WTAR	Wechsler Test of Adult Reading

CHAPTER ONE

Introduction

In the U.S., there are more than 200,000 diagnoses of breast cancer each year. Breast cancer is the 2nd leading cause of cancer-related deaths in women and accounts for 40,000 deaths per year (Hurria, Somlo, & Ahles, 2007). However, due to advances in the early diagnosis and treatment of breast cancer, survival rates have been rising since the 1990s. It is currently estimated that the combined overall 5-year survival rate for all stages of breast cancer is now at 89% (Altekruse et al., 2010). Of the 11.4 million cancer survivors in the U.S., breast cancer survivors account for 2.6 million people or 23% of the total cancer survivor population (Boykoff, Moieni, & Subramanian, 2009).

Chemotherapy is an important component in the treatment of many stages of breast cancer (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Castellon et al., 2004; van Dam et al., 1998; Wefel et al., 2004) and is the treatment of choice for systemic disease (Schagen, van Dam, Muller, Boogerd, Lindeboom & Bruning, 1999; Wefel et al., 2004). Various side effects have been attributed to this treatment, including nausea, vomiting, oral inflammation, hair loss, decreases in blood cell production, thromboembolism, muscle pain, fatigue, weight gain, and neuropathy (Love, Leventhal, Easterling & Nerenz, 1988; Partridge, Burstein & Winer, 2001). As the ability to detect and treat breast cancer advances, an increasing number of survivors experience the side-effects of chemotherapy during treatment and late- and long-term effects following treatment. Therefore, breast cancer patients must learn to adjust to the changes which may occur secondary to receiving chemotherapy as well as changes in their quality of life (Hurria et al., 2007).

One side- and long-term effect which some breast cancer patients report as disruptive to their quality of life is changes in their cognitive function after receiving chemotherapy (Wefel et al., 2004). These cognitive symptoms have been reported to cause a range of dysfunction from mild to severe.

(Hurria et al., 2007). Because these cognitive changes are considered to be a side-effect of chemotherapy, the cognitive dysfunction has commonly been referred to as "chemo brain."

Chemo Brain

Chemo brain is often described by cancer patients as a mental slowing or an impairment in the ability to multitask with the same proficiency as prior to their cancer diagnosis (Hurria et al., 2007). It is also known as chemotherapy-induced cognitive impairment (CICI) or "chemo fog." Evidence of this phenomenon has grown in the medical literature within recent years and is now recognized as an adverse effect of chemotherapy used to treat cancers of the lung, breast, ovaries, and prostate (Argyriou, Assimakopoulos, Iconomou, Giannakopoulou, & Kalofonos, 2011). Symptoms include an inability to concentrate, difficulty in thinking, loss of memory, and other changes in cognitive function (Argyriou et al., 2011; Boykoff et al., 2009). CICI may also impact learning, reasoning, visuospatial skills, and executive function both during and after completion of treatment (Argyriou et al., 2011). Often, impairment is short-term and produces subtle cognitive effects. However, in some cases, impairment may produce sustained, long-term effects on cognition (Argyriou et al., 2011).

Research has shown cognitive changes in numerous patients who receive adjuvant treatment (Brezden et al., 2000; Hurria et al., 2006; Schagen et al., 1999; van Dam et al., 1998), with rates of impairment ranging from 12%-75% (Ahles et al., 2002; Argyriou et al., 2011; Hermelink et al., 2007; Vardy, Rourke, & Tannock, 2007). Unfortunately, due to methodological differences and limitations in the literature, there is not yet consensus as to how many individuals are affected by this condition (Schagen et al., 1999; Argyriou et al., 2011; Wefel et al., 2004). Those who do not report cognitive changes either truly do not experience the phenomenon, or may experience it but refrain from reporting from fear of being labeled as having "chemo brain" and the implications of this label on their abilities

to resume employment, find new employment, or engage in activities necessitating greater levels of cognitive functioning (Hurria et al., 2007).

The mechanisms behind CICI are not yet known, although several possible mechanisms have been proposed, including: genetic predisposition, hormonal changes due to cancer treatments, DNA damage from oxidative stress, anemia related to cancer, immune dysregulation from cancer or chemotherapy, neurotoxic damage to the central nervous system especially to progenitor cells, and genetic variations in blood-brain barrier transporters that allow small doses of chemotherapeutic agents to cross into the brain resulting in cell damage and a decrease in the division of cells (Argyriou et al., 2011). Although chemo-brain has been linked to chemotherapy, a direct causal relationship has not yet been established (Boykoff et al., 2009). The reason for this may lie in the myriad of factors which might play a role in decreasing a breast cancer patient's cognitive functioning including but not limited to anesthesia, hormonal therapies, anxiety, depression, menopause, fatigue, and/or medications (Ahles & Saykin, 2001; Hurria et al., 2006; Hurria et al., 2007).

Subjective Cognitive Dysfunction

Research regarding chemotherapy-related cognitive impairment has sought to understand the subjective experience of individuals with reported symptoms. In a meta-analysis of literature regarding subjective cognitive dysfunction in breast cancer patients, Pullens and colleagues (2010) examined 27 studies and reported that five out of the 27 studies demonstrated significantly greater subjective cognitive impairment in patients treated with chemotherapy (sometimes additionally given hormone therapy and/or radiotherapy) than in healthy control groups (Pullens, Vries, & Roukema, 2010). One study showed greater subjective cognitive dysfunction in those receiving chemotherapy coupled with hormonal therapy, compared to chemotherapy alone and another study found greater subjective

dysfunction in individuals receiving CMF chemotherapy than those receiving no chemotherapy treatment (Pullens et al., 2010).

Shillings and Jenkins (2007) interviewed 142 breast cancer patients receiving chemotherapy to examine the subjective experience of cognitive impairment. Results indicated 71% of patients in this sample reported problems with their memory at six months post-chemo, and 60% reported problems at 18 months post-chemo. Concentration problems were reported in 64% of the sample at six months, and 42% at 18 months. Women who reported trouble with memory or concentration specifically mentioned difficulties recalling names of people, things, memories, information, and events. Women also reported forgetting why they went into a store, what they had been told by someone just a little while earlier, threads of conversations, where they had previously placed things, birthdays, and other events. Some stated that they found it hard to concentrate and one woman described her experience as though her mind was "jumping" (Shilling & Jenkins, 2007).

In another study, Boykoff and colleagues (2009) interviewed 74 Caucasian and African American female breast cancer patients to further examine cognitive dysfunction secondary to chemotherapy. Results demonstrated common themes in their subjective complaints, which included: getting lost in familiar areas, misplacing items such as house and car keys, and having trouble paying bills, not because of financial troubles, but due to problems in their ability to remember and to perform simple cognitive tasks that they once performed easily. One woman reported having been afraid of hurting herself while driving because she could not remember if she looked at the stoplight, thus feeling that she frequently placed herself in potentially harmful situations. Women attending educational coursework reported difficulties learning and processing new concepts and some reported that cognitive impairment affected their ability to read.

Cognitive impairment can also impede an individual's job performance. Some breast cancer survivors report decreases in the ability to focus, which consequently makes their job-related tasks much more challenging. They also reported diminished efficiency in job performance and therefore a perceived reduction in the likelihood of promotion or being assigned new projects. Many reported that their employers were aware of their inability to manage the same level of work that they managed prior to treatment. Some reported an increase in the severity of their symptoms during stressful situations such as interviews, and others believe memory loss prevented them from obtaining employment (Boykoff et al., 2009).

Emotional well-being is also often affected by cognitive impairment. Some survivors report increases in stress, particularly in their work environments. Some also reported feelings of insecurity and avoidance of social situations because of their insecurity as well as fears of being embarrassed. Many survivors also report feeling emotionally-drained, scared, and dependent on others (Boykoff et al., 2009).

Objective Cognitive Dysfunction

Studies have been conducted to assess objective cognitive impairment through the use of neuropsychological assessments (Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998). Results have demonstrated impairments in various areas of cognitive functioning including memory, attention/concentration, visual-motor skills, and aspects of language (Brezden et al., 2000; Schagen et al., 1999). Additionally, research suggests a relationship between cognitive impairment and brain volume and some studies have thus used brain imaging to measure brain volume in individuals who have received chemotherapy compared to those who have not (Inagaki et al., 2007). Inagaki and colleagues (2007) reported differences in regional brain volume in the superior and middle frontal gyri, cingulate gyrus, and parahippocampal gyrus. Smaller superior prefrontal gyri are associated with

cognitive functions such as attention/concentration and visual memory. The prefrontal cortex is associated with cognitive functions such as planning, memory, inhibition, and execution. These changes in volume were not observed at more than three years following chemotherapy, suggesting that changes in brain volume associated with chemotherapy may be restored with time. If brain volume is indeed associated with cognitive functioning, then this study suggests that chemotherapy may possibly have a temporary impact on cognitive functioning (Inagaki et al., 2007).

Despite common reports of cognitive symptoms, most studies have not shown a link between measures of subjective cognitive dysfunction and objective cognitive impairment (Shilling & Jenkins, 2007; Vardy, 2009). Those who reported either concentration or memory difficulties were not more likely to demonstrate objective impairment on testing. This inconsistency between subjective and objective measures may be due to variety of reasons including but not limited to insensitivity of neuropsychological assessments to detect more subtle cognitive changes or unreliability of self-report measures (Shilling & Jenkins, 2007).

Need for Potential Treatments

Although science in medicine has advanced to produce aggressive treatments to combat cancer, these treatments often produce late- and long-term side-effects that adversely impact the quality of life of patients. Many women report trouble performing in their family life and/or their professional or educational pursuits secondary to the cognitive impairment reportedly experienced after chemotherapy (Ahles & Saykin, 2001). In addition, difficulties maintaining employment may often arise which can significantly impact their financial security, especially if they are the sole breadwinners in their families (Boykoff et al., 2009). As the survival rate for breast cancer increases, more women must learn to manage the adverse effects of both breast cancer and its treatment (Pullens et al., 2010). As such it is becoming increasingly important to identify methods of managing these adverse effects of

cancer treatment. And while there are still many questions regarding cognitive impairment secondary to chemotherapy, cognitive impairment is one such symptom reported by women undergoing cancer treatment. A growing body of research suggests that there may be a relationship between physical activity and improvement in cognitive functioning (Baker et al., 2010; Fardell, Vardy, Shah, & Johnston, 2012; Hassmen, Ceci, & Backman, 1992; Podewils et al., 2005)

CHAPTER TWO

Review of the Literature

Chemobrain and its Effects

The term "chemo brain" refers to the changes in cognitive function that many cancer patients report after undergoing chemotherapy and rates of impairment are estimated at anywhere from 20-30% of patients (Hafner, 2009) to 12-75% (Vardy, Wefel, Ahles, Tannock, & Schagen, 2007; Argyriou et al., 2011; Hermelink et al., 2007). Cognitive impairment secondary to chemotherapy was first identified in the 1980s when patients complained of problems with cognitive functions during and after treatment (Hafner, 2009). Many cancer patients today report deficits in their ability to perform general cognitive functions such as thinking, remembering, and concentrating (Brezden et al., 2000; Partridge et al., 2001; van Dam et al., 1998). Schagen et al. (1999) reported cognitive functions such as mental flexibility; information processing speed, motor function, and visual memory are also impacted. Raffa et al., (2006) concluded that cognitive functioning deficits occurred in attention, multitasking, and ability to organize information. Specific effects often exhibited by those with chemo brain include poor recall of words or names, trouble maintaining focus, decreased ability to learn new information, diminished ability to manage daily tasks and activities, and diminished capacity to multitask. Patient accounts of the phenomenon also describe feeling as if "in a fog" that does not lift (Hafner, 2009).

A study by Brezden and colleagues (2000) examined differences in cognitive functioning, specifically in the areas of memory, language, visual-motor, spatial, attention and concentration, and self-regulation and planning, between 31 breast cancer patients currently receiving either CEF (cyclophosphamide, epirubicin, and fluorouracil) or CMF (cyclophosphamide, methotrexate, and fluorouracil) adjuvant chemotherapy, 40 who had completed adjuvant chemotherapy on an average of two years prior to the study, and 36 healthy controls. Results showed significant differences in the

group receiving adjuvant chemotherapy when compared to the healthy control group (p=.046), even after factoring in demographic covariates. More specifically, the patients in the group receiving adjuvant chemo and the group who had completed adjuvant chemo demonstrated moderate to severe cognitive impairment compared to the healthy group, based on scores from the High Sensitivity Cognitive Screen (HSCS) they had been administered. Additionally, those individuals currently receiving adjuvant chemotherapy demonstrated impairment in areas of language (p=.033) and memory (p=.024) functions compared to controls, while those who had previously completed chemotherapy exhibited impairment in the areas of visual-motor skills (p=.024) and language (p=.047), when compared with controls (Brezden et al., 2000).

Van Dam et al. (1998) observed cognitive functioning in patients with high-risk breast cancer. The design of this investigation involved random assignment into the following three groups: the first group received four cycles of FEC (fluorouracil, epirubicin, and cyclophosphamide) chemotherapy and a fifth course of high-dose combination chemotherapy (CTC) and tamoxifen, the second group received 4-5 cycles of FEC standard-dose adjuvant chemotherapy and tamoxifen, and the third group consisted of control patients with stage 1 breast cancer not treated with chemotherapy. Each group was given a battery of neuropsychological tests, and results indicated that the high-dose chemotherapy group demonstrated greater cognitive impairment than the standard-dose chemotherapy group. Thirty-two percent of patients who received high-dose chemo displayed cognitive impairment, while 17% of those receiving standard-dose and 9% of controls showed cognitive impairment. Van Dam and colleagues performed a logistic regression analysis to ascertain risk of cognitive impairment. High-dose chemo appeared to increase risk of impairment by 3.5 times in comparison with those who received standard-dose chemotherapy and 8.2 times in comparison with the controls (van Dam et al., 1998).

Schagen and colleagues (1999) assessed the late effects of CMF adjuvant chemotherapy on the neuropsychological functioning of breast cancer patients. The study involved two groups: 39 patients who were given adjuvant CMF, some of whom also received 20 mg daily of hormonal therapy (tamoxifen) for three years, and 34 control patients who received no adjuvant treatment. Participants were administered questionnaires to measure subjective cognitive impairment as well as neuropsychological assessments to measure objective impairment. Results indicated that patients who were given CMF reported significantly more concentration and memory problems than the controls (p=0.007 and p=0.022, respectively). When compared to controls, patients who had received chemotherapy displayed significantly lower scores on subtests measuring attention and concentration, slowed mental ability, slower reaction time on a task of basic perceptuomotor performance and significantly slower motor speed. These patients also exhibited reduced verbal fluency than controls. Additionally, 28% of patients given chemotherapy showed impaired cognitive function, versus 12% of controls (p=0.013). Hormonal therapy did not appear to have any effect on cognitive function or patient's subjective reports of symptoms. The authors concluded that patients treated with adjuvant CMF chemotherapy have a greater risk of cognitive impairment than those who did not receive such treatment (Schagen et al., 1999).

The above provide just a few pieces of evidence, among many other studies, in support for the existence of the phenomenon known as chemo brain (Ahles et al., 2002; Bender et al., 2006; Fan et al., 2005; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006; Tannock, Ahles, Ganz, & Van Dam, 2004). As many of these studies suggest, countless breast cancer patients who undergo chemotherapy report adverse changes in their memory, attention/concentration, and processing speed as well as various other cognitive functions (Ahles et al., 2002; Bender et al., 2006; Brezden et al., 2000; Fan et al., 2005; Schagen et al., 2006; Schagen et al., 1999; Tannock et al., 2004; van Dam et al.,

1998). As the number of breast cancer survivors increases and research in this area of study continues to grow, it is likely that some of the questions still surrounding the nature of this phenomenon will be elucidated.

Currently, there is no treatment for cognitive impairment due to chemotherapy, although a growing body of research supports the role of physical activity as a way of sustaining cognitive performance (Podewils et al., 2005). In other clinical populations (Hassmen et al., 1992; Prakash et al., 2007) such as elderly adults and multiple sclerosis patients, exercise has been shown to help maintain and/or improve cognitive functioning. In the breast cancer population, research on the relationship between physical activity and cognitive function after chemotherapy is still growing. Therefore the current study will explore this potential relationship between exercise and cognitive functioning in breast cancer survivors post-adjuvant chemotherapy treatment.

Exercise and Chemotherapy

Fardell and colleagues (2012) examined the effects of two specific types of chemotherapy agents, 5FU and OX, on cognition in rats as well as the impact of exercise on cognitive deficits following treatment. Sixty lab rats were given either a single injection of OX at 8mg or 12mg, 5FU at 75 mg/kg, or a combination of 5FU and OX in two injections. Rats assigned to the exercise group were provided access to a running wheel, while rats assigned to the sedentary group were not. Cognitive functioning was assessed using contextual and cued fear conditioning, a novel object recognition test and a Morris water maze task. Results showed that both types of chemotherapy had adverse effects on cognitive functioning in rats, with the most adverse effects observed in those given the combination treatment. Importantly, rats in the exercise group showed significant improvement in behavioral task performance. On behavioral measures, their performance nearly matched those of the control group.

These results suggest that exercise may have the therapeutic potential to ameliorate cognitive impairment induced by chemotherapy (Fardell, Vardy, Shah, & Johnston, 2012).

Exercise and Whole Brain Irradiation

Although research on the impact of exercise on cognitive function in the human breast cancer population after chemotherapy is scarce, research has been conducted on animals that received whole brain irradiation (WBI), a different cancer treatment that often causes impairment in cognitive functioning, similarly to chemotherapy. WBI therapy is a form of radiation treatment for those with primary, metastatic, or advanced solid tumors of the brain. Despite its benefits, WBI is often associated with learning and memory deficits in patients.

Wong-Goodrich and colleagues (2010) examined the relationship between exercise and brain functioning in mice receiving WBI. Forty female adult mice were randomized to receive either 5 Gy of WBI or sham WBI. All mice were trained in a Barnes maze for 2.5 weeks to four months after WBI. One month after beginning either WBI or sham, half of the mice were provided daily access to a running wheel. In the mice given access to the running wheel, researchers observed that daily running prevented significant decline in retention for spatial memory, and this effect lasted for months after completion of WBI. One measure, an immunosorbent assay, indicated increased expression of the brain-derived vascular endothelial growth factor and IGF-1 as well as some refurbishment in the dentate gyrus of newborn BrdUrd+/NeuN+ neurons. In this model of exercise and WBI, physical activity was found to be an effective aide in recovery of memory function and brain plasticity, although after an average of two months following exercise, there was no evidence for considerable recovery of BDNF in the hippocampus. Therefore physical activity has been postulated as a potentially beneficial therapeutic intervention for adults suffering from memory decline, spatial learning deficits, and possibly other symptoms of cognitive impairment (Wong-Goodrich et al., 2010).

Exercise and Elderly Populations

A growing body of research has examined the relationship between physical activity and its impact on the cognitive decline associated with aging. These findings support the theory that physical exercise may help delay the onset of neurodegenerative processes such as those involved in dementias, including Alzheimer's disease (Deslandes et al., 2009). In addition to the numerous physiological and health-related benefits of physical activity, exercise is also associated with better overall cognitive functioning (Baker et al., 2010; Hassmen et al., 1992; Lautenschlager et al., 2008; Weuve et al., 2004).

Hassmen, Ceci, and Backman (1992) grouped participants into three different intensities of exercise to examine the effects of exercise on both physical and cognitive performance in older women (N=30). Results showed that women in the high intensity exercise condition demonstrated better scores on a digit span task compared to the low exercise intensity group, suggesting better attention (Hassmen et al., 1992). Further support came from Weuve and colleagues (2004) who conducted a longitudinal study in which they observed the relationship between cognitive functioning and long-term regular physical activity in 16,466 older women. A telephone interview cognitive screen was administered along with exercise questionnaires. Areas of cognition assessed included: immediate and delayed paragraph recall, category fluency, attention and working memory. Results indicated that long-term regular physical activity was associated with less cognitive decline and better cognitive function on all areas of cognitive functioning measured. Furthermore, this association was not limited to those who engaged in vigorous exercise; even walking at a pace of 21-30 min/mile at least 1.5 hours a week showed similar results (Weuve et al., 2004).

Baker and colleagues (2010) conducted a six-month clinical trial looking at outcome differences between high-intensity aerobic exercise versus a stretching control group. Relative to the stretching control group, a six month trial of aerobic exercise improved cognitive function in older

adults with mild cognitive impairment. Improvements were seen in the areas of speed of processing, efficiency of searching, multi-tasking, selective attention, and cognitive flexibility (Baker et al., 2010).

Exercise has also been shown to be beneficial for cognitive function in other groups, including elderly adults at risk for Alzheimer's. Lautenschlager and colleagues (2008) tested an exercise intervention to determine whether it would delay the progression of symptoms. By the end of the study, those in the exercise group had better scores on the Alzheimer's disease Assessment Scale—Cognitive Subscale (ADAS-Cog) than those in the usual care control group. Additionally, the exercise group displayed better delayed recall and lower Clinical Dementia Rating scores than controls. Improvements were visible after six months and continued for at least another year after the end of the intervention. These results suggest that exercise may improve cognitive function in older adults who are at risk for Alzheimer's, although methodological issues exist and the overall implications from this literature are not yet conclusive (Lautenschlager et al., 2008).

Exercise and Multiple Sclerosis

Not only has physical activity been shown to impact cognitive function in aging, but beneficial effects of exercise have been reported in other clinical populations. For example, a growing body of research has examined the link between exercise and cognitive function in multiple sclerosis (MS) patients (Feinstein, 2011; Prakash et al., 2007; Prakash, Snook, Motl, & Kramer, 2010).

Cognitive dysfunction is a symptom that is also commonly experienced by individuals with multiple sclerosis, a neurodegenerative disease, affecting 40-60% of those diagnosed with MS (Feinstein, 2011). Cognitive impairment is associated with a decline in gray and white matter volume in the brain. Areas of cognitive function that are commonly impaired are similar to impairments associated with chemo brain and include: memory, attention/concentration, and information processing speed (Prakash et al., 2007). Physical activity is observed to benefit individuals with multiple sclerosis

as cardiorespiratory fitness, a "physiological surrogate" (Prakash et al., 2010) of physical activity, appears to play a neuroprotective role (Prakash et al., 2007). In a different study, Prakash and colleagues (2010) examined whether higher fitness levels in patients with multiple sclerosis were associated with preserved integrity of gray and white matter. They recruited participants with relapse-remitting MS and compared them to a healthy control group that was matched for age, education, and gender. They examined the association between measures of gray and white matter atrophy and cardiorespiratory fitness. Results showed that higher fitness levels were linked to higher scores on a measure of information processing speed. Furthermore, higher processing speed was associated with preservation of gray matter, white matter, and included structures. Their research implies that fitness and physical activity may aide in slowing neurodegeneration (Prakash et al., 2010).

Biological Mechanisms of Exercise

In research with many different populations commonly affected by cognitive impairment, exercise is believed to have a protective effect on cognitive function (Feinstein, 2011; Prakash et al., 2007). Although the reason for this effect is poorly understood, Cotman & Engesser-Cesar (2002) suggest that the brain has the ability to produce molecules, called neurotrophic growth factors, that nourish neurons and enhance brain health. Brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1) are the two neurotrophic factors studied most extensively and have been associated with better cognitive functioning, plasticity, angiogenesis, and neurogenesis. BDNF has also been suggested to be related to brain plasticity, promoting differentiation and mediating synaptic efficacy within the brain (Deslandes et al., 2009).

In a study by Winter et al. (2007) researchers found that exercise accelerates learning and that in humans who ran at a high intensity demonstrated an increase in BDNF. Twenty-seven participants were subjected to three different conditions of exercise interventions: a relaxed group (control) who

spent 15 minutes being sedentary, a moderate exercise group consisting of 40 minutes of running maintaining a fixed heart rate, and an intense exercise group which required participants to complete two sprints of three minutes each with a two minute break in between. A task of vocabulary learning was given after each condition's intervention. Results showed that learning speed was faster after intense running compared to the sedentary condition. Peripheral levels of BDNF and catecholamines such as norepinephrine, epinephrine, and dopamine were analyzed before and after each intervention and results showed increased levels of catecholamines and BDNF. BDNF levels that were sustained after learning following intense exercise was associated with better short-term learning success. Participants with higher epinephrine levels following intense exercise showed better long-term retention, with retention of learned vocabulary lasting over 8 months (Winter et al., 2007). Neeper and colleagues (1996) used an animal model to determine whether exercise regulated BDNF in the hippocampus. In an experiment with rats (n=39) and a voluntary running wheel, researchers discovered after two to seven nights of running a 20% increase in BDNF mRNA levels as found when compared to levels observed prior to exercise, thus suggesting a neurotrophic up-regulation in the hippocampus which is the area of the brain responsible for learning and memory (Neeper, Gomez-Pinilla, Choi, & Cotman, 1996). These results further suggest that exercise has the added effect of enhancing synaptic capacity, making neural connections stronger and more efficient (Cotman & Engesser-Cesar, 2002; Neeper, Gomez-Pinilla, Choi, & Cotman, 1995; Neeper et al., 1996). Cotman & Engesser-Cesar (2002) further suggested that exercise can cause changes in several other genes that regulate synaptic efficiency and promote overall cognitive function.

IGF-1(Insulin-like Growth Factor-1), another neurotrophic factor, is associated with neurogenesis as well because its release causes production of progenitor cells in the brain region of the hippocampus where adult neurogenesis occurs, more specifically the subgranular zone. In older adults

with poor cognitive functioning, exercise increases IGF-1 levels, thereby improving cognitive performance. Research also suggests that strength training, which increases testosterone, may especially have many benefits, because testosterone may be a key to higher BDNF levels. In addition to the regulation of BDNF and IGF-1 levels, physical activity may play a role in the control of vascular endothelial growth factor, which has neuroprotective, neurogenic, and neurotrophic effects in addition to the control of proliferation of endothelial cells. It is also believed to be the main growth factor related to formation of capillaries in the developing brain (Deslandes et al., 2009). For these reasons, it is believed that exercise and other mechanisms that induce neurotrophic factors may enhance learning and protect brain function.

Exercise and Quality of Life

In addition to potentially sustaining cognitive functioning, much research has shown that exercise improves quality of life in human cancer survivors (Campbell, Mutrie, White, McGuire, & Kearney, 2005; Courneya, 2003; Courneya & Friedenreich, 1997; Courneya et al., 2003; Courneya et al., 2007; Schwartz, 1999; Segal et al., 2003). In a meta-analysis of the effects of physical activity on patients and survivors of breast cancer, three of 14 studies examined the effects of exercise on quality of life compared to quality of life outcomes with usual care (McNeely, Campbell et al. 2006). Two of the three studies (Courneya et al,. 2003; Campbell et al., 2005) displayed significant increases in scores on measures of quality of life. In the study by Courneya and colleagues (2003), researchers performed a prospective, randomized controlled trial to examine the role of exercise in quality of life outcomes. Participants were randomized into either an exercise group or a non-exercise control group. Quality of life outcomes were assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) and the Functional Assessment of Cancer Therapy- General (FACT-G). Results indicated significant improvements in scores on both the FACT-B and FACT-G in the exercising group. By the completion

of the study, overall quality of life had increased by an average of 9.1 points in the exercise group, versus a 0.3 point increase in controls (Courneya et al., 2003). Campbell and colleagues (2005) also conducted a randomized controlled trial of a group exercise program for women with breast cancer who were receiving adjuvant cancer treatment. The women were randomized into either a non-exercise group or an exercise group. The non-exercise group received their usual level of care and completed walking assessments and questionnaires. The exercise group, in addition to usual care, also engaged in an exercise intervention two times weekly for a total of 12 weeks. They measured quality of life, among other factors, both pre- and post- a 12-week intervention. After 12 weeks, women who participated in the exercise program showed significantly higher quality of life scores (Campbell et al. 2005).

Anna Schwartz (1999) also examined the effect of exercise on fatigue and quality of life in patients receiving chemotherapy. Quality of life was first assessed before the first chemotherapy treatment and final measurement occurred at the completion of chemotherapy. Although quality of life decreased as a whole for almost all participants, individuals who exercised exhibited increased functional ability and less decline in quality of life than those who did not engage in exercise (Schwartz, 1999).

The above studies provide just a few examples of ways that exercise has displayed useful effects on functioning. Exercise has shown to have many benefits, including the improvement of quality of life and enhancing neurogenesis in the brain (Campbell et al., 2005; Cotman & Engesser-Cesar, 2002; Courneya et al., 2003; Neeper et al., 1995; Neeper et al., 1996; Schwartz, 1999; Winter et al., 2007). Additionally, it has shown to be beneficial in animal models of WBI, aging adults, and multiple sclerosis (Baker et al., 2010; Hassmen et al., 1992; Lautenschlager et al., 2008; Prakash et al., 2007; Prakash et al., 2010; Wong-Goodrich et al., 2010). The purpose of this investigation is to explore

the impact of exercise on cognitive functioning following chemotherapy. It is hypothesized that those individuals who participated in greater physical activity following chemotherapy will show better cognitive functioning through scores on neuropsychological tests than those who participated in little or no exercise.

CHAPTER THREE

Methodology

Participants

Participants consisted of 60 women with a history of breast cancer recruited through the Harold C. Simmons Comprehensive Cancer Center at the University of Texas Southwestern Medical Center. All participants had completed treatment including adjuvant chemotherapy three months to two years preceding evaluation. Pre-, peri-, or post-menopausal individuals were eligible as well as women who were still receiving antihormonal therapy. All study participants were native English speakers, between 18 and 70 years of age, and all were required to have at least a minimum of a high school education or GED in order to participate. Those with a history of head injury with loss of consciousness greater than 20 minutes, solid brain metastasis, stroke, major surgeries within past six months unrelated to breast cancer treatment, untreated hypertension, untreated diabetes, pre-existing major Axis I psychiatric disorder, or other pre-existing condition with known cognitive impairments such as dementia or intellectual disability, were excluded.

Procedure

Following IRB approval, the electronic medical records were reviewed for those who had given consent. The researchers then contacted potential participants by telephone. If the individual expressed interest, the researchers determined if eligibility criteria were met and provided subjects with further information about the study as well as answered any study related questions via telephone and a verbal consent script. If eligibility requirements were met, the researcher scheduled a study visit. Mailed questionnaires included: the Hospital Anxiety and Depression Scale, FACT-G, FACT-F, FACT-COG, Godin Leisure Time Exercise Questionnaire (Before Diagnosis), and Godin Leisure Time Exercise Questionnaire (Post-Chemo). If the questionnaires were not completed, participants were given another

copy of the mailed packet to complete on site at the time of their visit. Upon completion of a one-page survey of demographic questions that was administered verbally, neuropsychological tests were administered to assess cognitive functioning and included the following measures: FAS Verbal Fluency task, WAIS-IV Digit Span Forward, WAIS-IV Digit Span Backward, WAIS-IV Digit Span Sequencing, WAIS-IV Digit Symbol Coding, PASAT (3" version), California Verbal Learning Test 2nd Edition (CVLT-II), and the Wechsler Test of Adult Reading (WTAR). All participant files were assigned an identification code so as to de-identify personal information and protect confidentiality.

Measures

Participants completed the protocol in a single visit that lasted approximately 70-90 minutes. The measures focused on two primary areas: (1) self-report measures of physical activity, and (2) tests of neurocognitive functioning. The neurocognitive measures were chosen based on their psychometric properties, time efficiency to minimize fatigue, and external validity. All cognitive measures provide norm-referenced scores and an index of level of functioning that is adjusted for age and education relative to the general population. All published tests were administered according to directions outlined in their respective testing manuals.

Measures of Cognitive Functioning

The FAS-Test (Heaton, Miller, Taylor, & Grant, 2004) is a measure of verbal fluency, which assesses a person's ability to produce words spontaneously while under a time-restricted condition (Strauss, Sherman, & Spreen, 2006). Total scores were converted into demographically adjusted T-scores for use in this study.

The California Verbal Learning Test- Second Edition, Standard Form (CVLT-II) is a measure of verbal learning and memory. It consists of a list-learning task that involves multiple learning trials.

Raw and standardized scores were computed using the CVLT-II scoring software and converted into T-scores adjusted for age and gender (Delis, Kaplan, Kramer & Ober, 2000).

The Digit Span subtest of the WAIS-IV measures attention and freedom from distractibility (Lezak, Howieson, Loring, Hannay, & Fischer, 2004) and consists of three different trials: Digit Span Forward, Digit Span Backward, and Digit Span Sequencing. Examiners present sets of numbers of increasing length and participants are required to repeat the sequences of numbers. Raw scores from Digit Span Forward, Digit Span Backward, and a total score of all three trials were converted into scaled scores adjusted for age.

The Paced Auditory Serial Addition Test-3" interval (PASAT-3; Gronwall, 1977) is a serial-addition task designed to evaluate auditory information processing speed, working memory, and sustained and divided attention. A series of one-digit numbers are presented and the examinee must consecutively add pairs of numbers so that each number is added to the one presented immediately prior to it. Total number of correct responses is recorded, with a maximum score of 60 and percentage of errors, including omissions, are computed (Strauss et al., 2006). Demographically corrected scores were computed into T-scores for the purposes of this investigation.

Digit Symbol Coding is a subtest of the Wechsler Adult Intelligence Test- Fourth Edition (WAIS-IV; Wechsler, 2008a; Wechsler, 2008b) that measures psychomotor processing speed and divided attention. Examinees are to fill in rows of squares, matching numbers to symbols under a time-restricted condition. Raw scores were converted into z-scores adjusted for demographically-normed data (Wechsler, 2008a; Wechsler, 2008b).

Premorbid functioning. The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) is used to estimate an adult's premorbid intellectual functioning. This test requires subjects to read and

pronounce 50 phonetically irregular words. The totals of number of words pronounced correctly were converted into standard scores which were transformed into estimated IQ scores.

Self-Report Measures

Exercise. The Godin Leisure-Time Exercise Questionnaire is a self-report measure that assesses an individual's average weekly leisure-time exercise (Godin & Shephard, 1985). A modified version of the Leisure Score Index (LSI) from the Godin Leisure-Time Exercise Questionnaire (GLTEQ) was used to evaluate post-chemotherapy exercise behavior.

The following neuropsychological measures were administered as part of a larger study but not used in current analyses: (a) Animal Naming test (Category Fluency), (b) DKEFS Color-Word Interference test, and (c) Trail Making Tests A & B. The following additional questionnaires were also administered but not used for primary aims of this current study: (a) Hospital Anxiety and Depression Scale (HADS), (b) Functional Assessment of Cancer Therapy- General (FACT-G), (c) Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog), and (d) Functional Assessment of Chronic Therapy-Fatigue (FACT-F). Physical activity levels prior to breast cancer diagnosis as well as physical activity levels after completion of chemotherapy were assessed using the Godin Leisure Time Exercise Questionnaire, however only the post-chemotherapy GLTEQ questionnaire was analyzed for the purposes of this study.

Data Analyses

The Statistical Package for Social Sciences (SPSS, Version 19) was used for descriptive statistics, bivariate correlation, analysis of variance (ANOVA), analysis of covariance (ANCOVA), and hierarchical multiple regression. Exercise behavior was categorized using the scoring method developed by Godin (Godin, 2011), which outlines a scoring method for the GLTEQ that divides the total Leisure Score Index into three categories: insufficiently active (LSI<14), moderately active (LSI

of 14-23), and active (LSI $\geq$ 24). Descriptive statistics were conducted for categorical variables, including percentages and frequencies, as well as means, standard deviations, and ranges for continuous variables. A Pearson correlation was performed to examine the association between each of the seven cognitive measures and the self-report measure of exercise after chemotherapy. ANOVA was used to determine differences in these seven cognitive tests among three after-chemotherapy exercise groups, namely, an insufficiently active/sedentary group, a moderately active group, and an active group. Further, ANCOVA, controlling for estimated IQ from the WTAR, was conducted to determine whether differences still existed when controlling estimated IQ among the three post-chemotherapy exercise groups. Given that cognitive performance could be associated with factors such as age, education, IQ, anxiety, depression, and exercise, the current analysis applied hierarchical regression to understand how such a set of predictors would explain performance on the cognitive tests. An alpha level was set at .05 for all analyses.

Hypotheses

Hypothesis 1: Breast cancer survivors with higher reported weekly exercise levels will have better cognitive performance than those with lower weekly exercise levels. Cognitive performance has been evaluated by seven solid-psychometric test scores: FAS, CVLT, Digit Span Forward, Digit Span Backward, Digit Span Total, PASAT, and Coding. Individuals who report greater levels of exercise will show higher scores on measures of cognitive performance than those who report lower levels of exercise.

H1a. After controlling for estimated IQ, breast cancer survivors with higher weekly exercise levels will have better cognitive performance than those who report lower weekly exercise levels.

Hypothesis 2: Cancer survivors' cognitive test performance will be explained by a set of logically related predictors supported by literature --age, education, estimated IQ, anxiety, depression, and post-chemotherapy exercise.

CHAPTER FOUR

Results

Demographic Characteristics of the Sample

The total sample was comprised of 60 female participants who ranged from 38 - 71 years of age. Mean age was 57.78 years (*SD*=8.64) and mean years of education was 15.07 (*SD*=2.36). Most participants were Caucasian (90%). Ten participants (16.7%) had a previous cancer diagnosis before their breast cancer diagnosis, of which eight individuals had received chemotherapy, while the remaining 50 (83.3%) participants had no previous cancer diagnosis. Of those with previous cancer diagnoses, six individuals had been diagnosed with breast cancer and one participant each had been diagnosed with basal cell carcinoma, pancreatic cancer, and skin cancer. At the time of study, considering the 53 participants who were within the working ages of 18-65 years old, 21 individuals (39.6%) were employed, while 23 (43.4%) were unemployed, and the remainder (*n*=9) declined to answer. The average time since completion of chemotherapy was 12.69 months (*SD*=6.91). Twenty-two participants (36.7%) had received DDAC+T, and other chemotherapy drug regimens received by participants included TC (20%), AC (1.7%), AC+T (10%), CEF/FEC+T (6.7%), and others (25%). The majority of women (76.7%) had received endocrine therapy of some form including Tamoxifen (18.3%), Arimidex (23.3%), Aromasin (1.7%), or Femara (28.3%). Most (70%) had received radiation as well. Fourteen (23.3%) reported having been treated with immunotherapy.

With regard to mental health within the sample, 13.3% reported having been diagnosed with depression or bipolar disorder prior to their cancer diagnosis; however, all of these individuals reported that their symptoms were being managed by treatment. When asked about family history of dementia 23 participants (38.3%) reported a family history of dementia while 37 (61.7%) did not (Table 1).

Subjective Evaluation of Chemo brain and Chemotherapy-related Symptoms

When asked about subjective impressions of cognitive symptoms, 31 participants (51.7%) reported believing that they had attention problems, 41 (68.3%) reported memory impairment, 24 (40%) endorsed difficulties in problem-solving ability, and 40 (66.7%) believed that they were suffering from chemo brain. With regard to fatigue, 31 participants (51.7%) believed that they felt more fatigued now than prior to chemotherapy, while 30 (50%) believed that fatigue had significantly impacted their ability to think clearly. Additionally, 26 individuals (43.3%) believed that chemotherapy had significantly impacted their exercise behavior (Table 2).

Group Characteristics for Sedentary, Moderately Active, and Active Exercise Groups

The sedentary group contained 24 participants. Mean age was 58.67 (*SD* = 9.30) and mean education was 14.75 years (*SD* = 2.79), with an estimated IQ mean of 105.33 (*SD*= 6.39). *The moderately active group* consisted of 18 participants. Mean age for this group was 57.33 (*SD* = 9.10), mean education was 15.06 years (*SD* = 1.92) and estimated IQ mean was 109.78 (*SD* = 5.93). *The active group* contained 18 participants. Mean age was 57.06 (*SD* = 7.57), mean education was 15.50 years (*SD* = 2.18), and estimated IQ was 104.22 (*SD* = 6.20). There were no significant differences in age or education across groups (Table 3).

Cognitive Functioning in Sedentary, Moderately Active, and Active Exercise Groups

All participants' overall means, standard deviations, and ranges of neuropsychological measures are reported in Table 4. Means, standard deviations, and ranges for neuropsychological scores between exercise groups are described in Table 5. Using ANOVA, only CVLT (p=.001) and Digit Span Backward (p=.057) showed significant or nearly significant differences between group scores. Upon further examination of the LSD post hoc tests, the significant differences on the CVLT were between the sedentary and moderately active groups, with a difference of -8.06 (p=.004) as well as

between moderately active and active groups with a difference of 10.56 (p=.001). On digit span backward, there was a significant difference in scores between sedentary and moderately active groups of 1.54 (p=.022).

Using ANCOVA and controlling for estimated IQ, both CVLT (p=.012) and Digit Span Backward (p=.004) still maintained significant differences between exercise groups. On the CVLT, differences were between the sedentary and moderately active groups (*mean difference*= -6.84, p=.018) as well as moderately active and active groups (*mean difference*=9.04, p=.004). On Digit Span Backward, differences were between sedentary and moderately active groups (*mean difference*=2.09, p=.002) as well as moderately active and active groups (*mean difference*= -1.97, p=.007). Additionally Coding showed significant differences (p=.055) between sedentary and active groups (*mean difference*= -0.45, p=.048) as well as moderately active and active groups (*mean difference*= -0.57, p=.027) after controlling for estimated IQ (Table 5).

Given that cognitive function can be related to factors such as age, education, IQ, anxiety, depression, and exercise, these predictors were examined by hierarchical regression, using the following regression steps: step 1 (age and education), step 2 (estimated IQ), step 3 (anxiety and depression), and step 4 (exercise after chemotherapy). The bivariate correlations showed that post-chemotherapy exercise was significantly correlated with PASAT (r=-.21, p=.050), but did not have significant correlations with any other cognitive test measures. Estimated IQ, however, was significantly correlated with FAS (r=.33, p=.006), CVLT (r=.32, p=.006), Digit Span Backward (r=.22, p=.044), Digit Span Total (r=.35, p=.003), PASAT (r=.38, p=.001), and Coding (r=.38, p=.001). Estimated IQ showed moderate correlations with the above cognitive tests. Age was significantly correlated with PASAT (r=-.22, p=.049), education was significantly correlated with Coding (r=.27, p=.019), and anxiety was significantly correlated with CVLT (r= -.26, p=.023).

Depression was significantly correlated with Coding (r=-.24, p=.034). Detailed data regarding correlations between these predictors and cognitive tests may be found on Table 6.

CVLT and three post-chemotherapy exercise groups. On the CVLT, means were 52.17 (*SD*=10.04), 60.22 (*SD*=7.31), and 49.67 (*SD*=7.92) for the sedentary, moderately active and active groups, respectively. Using ANOVA to test the hypothesis that individuals who report greater levels of exercise will show higher scores on measures of cognitive performance than those who report lower levels of exercise, results revealed significant differences among after-chemotherapy exercise groups (F=7.40, p=.001). Further, according to the LSD post hoc tests, the significant differences were between the sedentary and moderately active groups (*mean difference*= -8.06, p= .004) as well as the moderately active and active groups (*mean difference*=10.56, p=.001). When estimated IQ was used as a covariate (F(1,56)=2.21, p=.142, η=.19), the significant differences in CVLT between exercise groups remained F(2,56)=4.19, p=.012 , η=.38. Using hierarchical regression, we found that the 28% of variance in CVLT scores could be explained by the set of the predictors. Estimated IQ significantly explained 16% of the variance in the CVLT (p= .001) and the anxiety and depression explained 9% of the variance in the CVLT (p= .036) (Table 7).

FAS and three post-chemotherapy exercise groups. The mean scores for the sedentary, moderately active, and active groups on the FAS Verbal Fluency test were 46.25 (*SD*=7.51), 44.50 (*SD*=7.16), 47.33 (*SD*=9.20), respectively. No significant differences were found among the three post-chemotherapy exercise groups (F=0.58, p=0.561) on the FAS verbal fluency test. After controlling for estimated IQ (F(1,56)=10.95, p=.002 , η=.40), there were still no significant differences between the three exercise groups F(2,56)=2.56, p=.087, η=.29.Using hierarchical regression, we found that 14% of the variance in FAS scores could be explained by the set of predictors of age, education, IQ, anxiety, depression, and post-chemotherapy exercise**.**

Digit Span Forward and three post-chemotherapy exercise groups. On Digit Span Forward, the means were 10.00 (*SD*=2.47), 10.00 (*SD*=2.77), and 10.50 (*SD*=2.28) for the sedentary, moderately active, and active groups, respectively. No differences were significant (F=0.25, p=0.779) on the Digit Span Forward test. After controlling for estimated IQ (F(1,56)=2.61, p=.112, η=.21), there were still no significant differences between exercise groups F(2,56)=0.64, p=.530, η= 0.15.Using hierarchical regression, 6% of the variance in Digit Span Forward scores could be explained by the set of predictors of age, education, IQ, anxiety, depression, and post-chemotherapy exercise.

Digit Span Backward and three post-chemotherapy exercise groups. On Digits Backward, means were 10.38 (*SD*=1.84), 8.83 (*SD*=2.23), and 10.11 (*SD*=2.27) for the sedentary, moderately active, and active groups, respectively, which resulted in a nearly significant difference (F=3.01, p=0.057) on the Digit Span Backward test. According to the LSD post hoc tests, the significant difference was between the sedentary and moderately active groups (*mean difference*= 1.54, p=.022). Using ANCOVA to control for estimated IQ (F(1,56)=8.67, p=.005, η=.37), the significant differences between exercise groups remained F(2,56)=5.98, p=.004, η=.42. Additionally, using hierarchical regression, 22% of the variance in Digit Span Backward scores could be explained by the following predictors: age, education, estimated IQ, anxiety, depression, and post-chemotherapy exercise. Anxiety and depression symptoms significantly explained 11% of the variance of Digit Span Backward scores (p=.032).

Digit Span Total Score and three post-chemotherapy exercise groups. On Digit Span total score, means were 10.63 (*SD*=2.34), 10.00 (*SD*=2.20), and 10.33 (*SD*=2.11) for the sedentary, moderately active, and active groups, respectively. There was no significant difference among the three post-chemotherapy exercise groups (F=0.40, p=0.669). After controlling for estimated IQ (F(1,56)=11.20, p=.001, η=.41), there were still no significant differences between exercise groups,

$F(2,56)=1.99$, $p=.146$, $\eta= .26$.Using hierarchical regression, 17% of the variance in Digit Span Total scores could be explained by the set of predictors of age, education, estimated IQ, anxiety, depression, and post-chemotherapy exercise. Estimated IQ significantly explained 9% of the variance in Digit Span Total scores ($p=.020$) and was the significant predictor in the regression model of Digit Span Total scores ($\beta= 0.33$, $p= .020$).

PASAT and three post-chemotherapy exercise groups. On the PASAT, means for the sedentary, moderately active, and active groups were 45.49 ($SD=10.60$), 42.11 ($SD=13.35$), and 36.19 ($SD=18.77$) respectively. No significant differences among the three post-chemotherapy exercise groups were seen ($F=2.20$, $p=0.121$) on the PASAT. When estimated IQ was used as a covariate ($F(1,56)=10.12$, $p=.002$, $\eta=.39$), no significant differences were observed between three exercise groups, $F(2,56)=2.52$, $p=.090$, $\eta=.29$. Additionally, using hierarchical regression, 30% of the variance in PASAT scores could be explained by the following predictors: age, education, estimated IQ, anxiety, depression, and post-chemotherapy exercise. Estimated IQ significantly explained 16% of the variance ($p=.001$) and total post-chemotherapy exercise significantly explained 6% of the variance ($p=.041$).

Coding and three post-chemotherapy exercise groups. On Coding, means were 0.56 ($SD=0.78$), 0.69 ($SD=0.65$), and 0.94 ($SD=0.91$) for the sedentary, moderately active and active groups, respectively. No significant differences were found among the three post-chemotherapy exercise groups ($F=1.27$, $p=0.290$) on the Coding test. However, after controlling for estimated IQ ($F(1,56)=13.72$, $p=.000$, $\eta=.44$), significant differences were observed between exercise groups, $F(2,56)=3.05$, $p=.055$, $\eta=.31$. Using hierarchical regression, 19% of the variance in Coding scores could be explained by the set of predictors of age, education, estimated IQ, anxiety, depression, and

post-chemotherapy exercise. Estimated IQ significantly explained 9% of the variance in Coding scores (p=.015).

CHAPTER FIVE

Discussion

The current study aimed to examine the relationship between cognitive functioning and self-reported exercise behaviors in breast cancer survivors who had undergone chemotherapy. Findings demonstrated significant differences between exercise groups on measures of declarative verbal memory (CVLT), working memory (Digit Span Backward), and processing speed (Coding). On the CVLT, significant differences occurred between the moderately active and active groups, with the moderately active group having a higher mean score than the active group. Significant differences were also seen between the moderately active and sedentary group, with the moderately active group having a higher mean score than the sedentary group. After controlling for estimated IQ, both the CVLT and Digit Span Backward still maintained significant differences between exercise groups. On the CVLT, differences were between the sedentary and moderately active groups as well as moderately active and active groups. On Digit Span Backward, differences were between sedentary and moderately active groups and also between moderately active and active groups, with the active group having a higher mean score than the moderately active group. In addition to these two tests, Coding also showed significant differences between sedentary and active groups as well as between moderately active and active groups after controlling for estimated IQ. On Coding, however, the active group had a significantly higher mean than both moderately active and sedentary groups.

Results from this current investigation cannot easily be compared with existing literature, which has primarily focused on cognitive functioning and active exercise interventions in other clinical populations (Deslandes et al., 2009; Feinstein, 2011; Podewils et al., 2005). Most research has assessed cognitive functioning in individuals with neurological diseases such as multiple sclerosis or Alzheimer's disease after an exercise intervention, and far fewer studies have used retrospective self-

report measures of exercise (Baker et al., 2010; Hassmen et al., 1992; Lautenschlager et al., 2008). However, the general conclusions from existing literature with these other clinical populations, despite differences in study design, support the notion that cognitive functioning is positively correlated with exercise activity. While study design differences limit comparability with the majority of available literature, it is still surprising that exercise groups in this study did not show differences in cognitive function in relation to levels of self-reported exercise as expected and one possible explanation is that a self-report measure of exercise was used to assess physical activity. When an exercise *intervention* is used as part of a study design, versus a self-report of exercise history, outcomes may differ. For example, during an exercise intervention, exercise group participants may perform monitored, regular exercise per prescription of a researcher at levels which may or may not be similar to their typical exercise behavior. Therefore exercise performed during interventions may not be reflective of a person's "average" or typical everyday exercise behaviors. The results from this investigation, however, do suggest the potential for a dosing effect of exercise, wherein too little or too much exercise may not be related to cognition, though a moderate amount of exercise may be associated. For example, by observing which exercise groups displayed significant differences in cognitive test scores, we can see that in the CVLT, the moderately active group, had an overall higher mean score than both sedentary and active groups. This of course may relate to the nature of the current samples and the higher mean IQ found in the moderate exercise group. Nevertheless, it is difficult to know why some of the results of this investigation are counterintuitive and it is possible that this may be related to the limitations of the study itself.

Further, a set of logically related predictors such as, age, education, estimated IQ, anxiety, depression, and total LSI exercise score explained a small proportion of variance in scores on cognitive measures. The most influential predictor appears to be an estimate of pre-morbid IQ, which explained

variance in scores on six out of the seven cognitive measures examined. However, the remaining predictors played a significant role in scores on at least one measure as well. It is possible that there was not sufficient variability in cognitive performance to identify significant predictors, as scores on cognitive tests fell within a relatively small range of (generally normal) scores. Additionally, participants in the sample had similarly high education levels, which may have restricted the observed correlations.

Implications for the Breast Cancer Survivor Population

In order to understand these differences in cognitive performance between groups and how they may impact cancer survivors in their daily living, it is essential to recognize the cognitive domains and skills fundamental to the measures that displayed significant differences. The CVLT measures verbal learning and episodic memory (Delis et al., 2000). Impairment in verbal learning and episodic memory can make it difficult for individuals to follow verbal instructions, whether on the job, at school, or within interpersonal relationships. For example, names of people, information acquired during important meetings, locations, and times all are types of information in which episodic memory is utilized. Reductions in episodic memory can impact what a person remembers about their day-to-day living, including information relevant to personal relationships, career and academic matters. Digit Span (i.e., digit span forward and digit span backward) measures simple attention and working memory (Wechsler, 2008a; Wechsler, 2008b). Working memory can be described as the holding of most recently activated portion of long-term memory and the manipulation of this information over a short period of time (Sternberg, 2009). Related difficulties may include trouble keeping in memory a set of verbal instructions or information someone has just given such as a phone number or grocery list. WAIS Coding (Wechsler, 2008a; Wechsler, 2008b), which showed significant differences between exercise groups after controlling for estimated IQ, measures information processing speed.

Processing speed encompasses the time it takes an individual to both react as well as respond to presented stimuli (Wiig, 2009). Individuals with reduced processing speed may take longer to scan visually presented material such as documents and/or have difficulty performing basic arithmetic calculations or simple reasoning and problem solving tasks, as well as other difficulties. Each of these neuropsychological tests measures cognitive domains that affect practical aspects of an individual's daily functioning. If differences in memory, processing speed and their related functions truly exist in breast cancer patients and vary with exercise levels, this finding may have important implications for rehabilitation after cancer treatment. Namely, exercise at optimal dosages may have benefits within these specific cognitive domains for recovering patients who show difficulties.

Limitations

Several limitations to the present study should be considered. First, the sample size was small, predominantly Caucasian, and of similar educational and socioeconomic background, which may have an impact on generalizability. The range in cognitive test scores for this sample was also narrow, with most participants scoring in the normal range on most neuropsychological measures. As such, this was a generally non-cognitively impaired sample, which may also have affected results, since most of the exercise literature supports beneficial effects of exercise in cognitively impaired populations.

A second limitation was the inherent bias in responding to self-report measures, including the GLTEQ. Participants' self-reports of their exercise behavior may consciously or unconsciously be influenced by recall biases as well as factors such as social desirability. Therefore, more objective measures of exercise may be preferable. Previous studies in other clinical populations have incorporated more of a randomized controlled trial design. For example, Lautenschlager and colleagues (2008) used a usual care control group and a physical activity group in which exercise group participants had to perform 150 minutes of moderate-intensity physical activity per week, to

determine impact of exercise on cognitive performance on tests. In another study, Prakash and colleagues (2007) assessed the role of exercise by measuring peak oxygen consumption and having participants undergo an exercise test on a cycle ergometer. Future studies examining exercise effects should similarly utilize randomized controlled trial designs that include objective measurements, such as a pedometer, to assess and monitor exercise activity.

Despite these limitations, to our knowledge, this study is the first of its kind to examine the relationship between cognitive functioning and a self-reported history of exercise within the breast cancer survivor population.

Future Directions

Future research should include larger samples, the use of objective measures (e.g., pedometer, fitness assessments), and should examine what exercise level provides optimal benefits for cognitive health and overall wellbeing. Physical activity has shown many benefits for a vast array of clinical populations and its role in cognitive functioning in breast cancer survivors is an area that continues to warrant further exploration.

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Table 1

Participants' Characteristics (n=60)

Variable	*Mean (SD)*	*Range*
Age (years)	57.78 (8.64)	38-71
Education (years)	15.07 (2.36)	9-20
Estimated Premorbid IQ	106.33 (6.52)	90 - 119
Time Since Completion of Chemotherapy (months)	12.69 (6.91)	3 – 23.8
Variable	Frequency [a] *n*,(%)	
Race/Ethnicity		
White	54 (90%)	
Non-White	6 (10%)	
Stage of Cancer at Diagnosis		
I	11 (18.3%)	
II	32 (53.3%)	
III	14 (23.3%)	
Radiation	42 (70%)	
Hormone Therapy	46 (76.7%)	
Employment	25 (41.7%)	
Employment in those within working age (<66 years)	21 (39.6%)	
Previous Cancer Diagnosis	10 (16.7%)	
Treated with Chemo for previous cancer	8 (13.3%)	
Type of Previous Cancer Diagnosis		
Basal Cell Carcinoma	1 (1.7%)	

Breast	6 (10.0%)
Pancreatic	1 (1.7%)
Family History of Dementia	23 (38.3%)
MDD/ Bipolar Disorder	8 (13.3%)
Receiving Treatment for MDD/Bipolar	8 (13.3%)
Chemo Drugs Used	
AC	1 (1.7%)
AC+T	6 (10.0%)
DDAC+T	22 (36.7%)
CEF/FEC+T	4 (6.7%)
TC	12 (20.0%)
Unknown	5 (8.3%)
Other	10 (16.7%)
Menopausal Status at Time of Testing	
Pre-	3 (5.0%)
Peri-	1 (1.7%)
Post-	50 (83.3%)
Endocrine Regimen	
Tamoxifen	11 (18.3%)
Arimidex	14(23.3%)
Aromasin	1 (1.7%)
Femara	17 (28.3%)
Surgery	59 (98.3%)

Immunotherapy/BRMs	14 (23.3%)

Note. [a.] indicates that responses are positive, %yes

Table 2

Subjective Report of Chemo Brain-Related Symptoms

Variable	Frequency[a] *n* (%)
Attention Problems	31 (51.7%)
Memory Problems	41 (68.3%)
Problem-Solving Ability Problems	24 (40.0%)
Chemo brain	40 (66.7%)
Increased Fatigue Since Chemotherapy	31 (51.7%)
Fatigue Impacts on Thinking Ability	30 (50.0%)
Exercise Level Affected by Chemotherapy	26 (43.3%)

Note. [a]·indicates that responses are positive, %yes

Table 3

Exercise Groups Sample Characteristics

	Group (*n*, % of sample)		
	Sedentary (24, 40%)	Moderately Active (18, 30%)	Active (18, 30%)
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Age	58.67 (9.30)	57.33 (9.10)	57.06 (7.57)
Years of Education	14.75 (2.79)	15.06 (1.92)	15.50 (2.18)
Estimated IQ	105.33 (6.39)	109.78 (5.93)	104.22 (6.20)

Table 4

Descriptive Statistics for Neuropsychological Measures: Entire Sample

Measure	**Mean (*SD*)**	**Range**
Digit Span		
DSFSS (Digit Span Forward Scaled Score)	10.15 (2.48)	5 – 19
DSBSS (Digit Span Backward Scaled Score)	9.83 (2.16)	5 – 15
DSTotalSS (Digit Span Total Scaled Score)	10.35 (2.21)	6 – 17
PASAT		
PTscore (PASAT T Score)	41.68 (14.55)	1 – 59
Coding		
CDz (Coding z score)	0.71 (0.79)	-1.33 – 2.33
FAS T score	46.05 (7.90)	29 – 61
CVLT total T Score	53.83 (9.57)	30 – 71
WTAR		
Standard Score	109.02 (9.01)	86 – 126
Estimated IQ	106.33 (6.52)	90 - 119

Note. PASAT=Paced Auditory Serial Addition Test; FAS=F-A-S Verbal Fluency Task; CVLT= California Verbal Learning Test; WTAR= Wechsler Test of Adult Reading

Table 5

Neuropsychological Test Results by Exercise Groups

Test	**Sedentary (*n*=24)** **Mean (*SD*)**	**Moderately Active (*n*=18)** **Mean (*SD*)**	**Active (*n*=18)** **Mean (*SD*)**	***F***	***P***
FAS					
Unadjusted	46.25 (7.51)	44.50 (7.16)	47.33 (9.20)	0.58	0.561
Adjusted	46.77 (1.51[a])	42.71 (1.81 [a])	48.43 (1.76 [a])	2.56	.087
CVLT					
Unadjusted	52.17 (10.04)	60.22 (7.31)	49.67 (7.92)	7.40	.001
Adjusted	52.44 (1.76 [a])	59.28 (2.12 [a])	50.24 (2.06 [a])	4.19	.012
Digit Span Total					
Unadjusted	10.63 (2.34)	10.00 (2.20)	10.33 (2.11)	0.40	.669
Adjusted	10.77 (0.42 [a])	9.49 (0.51 [a])	10.64 (0.49 [a])	1.99	.146
DS Forward					
Unadjusted	10.00 (2.47)	10.00 (2.77)	10.50 (2.28)	0.25	.779
Adjusted	10.09 (0.51 [a])	9.71 (0.61 [a])	10.68 (0.59 [a])	0.64	.530

DS Backward					
Unadjusted	10.38 (1.84)	8.83 (2.23)	10.11 (2.27)	3.01	.057
Adjusted	10.50 (0.40 [a])	8.41 (0.49 [a])	10.37 (0.47 [a])	5.98	.004
PASAT					
Unadjusted	45.49 (10.60)	42.11 (13.35)	36.19 (18.77)	2.20	.121
Adjusted	46.39 (2.72 [a])	39.01 (3.27 [a])	38.09 (3.18 [a])	2.52	.090
Coding					
Unadjusted	0.56 (0.78)	0.69 (0.65)	0.94 (0.91)	1.27	.290
Adjusted	0.61 (0.15 [a])	0.49 (0.18 [a])	1.06 (0.17 [a])	3.05	.055

Note. FAS=F-A-S Verbal Fluency Task; CVLT=California Verbal Learning Test; DS=Digit Span; PASAT=Paced Auditory Serial Addition Test; [a] refers to standard error; "Adjusted" refers to data adjusted to control for estimated IQ.

Table 6

Correlations between Predictors and Performance on Cognitive Measures

	FAS	CVLT	Digit Span Forward	Digit Span Backward	Digit Span Total	PASAT	Coding
	r	*r*	*r*	*r*	*r*	*r*	*r*
Age	.11	-.10	.09	.15	.07	**-.22***	-.02
Education	.09	-.08	.02	.16	.15	.12	**.27***
Estimated IQ	**.33***	**.32***	.18	**.22***	**.35****	**.38****	**.38****
Anxiety	.033	**-.26***	-.10	.19	.08	.00	-.10
Depression	-.12	-.06	-.07	-.08	-.11	-.18	**-.24***
Total LSI	.07	-.08	.12	-.12	-.04	**-.21***	.17

Note: * indicates $p \leq .05$, ** indicates $p \leq .005$; PASAT=Paced Auditory Serial Addition Test; FAS=F-A-S Verbal Fluency Task; CVLT= California Verbal Learning Test; LSI= Leisure Score Index

Table 7

Hierarchical Multiple Regression

	CVLT		FAS		DSF		DSB	
	ΔR^2 (*p*)	***B* (*p*)**	**ΔR^2 (*p*)**	***B* (*p*)**	**ΔR^2 (*p*)**	***B* (*p*)**	**ΔR^2 (*p*)**	***B* (*p*)**
Step 1	.02 (.554)		.03 (.473)		.01 (.738)		.07 (.149)	
Age		-.12 (.374)		.14 (.315)		.10 (.450)		.20 (.131)
Edu		-.11 (.419)		.12 (.364)		.05 (.725)		.21 (.120)
Step 2	.16 (.001**)		.09 (.024*)		.03 (.218)		.02 (.267)	
IQ		.44 (.001**)		.32 (.024*)		.18 (.218)		.16 (.267)
Step 3	.09 (.036*)		.03 (.434)		.01 (.850)		.11 (.032*)	
Anxiety		-.45 (.012*)		.25 (.199)		-.11 (.571)		.49 (.009*)
Depression		.41 (.029*)		-.18 (.364)		.08 (.702)		-.36 (.067)
Step 4	.00 (.922)		.00 (.672)		.02 (.310)		.03 (.168)	
Exercise		-.01 (.922)		.06 (.672)		.14 (.310)		-.18 (.168)
R^2	.28		.14		.06		.22	

	DS Total		PASAT		Coding	
	ΔR^2 (*p*)	***B* (*p*)**	**ΔR^2 (*p*)**	***B* (*p*)**	**ΔR^2 (*p*)**	***B* (*p*)**
Step 1	.03 (.388)		.05 (.217)		.07 (.113)	
Age		.11 (.412)		-.20(.141)		.04 (.737)
Edu		.17 (.208)		.08 (.556)		.28 (.038*)
Step 2	.09 (.020*)		.16 (.001**)		.09 (.015*)	
IQ		.33 (.020*)		.44 (.001**)		.33 (.015*)
Step 3	.04 (.251)		.03 (.406)		.01 (.721)	
Anxiety		.31 (.102)		.24 (.185)		.08 (.677)
Depression		-.20 (.313)		-.20 (.279)		-.15 (.436)
Step 4	.00 (.609)		.06 (.041*)		.02 (.329)	
Exercise		-.07 (.609)		-.25 (.041*)		.13 (.329)
R^2	.17		.30		.19	

Note: * indicates p≤.05, ** indicates p≤.005; Edu= Education; PASAT=Paced Auditory Serial Addition Test; FAS=F-A-S Verbal Fluency Task; CVLT= California Verbal Learning Test; DSF=Digit Span Forward; DSB=Digit Span Backward; DS Total= Digit Span Total

Appendix

Characteristics and Psychometric Properties of Measures

The assessments used in this study were chosen based on their psychometric properties, utility in measuring specific aspects of cognitive functioning, and use among other relevant clinical populations.

A. Measures of Cognitive Functioning

The FAS-Test is a measure of verbal fluency. The FAS-Test, specifically, measures phonemic fluency, which assesses a person's ability to produce words spontaneously while under a time restricted condition (Strauss, Sherman, & Spreen, 2006). Total scores were converted into T-scores adjusted for demographic data for use in this study.

On the FAS-Test, an examinee must say as many words as possible that begin with the designated letter for that trial within 60 seconds. This procedure is repeated for three trials, with one trial for each of the letters F, A, and S (Strauss et al., 2006). Repetitions, proper nouns, and wrong words, and variations of the same word are not permitted. The total score is determined by the sum of the total number of acceptable words for the three trials (Strauss et al., 2006). Internal consistency reliability is high (r=.83) (Tombaugh, Kozak, & Rees, 1999). Studies also indicate adequate test-retest reliability (r=.74) (Tombaugh et al., 1999). The FAS verbal fluency task is highly correlated with other tasks of phonemic fluency. This measure appears sensitive to traumatic brain injury as well as cognitive slowing associated with mood or thought disorders such as depression (Strauss et al., 2006).Because the FAS test has demonstrated an ability to assess cognitive dysfunction in various populations, it will also likely be

useful in detecting cognitive impairment within cancer populations, specifically in individuals who have completed chemotherapy for breast cancer.

The California Verbal Learning Test- Second Edition, Standard Form (CVLT-II) is a measure of verbal learning and memory. It consists of a list-learning task that involves multiple trials. Raw and standardized scores were computed using the CVLT-II scoring software and converted into T-scores adjusted for age and gender (Strauss et al., 2006).

It can be administered to individuals ages 16-89. In this test, the subject is verbally presented with word List A, which consists of 16 items, and then immediately asked to recall words from the list. This process is repeated for five trials. The first list contains 16 words from four different categories: furniture, ways of traveling, vegetables, and animals. After these first five trials, a second 16-word list (List B) is presented, containing words from categories such as vegetables, animals, musical instruments, and parts of a house. This is followed by short-delay free-recall as well as short-delay cued recall of List A. After a 20-minute delay, during which the subject participates in other cognitive tasks, the subject is administered long-delay free-recall, long-delay cued-recall, and recognition trials of the first list (List A). Raw and standardized scores are computed using the CVLT-II scoring software and converted into T-scores adjusted for age and gender (Strauss et al., 2006).

Reliability studies indicate high internal consistency for the five immediate recall trials. Split-half reliability is high for normative samples (r=. 94) as well as clinical samples (r=.96). Cronbach's alphas are also high for the five immediate-recall trials for both the normative (r=.82) as well as clinical (r=.83) samples. The CVLT-II demonstrates

high test-retest reliability for scores measuring overall achievement level such as Total Recall on trials 1-5, Short Delay Free Recall, Long Delay Free Recall, and Total Recognition Discriminability (Strauss et al., 2006).

Digit Span is a subtest of the Wechsler Adult Intelligence Scale- Fourth Edition (WAIS-IV) and measures attention and freedom from distractibility (Lezak et al., 2004) and consists of three different trials. Examiners present increasing sets of numbers and participants are required to repeat the sequences of numbers.

Digit Span comprises three different trials: Digits Forward, Digits Backward, and Digits Sequencing. Each of these three trials consists of seven pairs of random number sequences which the examiner reads aloud at a rate of one number per second. Examinees repeat the numbers back in the exact sequence that they were first recited. The task is discontinued once an examinee makes an error in both sequences in a pair. The number of digits that an examinee can recall correctly is their span. A raw score for each individual trial is calculated by counting the number of digits that are recalled correctly. The raw scores for each trial are also added together to form a total score, which is transformed into a scale score adjusted for age based on normative data (Wechsler, 2008). For this present study, raw scores for Digit Span Forward, Digit Span Backward, and a total score of all three trials were converted into scaled scores adjusted for age.

The Digit Span subtest demonstrates a split-half reliability of r=.93 and a test-retest reliability of r=.83 (Kaufman & Lichtenberger, 1999). Research demonstrates a moderate correlation between Digit Span Total Score and other WAIS-IV measures of memory including Letter-Number Sequencing (r=.69) and Arithmetic (r=.60). It is also

moderately correlated with the RBANS Attention composite score (r=.65) (Wechsler, 2008).

The Paced Auditory Serial Addition Test- 3" interval (PASAT-3) is a serial-addition task designed to evaluate auditory information processing speed, working memory, and sustained and divided attention (Strauss et al., 2006). A series of one-digit numbers are presented and the examinee must consecutively add pairs of numbers so that each number is added to the one presented immediately prior to it. Total number of correct responses is recorded, with a maximum score of 60 and percentage of errors, including omissions, are computed (Strauss et al., 2006). Demographically corrected scores were computed into T-scores for the purposes of this investigation.

Although two versions of the PASAT are available, the 3-second version was selected for this study. The examinee is not required to keep a running total, but rather add each digit to the digit before it. The numbers are presented at the rate of one number every three seconds through a compact disk recording. A practice trial is administered first, followed by the 61-item test (Strauss et al., 2006). Scores on the four PASAT trials have demonstrated a very high Cronbach's alpha (r=.90) (Crawford, Obonsawin, & Allan, 1998) and are highly correlated even across the different pacings (r=.75-.95) (Macleod & Prior, 1996). Correlations for test-retest with short intervals between testing was high (r>.90) (McCaffrey et al., 1995). Correlations for test-retest over longer intervals appears to be slightly lower, but still sufficient (r=.73) (Schachinger, Cox, Linder, Brody, & Keller, 2003). Three-month long-term stability is also high (r=.83-.96) (Sjogren, Thomsen, & Olsen, 2000). The PASAT is moderately correlated to tests such as the d2 Test, Trail Making Test, Digit Span, Auditory Consonant Trigrams, Visual Search

and Attention Test, and the Stroop test, which are all measures of attention (Strauss et al., 2006).

The PASAT is sensitive to head-injury. Research suggests that it may be a better indicator of information-processing capacity than other measures of attention such as the Trail Making Test, Digit Span, and the attention/concentration subtest of the WMS-R (Cicerone & Azulay, 2002; Strauss et al., 2006). The PASAT is sensitive to and has commonly been used to measure cognitive functioning in individuals with multiple sclerosis (Kalmar, Bryant, Tulsky, & DeLuca, 2004; 1997). It is also sensitive to impairment in patients with moderate hypoglycemia, chronic fatigue syndrome, schizophrenia spectrum disorders, and schizotypal personality disorder. It can also assess cognitive functioning in chronic pain patients (Strauss et al., 2006). Based on its effectiveness in the detection of cognitive functioning across varied sample populations, the PASAT will likely also be of use within the population currently being studied.

Digit Symbol Coding is a subtest of the Wechsler Adult Intelligence Test- Fourth Edition (WAIS-IV) that measures psychomotor processing speed and divided attention. Examinees are to fill in rows of squares, matching numbers to symbols under a time-restricted condition (Wechsler, 2008). Raw scores were converted into z-scores for use in this investigation.

In the Coding task, examinees are presented with rows of blank squares, each paired with a randomly assigned number from one to nine. At the top of the page, there is a key containing numbers one through nine, each paired with a random symbol. The examinees are to fill-in the empty squares with the symbol that corresponds to each number. The number of squares filled in determines the raw score (Lezak et al., 2004),

which is converted into a scaled score adjusted for demographically-normed data. The Coding subtest demonstrates a test-retest reliability of r=.86 (Strauss et al., 2006). Furthermore, it is moderately correlated with other tests of processing speed such as Symbol Search of the WAIS-IV (r=.65) and tests of attention such as the RBANS attention component (r=.56) (Wechsler, 2008).

The Coding subtest has demonstrated sensitivity in the assessment of a variety of clinical populations including dementia, individuals with tumor, chronic alcoholism and hypertension. It has been considered more sensitive in the detection of brain damage than other subtests of the Wechsler. Research suggests that even minor brain damage will result in lowered scores (Lezak et al., 2004). For these reasons, it was chosen for use within the breast cancer population in this study.

The Wechsler Test of Adult Reading (WTAR) is used to estimate an adult's premorbid overall intellectual functioning. This test requires a subject to read and pronounce correctly 50 phonetically irregular words on a list (Strauss et al., 2006). A raw score was first calculated by adding up total number of words pronounced correctly and was then converted into a standard score (Strauss et al., 2006), which as further transformed into an estimated IQ score.

The WTAR has shown good internal consistency (.90-.97) for an adult sample from the United States (Strauss et al., 2006). It has also demonstrated stability in performance over time with correlations of r >.90 for test-retest with small practice effects. WTAR is highly correlated with other measures used to assess reading, demonstrating correlations of r=.90 and r=.73 with the AMNART and the WRATR, respectively (Lezak et al., 2004). WTAR is moderately correlated with other measures of

memory such as the WMS-III (General memory, r=.49, Immediate memory, r=.47, working memory, r=.51) for a standardized sample (Strauss et al., 2006).

B. Self-Report Measures:

The Godin Leisure-Time Exercise Questionnaire (GLTEQ) is a self-report measure that assesses an individual's average weekly leisure-time exercise (Godin & Shephard, 1985). A modified version of the Leisure Score Index (LSI) from the Godin Leisure-Time Exercise Questionnaire (GLTEQ) was used to evaluate exercise behavior.

The GLTEQ contains two parts, the first consisting of open-ended questions regarding the average frequency of mild, moderate, and strenuous exercise that an individual engages in on a typical seven-day period (a week). It also includes descriptions of each category: mild (minimal effort), moderate (not exhausting), and strenuous (heart beats rapidly) as well as examples of types of activities that fall under each intensity category: mild (e.g. yoga, archery, bowling, golf, easy walking), moderate (e.g. fast walking, easy swimming, baseball), and strenuous (e.g. running, jogging, basketball). The second part consists of a multiple-choice question with the following choices: often, sometimes, never/rarely, to gauge how often an individual engages in regular activity long enough to perspire (Godin & Shephard, 1985). Additionally, we modified the questionnaire to inquire about the average length of time spent in each exercise session, allowing us to determine the average exercise time per week by multiplying the average frequency by the average duration engaged in exercise. The questionnaire is scored by multiplying the weekly frequencies of the various intensity levels of light, moderate, and strenuous exercise by three, five, and nine metabolic equivalents of task (METs), respectively.

The GLTEQ compares favorably in reliability and validity to other self-report measures of physical activity level (Milne, Gordon, Guilfoyle, Wallman, & Courneya, 2007; Rogers et al., 2006; Stevinson et al., 2007). The Leisure Score Index of the GLTEQ has demonstrated test-retest reliability of .62, after one month. Concurrent validity with maximum oxygen consumption and an accelerometer are .56 and .32, respectively (Jacobs, Ainsworth, Hartman, & Leon, 1993; Karvinen, Courneya, North, & Venner, 2007).

BIOGRAPHICAL SKETCH

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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Texas Christian University	B.S.	2010	Psychology
The University of Texas Southwestern School of Health Professions	M.R.C.	2013	Rehabilitation Counseling Psychology

Clinical Experience

2011-2012 UT Southwestern University Rehabilitation Services – Graduate Intern
2011-2012 Zale Lipshy University Hospital –Inpatient Psychiatric Unit Graduate Intern
2012 UT Southwestern Bariatric Surgery Clinic – Psychological Services Graduate Intern