ANALYSIS OF NEUROCOGNITIVE ELEMENTS OF ATTENTION

FOLLOWING CHEMOTHERAPY TREATMENT

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DEDICATION

to my family

Tim, Jolene, Kevin, Teresa, and Emma

we rock

ANALYSIS OF NEUROCOGNITIVE ELEMENTS OF ATTENTION FOLLOWING CHEMOTHERAPY TREATMENT

by

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Breast cancer affects approximately 123 out of 100,000 women per year in the United States, with 207,090 new cases estimated each year (Altekruse et al., 2010). Adjuvant chemotherapy has become a staple of care to improve long-term outcomes for several types of breast cancers (de Boer, Taskila, Ojajärvi, van Dijk, & Verbeek, 2009). Because of advances in treatment, the overall 5-year survival rate for breast cancer patients is now estimated at 89% (Altekruse et al., 2010). With increased survival comes a greater concern for issues related to quality of life, including cognitive function. Unfortunately, cancer treatments may result in cognitive changes or impairment, with

deficits ranging from minor to debilitating (Argyriou, Assimakopoulos, Iconomou, Giannakopoulou, & Kalofonos, 2011). The phenomenon of cognitive dysfunction following cancer treatment is often called "chemo-brain" by patients and in the media. Despite an increase in the number of published studies in recent years, many aspects of chemotherapy-related cognitive dysfunction remain poorly understood. The pattern of cognitive impairment and neurological damage (as seen on neuroimaging) is reflective of disruption of frontal subcortical networks (Meyers, 2008). Because attention and related constructs are of central importance in this so-called "subcortical profile," it is important to have a thorough understanding of how these domains are impacted by chemotherapy. However, available literature is difficult to interpret, in part because of various methodological factors, including the use of singular or otherwise limited neuropsychological tests, inconsistent use of tests across studies, and variability in the conceptualization of domains believed to be affected by chemotherapy (such as attention and related constructs). Thus, conclusions regarding attentional impairment in women treated for breast cancer are limited, and its role in the clinical syndrome known as chemo-brain remains poorly understood.

TABLE OF CONTENTS

CHAPTER ONE: Statement of the Problem 1

CHAPTER TWO: Review of the Literature 4

CHAPTER THREE: A Meta-Analysis of Neuropsychological Tests used to Detect Chemotherapy-Related Cognitive Dysfunction in Prospective Studies 32

CHAPTER FOUR: Analysis of Attention and Executive Function in Breast Cancer Survivors Exposed to Chemotherapy 65

CHAPTER FIVE: General Conclusions 101

APPENDIX A: Characteristics and Psychometric Properties of Measures 103

APPENDIX B: Additional Analyses 118

REFERENCES 134

LIST OF FIGURES

CHAPTER FOUR

FIGURE 1: Frequency of Clinically Significant Scores on Self-Report Measures... 79

FIGURE 2: Percentage of Impaired Scores by Neuropsychological Test..... 83

FIGURE 3: Rank Performance on Tests of Attention/Executive Function..... 86

LIST OF TABLES

CHAPTER TWO

TABLE 1: Mirsky and Duncan's Factors of Attention and Corresponding Neuropsychological Tests 21

TABLE 2: Selected Neuropsychological Tests Reported to Measure Various Domains of Cognitive Function 28

CHAPTER THREE

TABLE 1: Description of Studies Included in Meta-Analysis 40

TABLE 2: Participants' Demographic Data and Cancer-Related Characteristics 44

TABLE 3: Effect Sizes of Neuropsychological Tests by Domain 45

TABLE 4: Comparison of Effect Sizes and Practice Effects in Cancer and Control Groups 51

CHAPTER FOUR

TABLE 1: Sample Characteristics 78

TABLE 2: Self-Report Measures of Well-Being 80

TABLE 3: Descriptive Statistics for Neuropsychological Measures 81

TABLE 4: Frequency of Impaired Test Scores 82

TABLE 5: Demographic Characteristics (Mean, SD) by Impairment Status 84

TABLE 6: Mean (SD) and Frequency of Clinically Significant Self-Report Scores by Impairment Status 85

TABLE 7: Mean Rank Performance on Attention/Executive Function Tests 86

APPENDIX B

TABLE 1: Descriptive Statistics for Neuropsychological Measures at Different Criteria for Impairment 119

TABLE 2: Correlations between Neuropsychological and Self-Report Measures . 120

TABLE 3: Frequency of Endorsement of General Cognitive Complaints..... 122

TABLE 4: Frequency of Clinically Significant Self-Report Scores by Cognitive Complaint Status..... 123

TABLE 5: Neuropsychological Performance by Cognitive Complaint Status 125

TABLE 6: Neuropsychological Performance by Fatigue Level..... 127

TABLE 7: Frequency of Impaired Scores on Selected Tests in Impaired Group ... 128

TABLE 8: Group Differences on Self-Report Measures after Controlling for Premorbid IQ 130

TABLE 9: Neuropsychological Predictors of CVLT-II Total Score..... 132

TABLE 10: Self-Report Measures as Predictors of CVLT-II Total Score 133

LIST OF APPENDICES

APPENDIX A: Characteristics and Psychometric Properties of Measures 103

APPENDIX B: Additional Analyses 118

LIST OF ABBREVIATIONS

BDI	Beck Depression Inventory
CogOth	FACT-Cog: Comments from Others subscale
CogPCA	FACT-Cog: Perceived Cognitive Abilities subscale
Cog PCI	FACT-Cog: Perceived Cognitive Impairment subscale
CogQOL	FACT-Cog: Impact on Quality of Life subscale
CI	Confidence Interval
CNSVS	Central Nervous System Vital Signs computer test
CVLT	California Verbal Learning Test
D-KEFS	Delis-Kaplan Executive Function System
EWB	FACT-G: Emotional Well-Being subscale
FACT-Cog	Functional Assessment of Cancer Therapy: Cognitive module
FACT-F	Functional Assessment of Cancer Therapy: Fatigue module
FACT-G	Functional Assessment of Cancer Therapy: General module
fMRI	Functional Magnetic Resonance Imaging
FSIQ	Full Scale IQ
FWB	FACT-G: Functional Well-Being subscale
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
MS	Multiple Sclerosis
PASAT	Paced Auditory Serial Addition Test
PWB	FACT-G: Physical Well-Being subscale

QoL	Quality of Life
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SWB	FACT-G: Social Well-Being subscale
TMT	Trail Making Test
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WMS	Wechsler Memory Scale
WTAR	Wechsler Test of Adult Reading

CHAPTER ONE
Introduction

STATEMENT OF THE PROBLEM

Breast cancer affects approximately 123 out of 100,000 women per year in the United States, with 207,090 new cases estimated each year (Altekruse et al., 2010). Adjuvant chemotherapy has become a staple of care to improve long-term outcomes for several types of breast cancers (de Boer, Taskila, Ojajärvi, van Dijk, & Verbeek, 2009). Because of advances in treatment, the overall 5-year survival rate for breast cancer patients is now estimated at 89% (Altekruse et al., 2010). With increased survival comes a greater concern for issues related to quality of life, including cognitive function. Moreover, as more women are wanting to return to work and other activities following treatment, cognitive function becomes even more important (Wefel, Saleeba, Buzdar, & Meyers, 2010). Unfortunately, cancer treatments may result in cognitive changes or impairment, with deficits ranging from minor to debilitating (Argyriou, Assimakopoulos, Iconomou, Giannakopoulou, & Kalofonos, 2011). The phenomenon of cognitive dysfunction following cancer treatment is often called "chemo-brain" by patients and in the media. While the physical and neurological side effects of cancer treatments have been studied extensively, the effects on cognition remain unclear (Wefel et al., 2010).

Although research examining cognitive changes associated with chemotherapy has increased in the past decade and generally indicates that subtle cognitive deficits are present in at least a subgroup of cancer survivors, clear conclusions are difficult to draw. This is, at least in part, due to the wide range of results and the various methodological

challenges posed by work in this area. Some of these challenges include variability in study design, diversity of patient samples, use of appropriate comparison groups, definitions of impairment, neuropsychological tests included, and analytical methods used.

For example, there is no consensus as to what cognitive domains are primarily affected, although the domains most consistently reported to be affected are attention/concentration, working memory, verbal learning and memory, executive function, and processing speed (Correa & Ahles, 2008; Wefel, Witgert, & Meyers, 2008). Several longitudinal investigations have shown that cognitive function improves over time (e.g., Ahles et al., 2010; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009; Jansen, Cooper, Dodd, & Miaskowski, 2010), although other studies have reported residual deficits up to 10 years post-chemotherapy (de Ruiter et al., 2011). Estimates of the prevalence of cognitive impairment among patients who have received chemotherapy typically range from 15% to 75% across published reports (e.g., Argyriou et al., 2011; Vardy, Rourke, & Tannock, 2007), although other investigators have reported no deficits (e.g., Hermelink et al., 2007; Mehlsen, Pedersen, Jensen, & Zachariae, 2009). Moreover, cognitive impairment prior to the start of chemotherapy has been reported at rates as high as 35% (Ahles et al., 2008).

Additionally, there is often an apparent disconnect between patient-reported cognitive symptoms and objective findings on neuropsychological tests, but a relatively stronger correlation between subjective complaints and mood symptoms (Pullens, Vries, & Roukema, 2010). The reason for this discrepancy is unclear, although it is not uncommon in other disorders such as multiple sclerosis (Langdon, 2011), mild traumatic

brain injury (Spencer, Drag, Walker, & Bieliauskas, 2010), mild cognitive impairment (Monastero, Manglialasche, Camarda, Ercolani, & Camarda, 2009), and major depression (Christensen, Griffith, Mackinnon, & Jacomb, 1997). However, research is needed to further explore the relationship between objective cognitive dysfunction, subjective cognitive complaints, and other factors such as mood and fatigue in cancer patients (Hurria, Somio, & Ahles, 2007).

In sum, chemotherapy-related cognitive dysfunction appears to be a common yet poorly understood phenomenon. The need for a more complete understanding of this issue is not merely an academic one, but a practical one as well. The cognitive complaints associated with chemotherapy are distressing to patients (Hurricane Voices Breast Cancer Foundation, 2007) and, although level of actual impairment may vary, even a slight decline in cognitive function can have a significant impact on everyday functioning and quality of life (Boykoff, Moieni, & Subramanian, 2009). Moreover, the concern regarding cognitive decline may impact patients' decisions to include chemotherapy as part of their treatment regimen (Raffa et al., 2006). The potentially significant impact on quality of life and medical status indicates that a better understanding of the cognitive effects of chemotherapy is warranted.

CHAPTER TWO
Review of the Literature

CHEMOTHERAPY-RELATED COGNITIVE DYSFUNCTION

Methodological Challenges in Clinical Studies

In the past decade, there has been a significant increase in the number of studies examining the cognitive effects of chemotherapy in breast cancer survivors, with nearly 60 empirical reports published since 2000. Although a large body of literature is beginning to emerge examining cognitive effects of chemotherapeutic agents, this area of research is hampered by numerous methodological challenges, and many aspects of chemotherapy-related cognitive dysfunction remain poorly understood. While inconsistencies in the literature may result from the lack of robust cognitive impairment following chemotherapy treatment, it is also likely that mixed findings are a result of significant cross-study variations in methodology.

Given the multi-modal and multi-agent treatments often required, it is not surprising that samples are typically quite heterogeneous in terms of patient- (e.g., demographics, co-morbid diagnoses) and treatment-related (e.g., type and extent of treatment received) factors. To that end, composition of the treatment group (e.g., those who only received chemotherapy vs. those who received chemotherapy plus anti-hormonal therapy) and choice of control groups (e.g. cancer patients who do not receive chemotherapy vs. healthy controls) are often quite variable. Unfortunately, small sample size is a challenge that characterizes much of the literature in this area. For example, among reports published since 1995, 26 (41%) had sample sizes less than 40, and 16

(25%) had sample sizes under 30. When researchers attempt to control for patient- or treatment-related factors, they risk decreasing sample size even more, thereby further limiting the generalizability of results.

Study designs vary as well, with some investigators choosing cross-sectional designs (e.g., Ahles et al., 2008; Castellon et al., 2004; deRuiter et al., 2010; Schilder et al., 2010a) and other choosing prospective designs (e.g., Ahles et al., 2010; Hermelink et al., 2007; Hurria et al., 2006; Quesnel, Savard, & Ivers, 2009; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). While prospective studies theoretically provide an ideal model for examining cognitive decline, ambiguity exists among these studies as well, with rates of impairment ranging from 13% - 34% (e.g. Hermelink et al., 2007; Hurria et al., 2006; Jenkins et al., 2006; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006; Wefel et al., 2008). A related complication arises from the use of different measurement time points (i.e., time since treatment completion). Various investigations have assessed patient groups anywhere from one week (e.g., Jansen et al., 2010; Ruzich, Ryan, Owen, Delahunty, & Stuart-Harris, 2007) to 16 years (Yamada, Denberg, Beglinger, & Schultz, 2010) following treatment, making comparisons across studies difficult. Additionally, delayed-onset cognitive dysfunction has been reported in some patients. Wefel et al. (2010) assessed 42 breast cancer patients prior to and following treatment with standard dose chemotherapy and found that 65% of patients evidenced cognitive decline shortly after completion of chemotherapy (mean months since completion = 1.6). At a later interval (mean months since completion = 7.7), 61% of patients showed evidence of decline. Importantly, of the patients in this group, 29% had *not* shown evidence of cognitive decline at the acute interval, suggesting a delayed advent of cognitive

dysfunction. Given the paucity of empirical evidence regarding the temporal onset of symptoms in relation to chemotherapy, consistency in measurement time points will be important in future research.

Another methodologic issue is the operational definition of "cognitive impairment." Lack of a standardized definition of 'impairment' has been described as one of the largest obstacles to fully characterizing the rate of cognitive impairment following chemotherapy (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008). Among published reports, cognitive impairment has been defined by some as a decline in group performance on neuropsychological tests from baseline (Bender et al., 2006; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008), and by others as lower mean scores than a control group (Castellon, Silverman, & Ganz, 2005; Schagen et al., 2006; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005). Still other investigators have used mixed effects modeling (Ahles et al., 2010; Tager et al., 2010) or a Reliable Change Index (Mehlsen et al., 2009; Hermelink et al., 2007; Wefel et al., 2010) to define impairment. Schilder et al. (2010b) recently compared different criteria for determining cognitive impairment in 205 breast cancer patients and found rates of impairment ranging from 1% for the most strict to 37% for the least strict criterion relative to published norms. Compared to a healthy control group (N = 124), rates of impairment ranged from 14% to 45%, respectively, depending upon the criterion for impairment.

A related concern is the distinction between cognitive *impairment* and *decline*, particularly as cognitive deficits are often reported to be subtle. Scores obtained by chemotherapy-treated cancer patients often fall within the normal range but are lower than those of control groups (Ahles et al., 2008; Marín, Sánchez, Arranz, Auñón, &

Barón, 2009). For example, a longitudinal analysis of 61 female breast cancer patients (Stewart et al., 2008) reported that mean cognitive domain scores for patient groups were in the average range relative to published norms both before and after treatment. However, looking more closely at the individual change scores, they found that the chemotherapy patients were 3.3 times more likely to show cognitive decline than the patients who had received hormonal therapy but not chemotherapy ($N = 51$; 31% and 12%, respectively).

Given that *cognition* is being examined, neuropsychological test selection is clearly a crucial factor that unfortunately varies widely across studies as well. Test instruments should be chosen based on adequacy of psychometric properties, availability of appropriate normative data, sensitivity to the cognitive domains believed to be affected by chemotherapy, and ability to detect subtle changes in these domains (Freeman & Broshek, 2002). Because of the subtle nature of deficits related to chemotherapy (Wefel et al., 2008), screening measures may not be the most appropriate options to measure cognitive changes following chemotherapy. For example, Jansen et al. (2010) used the Repeatable Battery of Adult Neuropsychological Status (RBANS; Randolph, 1998), a brief neuropsychological screening battery, to assess 71 breast cancer patients prior to and following chemotherapy. They reported declines in the areas of visuospatial skill, attention, delayed memory, and motor function. However, declines were not seen in immediate memory, language, or executive function.

Calvio, Peugeot, Bruns, Todd, and Feuerstein (2010) used the Central Nervous System Vital Signs (CNSVS; Gualtieri & Johnson, 2006) as the main objective cognitive outcome. CNSVS is a computerized neurocognitive test battery that was developed as a

routine clinical screening instrument. No significant differences were found between mean scores of the breast cancer group (N = 122) and a control group (N = 113) on any CNSVS domains except complex attention, where the breast cancer group actually performed *better* than the control group ($p < .05$). In this case, a screening battery did not appear to differentiate the groups on most domains. Studies that have employed more traditional neuropsychological batteries have tended to find greater differences between chemotherapy and control groups (e.g., Shilling et al., 2005; Wefel et al., 2004). Thus, consistency in test selection is important to allow comparison of results across studies and facilitate clarification of the domains and skills affected by chemotherapy.

Cognitive Domains Affected

Despite challenges in methodology which complicate interpretation of findings across studies, the most common cognitive abnormalities among breast cancer survivors have been reported in the areas of verbal learning and memory, attention/concentration, working memory, executive function, and processing speed (Correa & Ahles, 2008; Hermelink et al., 2007; Hurria et al., 2006; Jenkins et al., 2006; Schagen et al., 2006; Stewart et al., 2008; Wefel et al., 2008; Wefel et al., 2010). Several meta-analyses of both cross-sectional and longitudinal studies have reported small to medium effect sizes across each of these cognitive domains, with the largest effect sizes reported for executive functioning and verbal memory (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006).

In one of the larger cross-sectional investigations, Jim et al. (2009) compared 187 breast cancer survivors with 187 age-matched controls without cancer. Of the survivors,

97 had received chemotherapy only, or chemotherapy plus radiation, and 90 had received radiation only. While overall means for the two survivor groups did not differ, results showed that survivors treated with chemotherapy were more likely than controls to show impairment (defined as ≤ 1.5 *SD* below the normative mean) on a measure of verbal learning and episodic memory (California Verbal Learning Test-Second Edition [CVLT-II]; Delis, Kaplan, Kramer, & Ober, 2000).

Von Ah et al. (2009) found that breast cancer survivors ($N = 52$) scored significantly lower on total learning and delayed recall scores from on another verbal list learning task (Rey Auditory Verbal Learning Test [RAVLT]; Schmidt, 1996) ($p = .01$ and .02, respectively), and trended towards lower performance on a verbal fluency task (Controlled Oral Word Association; Benton, Hamsher, & Sivan, 1994) ($p = .08$) compared to healthy controls ($N = 52$). However, no significant group differences were found on a measure of simple attention (Wechsler Adult Intelligence Scale-Fourth Edition [WAIS-IV; Wechsler 2008a] Digit Span subtest) or a commonly used and highly sensitive number-symbol substitution task (WAIS-IV Coding subtest) ($p = .89$ and .79, respectively).

Similarly, Quesnel et al. (2009) compared cognitive performance of breast cancer patients who had received chemotherapy ($N = 41$) with a group of healthy controls matched for age and education ($N = 23$). Performance was measured in both groups prior to chemotherapy, immediately following treatment, and three months later. At both time points after chemotherapy, breast cancer patients evidenced decreased verbal fluency and aspects of verbal memory compared to baseline. Specifically, on a verbal list learning

task (RAVLT), the chemotherapy group performed lower on total recall (learning) and free delayed recall, but not recognition.

Reid-Arndt, Yee, Perry, and Hsieh (2009) examined 46 female breast cancer survivors one month after the completion of chemotherapy using a brief battery of traditional neuropsychological tests. They reported significantly lower performance on measures of executive functioning (Trail Making Test-Part B [TMT-B; Reitan, 1958] and Stroop Color Word Test [Golden, 1978]) and verbal fluency compared to what would be expected given estimated premorbid intellectual abilities (Wide-Range Achievement Test-Third Edition [WRAT-3; Wilkinson, 1993] Reading subtest).

Whereas decreases in cognitive function have commonly been reported in verbal learning and memory, attention, processing speed, and aspects of executive function as noted above, some studies have reported declines in other cognitive domains. For example, in a recent prospective analysis, Vearncombe et al., (2009) found that 17% of breast cancer patients exposed to chemotherapy (N = 136) showed a significant decline in motor coordination and abstract reasoning, as well as verbal learning and memory. Jansen et al. (2008) examined a group of female breast cancer patients (N = 30) before and after chemotherapy. They found that 33% of the sample had a decrease of one or more standard deviations on two or more tests after the completion of chemotherapy. Domains most commonly reduced at this level included visuospatial skills (40%), motor function (13%), immediate memory (13%), language (13%), and delayed memory (13%).

Despite the fact that many investigations have reported evidence of cognitive dysfunction in breast cancer patients exposed to chemotherapy, several have found no impairment (e.g. Debess, Riis, Engebjerg, & Ewertz, 2010; Hermelink et al., 2007; Jim et

al., 2009). One such study found that cancer patients did not differ in cognitive performance from healthy controls before or after chemotherapy (Mehlsen et al., 2009). This study found that 29% of breast cancer patients (N = 34) showed decline on more than two cognitive measures versus 25% of cardiac patients (N = 12) and 17% of healthy controls (N = 12). In a recent longitudinal investigation, Tager et al. (2010) compared breast cancer survivors who had (N = 30) or had not (N = 31) received chemotherapy using a detailed battery of neuropsychological tests. A mixed-model analysis showed no differences in cognitive function between the groups over time, with the exception of motor function. Women who had received chemotherapy demonstrated a decline in motor performance over time compared to the no-chemotherapy group, although this decline only approached statistical significance (p = .08).

Subjective cognitive impairment

Subjective cognitive dysfunction refers to the cognitive difficulties patients report based upon their experience in daily life, as well as satisfaction with their current cognitive functioning (Pullens et al., 2010). Rates of self-reported cognitive impairment in breast cancer patients range from 30% to 70% in the current literature (Vardy, 2009). For example, a qualitative investigation of 74 breast cancer survivors showed that 70% of women reported cognitive impairment, with many considering it their most troubling post-treatment symptom (Boykoff et al., 2009). Another study (Shilling and Jenkins, 2007) found that 71% of breast cancer patients (N = 142) reported problems with their memory one month after the final chemotherapy session, and 60% at twelve months. Concentration difficulties were reported by 64% and 42%, respectively. Additionally, an

online survey of 471 cancer survivors indicated that 98% noticed changes in their thinking, memory, or attention during or just after chemotherapy, with over 50% indicating that the symptoms were moderate to severe. Furthermore, 92% of patients who were five or more years post-chemotherapy reported continuing difficulties with cognitive function (Hurricane Voices Breast Cancer Foundation, 2007).

Overall, investigations of subjective cognitive dysfunction following chemotherapy have consistently indicated that the most common complaints involve difficulties with attention/concentration, short-term memory loss, word recall, organization of daily tasks, and multitasking (Castellon et al., 2005; Mehlsen et al., 2009; Shilling & Jenkins, 2007; Von Ah et al., 2009; Weis, Poppelreuter, & Bartsch, 2009). However, there does not appear to be a consistent association between self-reported cognitive decline and impaired performance on objective neuropsychological measures, particularly when depression, anxiety, and fatigue are statistically controlled (Ahles & Saykin, 2007; Bender et al., 2006).

Effects of mood and fatigue

In general, current research does not support an association between objective cognitive performance and self-reported anxiety, depression, or fatigue (Argyriou et al., 2011; Pullens et al., 2010; Raffa, 2010; Vardy et al., 2006; Wefel et al., 2010), although there are a few exceptions that deserve note. For example, Mehlsen et al. (2009) found that higher depression scores (as measured by the Beck Depression Inventory-Second Edition [BDI-II; Beck, Brown, & Steer, 1996]) were associated with poorer working memory and verbal memory scores ($p < .05$) among breast cancer patients ($N = 34$).

However, given that the BDI-II has several items addressing physical symptoms of depression, which cancer patients often experience as part of treatment, these scores may be artificially inflated. Stewart et al. (2008) examined a group of 61 breast cancer patients before and after chemotherapy and found that patients whose cognitive performance declined (31%) had higher baseline depression scores (as measured by the Profile of Mood States [McNair, Lorr, & Droppleman, 1981]) than patients whose cognitive performance did not decline. Depression scores at follow-up (post-chemotherapy) did not differ between the groups, however. Based on this, the researchers suggested that characterological factors such as poor stress tolerance may be risk factors for cognitive impairment following chemotherapy. Overall, it appears that the cognitive dysfunction seen following chemotherapy is not simply an artifact of anxiety, depression, or fatigue, but may represent an independent phenomenon.

In contrast to the lack of association between psychological factors and objective cognitive performance, elevated fatigue and mood symptoms have been consistently associated with *self-reported* cognitive function among cancer patients (Ahles et al., 2008; Debess et al., 2010; Shilling & Jenkins, 2007; Vardy, 2009). For example, Weis et al. (2009) reported significant correlations between measures of self-reported cognitive function and mood symptoms (r = .30 - .50, respectively) in a sample of 90 breast cancer patients who had completed treatment an average of 9 months earlier. It should be noted that this finding is not exclusive to cancer populations and has been reported in many other disorders such as multiple sclerosis (Langdon, 2011), mild traumatic brain injury (Spencer et al., 2010), mild cognitive impairment (Monastero et al., 2009), and major depression (Christensen et al., 1997).

Evidence from Neuroimaging Research

Cerebral white matter has been frequently identified as being vulnerable to toxic effects of chemotherapy (Morgan and Ricker, 2008; Lezak, Howieson, Bigler, & Tranel, 2012; Wefel et al., 2008), and most neuroimaging studies have shown that chemotherapy has an adverse effect on central nervous system structure. Inagaki et al. (2007) found reduced gray and white matter volumes in the prefrontal, parahippocampal, cingulate gyrus, and precuneus regions in breast cancer survivors (N = 51) one year after treatment compared to controls. Furthermore, the reduced volumes were correlated with poorer performance on cognitive measures of attention, concentration, and visual memory. Using diffusion tensor imaging, Abraham et al. (2008) found that women who had received standard-dose chemotherapy evinced decreased anterior white matter integrity, which was associated with significantly poorer performance on a measure of processing speed compared to controls. McDonald, Conroy, Ahles, West, and Saykin (2010) found decreased gray matter density in bilateral frontal, temporal, and cerebellar regions and right thalamus 1 month after chemotherapy compared to baseline (N = 17). Additionally, several studies have reported atrophy, both diffusely and more focally in the hippocampal regions, which are involved in new learning and memory (Dietrich, Han, Yang, Mayer-Pröschel, & Noble, 2006; Vearncombe et al., 2009; Wefel et al., 2008).

Another recent investigation compared a group of breast cancer survivors 10 years after completion of high-dose chemotherapy (N = 19) with a control group of breast cancer survivors with similar time since treatment but for whom chemotherapy had not been indicated (N = 15; de Ruiter et al., 2011). Results indicated that compared to

controls, the chemotherapy group showed hyporesponsiveness in the dorsolateral prefrontal cortex and parahippocampal gyrus, brain regions associated with executive function and memory encoding. Additionally, whole-brain analyses showed decreased activation bilaterally in the posterior parietal cortex, a region associated with attention.

Several functional magnetic resonance imaging (fMRI) studies of post-chemotherapy cancer survivors have found decreased activation in the mid frontal regions of the brain during working memory tasks, particularly as the task becomes more difficult (e.g. Ahles & Saykin, 2007; Silverman et al., 2007). Ferguson, McDonald, Saykin, and Ahles (2007) used fMRI with a similar working memory task to examine two monozygotic twins who were discordant for breast cancer and chemotherapy. They found that the twin who had received chemotherapy had increased activation of larger regions of the frontal and parietal lobes, suggesting that, although she was able to perform the working memory task, additional areas of the brain were recruited in order to compensate. Other investigations have replicated the finding of compensatory activation of other brain regions (which are not typically utilized for a given task), which may partially explain why objective performance on cognitive measures is often in the normal range for breast cancer survivors, even with altered cortical activation (Correa & Ahles, 2008; Silverman et al., 2007; Vardy et al., 2008).

Frontal Subcortical Profile

As evident from the ambiguity in the literature, research is needed in order to clarify specific patterns of cognitive impairment following chemotherapy. However, given the types of cognitive difficulties reported as well as findings from neuroimaging

studies, several leaders in the field are now suggesting a frontal/subcortical profile of chemotherapy-related cognitive dysfunction (Correa & Ahles, 2008; Meyers, 2008; Vardy et al., 2008; Wefel, Vardy, Ahles, & Schagen, 2011). As noted above, the most common cognitive abnormalities among breast cancer survivors have been reported in the areas of verbal learning and memory, attention, processing speed, working memory, and aspects of executive function, all of which are thought to have diffuse frontal-subcortical underpinnings (Wefel & Schagen, 2012). In terms of verbal memory, deficits are typically seen in encoding and retrieval, with the relative preservation of recognition memory (Quesnel et al., 2009; Von Ah et al., 2009), which is a classic pattern of so-called "subcortical dysfunction" and implies a disruption of the supportive processes involved in the initial acquisition of information (Stuss & Knight, 2002; Meyers, 2008). These supportive processes may include aspects of executive functions and related foundational skills such as attention, processing speed, and working memory.

Moscovitch (2004) described the way in which various cognitive functions work to support memory, suggesting that they "control the information delivered to the medial temporal and diencephalic system at encoding, initiate and guide retrieval, monitor, and help interpret and organize the information that is retrieved" (p. 8). Because adequate functioning of these skills is so intricately linked to adequate memory performance, it is important to understand the nature of any dysfunction in those areas. However, these skills are inherently difficult to measure in isolation (see below) and therefore, we lack a thorough understanding of attentional impairment in chemotherapy-related cognitive dysfunction.

Other disorders with subcortical abnormalities

Because examination of cognitive function is still a relatively new area of research in the cancer field, it is helpful to examine the literature pertaining to other disorders with white matter involvement and subcortical abnormalities. In particular, it will be important to examine patterns of attentional dysfunction and the ways in which it has been measured in these populations, in order to help inform and guide future research on attentional dysfunction in patients exposed to chemotherapy.

Multiple sclerosis (MS), an autoimmune disease affecting the brain and spinal cord, is pathologically characterized by demyelination of the neurons and diffuse damage of white and gray matter regions (Hoffman, Tittgemeyer, & Von Cramon, 2007). With respect to cognitive impairment, Johnson (2007) reported that, "simple attentional tasks, such as immediately reciting back a list of numbers or words, are intact in MS patients. However, with increased task complexity, MS patients tend to demonstrate impaired performance" (p 173). For example, impairment is more common on tasks of sustained, selective, divided, and alternating attention (Amato et al., 2010; Chiaravalloti & Deluca, 2008).

Human Immunodeficiency Virus (HIV) is a retrovirus that directly invades the brain shortly after infection, causing inflammatory and neurotoxic responses (Piot, 2007). Preferential damage to white matter has been consistently demonstrated using various neuroimaging techniques (Gongvatana et al., 2009). Cognitive skills typically affected include learning, attention, and processing speed; in particular, complex attentional tasks requiring greater allocation of resources (Heaton et al., 1995). Deficits have been shown

in several attentional processes, such as divided attention, visuospatial orienting, and response inhibition (Hardy & Hinkin, 2002; Levine et al., 2008).

The pattern of cognitive impairment in HIV and MS—specifically, that certain components are differentially impacted—suggests that diseases affecting the white matter do not have a singular effect on cognition, although elements of attention, particularly "executive aspects of attention" (Anderson, 2002, p. 320), are often implicated and serve as the foundation for many other cognitive abilities. Therefore, a detailed examination of these domains in cancer patients exposed to chemotherapy is warranted. However, attentional abilities in a post-chemotherapy sample have yet to be thoroughly investigated.

ATTENTION

Theoretical Models of Attention

Attention can be a challenging concept to define and operationalize, and it has been done in many different ways. Cognitive psychologist Alan Allport (1993) stated:

> There can be no simple theory of attention, any more than there can be a simple theory of thought. A humbler but also a more ambitious task [sic] will be to characterize [sic] as much as possible of this great diversity of attentional functions (p. 206).

In daily language, use of the term "paying attention" has many different connotations, often suggesting effort and referring to aspects of directed and selective perception (Van Zomeren & Brouwer, 1994).

Several models of attention have been proposed by various leaders in the field, all of which attempt to explain the various component processes of this complex domain. Most of these conceive of attention as "a system in which processing occurs sequentially in a series of stages within different brain systems" (Lezak et al., 2012, p. 36).

Sohlberg and Mateer (1989) proposed a popular model of attention comprised of five hierarchical levels. This model was based upon clinical observation of patients recovering from coma and the attentional abilities they attained as recovery progressed. The first level is *focused attention*, which is described as the ability to respond to a specific stimulus. The second level is *sustained attention*, which is the ability to maintain a consistent response for an appreciable length of time. The third level is *selective attention*, or the ability to maintain focus on a task in the presence of distracting stimuli. The fourth level is *alternating attention*, described as the ability to shift attention from one aspect of a stimulus to another. The fifth and most complex level is *divided attention*, the ability to respond simultaneously to multiple competing tasks. This remains one of the most commonly referenced models of attention, and the idea of a hierarchy of attention components has been reflected in other models as well.

Mirsky, Anthony, Duncan, Ahearn, and Kellam (1991) used exploratory factor analysis to identify underlying components of a variety of commonly used neuropsychological measures of attention. Their sample consisted of a mixed group of 203 adults, including both inpatients and outpatients with various psychiatric and neurological disorders, as well as normal volunteers. Four factors were initially found which explained approximately 80% of the variance across tests (see Table 1). The factors are remarkably similar to the levels proposed by Sohlberg and Mateer (1989),

providing additional support for the theoretical soundness of both models. The first of these, termed *focus/execute*, is described as the capacity to selectively attend to a stimulus and quickly initiate a response. The second factor, *shift*, describes the ability to shift focus from one aspect of a complex stimulus to another. The third factor, labeled *sustain*, is assumed to reflect the capacity to maintain attentional focus for an extended period of time. The fourth factor, *encode*, is described as the ability to briefly hold information in memory while performing some sort of mental manipulation. This factor has been likened by others to working memory (Levine et al., 2008). More recently, Mirsky and Duncan (2001) reported a five-factor model of attention, with the addition of a *stabilize* element, which is described as measuring the consistency of responses over time (see Table 1).

Table 1. *Mirsky and Duncan's Factors of Attention and Corresponding Neuropsychological Tests*

Factor	Description	Tests Loading on Factor
Focus/Execute	Capacity to selectively attend to a stimulus and quickly initiate a response	WAIS Digit-Symbol Coding Letter Cancellation Trail Making Test A and B Stroop Color Word Test
Shift	Ability to shift focus from one aspect of a complex stimulus to another	WCST Categories Completed WCST Percent Correct WCST Number of Errors Reciprocal Motor Programs Test
Sustain	Capacity to maintain attentional focus for an extended period of time	CPT Correct Responses CPT Commission Errors CPT Reaction Time
Encode	Ability to briefly hold information in memory while manipulating other information	WAIS Digit Span WAIS Arithmetic
Stabilize	Consistency of responses over time	CPT Variance of Reaction Time

Note. Adapted from "A Nosology of Disorders of Attention," by A.F. Mirsky and C.C. Duncan, 2001, *Annals of the New York Academy of Sciences, 931,* p. 19. Copyright 2001 by the New York Academy of Sciences.

The model proposed by Mirsky and Duncan (2001) has a sound theoretical basis, included a large sample, utilized widely-used clinical tests, and appears to have good psychometrics. A replication of the adult model (Kelly, 2000) with 100 children ages 7-13 years found the same four factors (sustain, encode, focus-execute, and shift). Replication of the child model with the same sample produced a three-factor model in which the encode and focus-execute factors are combined. However, Strauss, Thompson, Adams, Redline, and Burant (2000) used structural equation modeling to examine the model and did *not* find support for the same four factors, suggesting that the model did not completely explain the components of attention as measured by these particular neuropsychological tests. Nevertheless, Levine et al. (2008) were able to replicate the five-factor structure proposed in the updated model (Mirsky & Duncan, 2001) in a sample of HIV patients. These replications of a similar factor structure support the concept of a group of attention elements, similar to those found by Mirsky and colleagues.

Posner and Petersen (1990) provide another model in which the orienting of attention is described in three stages. The first step is disengagement from the current focus. Second is physical shifting (e.g., of visual or auditory processes) from one stimulus to another. The final step is focusing attention on the new stimulus. A sequential and hierarchical process, this model is organized such that the early stages are modality-specific (e.g., vision or audition), while the final stage involves the interface of several different modalities.

Lezak and colleagues (Lezak et al., 2012, p. 36) conceptualize attention as being comprised of three distinct but intertwined components, which are described in terms of

deficits in each. At the lowest level of complexity are pure attentional deficits, which appear as distractibility or impaired focus. At the next level are concentration problems, which may be a result of difficulty with pure attention, ability to maintain focus, or both. At the highest level of complexity are tracking problems. Again, these may be due to deficits in pure attention, concentration, the ability to maintain focus while engaging in other tasks (such as solving problems or following a sequence of ideas), or by all three. Not only do these three components build on each other, they also require increasing involvement of various brain systems. Lezak and colleagues also state that less complex aspects of attention (e.g., simple immediate span of attention) are often unaffected by aging or other brain damage; however, complex aspects of attention are much more sensitive and fragile (Lezak et al., 2012, p. 36). Additionally, they emphasize that impaired attention is not necessarily a global impairment; rather, deficits can reflect involvement of certain components of attention and not others.

While each of these models differs in the details of their organization, all conceptualize attention as a multi-faceted construct consisting of several processes, some of which are considered higher order than others. Several researchers have conceptualized these higher-order processes as "executive aspects of attention" (Anderson, 2002, p. 320; Stuss, 1992; Stuss & Alexander, 2000; Wefel et al., 2011).

Measurement of Attention

The field of cognitive science has furthered our understanding of attention by breaking down the domain into isolated component parts and measuring these parts using very simple tasks. Rather than a single entity, cognitive psychology shows that attention

is more likely a set of numerous inter-related components. (Pashler, 1998). Neuropsychology tends to utilize more complex psychological tasks that are interpreted in terms of attention concepts (Lezak et al., 2012; Strauss et al., 2000). One challenge facing clinical neuropsychology is that attention processes cannot easily be assessed in isolation. Traditional measures have significant overlap with other cognitive domains (e.g., auditory or visual systems), as they inherently require the examinee to attend to something (Levine et al., 2008; Strauss, Sherman, & Spreen, 2006). For this reason, it is difficult to determine whether deficits are due to impairment in attention or in the overlapping domain. Additionally, there tends to be a low correlation between performance on different attention tasks, highlighting the inherent difficulty in measuring attention (Van Zomeren & Brouwer, 1994). Given all of this information, it seems clear that attention cannot be reduced to a single definition, nor can it be assessed with a single test. Several terms closely intertwined with and critical to the understanding of attention are discussed below.

Executive function is generally seen as a control mechanism used to modulate the operation of cognitive sub-processes and thereby guide behavior toward a goal (Miyake, Emerson, & Friedman, 2000). However, this general term comprises a number of different abilities, and the extent to which these abilities reflect diverse constructs or a single, unitary construct is a matter of debate in the field. These abilities include prioritizing and sequencing behavior, inhibiting familiar or stereotyped behaviors, creating and maintaining an idea of what task or information is most relevant for current purposes (often referred to as an attentional or mental set), providing resistance to information that is distracting or task irrelevant, switching between task goals, utilizing

relevant information in support of decision making, categorizing or otherwise abstracting common elements across items, and handling novel information or situations (Banich, 2009). As noted above, more "complex aspects of attention" (Wefel et al., 2011, p. 3) are often referred to as executive functions (Anderson, 2002, p. 320; Stuss, 1992; Stuss & Alexander, 2000).

Working memory is the ability to simultaneously store, process, and manipulate information, and it overlaps conceptually with various aspects of attention (Oberauer, 2002; Strauss et al., 2006). In fact, it is often used interchangeably with some aspects of attention (Levine et al., 2008). It has been postulated by some researchers that working memory is actually the first step in the process of encoding information into long-term memory and that learning trials, particularly initial trials, may reveal more about working memory and attention than overall learning or memory ability (Janculjak, Mubrin, Brinar, & Spilich, 2002; Strauss et al., 2006). Successful encoding, then, relies heavily upon intact attention and working memory, and without successful encoding, later stages in memory processing (such as retrieval and recall) are adversely affected (Blumenfeld, 2002; Lezak et al., 2012). For example, Deluca, Gaudino, Diamond, Christodoulou, and Engel (1998) found strong negative correlations between the number of learning trials to reach criterion and subsequent verbal memory in MS patients. While conclusions cannot be drawn from this finding alone, it does provide support for the importance of successful acquisition and encoding in memory paradigms.

Processing speed is the ability to rapidly process information, both simple and complex, (Freeman & Broshek, 2002) and is closely related to learning and memory, as well as working memory and attention (Johnson, 2007). Some researchers have posited

that deficits in working memory are mediated by processing speed abilities (Morgan & Ricker, 2008). Working memory capacity is dependent on processing speed because encoding, transforming, and retrieving information within working memory requires time, and the faster the rate of processing, the greater amount of information that can be processed (Conway, Cowan, Bunting, Therriault, & Minkoff, 2002). For example, Fry and Hale (1996) found that in children, adolescents, and young adults, overall improvement in working memory was mediated by developmental changes in processing speed. Moreover, individual differences in processing speed had a strong, positive, and direct effect on working memory.

Attention and Chemotherapy

As discussed above, the definition of attention is not always straightforward, and there is inherent overlap in tests used to assess attention, which creates problems for accurate and consistent measurement. It is difficult to draw conclusions about attentional functioning when tests are labeled as measures of attention but in fact may have a stronger emphasis on psychomotor speed or executive functioning, for example (Chiaravalloti & Deluca, 2008; Strauss et al., 2006). This becomes problematic because many studies utilize domain composite scores to compare performance, and without consensus on which tests are measures of which domain, those composite scores lose value in their ability to help draw conclusions about the cognitive effects of chemotherapy. Additionally, differences in the cognitive tests used across studies may contribute to discrepant findings, both in terms of rate and type of impairment (Wefel et al., 2010).

Two meta-analyses examining the frequency of use and categorization of neuropsychological tests highlight the confusion surrounding this matter (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Jansen, Miaskowski, Dodd, & Dowling, 2007). Across the studies included in those meta-analyses and more recent studies examined qualitatively by this author, tests purported to measure attention and other closely related domains were quite variable (see Table 2).

Table *2. Selected Neuropsychological Tests Reported to Measure Various Domains of Cognitive Function*

Test	Domain				
	Attention	Working Memory	Processing Speed	Executive Function	Other
Auditory Consonant Trigrams	✓	✓			
Booklet Category Test				✓	
Continuous Performance Test	✓		✓		
Controlled Oral Word Association Test				✓	✓
D-KEFS Color Word Interference			✓	✓	
D-KEFS Sorting Test				✓	
D-KEFS Trail Making Test			✓	✓	
d2 Test of Attention	✓		✓		
Digit Vigilance	✓				
Grooved Pegboard			✓		✓
Paced Auditory Serial Addition Test	✓	✓	✓	✓	
Ruff 2&7 Test	✓				
Stroop Color and Word Test	✓			✓	
Trail Making Test	✓		✓	✓	
WAIS Arithmetic	✓	✓			
WAIS Digit Span	✓	✓			
WAIS Digit Symbol Coding	✓		✓	✓	
WAIS Letter Number Sequencing		✓			
WAIS Similarities				✓	✓
WAIS Symbol Search			✓		
Wisconsin Card Sorting Test				✓	
WMS Spatial Span	✓	✓			

Note. D-KEFS = Delis Kaplan Executive Function System; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale.

Given the significant variability in the tests chosen to measure different domains of cognitive function, it is not difficult to see why findings regarding attention and related cognitive abilities have been ambiguous.

Another recent meta-analysis of six studies and 208 breast cancer survivors (Falleti et al., 2005) indicated that, compared to control groups, survivors who had received chemotherapy showed poorer cognitive function across several domains. Small to moderate effect sizes were found (d = -.18 to -.51) for each of the domains assessed, with the notable exception of attention (d = -.03). Interestingly, a similar meta-analysis (Stewart et al., 2006) of seven studies (five of which overlapped with those included in the Falleti et al. [2005] paper) found small to medium effect sizes for each of the cognitive domains examined, without exception. One possible explanation for these different findings may be the way in which each study grouped neuropsychological measures into cognitive domains—attention and similar domains in particular. Falleti and colleagues used only two domain labels, *attention* and *executive function*, while Stewart and colleagues utilized more specific labels of *simple attention*, *working memory*, *speed of processing*, and *language*. The latter study found greater effect sizes for working memory (d = -.24, $p < .05$), speed of processing (d = -.22, $p < .05$), and language (d = -.37, $p < .005$) than simple attention (d = -.13, $p > .05$), which suggests that effect sizes are impacted by the grouping of tests, and that breaking tests into a greater number of domains by their component parts results in different effect sizes for different components. This supports the idea proposed by many leaders in the field (e.g., Blumenfeld, 2002; Lezak et al., 2012) that certain aspects of attention may be more impacted than others in the context of cognitive dysfunction, and that a general label of

attention may not be sufficient to explain the cognitive impairment experienced after chemotherapy. Attention is a multi-dimensional domain that has a close relationship to many other important cognitive domains. In order to distinguish between deficits in these various dimensions or related cognitive domains, Lezak and colleagues (2012) emphasize the inclusion of several neuropsychological tests requiring the involvement of various components of attention. Without this, it is difficult to clarify the nature of attentional problems following chemotherapy.

Another obstacle to the thorough and accurate understanding of attentional deficits following chemotherapy is the mild nature of the dysfunction. As discussed above, many studies have found that, although decline may be seen at an individual level, test performance may still fall in the normal or average range (Ahles et al., 2008; Marín et al., 2009; Stewart et al., 2008). This finding, in addition to the discrepancy between subjective report of cognitive dysfunction and objective results on neuropsychological tests, as well as findings on imaging studies that support neuropathological changes following chemotherapy, suggests that many of the measures currently in use (or at least most frequently used) may not be sensitive enough to test the limits of cognitive capacity (Correa & Ahles, 2008; Raffa, 2010). It has been suggested that "more resource-demanding neurocognitive tasks [may be] necessary to elicit performance problems and the difficulty of the task may be more important than the domain being assessed" (Castellon et al., 2005, p. 204). However, due to the lack of test consistency across research studies, this is difficult to determine.

OVERALL AIMS

Despite an increase in the number of published studies in recent years, many aspects of chemotherapy-related cognitive dysfunction remain poorly understood. The pattern of cognitive impairment and neurological damage (as seen on neuroimaging) is reflective of disruption of frontal subcortical networks (Meyers, 2008). Because attention and related constructs are of central importance in this so-called "subcortical profile," it is important to have a thorough understanding of how these domains are impacted by chemotherapy. However, available literature is difficult to interpret, in part because of various methodological factors, including the use of singular or otherwise limited neuropsychological tests, inconsistent use of tests across studies, and variability in the conceptualization of domains believed to be affected by chemotherapy (such as attention and related constructs). Thus, conclusions regarding attentional impairment in women treated for breast cancer are limited, and its role in the clinical syndrome known as chemo-brain remains poorly understood. The following two studies address these issues in an attempt to increase our understanding of attention and related constructs in chemotherapy-related cognitive dysfunction.

CHAPTER THREE
Study One

A META-ANALYSIS OF NEUROPSYCHOLOGICAL TESTS USED TO DETECT CHEMOTHERAPY-RELATED COGNITIVE DYSFUNCTION IN PROSPECTIVE STUDIES

Abstract

Objective: Chemotherapy treatment for breast cancer has been associated with cognitive dysfunction (Wefel & Schagen, 2012), but findings are mixed regarding the frequency, severity, and nature of cognitive impairment. Although a variety of neuropsychological tests are available to measure cognitive change, little is known about their sensitivity to individual change in this population. The current paper applies meta-analytic techniques to prospective longitudinal studies examining cognitive function in breast cancer patients before and after chemotherapy treatment.

Method: A total of 13 studies with 725 subjects were included in the meta-analysis based on the following eligibility criteria: inclusion of breast cancer patients exposed to chemotherapy, use of a prospective design, and use of standard neuropsychological tests. From these, within-subjects comparisons were used to generate Cohen's *d* effect sizes for 31 neuropsychological tests.

Results: Effect sizes for each test ranged from -.56 to .68. Using a fixed effects model, semantic fluency and SDMT were the only measures that declined significantly following chemotherapy treatment. In contrast, significant *improvements* were observed on 13 of the 31 variables, which may be related to practice effects. However, improvements were

smaller than expected on several tests, which may in fact reflect a subtle decline in performance.

Conclusion: The current meta-analysis provides initial data regarding within-subjects change on neuropsychological tests following chemotherapy for breast cancer. However, questions still remain and further research is needed to explore the cognitive effects of chemotherapy. While longitudinal comparisons appear to be relevant in this population given reports of pre-chemotherapy cognitive impairment, the effect of practice cannot be underestimated and deserves further empirical exploration and clinical consideration.

A Meta-Analysis of Neuropsychological Tests used to Detect Chemotherapy-Related Cognitive Dysfunction in Prospective Studies

Breast cancer affects approximately 123 out of 100,000 women per year in the United States, with 207,090 new cases estimated each year (Altekruse et al., 2010). Because of advances in treatment, which generally includes a combination of surgery, radiation, chemotherapy, and immunotherapy, the overall 5-year survival rate for breast cancer patients has increased dramatically, recently estimated at 89% (Altekruse et al., 2010). Unfortunately, because most cancer treatments are not highly specific, they pose a danger to healthy tissue, including that of the nervous system. While the potential cognitive effects of radiation have long been discussed, research examining cognitive effects of chemotherapy has only recently begun to receive greater recognition. Despite an increase in the number of empirical studies, this area of research is plagued by numerous methodological challenges, and many aspects of chemotherapy-related cognitive dysfunction remain poorly understood.

For example, wide variation in the frequency, severity, and nature of cognitive impairment has been reported. Estimates of the prevalence of cognitive dysfunction in patients diagnosed with non-central nervous system tumors vary considerably, ranging from 19% to 78% (e.g. see Wefel & Schagen, 2012). In most cases, cognitive symptoms begin shortly after treatment is started and may last months or even years after the completion of treatment (e.g., Ahles et al., 2010; de Ruiter et al., 2011). However, cognitive impairment *prior to* the start of chemotherapy has been reported in up to 35% of breast cancer patients in one investigation (Ahles et al., 2008).

The most common cognitive abnormalities among breast cancer survivors have been reported in the areas of verbal learning and memory, attention, processing speed, working memory, and executive function (e.g., Jim, Donovan, Small, Andrykowski, Munster, & Jacobsen., 2009; Reid-Arndt, Yee, Perry, & Hsieh, 2009; Quesnel, Savard, & Ivers, 2009; Von Ah et al., 2009). However, these findings have not been universally supported. For example, Tager et al. (2010) reported a decline in motor performance (as compared to baseline) but not attention/concentration in breast cancer patients following chemotherapy. Moreover, some studies have reported no evidence of cognitive impairment following chemotherapy, in any domain (e.g., Debess, Riis, Engebjerg, & Ewertz, 2010; Mehlsen, Pedersen, Jensen, & Zacharaiae, 2009; Ruzich, Ryan, Owen, Delahunty, & Stuart-Harris, 2007).

While inconsistencies in the literature may result from the lack of a robust cognitive impairment following chemotherapy treatment, it is also likely that mixed findings are a result of significant cross-study variations in methodology. For example, given the multi-modal and multi-agent treatments often required, it is not surprising that patient samples are typically quite heterogeneous in terms of the type and extent of treatment received. Small sample size and variability in such factors as study design (e.g., measurement time points), analytical methods, comparison group, and definition of impairment also complicate matters. Given that *cognition* is being examined, neuropsychological test selection is clearly a crucial factor that may influence results. The instruments should be chosen based on adequacy of psychometric properties, availability of appropriate normative data, sensitivity to the cognitive domains believed to be affected by chemotherapy, and ability to detect subtle changes in these domains.

Unfortunately, significant cross-study variability exists in the tests chosen to measure cognition.

Furthermore, most neuropsychological studies of cancer report results in terms of composite cognitive domain scores that combine scores from several tests. While such summary scores reflect a convenient way to summarize findings and are sometimes necessary for data reduction, discrepancies exist in terms of what cognitive domain - specific tests are included in each domain and what they purport to measure, making results across studies sometimes difficult to interpret.

Meta-analysis is a statistical approach for combining results from multiple independent studies (Gliner, Morgan, & Harmon, 2003). It uses a quantitative technique to assess the strength of the relationship between a treatment (here, chemotherapy) and outcome measures (such as neuropsychological test performance). Meta-analyses are an important part of systematic reviews of a body of literature and offer several important advantages. First, they provide a quantitative estimate of net findings aggregated across multiple studies, which increases the power to detect significant treatment effects, even those that may be subtle in nature (Lipsey & Wilson, 2001). Additionally, meta-analyses can help to increase external validity of results (Lipsey & Wilson, 2001). Because of the heterogeneous nature of patient samples included in studies of chemotherapy-related cognitive dysfunction, generalizability of results may be limited. Including multiple studies increases the variation of the sample, thereby increasing generalizability and, in a sense, helping to control for confounding factors such as type of chemotherapy regimen.

Three earlier meta-analyses have examined cognitive impairment associated with chemotherapy treatment for breast cancer (Falleti, Sanfilippo, Maruff, Weih, & Phillips,

2005; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006; Jansen, Miaskowski, Dodd, & Dowling, 2007). Falleti et al. (2005) analyzed five studies that compared cancer patients to healthy controls on 55 neuropsychological tests that were grouped into six cognitive domains (motor function, memory, executive function, language, spatial ability, and attention). Stewart et al. (2006) analyzed seven studies that used either control, normative, or baseline comparisons on 48 neuropsychological tests in eight domains (simple attention, working memory, short-term memory, long-term memory, processing speed, language, spatial skill, and motor abilities). Both of these meta-analyses found small to medium effect sizes for all cognitive domains except attention, which resulted in negligible effect sizes in both reports. Falleti et al. noted that patients treated with chemotherapy actually scored better than the comparison group on some tests of attention but worse on others. They postulated several explanations for this finding, one being that only some aspects of attention are adversely affected by chemotherapy. However, there is an important limitation to these studies that deserves note. Both studies used a combination of test results to represent cognitive-domains, and the neuropsychological tests included in each domain (in particular, the attention domain) differed. Since neither of these meta-analyses provided effect sizes for individual neuropsychological tests, the findings are difficult to interpret. In the only meta-analysis to examine the sensitivity of individual neuropsychological tests in patients with breast cancer, Jansen et al. (2007) found six tests were sensitive to chemotherapy-related cognitive dysfunction (Grooved Pegboard, FePsy 'The Iron Psyche' Finger Tapping, Rey Complex Figure Test (RCFT) – copy score, and Wechsler Adult Intelligence Test [WAIS] Block Design).

In each of these meta-analyses, cross-sectional investigations were the basis for the majority of effect sizes generated. The two earlier studies (Falleti et al., 2005; Stewart et al., 2006) reported on exclusively cross-sectional comparisons (with the exception of one longitudinal study, which was analyzed separately [Falleti et al., 2005]). Although Jansen et al. (2007) included several longitudinal studies, the majority of them were cross-sectional. Since the publication of these three meta-analyses, numerous longitudinal studies have been published that would allow for within-subject comparisons (i.e., before and after chemotherapy). Also since the publication of these meta-analyses, several investigators have reported cognitive impairment *before* the start of chemotherapy (Ahles et al., 2008; Hermelink et al., 2007; Quesnel et al., 2009; Wefel, Saleeba, Muzdar, & Meyers, 2010; Cimprich et al., 2010). These findings highlight the importance of within-subject comparisons to account for pre-chemotherapy cognitive impairment.

Given the drastic increase in the number of prospective studies in the past few years, as well as recent findings suggestive of possible cognitive impairment before the start of chemotherapy, it is the aim of this paper to examine the literature with respect to the sensitivity of neuropsychological tests using longitudinal within-subject comparisons (i.e., before and after chemotherapy treatment) in breast cancer patients.

Method

Literature Search

To locate relevant studies, we conducted database searches of PsycINFO and PubMed. Searches were conducted using terms such as cancer, chemotherapy, antineoplastic agents, chemo-brain, cognition, cognitive, neuropsychology, and

neuropsychological. The initial search was deliberately kept broad to ensure that all relevant studies were captured.

All potentially relevant studies were manually reviewed and screened against the inclusion criteria (specified below), with particular emphasis on those that adopted a longitudinal design. The reference lists of these articles were also examined to identify additional potentially relevant studies. Likewise, subsequent citations of these papers were also examined.

For a study to be eligible for inclusion into the current meta-analysis, it had to meet the following criteria:

1. Examined a group of participants diagnosed with breast cancer who had received chemotherapy
2. Original study data from valid and reliable neuropsychological tests with published standardized administration procedures and normative data
3. Utilized a longitudinal design where participants were assessed at baseline (i.e., before the initiation of chemotherapy) and at least once during the 12 months following completion of chemotherapy
4. Study published in an English-language, peer-reviewed journal

All possibly eligible studies published by the same group were carefully examined to ensure that no overlapping data were included that would inflate homogeneity of the meta-analytic findings. If more than one study reported on the same sample, only the largest sample was incorporated into the analyses. Studies that did not distinguish patients with breast cancer from those with other types of cancer were excluded. A total of 13 studies with 725 subjects were included in the final analysis (see Table 1).

Table 1. *Description of Studies Included in Meta-Analysis*

		Age		Education		Est. IQ	Cancer Stage (%)			Treatment (%)	
Citation	*N*	M (*SD*)	Range	M (*SD*)	Range	M (*SD*)	I	II	III	Radiation	Hormone
Bender et al., 2006	34	41.9 (23.2)	NR	14.4 (11.8)	NR	NR	35	65	0	NR	44
Hermelink et al., 2007; 2008	101	48.6 (9.7)	NR	NR	NR	107.7 (14.7)		NR		NR	28
Hurria et al., 2006	28	71.0 (5.0)	65-84	NR	NR	113.6 (6.7)	39	50	11	NR	89
Jansen et al., 2010	67	50.3 (8.8)	30-65	15.7 (3.0)	11-24	NR		NR		NR	61
Jenkins et al., 2006	85	51.5 (9.6)	NR	12.0 (2.6)	NR	109.9 (12.3)	5	36	59	84	71
Mehlsen et al., 2009	34	48.6 (8.0)	29-65	14.0 (2.7)	NR	NR		NR		NR	NR
Quesnel et al., 2009	38	50.3 (7.2)	NR	NR	NR	NR	34	49	17	93	76
Ruzich et al., 2007	35	50.6 (8.3)	30-66	14.1 (2.3)	9-20	110.9 (9.0)		NR		NR	NR
Schagen et al., 2006	61	48.1 (7.0)	NR	NR	NR	102.1 (16.1)		NR		NR	NR
Stewart et al., 2008	61	57.5 (3.7)	50-66	14.5 (3.2)	8-23	107.6 (10.1)	30	66	5	5	20
Vearncombe et al., 2011	121	49.6 (8.1)	25-68	13.2 (3.5)	NR	111.1 (7.9)	26	74		76	98
Wefel et al., 2004	18	45.4 (6.7)	34-63	14.0 (2.6)	12-18	NR	50	39	11	33	NR
Wefel et al., 2010	42	48.8 (8.1)	33-65	13.0 (2.5)	8-18	NR	19	55	26	57	NR

Note. N = number of participants in each study; NR = not reported.

Data Extraction and Preparation

Data extracted from each study included demographic variables (e.g., age, education), sample size, information relating to medical status (e.g., stage of cancer) and cognitive tests used, and summary statistics for the calculation of effect sizes. If these data were not included in the article, the study authors were contacted to request this information. Data could not be obtained from two otherwise eligible studies (Ahles et al., 2010; Tager et al., 2010) and, therefore, these studies were excluded from analysis. When participants were assessed at more than one time point in the 12 months following chemotherapy, we used only data from the earliest time point to minimize the potential influence of practice effects. One group published baseline data in one paper (Hermelink et al., 2007) and follow-up data in another (Hermelink et al., 2008).

Several studies stratified participants by treatment type or menopausal status, in which case the groups were collapsed before calculating effects sizes so that analyses were based upon only one group per study. Specifically, Schagen, Muller, Boogerd, Mellenbergh, and van Dam (2006) stratified participants by chemotherapy dose (standard versus high), Bender et al. (2006) distinguished between participants who had received tamoxifen in addition to chemotherapy and those who had not, and Vearncombe et al. (2011) distinguished between pre-menopausal, chemotherapy-induced menopause, and post-menopausal groups.

Effect Size Calculations and Analysis

Comprehensive Meta-Analysis (version 2) software was used for all analyses. Cohen's *d* effect sizes (Cohen, 1988) were calculated to measure differences in cognitive

functioning before and after chemotherapy treatment. Given the challenges associated with grouping neuropsychological tests into discrete cognitive domains, each neuropsychological test was first analyzed separately. Each test was also assigned to a single cognitive domain and an effect size was generated for the domain as a whole.

All effect sizes were coded such that negative effect values indicate a decline in performance after chemotherapy, and positive effects indicate improved performance. In cases where a higher score reflected greater impairment (e.g., timed tasks), the direction of the effect size was transformed so that a negative effect still indicated a decline in performance, thereby ensuring that all effect sizes could be interpreted consistently.

The effect sizes for all test scores were aggregated across studies to calculate a mean effect size (and standard deviation [*SD*]) for that test. All effect sizes were weighted to account for sample size. Ninety-five percent confidence intervals (CI) were additionally calculated and indicate the range within which the effect size is expected to fall 95% of the time. Generally, a small effect size for independent t-tests is defined as $d = .20$, a medium effect as $d = .50$, and a large effect as $d = .80$ (Cohen, 1992). However, these categorizations are broad and do not necessarily indicate levels of practical significance. For the purpose of additional interpretation, the *Z* statistic was calculated as an indication of whether the effect size is statistically significant or not. The Q statistic tests the degree of homogeneity within each aggregated effect size. This statistic indicates whether the amount of variance in the studies used in the current meta-analysis is greater than what would be expected based upon sampling error alone (Hedges & Olkin, 1985).

In computing these effect size statistics, both fixed and random effects models were calculated. In the absence of significant heterogeneity, the use of a fixed effects

model is appropriate and may provide greater statistical power than a random effects model, particularly when the number of comparisons is small (Hedges & Vevea, 1998). Therefore, results from the fixed effects model are utilized whenever possible (when data are homogeneous). For heterogeneous data, results from the random effects model are reported. Although there are other procedures available for examining heterogeneous data, such as identifying outliers, given the small number of comparisons used in many of the analyses, this was not a feasible option.

One of the criticisms of meta-analysis is that it does not always take unpublished studies into consideration. There is a risk that the studies included in this meta-analysis account for only a subset of the existing research in this area. Thus, a fail-safe *n* statistic was computed to estimate the number of additional studies with null results that would be needed to reduce the weighted combined mean effect size to a non-significant level (Orwin, 1983).

Results

Participant Characteristics

Data from a total of 725 individual subjects was included in this meta-analysis. Table 2 presents demographic and relevant disease-related data for all included participants. The average age of the sample was 50.6 (*SD* = 10.6) and average education was 13.7 years (*SD* = 4.4). Each stage of cancer (I-III) was similarly represented. A small majority of patients received radiation (63%) and hormonal therapy (62%). Roughly 85% of the studies reported screening out participants who had received previous chemotherapy. Presence of metastatic disease was a criterion for exclusion in 69% of studies.

Table 2. *Participants' Demographic Data and Cancer-Related Characteristics*

	k	*N*	M (*SD*)	Range
Age	13	725	50.6 (10.6)	25 - 84
Education	9	497	13.7 (4.4)	8 - 24
Estimated IQ	7	492	108.8 (13.7)	NR
Test-Retest Interval (months)	13	725	9.4 (3.6)	6 - 18
% Stage				
I	8	106	25	0 - 59
II	7	306	29	36 - 66
III	7	306	25	0 - 59
% Radiation	6	365	63	5 - 93
% Hormone Therapy	8	535	62	20 - 98

Note. k = number of studies contributing to calculation; N = number of participants contributing to calculation; NR = not reported.

Neuropsychological Test Characteristics

Overall, scores from 52 different cognitive tests and subtests were reported. To ensure stability of meta-analytic outcome, measures that were reported in fewer than two studies were not incorporated into the meta-analysis, resulting in a total of 23 different cognitive tests that were amenable to analysis. When scores were obtained from different editions of a test (e.g., WAIS; Wechsler, 1981, 1997a, 1999, 2008a), these were combined for the purposes of calculating mean effect sizes. In several cases, multiple test scores were reported for a single measure (e.g., Copy, Immediate Recall, and Delayed Recall trials of the RCFT [Rey, 1964]) and separate effect sizes were reported for each score. If a test score was reported by at least 2 studies, effect sizes were generated for each score. After pooling test scores as described above, a total of 31 cognitive test scores were used in the final analysis (see Table 3).

Table 3. *Effect Sizes of Neuropsychological Test by Domain*

	Effect size and 95% confidence interval					Test of null (2-tail)	
	k	N	*d*	LL	UL	Z	*p*
Attention/Executive Function							
Arithmetic (WAIS)	4	148	0.11	-0.12	0.34	0.93	0.35
Digit Span (WAIS)[†]	4	156	0.13	-0.10	0.37	1.12	0.26
Digit Span Forward (WAIS)[*]	4	157	0.55	-0.15	1.26	1.54	0.12
Digit Span Backward (WAIS)[§]	5	278	**0.17**	0.01	0.34	2.04	0.04
Letter Number Sequencing (WAIS)	4	215	0.06	-0.13	0.25	0.60	0.55
Phonemic Fluency[*§]	9	478	0.20	-0.14	0.54	1.17	0.24
Semantic Fluency[*§]	3	196	-0.45	-1.11	0.20	-1.36	0.18
Spatial Span (WMS)	3	184	0.01	-0.19	0.21	0.10	0.92
Stroop Color Word Test	6	396	0.04	-0.10	0.18	0.55	0.58
Trail Making Test B	8	317	**0.19**	0.03	0.35	2.36	0.02
Wisconsin Card Sorting Test	2	96	-0.06	-0.35	0.24	-0.38	0.70
Speed of Information Processing							
Digit Symbol Coding (WAIS)	8	380	**0.16**	0.02	0.31	2.23	0.03
Grooved Pegboard	4	267	-0.01	-0.18	0.16	-0.13	0.90
Symbol Digit Modalities Test (Oral)[*]	2	159	-0.26	-0.80	0.28	-0.94	0.35
Symbol Search	2	95	0.22	-0.06	0.51	1.52	0.13
Trail Making Test A	8	317	**0.24**	0.09	0.40	3.02	<0.001

Note. Significant effect sizes (*d*) are in boldface. k = number of studies contributing; N = number of subjects contributing; LL = lower limit of confidence interval; UL = upper limit of confidence interval. [*]Results from random effects model reported. [§]Alternate forms were used in some studies. [†]Studies did not specify whether test was forward or backward.

Table 3 (Continued). *Effect Sizes of Neuropsychological Test by Domain*

		Effect size and 95% confidence interval				Test of null (2-tail)	
	k	N	*d*	LL	UL	Z	*p*
Language							
Boston Naming Test	2	89	0.16	-0.14	0.46	1.04	0.30
Visuospatial Skill							
Block Design (WAIS)	4	142	0.18	-0.06	0.42	1.49	0.14
Rey-Osterrieth Complex Figure Test: Copy	3	100	-0.15	-0.43	0.13	-1.06	0.29
Visual Memory							
Family Pictures II (WMS)*	2	96	0.48	-0.30	1.26	1.21	0.23
Rey-Osterrieth Complex Figure Test: Immediate Recall[§]	5	219	**0.42**	0.21	0.63	3.92	<0.001
Rey-Osterrieth Complex Figure Test: Delayed Recall[*§]	5	219	0.21	-0.14	0.55	1.18	0.24
Visual Reproduction I (WMS)	2	182	0.14	-0.06	0.35	1.4	0.16
Visual Reproduction II (WMS)	2	182	**0.25**	0.05	0.46	2.46	0.01
Verbal Memory							
California Verbal Learning Test: Delayed Recall	2	122	0.14	-0.1	0.39	1.16	0.25
California Verbal Learning Test: Recognition	2	122	**0.26**	0.02	0.51	2.09	0.04
Hopkins Verbal Learning Test: Total[§]	2	46	-0.26	-0.63	0.11	-1.39	0.17
Logical Memory I (WMS)[*]	4	255	**0.38**	0.05	0.72	2.25	0.02
Logical Memory II (WMS)	5	316	**0.48**	0.27	0.69	4.54	<0.001
Rey Auditory Verbal Learning Test: Total Learning[*§]	5	312	-0.03	-0.32	0.26	-0.19	0.85
Rey Auditory Verbal Learning Test: Delayed Recall[*§]	6	347	0.10	-0.32	0.53	0.48	0.63

Note. Significant effect sizes (*d*) are in boldface. k = number of studies contributing; N = number of subjects contributing; LL = lower limit of confidence interval; UL = upper limit of confidence interval. [*]Results from random effects model reported. [§]Alternate forms were used in some studies. [†]Studies did not specify whether test was forward or backward.

Effect Sizes

Table 3 displays the mean weighted effect sizes, 95% CIs, and *Z* statistic for each neuropsychological test across studies. Each test was analyzed independently; however, the results are presented according to cognitive domains for clarity. The mean effect sizes for each test across the 13 studies ranged from *d* = -.56 to .68. Using a fixed effects model, semantic fluency and Symbol Digit Modalities Test (SDMT; Smith, 1982) were the only measures that declined significantly following chemotherapy treatment. In contrast, significant *improvements* were observed on 13 of the 31 variables. Falleti et al. (2005) found improvements in all domains when analyzing baseline comparisons, results that are similar to our own. However, their results should be interpreted with caution as the effect sizes were based on only one longitudinal study. The following sections outline results of individual tests, organized by cognitive domain for ease of comprehension.

Attention/concentration and executive function

The selected articles contained data for seven neuropsychological tests that are generally considered to measure attention/concentration and executive function. Effect sizes ranged from *d* = -.06 (Wisconsin Card Sorting Test [WCST]; Heaton et al., 1993) to *d* = .68 (WAIS Digit Span Forward), with only Digit Span Forward, Digit Span Backward, and Trail Making Test-Part B (TMT-B; Reitan, 1958) being significant.

The WAIS Digit Span subtest was reported as a total score in some studies and broken down into Forward and Backward scores in others. These scores were first examined separately, and significant positive effects were observed for both Digit Span Forward and Digit Span Backward. The data for the Digit Span Forward task were

heterogeneous, so a random effects model was examined and resulted in a non-significant effect size. When an aggregate effect size was calculated (i.e., Digit Span Forward and Digit Span Backward were pooled), a small but significant positive effect was also observed.

Measures of phonemic and semantic fluency were heterogeneous (i.e., highly variable); thus, a random effects model was employed, resulting in non-significant results. The effect size observed for semantic fluency approached one half SD and was the largest negative effect (d = -.45) in any domain. This suggests some potential for semantic fluency as an important tool in examining cognitive dysfunction related to chemotherapy treatment.

Speed of information processing

Five tests were classified as measures of information processing speed. Significant improvement was seen on WAIS Digit Symbol Coding and Trail Making Test-Part A (TMT-A). A negative effect was observed for the oral SDMT; however, these data were based upon only two studies and were heterogeneous; when a random effects model was examined, the effect size was no longer significant.

Language

In the studies included in this analysis, only one test, the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), was identified as measuring language, and it did not result in a significant effect size.

Visuospatial skill

Two tests were included as measures of visuospatial skill (WAIS Block Design and RCFT Copy) but neither resulted in a significant effect size.

Visual memory

The selected articles contained data for five variables from three tests examining various aspects of visual memory. With the exception of Wechsler Memory Scale (WMS; Wechsler, 1987, 1997b) Visual Reproduction I, all resulted in significant, small positive effect sizes. When a random effects model was examined for those measures with heterogeneous data (WMS Family Pictures II and RCFT Delayed Recall), the resulting effect sizes were no longer significant.

Verbal memory

Seven variables from four neuropsychological tests assessing aspects of verbal memory were reported. Of these, California Verbal Learning Test (CVLT; Delis, Kaplan, Kramer, & Ober, 1987, 2000) Recognition, WMS Logical Memory I, and WMS Logical Memory II were significant in the positive direction. Only data from Logical Memory I were heterogeneous, and the random effects model indicated a non-significant effect size for this test.

Potential Role of Practice Effects

Practice effects are defined as improvements in performance secondary to repeated exposure to a task (McCaffrey, Duff, & Westervelt, 2000). Given the large number of

positive effect sizes observed in this meta-analysis, it is possible that practice effects played a role in the results. To examine this, we compared the effect sizes found in our analysis with results from a recent meta-analysis of practice effects on commonly used neuropsychological tests (Calamia, Markon, & Tranel, 2012). In this paper, Calamia et al. (2012) conducted meta-analyses of individual neuropsychological tests using linear mixed-effects models. To generate a baseline model, predictors were centered such that the intercept represents the estimated score increase made by a 40-year-old healthy person retested after one year. This provided a baseline intercept (β) for each test. Additionally, mean age of participants was used as fixed-effects predictor of differences in effect sizes. The resulting β weight (-0.004) can be used to calculate the effect of age on the estimated score change. Since the mean age of our sample was 50.6 (which is 10.6 years greater than the mean of 40 in the baseline model), the expected score gain would be equal to the baseline intercept for a given test added to 10.6 times the 0.004/year effect of age. Table 4 lists the adjusted β weights of tests for which intercepts were provided by Calamia et al., as well as the difference between the adjusted β weight and the effect size generated in the current meta-analysis.

Table 4. *Comparison of Effect Sizes and Practice Effects in Cancer and Control Groups*

	Adjusted β	*d*	Difference
Attention/Executive Function			
Arithmetic (WAIS)	0.12	0.14	0.02
Digit Span (WAIS)	0.22	0.28	0.06
Letter Number Sequencing (WAIS)	0.13	0.02	-0.11
Phonemic Fluency	0.22	0.26	0.04
Trail Making Test B	0.17	0.19	0.02
Wisconsin Card Sorting Test	0.12	-0.05	-0.17
Speed of Information Processing			
Digit Symbol Coding (WAIS)	0.26	0.18	-0.08
Trail Making Test A	0.15	0.08	-0.07
Language			
Boston Naming Test	0.23	0.16	-0.07
Visuospatial Skill			
Block Design (WAIS)	0.20	0.13	-0.07
Rey-Osterrieth Complex Figure Test: Copy	-0.04	-0.15	-0.11
Visual Memory			
Rey-Osterrieth Complex Figure Test: Immediate Recall	0.22	0.42	0.20
Rey-Osterrieth Complex Figure Test: Delayed Recall	0.34	0.23	-0.11
Verbal Memory			
California Verbal Learning Test: Delayed Recall	0.53	0.14	-0.38
California Verbal Learning Test: Recognition	0.30	0.26	-0.03
Rey Auditory Verbal Learning Test: Total Learning	0.44	-0.11	-0.55
Rey Auditory Verbal Learning Test: Delayed Recall	0.20	-0.08	-0.29

Note. β = intercepts, as reported in Calamia et al. (2012), represent the expected change after one year and have been adjusted for age; d = effect sizes calculated in the current meta-analysis.

Test variables showing a possible practice effect in cancer survivors fell into two categories: those for which both clinical and control groups showed similar improvement, and those for which the improvement was smaller than expected in the cancer group. Those variables falling in the latter category are ones for which the cancer group did not make the expected gains (i.e., they fell below the expected practice effect level for

controls as reported by Calamia et al., 2012). Variables for which expected gains were not seen included WAIS Letter Number Sequencing, WCST, WAIS Digit Symbol Coding, TMT-A, Boston Naming Test, WAIS Block Design, RCFT Copy and Delayed Recall, CVLT Delayed Recall, Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) Total Learning, and RAVLT Delayed Recall. The largest discrepancies (i.e., the cancer group performed significantly worse than the expected practice effect) were seen on measures of verbal learning and memory—specifically, CVLT Delayed Recall, RAVLT Total Learning, and RAVLT Delayed Recall.

Fail Safe *n*

The potential effects of publication bias were examined with the calculation of a fail-safe *n* (Orwin, 1983). Results of this calculation indicate that an additional nine studies with null results (i.e., studies with a mean effect size of zero) would be needed to reduce the overall weighted effect size to a non-significant level. Although this meta-analysis contains a small number of studies (13), this result calls into question the robustness of the current meta-analysis. However, given the lack of large effect sizes, this result is not altogether surprising and highlights the need for additional research in this area.

Discussion

A number of reviews (e.g., Castellon, Silverman, & Ganz, 2005; Dutta, 2011; Wefel and Schagen, 2012) and several meta-analyses (Falleti et al., 2005; Stewart et al., 2006; Jansen et al., 2007) have been published on the topic of cognitive dysfunction

related to chemotherapy treatment in patients with breast cancer. Overall, many inconsistencies in findings exist, and methodological variability (e.g. heterogeneous samples, treatments, etc.) has been implicated as a factor contributing to the wide variability in reports of cognitive impairment in this population. Of particular importance is test selection and assignment of domains. One limitation of previous reviews and meta-analyses is that results are often presented as composite domain scores. While these domains certainly help us understand cognitive function in a broad way, a great deal of information is at risk of being lost when tests are combined. All neuropsychological tests require the use of more than one facet of cognition, and it is important to our understanding of chemotherapy-related cognitive dysfunction to be able to differentiate between these various components. Thus, we analyzed each neuropsychological test separately in an attempt to examine the effect of chemotherapy on more specific aspects of cognitive functioning.

To our knowledge, this is the first meta-analysis of neuropsychological data exclusively focusing on longitudinal observations in breast cancer patients treated with chemotherapy. Results indicate general *improvements* in the performance of patients treated with chemotherapy on the majority of neuropsychological tests analyzed. These observed improvements may result from real improvements in cognition, possibly related to decreased psychological stress after the initiation of curative treatment. However, given that most studies have found minimal correlation between self-reported mood symptoms and objective cognitive performance (e.g., Argyriou, Assimakopoulos, Iconomou, Giannakopoulou, & Kalofonos, 2011; Pullens, Vries, & Roukema, 2010; Raffa, 2010), this explanation may not account for observed improvement in cognitive

functioning following chemotherapy. Rather than representing real improvements in cognition, positive effect sizes may reflect measurement artifact. For example, it has generally been found that only a subset of patients demonstrates cognitive impairment following chemotherapy treatment; therefore, the appropriateness of group-level analysis of change over time is questionable (Ouimet, Stewart, Schindler, & Bielajew, 2009), as it may mask impairment in that subset of individuals.

Alternatively, positive effect sizes may be related to practice effects, a limitation inherent in prospective studies, even when alternate test forms are used (Calamia et al., 2012). These results suggest that, for most variables, practice effect alone might account for the improvement observed in cancer patients and may in fact mask deterioration in cognitive functioning following chemotherapy. Keeping this in mind, it may be worth examining not just effect sizes themselves, but the difference between the effect size and the expected practice effect for each neuropsychological test. Attenuation of practice effects in cancer patients has been reported by other researchers as well and provides support for the subtle nature of cognitive deficits in this population (Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009; Tager et al., 2010). In our meta-analysis, the variables that showed the greatest discrepancy from the expected practice effect were measures of verbal learning and memory—specifically, CVLT Delayed Recall, RAVLT Total Learning, and RAVLT Delayed Recall. Although further research is needed, these preliminary data suggest that measures of verbal learning and memory may be especially sensitive to chemotherapy-related cognitive decline. This is generally in line with the literature, which suggests verbal learning and memory as a domain often affected in this population. However, another common domain reported as affected is executive function,

which did not emerge as an area of significant decline in this meta-analysis. One possible explanation for this may be the measurement difficulties inherent to traditional executive function measures (e.g., the requirement of a novel response or problem-solving strategy). Because of this, it is generally thought that tests of executive function are among the most likely to show large practice effects (Calamia et al., 2012; Lezak et al., 2012), and therefore, effect sizes generated for these tests should be interpreted with caution.

Additionally, the pattern of memory impairment generally reported in the literature on chemotherapy-related cognitive dysfunction appears as deficits in encoding and retrieval, with relative preservation of recognition memory (e.g., Quesnel et al., 2009; Von Ah et al., 2009). A similar pattern was seen in the results of this meta-analysis, with CVLT Recognition scores showing improvement in line with that of healthy controls. Such a pattern of recognition being superior to recall suggests damage to frontal subcortical networks (Stuss & Knight, 2002), of which executive functions are a large part (Wefel & Schagen, 2012). As such, it is possible that difficulties in executive function may be related to and/or impact memory functioning. However, the relationship between executive function and memory has yet to be fully explored in this population and will be an important area of future research.

One limitation of the current study was the relatively small fail-safe *n*, which suggests that the lack of inclusion of unpublished studies with null results may have a significant impact on our findings. In part, this is likely related to our lack of large effect sizes. However, as discussed above, these effect sizes may reflect an underestimate of the true impact of chemotherapy on cognitive function due to practice effects, which

artificially inflate test scores. Another limitation is the small number of prospective studies that met inclusion criteria (in particular, having a longitudinal design), therefore limiting our ability to perform analyses of moderator variables such as age and test-retest duration.

Both of these limitations should be addressed in future research, specifically meta-analyses that include control groups. We chose to limit this analysis to longitudinal (pre/post) data in an effort to examine within-subject changes as these may be more representative of chemotherapy-related cognitive changes than cross-sectional comparisons, which may mask more subtle findings. However, including studies utilizing control groups will increase the available sample size and moderate the effect of practice. Examining comparisons with different control groups (i.e., healthy controls, cancer survivors who did not receive chemotherapy) will also be important in helping to determine the most appropriate control group for this population.

The current meta-analysis provides initial data regarding within-subjects change on neuropsychological tests following chemotherapy for breast cancer. However, questions still remain and further research is needed to explore the cognitive effects of chemotherapy. The attenuation of practice effects from baseline to post-chemotherapy suggests a decline in function, albeit a subtle one. For this reason, research examining the sensitivity of various neuropsychological tests to chemotherapy-related cognitive dysfunction will be essential to understanding this complex phenomenon. While longitudinal comparisons appear to be relevant in this population given reports of pre-chemotherapy cognitive impairment, the effect of practice cannot be underestimated and deserves further empirical exploration and clinical consideration.

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CHAPTER FOUR
Study Two

ANALYSIS OF ATTENTION AND EXECUTIVE FUNCTION IN BREAST CANCER SURVIVORS EXPOSED TO CHEMOTHERAPY

Abstract

Objective: The pattern of cognitive dysfunction associated with chemotherapy treatment is reflective of disruption of frontal subcortical networks (Meyers, 2008). Because attention and executive function are of central importance in this so-called "subcortical profile," it is important to have a thorough understanding of how they may be impacted by chemotherapy. However, current knowledge of these cognitive domains in cancer patients is difficult to interpret. The current study attempts to clarify the literature with respect to executive function and its component parts in chemotherapy-related cognitive dysfunction.

Method: Seventy-two female breast cancer survivors between the ages of 40 and 70 were administered a battery of neurocognitive tests of attention and executive function an average of one year following chemotherapy treatment. Frequency of impairment and rank performance was examined on each neuropsychological test. Impaired (N = 13, defined as $\geq$ 2 tests $\leq$ 1.5 *SD* below the mean) participants were compared to non-impaired (N = 59) on demographic factors and self-report measures of mood, quality of life, and cognitive function.

Results: The overall rate of impairment in our sample was approximately 18%. Those tests with the greatest frequency of impairment were PASAT (22.2%) and FAS (13.9%),

which were also consistently ranked lowest (with Category Fluency). Notably, none of the participants obtained an impaired score on WAIS-IV Coding. Impairment status was not associated with age, education, time since treatment, or self-reported symptoms of depression, anxiety, or fatigue. However, estimated premorbid IQ was significantly lower among subjects who showed evidence of cognitive impairment.

Conclusion: Those tests on which participants consistently scored lowest all require verbal output under time pressure (FAS, PASAT, and Animal Fluency). Our results suggest that there may be an executive-based verbal component to chemotherapy-related cognitive dysfunction. Although this is highly consistent with patient complaints, this concept has yet to be explored in the literature and merits further investigation.

Analysis of Attention and Executive Function in Breast Cancer Survivors Exposed to Chemotherapy

Worldwide, it is estimated that more than 12 million new cancer cases occur each year. Breast cancer is the most frequently diagnosed cancer in females, accounting for 23% (1.38 million) of new cancer cases (Jemal et al., 2011). Due to advances in treatment, including aggressive, multi-modal regimens, long-term survival rates have drastically increased in the past several decades (Altekruse et al., 2010). With prolonged survival comes a greater concern for issues related to quality of life, including cognitive function.

Reports by cancer patients of cognitive problems following treatment were initially attributed to mood-related factors such as anxiety or depression (Meyers, 2008), and were often dismissed by clinicians. However, an emerging body of literature is providing insight into measurable cognitive changes following chemotherapy treatment in breast cancer survivors. The phenomenon of cognitive dysfunction following cancer treatment is often called "chemo-brain" by patients and in the media. In the past decade, there has been a significant increase in the number of studies examining the cognitive effects of chemotherapy in this population, with nearly 60 empirical reports published since 2000. The majority of these studies have reported at least some evidence of mild cognitive difficulties, although this remains poorly understood, with the prevalence of reported cognitive deficits ranging from roughly 15% to 75% across published reports (Wefel, Vardy, Ahles, & Schagen, 2011). The literature suggests that cognitive deficits

tend to be subtle in breast cancer patients who have completed chemotherapy, and the presence of severe deficits is rare (Wefel & Schagen, 2012).

The most common cognitive abnormalities among breast cancer survivors have been reported in the areas of learning and episodic memory, in addition to attention, processing speed, working memory, and aspects of executive function (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006; Wefel & Schagen, 2012). Further exploration into the specific nature of these deficits reveals a pattern suggestive of adverse effects on frontal subcortical networks (Meyers, 2008). For example, on tasks of verbal memory, deficits are typically seen in encoding and retrieval, with the relative preservation of recognition memory (Quesnel, Savard, & Ivers, 2009; Von Ah et al., 2009), which is a classic pattern of so-called "subcortical dysfunction." Results from neuroimaging studies provide additional support for this observation. Studies using diffusion tensor imaging have consistently reported decreased integrity of frontal and temporal white matter (Abraham et al., 2008; de Ruiter et al., 2011). Results from functional imaging studies have supported a subcortical pattern of dysfunction as well. For example, Kesler, Bennett, Mahaffey, & Spiegel (2009) showed reduced prefrontal cortex activation on functional magnetic resonance imaging (fMRI) during memory encoding in a sample of chemotherapy-treated breast cancer survivors. Additionally, they found increased spatial extent of cortical activation during the recall phase. Since the prefrontal cortex has been shown to be important in attention and organizational skills, the authors posited that their findings might reflect a decrease in these abilities during the encoding phase, thus setting the stage for subsequent difficulty with recall. The widespread activation they found indicates

recruitment of brain regions not typically utilized during memory recall. Essentially, because the information was not properly encoded, remembering it after a delay required additional effort. Several other fMRI studies have replicated this finding (Ferguson, McDonald, Saykin, & Ahles, 2007; Silverman et al., 2007).

While the hippocampus is often implicated in memory dysfunction, this does not appear to be the case in chemotherapy-related cognitive dysfunction (Meyers, 2008). Damage to the medial temporal lobe produces generalized memory loss that is manifested as impaired recall and recognition. The available research, as described above, indicates that the pattern of performance seen in chemotherapy-related cognitive dysfunction is, by contrast, likely related to a disruption of the supportive processes involved in the initial acquisition and efficient retrieval of information (Stuss & Knight, 2002; Meyers, 2008). These supportive processes may include aspects of executive functions and related foundational skills such as attention, processing speed, and working memory. It is not surprising, then, that these are some of the most commonly-reported domains to be affected following chemotherapy, particularly executive function. However, this finding is far from universal in the literature.

Even as numerous studies have reported deficits in attention, working memory, processing speed, and executive function in breast cancer survivors (Ahles et al., 2010; Bender et al., 2006; Jansen, Cooper, Dodd, & Miaskowski, 2010; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006; Stewart et al., 2008), others have reported negative findings in all of these areas (Debess, Riis, Engebjerg, & Ewertz, 2010; Jenkins et al., 2006; Jim et al., 2009; Mehlsen, Pedersen, Jensen, & Zachariae, 2009; Tager et al., 2010). One investigation even reported *improvements* in executive function in a cancer

group after chemotherapy (Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008). This particular inconsistency may simply be a result of different study designs or definitions of impairment; however, this does not appear to be the case. If study-specific factors, such as definition of impairment or choice of comparison group, were of singular importance in whether deficits were found or not, it could be expected that studies with similar designs would produce similar findings. This is not the case, however. Studies by Jim et al. (2009) and Wefel, Lenzi, Theriault, Davis, & Meyers (2004) both assessed the domain of attention, used a longitudinal design to assess breast cancer patients before and after chemotherapy, and defined impairment as ≥ 1.5 standard deviations (*SD*) on ≥ 2 tests. Wefel et al. reported impairment in attention, while Jim et al. did not. Although similar in terms of design and definition of impairment, the studies differed in the tests chosen to measure attention. While study design is certainly relevant, the importance of consistency in other methodological factors such as composition of neuropsychological test batteries cannot be overlooked.

As evidenced by this example, variability in the choice of tests used to represent various cognitive domains can obfuscate our understanding of chemo-brain. Consistency in test selection is important to allow comparison of results across studies and facilitate clarification of the domains and skills affected by chemotherapy. Adequate test selection not only requires an understanding of the population of interest (especially with regard to cognitive aspects of the disease or treatment), but a thorough understanding of the psychometric properties of various tests as well (Freeman & Broshek, 2002). Of particular importance to cancer research is the tests' ability to detect subtle cognitive dysfunction (Wefel et al., 2011). Unfortunately, there is a paucity of information

available regarding the sensitivity and specificity of neuropsychological tests to detect cognitive changes following chemotherapy (Freeman & Broshek, 2002; Jansen, Miaskowski, Dodd, & Dowling, 2007). Researchers are therefore left with little guidance on which tests to choose, and variability is an inevitable result.

An additional challenge facing researchers in this area is that traditional neuropsychological tests capture multiple facets of cognition. For this reason it is sometimes difficult to summarize neuropsychological findings in a research report, as an impaired score may have one of many underlying causes. Clinically, neuropsychologists are trained to examine qualitative aspects of performance to understand the underlying cause for an impaired score. However, in large-scale research protocols this is not always possible, making the "label" very important. For example, Grooved Pegboard (Trites, 1989), a common test in neuropsychological assessment, has been characterized as a test of motor functioning (Collins et al., 2009) or processing speed (Ahles et al., 2010), depending on the study. Certainly, successful performance on this task requires both intact motor functioning and psychomotor speed, but the label it is assigned in a given investigation will influence the reported findings (i.e., determine whether the study reports impairment in motor skills or processing speed). Therefore, it is possible that some divergence between theoretical cognitive domains and clinical patterns is accountable, at least in part, for discrepant reports in the literature.

This issue is ameliorated somewhat when we have a clear understanding and conceptualization of the domain in question, but for many areas, this is not the case. An example of one such area is executive function, a concept that still lacks a formal definition (Jurado & Rosselli, 2007). Similar problems are found with constructs such as

attention, working memory, and processing speed, which also lack clear definitions (Baddeley, 2003; Petersen & Posner, 2012). However, even among variable definitions of these constructs, relative agreement exists in terms of their multi-faceted nature and their respective roles as supportive functions (Jurado & Rosselli, 2007; Lezak, Howieson, Bigler, & Tranel, 2012; Miyake, Emerson, & Friedman, 2000). Therefore, the very nature of these skills makes them particularly difficult to isolate via neuropsychological tests and subsequently difficult to categorize into discrete domains.

As noted above, the pattern of cognitive impairment and neurological damage (as seen on neuroimaging) is reflective of disruption of frontal subcortical networks (Meyers, 2008). Because executive function and related constructs are of central importance in this so-called subcortical profile, it is important to have a thorough understanding of how these domains are impacted by chemotherapy. Current knowledge regarding the effects of chemotherapy on executive function and related domains is difficult to interpret, in part because of various methodological factors, including inconsistent use of tests across studies and variability in the conceptualization of each construct. Thus, conclusions regarding impairment in these domains are limited, and their role in the clinical syndrome known as chemo-brain remains poorly understood. The current study attempts to clarify the literature and pave the way for more thorough investigations of executive function and its component parts in chemotherapy-related cognitive dysfunction.

Methods

Participants

The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center (UT Southwestern). Participants were recruited through the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern. Female breast cancer patients who completed adjuvant chemotherapy treatment between three to twenty-four months prior were administered a battery of neuropsychological tests and self-report measures. All participants were disease-free at the time of testing, were native speakers of English, had minimum of a high school education (or GED equivalent), and were between 40 and 70 years old. Patients with a history of stroke, head injury with loss of consciousness greater than 30 minutes, brain metastasis, untreated diabetes, untreated hypertension, major surgeries within the past six months unrelated to their breast cancer treatment, and pre-cancer major Axis I psychiatric disorder or other disorder with known cognitive impairments (e.g. dementia, epilepsy, intellectual disability) were excluded. Subjects were not excluded on the basis of other treatments received (e.g., radiation, hormone therapy). A total of 800 women were identified for initial screening and 75 were enrolled (175 unable to contact, 12 refused, 538 ineligible). Of the enrolled participants, 3 were found to have neurologic complications that were unknown at the time of enrollment and were therefore excluded from analysis.

Measures

Neurocognitive tests were selected based on their ability to measure various components of attention and executive function, as well as psychometric properties, common clinical use, and time efficiency to minimize fatigue. The following tests (listed in order of administration) were given as part of a larger battery: 1) *FAS* (Heaton, Miller, Taylor, & Grant, 2004) is a test of verbal fluency that evaluates the spontaneous production of words beginning with a given letter. T-scores will be used in the current study and are based on the total number of words generated. 2) *Category fluency* (Heaton et al., 2004) is a similar task that requires the production of words within a semantic category (animals). T-scores will be used and are based on the total number of words generated. 3) *Digit Span* from the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV; Wechsler, 2008a) is used to measure basic auditory attention and working memory. This test is given in three trials, where participants are asked to repeat strings of numbers forward, backward, and in sequential order. Scaled scores from the forward and backward condition were used in the current analysis. 4) *Color Word Interference Test* from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) is a version of the Stroop paradigm and assesses response inhibition, impulse control, selective attention, and cognitive flexibility. Scaled scores from the Inhibition trial were used in the present study. 5) *Paced Auditory Serial Addition Test* (PASAT; Gronwall, 1977) is a measure of divided attention, auditory information processing speed, mental flexibility, and working memory. Single digits are presented aurally every 3 seconds, and the participant is required to add each new digit to the one presented immediately prior to it. 6) *Coding* from the WAIS-IV (Wechsler, 2008a) is a

number/symbol substitution task that measures divided attention, visual scanning, and processing speed. 7) *Trail Making Test* (TMT; Reitan, 1958) is a measure of visual attention, processing speed, and mental flexibility. The test is given in two parts, A and B, and requires sequencing of numbers and letters. Standard scores from each part were used in the current [1]analysis.

Additionally, the *Wechsler Test of Adult Reading* (WTAR; Wechsler, 2001b) was used to provide an estimate of premorbid intellectual functioning. Participants' perception of their own functioning was measured using the following self-report instruments. Unless noted otherwise, a total score was generated for each measure and used in the present study. The *Hospital Anxiety and Depression Scale* (HADS; Zigmond & Snaith, 1983) is a 14-item screening measure of depression and anxiety symptoms in medical populations. *Functional Assessment of Cancer Therapy—General* (FACT-G; Cella et al., 1993) is a 27-item measure of quality of life in cancer patients within the domains of physical well-being, functional well-being, social well-being, and emotional well-being. *Functional Assessment of Cancer Therapy—Cognitive Function* (FACT-Cog; Wagner, Sweet, Butt, Lai, & Cella, 2009) is a brief measure of cognitive function for patients who have received cancer treatment. Four subscales are calculated and include Perceived cognitive impairment (CogPCI); Impact on quality of life (CogQOL); Comments from others (CogOth); and Perceived cognitive abilities (CogPCA). *Functional Assessment of Cancer Therapy—Fatigue* (FACT-F; Yellen, Cella, Webster,

[1] Additional neuropsychological tests administered included the *California Verbal Learning Test—Second Edition* (CVLT-II; Delis, Kaplan, Kramer, & Ober, 2000) and the *Texas Assessment of Processing Speed* (TAPS; Grosch et al., 2012).

Blendowski, & Kaplan, 1997) is a 13-item measure of fatigue-related symptoms in cancer patients.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS, Version 19) was used for all statistical analyses. Frequency of impairment was examined on each of the nine measures of attention/executive function described above. Based on the recommendations of the International Cognition and Cancer Task Force, overall impairment was defined as two or more scores falling at or below -1.5 *SD* from the normative mean (Wefel et al., 2011). One-sample proportions tests were used to determine if the observed rate of impairment exceeded expectation. In a healthy, normal population, 6.7% of the population would be expected to have scores falling below -1.5 *SD* on any one measure, assuming the population was normally distributed. By using curves based on the binomial probability distribution assuming independent, normally distributed test scores, it was determined that in a battery of nine independent tests, 10% of the population is expected to fall 1.5 *SD* below the mean on two measures. It should be noted that Ingraham and Aiken (1996) have found this estimate is reliable even when test scores are correlated.

The literature suggests that cognitive deficits tend to be subtle in breast cancer patients who have completed chemotherapy, and the presence of severe deficits is rare (Wefel & Schagen, 2012). Because reported rates of impairment in breast cancer patients exposed to chemotherapy are quite variable, we chose to examine rank performance as well as frequency of impairment. To that end, scores on each of the nine attention/executive function measures were converted to *z*-scores and ranked from lowest

to highest for each individual participant. A Friedman Two Way Analysis of Variance test was used to examine if there was a consistent rank order among the tests. Friedman's test is a nonparametric alternative to a repeated-measures analysis of variance that uses the ranks of the data rather than their raw values to calculate the test statistic. The size of the test statistic reflects subject-to-subject consistency with respect to performance (i.e., subjects tend to score highest on the same measure, second highest on the same measure, etc.). As subject-to-subject consistency increases, mean differences in rank order across measures will increase, indicating that there is a consistency to the order of scores. In the presence of a significant overall test, follow-up pairwise comparisons were performed using the Wilcoxon Test for Pairs, with the p-values adjusted using the Bonferroni correction to maintain an overall .05 comparison rate.

Results

Sample Characteristics

Sample characteristics are described in Table 1. The sample consisted of 72 female participants between the ages of 40 and 70. Mean age was 57.0 (*SD* = 8.8) and mean education was 15.2 (*SD* = 2.3). Only two participants had less than 12 years of education, and both had obtained a GED. The overall estimated IQ of the sample (as measured by the WTAR) was within the average range (*M* = 108.9, *SD* = 9.6). The majority of the sample was white (87.5%) and right handed (87.5%). Most participants had early stage breast cancer (75% at Stage II or lower). Mean time since completion of chemotherapy treatment was 12.9 months (*SD* = 7.3). All had undergone surgery and the majority had received radiation therapy (77.8%) and hormone therapy (76.4%).

Table 1. *Sample Characteristics (N=72)*

Age (years)	
Mean (*SD*)	57.0 (8.8)
Range	40 - 70
Education (years)	
Mean (*SD*)	15.2 (2.3)
Range	9 - 20
Estimated Premorbid IQ	
Mean (*SD*)	108.9 (9.6)
Range	86 - 126
Race/Ethnicity (*N*, %)	
White	63 (87.5)
Non-White	9 (12.5)
Stage of Cancer at Diagnosis (*N*, %)	
I	12 (16.7)
II	42 (58.3)
III	18 (25.0)
Time Since Completion of Chemotherapy (months)	
Mean (*SD*)	12.9 (7.3)
Range	3 - 24
Radiation (*N*, % Yes)	56 (77.8)
Hormone Therapy (*N*, % Yes)	55 (76.4)

Self-reported Well-being

As shown in Figure 1, levels of self-reported anxiety and depression were generally low overall, although about 29% of the group reported clinically significant symptoms of anxiety. Symptoms of fatigue were endorsed by approximately 35% of the sample, with the mean score of the group as a whole falling slightly above the cutoff for "clinical significance" on this variable. Overall quality of life ratings were average (see Table 2 for means and *SD*).

Figure 1. *Percentage of Clinically Significant Scores on Self-Report Measures*

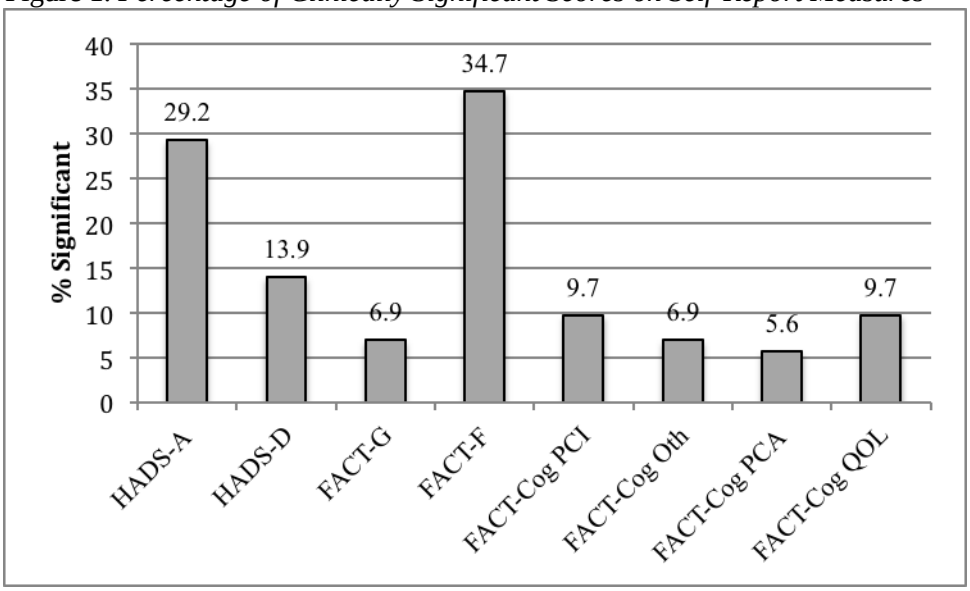


Table 2. *Self-Report Measures of Well-Being (N=72)*

Variable	Mean (*SD*)	Possible Range
HADS[§a]		
Anxiety	5.26 (4.20)	0-21
Depression	3.17 (3.48)	0-21
FACT-G Total[†]	53.71 (8.67)	0-108
FACT-F[§b]	38.61 (11.84)	0-52
FACT-Cog[§c]		
Perceived Cognitive Impairment	47.38 (16.34)	0-72
Comments from Others	14.93 (2.24)	0-16
Perceived Cognitive Abilities	18.31 (5.61)	0-28
Impact on Quality of Life	12.69 (3.27)	0-16

Note: [a]Cutoff score = 8, with higher scores indicating higher levels of anxiety or depression. [b]Cutoff score = 36, with higher scores indicating lower levels of fatigue. [c]Sample mean and SD were used to determine frequency of significant scores. Lower scores indicate greater cognitive complaints. [§]Means reported as raw scores. [†]Means reported as T-scores.

Cognitive Function

Descriptive statistics for all neuropsychological measures can be found in Table 3. Although examination of the group mean scores for individual tests suggests subtle findings overall, it is important to note the large range of scores on most tests, with some ranging from above average to severely impaired.

Table 3. *Descriptive Statistics for Neuropsychological Measures (N=72)*

Variable	Mean (*SD*)	Median	Range
FAS Total[†]	45.7 (9.1)	46	23 - 66
Category Fluency Total[†*]	46.9 (11.1)	50	9 - 63
WAIS-IV Digit Span			
Forward[§]	10.3 (2.7)	10	5 - 19
Backward[§]	10.0 (2.2)	10	5 - 16
D-KEFS Color Word Interference Test (Inhibition)[§]	10.6 (3.0)	11	1 - 17
PASAT Total[†]	43.1 (13.1)	45	9 - 60
WAIS-IV Coding[§]	12.2 (2.5)	12	6 - 17
Trail Making Test			
Part A[†]	49.7 (9.5)	50	19 - 71
Part B[†]	51.2 (10.1)	54	13 - 71

Note. [§]Means reported as Scaled scores; [†]Means reported as T-scores. [*]*N* = 69.

Frequency of cognitive impairment

Overall impairment was defined as two or more scores at or below -1.5 *SD* from the normative mean for that measure. By direct calculations based on the binomial distribution assuming independent, normally distributed test scores, it was determined that in a battery of nine tests, 10% of the general population would be expected to fall 1.5 *SD* below the mean on two or more measures. In our sample, 18.1% (*N* = 13) met this criterion, which is significantly greater than the expected frequency ($p = .02$; see Table 4). Table 4 also shows the number of participants with impaired scores on one, two, three, etc. tests.

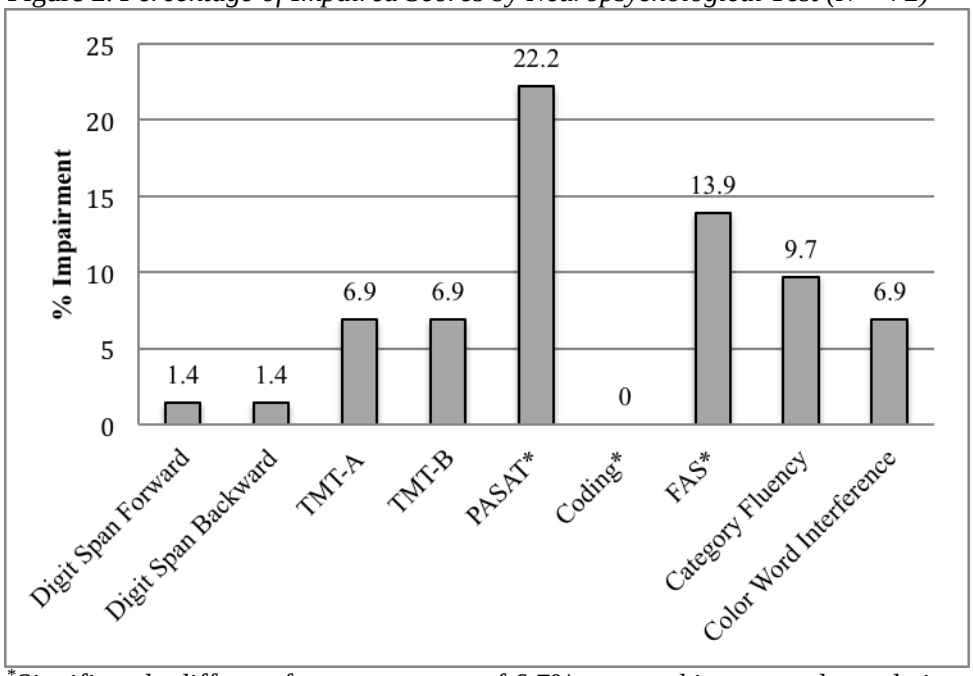
Table 4. *Frequency of Impaired Test Scores*

Number of Tests Impaired	Observed Frequency (*N*, %)	p^*
0	46 (63.9)	
1	13 (18.1)	
2	8 (11.1)	
3	1 (1.4)	
4	2 (2.8)	
5	2 (2.8)	
6 - 9	0 (0.0)	
≥ 2	13 (18.1)	0.02

*One-sample proportions test

Those tests with the greatest frequency of impairment were the PASAT (22.2%) and FAS (13.9%; see Figure 2). Notably, none of the participants obtained an impaired score on WAIS-IV Coding, and only three (4.2%) had a score that fell at or below -1 *SD* on this measure.

Figure 2. *Percentage of Impaired Scores by Neuropsychological Test (N = 72)* [†]



[*]Significantly different from percentage of 6.7% expected in a normal population
[†]N = 69 for Category Fluency.

Comparison of impaired versus non-impaired groups.

The impaired (N = 13) and non-impaired (N = 59) groups did not significantly differ in terms of age, education, or time since completion of chemotherapy treatment. However, estimated premorbid IQ was significantly lower in the impaired group ($p <$ .001; see Table 5). The groups did not differ significantly on measures of self-reported mood, quality of life, or cognitive function (see Table 6).

Table 5. *Demographic Characteristics (Mean, SD) by Impairment Status*

	Impaired (N = 13)	Non-Impaired (N = 59)	p^*
Age	59.0 (9.2)	56.5 (8.7)	0.37
Education	14.9 (2.6)	15.3 (2.3)	0.65
Estimated Premorbid IQ	98.2 (5.5)	111.3 (8.6)	**<0.001**
Time since completion of chemotherapy (months)	14.5 (7.9)	12.4 (7.0)	0.34

Note. p-values <.05 are in boldface. *Independent samples t-test

Table 6. *Mean (SD) and Frequency of Clinically Significant Self-Report Scores by Impairment Status*

	Impaired (*N* = 13)		Non-Impaired (*N* = 59)		
	M (*SD*)	Elevated (*N*, %)	M (*SD*)	Elevated (*N*, %)	*p*[*]
Mood					
HADS[§a]					
Anxiety	5.5 (5.8)	4 (30.8)	5.2 (3.8)	17 (28.8)	0.80
Depression	3.9 (4.6)	3 (23.1)	3.0 (3.2)	7 (11.9)	0.39
Total	9.5 (10.2)	4 (30.8)	8.2 (6.4)	19 (32.2)	0.57
QoL					
FACT-G[†]					
Personal Well-Being	48.9 (11.5)	2 (15.4)	50.9 (9.3)	5 (8.5)	0.50
Social Well-Being	51.5 (9.6)	1 (7.7)	54.3 (7.9)	3 (5.1)	0.27
Emotional Well-Being	50.9 (7.1)	0 (0.0)	49.9 (7.2)	5 (8.5)	0.67
Functional Well-Being	54.8 (10.0)	1 (7.7)	55.2 (7.0)	0 (0.0)	0.85
Total	52.3 (11.1)	1 (7.7)	54.0 (8.1)	4 (6.8)	0.52
FACT-F[§b]	42.0 (12.4)	2 (15.4)	37.9 (11.7)	23 (39.0)	0.26
Cognitive Function					
FACT-Cog[§c]					
Perceived Cognitive Impairment	52.8 (15.7)	1 (7.7)	46.2 (16.4)	6 (10.2)	0.19
Comments from Others	14.8 (2.4)	2 (15.4)	15.0 (2.2)	3 (5.1)	0.78
Perceived Cognitive Abilities	19.8 (4.6)	0 (0.0)	18.0 (5.8)	4 (6.8)	0.29
Impact on Quality of Life	14.2 (2.2)	0 (0.0)	12.3 (3.4)	7 (11.9)	0.06

Note. [a]Cutoff score = 8, with higher scores indicating higher levels of anxiety or depression. [b]Cutoff score = 36, with higher scores indicating lower levels of fatigue. [c]Sample mean and SD were used to determine frequency of significant scores. Lower scores indicate greater cognitive complaints. [*]Independent samples t-test.

Rank order of tests based on performance

We examined the rank order of each of the nine measures of attention/executive function to determine if there was a consistency to the ranks of tests with greater vs lower rates of impairment. As indicated in Table 7, Friedman's Two Way Analysis of Variance test revealed that the nine measures differed significantly with respect to rank order *z*-score ($\chi^2[8] = 113.4$; $p < .001$). The test resulting in the lowest overall ranked score was FAS.

Table 7. *Mean Rank Performance on Attention/Executive Function Tests*

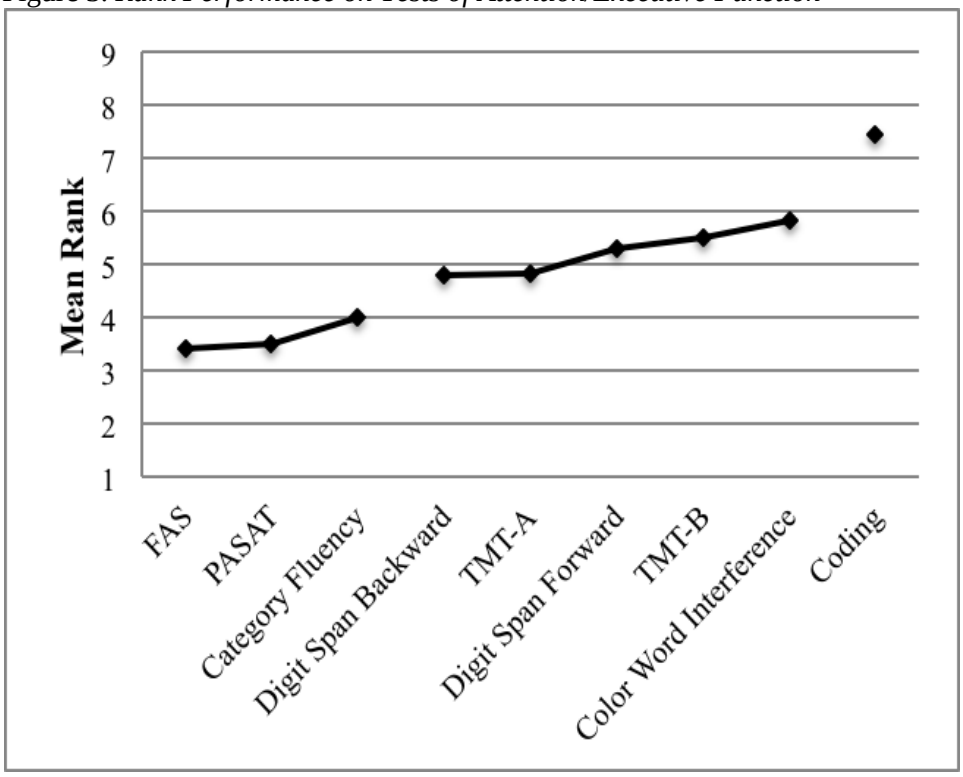
Variable	Mean Rank (N=69)	χ^2	*p**
FAS	3.42		
PASAT	3.51		
Category Fluency	4.01		
WAIS-IV Digit Span Backward	4.80		
Trail Making Test A	4.81		
WAIS-IV Digit Span Forward	5.28		
Trail Making Test B	5.49		
D-KEFS Color Word Interference (Inhibition)	5.83		
WAIS-IV Coding	7.44		
		113.40	<0.001

*Friedman's Two-Way Analysis of Variance Test

Multiple comparisons indicate that FAS, PASAT, and Category Fluency had consistently lower score ranks than the other tests, but there was no significant difference between them. Interestingly, Coding had the highest average score rank and was significantly different than all of the other tests. Multiple comparisons indicated that there

were no significant differences between the remaining five tests (Digit Span Backward, TMT-A, Digit Span Forward, TMT-B, and Color Word Interference; see Figure 3).

Figure 3. *Rank Performance on Tests of Attention/Executive Function*



Discussion

The overall rate of impairment in our sample of breast cancer survivors treated with chemotherapy was approximately 18%, which is greater than what would be expected in a healthy population and is generally consistent with other studies examining

chemotherapy-related cognitive dysfunction, albeit at the lower end of the reported range (Wefel & Schagen, 2012).

Importantly, our findings of cognitive dysfunction cannot be attributed to self-reported symptoms of depression, anxiety, or fatigue, which is highly consistent with other reports (Ahles et al., 2010; Collins et al., 2009; Hermelink et al., 2007; Jansen et al., 2008). Impairment status was also unrelated to age, education, or time since completion of treatment. This finding is generally consistent with the current literature, as most studies have failed to find a significant association between cognitive decline and demographic factors. However, our results showed that performance on the WTAR, an index of premorbid IQ, was significantly lower among subjects who showed evidence of cognitive impairment. Since the WTAR tends to be insensitive to acquired cognitive impairment (Lezak et al., 2012) and is much less sensitive than the other measures utilized, this merits explanation. Because of its resistance to change after brain damage, this test is often used as an indicator of cognitive reserve. *Cognitive reserve* describes the brain's resilience to damage and has been characterized as its ability to optimize performance through differential recruitment of neural networks. It is thought to be related to numerous factors including genetics, education, and lifestyle (Stern, 2009). Low cognitive reserve has been identified as a risk factor for cognitive decline after a variety of insults to the brain such as traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003) or neurotoxic exposure (e.g., lead; Bleecker, Ford, Celio, Vaughan, & Lindgren, 2007) and increases vulnerability to the development of neurodegnerative disorders such as Alzheimer disease (Whalley, Deary, Appleton, & Starr, 2004). The same notion has been posited in breast cancer patients exposed to chemotherapy,

although further research is needed (Ahles et al., 2010; Wefel, Saleeba, Buzdar, & Meyers, 2010). Taken together, these findings highlight the importance of cognitive reserve in chemotherapy-related cognitive dysfunction and suggest further exploration of the potential impact of cognitive reserve is merited.

In terms of individual neurocognitive tests, the most common impairments were seen on the PASAT (about 22%) and FAS (about 14%). Surprisingly, none of the participants obtained an impaired score on Coding, and only three (4.2%) had a score that fell at or below -1 *SD* on this measure. Coding and related tests (such as Symbol Digit Modalities Test; Smith, 1982) are generally regarded as some of the most sensitive neuropsychological measures to brain damage (Lezak et al., 2012). Although its broad sensitivity to cognitive dysfunction is well established, Coding may not perform as well in the context of chemotherapy-related cognitive dysfunction. Despite its frequent use, Coding is often not reported as impaired in chemotherapy-treated cancer patients (Ahles et al., 2008; Castellon et al., 2004; de Ruiter et al., 2011; Donovan et al., 2005; Quesnel et al., 2009; Stewart et al., 2008; Von Ah et al., 2009; Wefel et al., 2010). In several cases, investigators have reported declines in verbal fluency in the context of unchanged performance on Coding (de Ruiter et al., 2011; Quesnesl et al., 2009; Von Ah et al., 2009). Importantly, of the four studies that have found a significant decline or difference in Coding performance, three report mean scores well within the average range (Abraham et al., 2008; Deprez et al., 2011; Hurria et al., 2006).

Because reported rates of impairment in breast cancer patients exposed to chemotherapy are quite variable, we chose to examine rank performance as well as frequency of impairment. Those tests on which participants consistently scored lowest

included FAS, PASAT, and Animal Fluency. In contrast, participants consistently achieved the highest score on Coding. Although all of these measures are generally considered to be some of the most sensitive to general cognitive dysfunction or decline (Lezak et al., 2012), there appears to be a difference in their relative sensitivity to chemotherapy-related cognitive dysfunction in our sample.

In attempting to understand these results, it is important to consider the underlying skills required to perform each of these tasks. Both Coding and PASAT are considered to be sensitive to deficits in information processing speed (Lezak et al., 2012); however, it is clear from our results that difficulties with processing speed alone do not explain the cognitive dysfunction in this population. The three tasks on which participants consistently scored lowest (FAS, PASAT, and Animal Fluency) all require speeded verbal output. These tasks also require the generation of *novel* information (or, in the case of PASAT, *new* information, although the responses are constrained/regulated), necessitating a verbal search and retrieval strategy. These task requirements are different from those required by the Color Word Interference test, which relies upon inhibition as a core ability (Delis et al., 2001). In contrast, Coding does not require any verbal *output* and little to no verbal ability (except as it relates to the numbers used on the stimulus).

This concept of a speeded verbal component to chemotherapy-related cognitive dysfunction has yet to be explored in the literature, although it is highly consistent with patient complaints. Downie, Mar Fan, Houede-Tchen, Yi, & Tannock (2006) completed semi-structured interviews with 21 women who had received adjuvant chemotherapy for breast cancer and found that verbal fluency and word-finding ability were among the most commonly reported cognitive changes post-treatment. None of the women reported

problems with verbal comprehension but instead related changes in language ability to slower information processing. An online survey of 471 cancer patients regarding self-reported cognitive symptoms after treatment yielded similar findings (Hurricane Voices Breast Cancer Foundation, 2007). Difficulty with word recall was reported by 95% of the sample, with 29% of that group rating the problem as "significant" and 49% rating it as "moderate." Of note, the other areas most frequently endorsed included "short-term memory loss" (94%), "lack of concentration" (93%), "inability to multi-task" (87%), and "inability to organize daily tasks" (87%). These results suggest that reported symptoms are not related to language abilities per-se, but rather to aspects of attention/concentration or executive function.

To our knowledge, the current study represents the first in-depth exploration of executive function and attention/concentration in breast cancer survivors. Because these constructs are of central importance in the subcortical profile of cognitive impairment, it is important to have a thorough understanding of how they may be impacted by chemotherapy. Future studies should incorporate large, representative samples and begin to address other important questions in this area such as potential risk factors for cognitive decline following chemotherapy and effects of demographic variables such as ethnicity.

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CHAPTER FIVE
General Conclusions

In the first study, we analyzed effect sizes for neuropsychological data based on longitudinal observations and found general *improvements* in performance following chemotherapy on the majority of neuropsychological tests analyzed. It is likely that practice effect might account for the improvement observed in cancer patients and may in fact mask deterioration in cognitive functioning following chemotherapy. However, attenuated practice effects were seen in several areas, including on measures of verbal learning and memory. Although further research is needed, these preliminary data suggest that measures of verbal learning and memory may be especially sensitive to chemotherapy-related cognitive decline. This is generally in line with the literature, which suggests verbal learning and memory as a domain often affected in this population. Although measures of executive function did not consistently show significant attenuation, measurement difficulties inherent to traditional executive function tasks make them particularly susceptible to practice effects. Therefore, effect sizes generated for these tests should be interpreted with caution.

In the second study, we identified that certain tests traditionally purported to measure attention/executive function appear to be more sensitive to chemotherapy-related cognitive dysfunction than others. Specifically, participants consistently scored lowest on FAS, PASAT, and Category Fluency, and scored highest on Coding. Both Coding and PASAT are considered to be sensitive to deficits in information processing speed (Lezak et al., 2012); however, it is clear from our results that difficulties with processing speed alone do not explain the cognitive dysfunction in this population. Those tests on which

participants consistently scored lowest all require verbal output under time pressure (FAS, PASAT, and Animal Fluency). Our results suggest that there may be a speeded verbal component to chemotherapy-related cognitive dysfunction. Although this is highly consistent with patient complaints, this concept has yet to be explored in the literature and merits further investigation.

APPENDIX A
Characteristics and Psychometric Properties of Measures

Tests were selected based on dimensions of attention (e.g. measures tapping attentional components of various complexity) as well as psychometric properties and common clinical use in cancer populations or other relevant populations. All neurocognitive measures have all been inconsistently reported to be sensitive in post-chemotherapy patients.

Neurocognitive

Wechsler Test of Adult Reading (WTAR)

The WTAR (Wechsler, 2001b) is a single-word reading test that is used to measure the examinee's word knowledge and literacy prior to experiencing a change in cognitive functioning. This test requires the examinee to read and pronounce irregularly-spelled words, but does not require comprehension or knowledge of word meaning. Rather, the utilization of words with irregular pronunciation minimizes the assessment of current ability to apply standard pronunciation rules and maximizes the assessment of previous learning of the word. Unlike many intellectual and memory abilities, reading recognition is relatively stable in the presence of cognitive declines associated with normal aging or brain insult. The number of words pronounced correctly is counted to determine a total score, which is then used in conjunction with demographic information to estimate level of premorbid intellectual functioning in the form of a standard score (Wechsler, 2001b).

The WTAR is a well-validated measure of premorbid functioning, and is co-normed with the WAIS-IV. Reliability of the WTAR is very high, reported at an average of .98. The WTAR is highly correlated with WAIS-IV Full Scale IQ (FSIQ; *r*=.70) and Verbal Comprehension Index (*r*=.75). The WTAR is also highly correlated with the Wechsler Individual Achievement Test—Second Edition (Wechsler, 2001a), a measure of achievement (Reading composite score, *r*=.82; Total composite score, *r*=.80). Furthermore, when comparing actual FSIQ scores on the WAIS-IV and estimated scores generated by the WTAR prediction equation, the mean differences were close to zero. For FSIQ, 46.4% of the prediction sample had estimated scores within 5 points of the actual score, and 75.1% were within 10 points (Wechsler, 2001b).

Trail Making Test (TMT)

The TMT (Reitan, 1958) is a well-validated measure of visual attention and tracking, working memory, motor processing speed, and cognitive flexibility (Strauss et al., 2006). The test is given in two parts, A and B. The examinee is required to draw lines connecting consecutively numbered circles on a sheet of paper in part A, and to connect consecutive numbered and lettered circles in alternating order in part B. The examinee is prompted to complete these tasks as quickly as possible without lifting the pencil from the paper. Raw scores are based on time to complete each trial. Examinees who are not able to complete part B within 5 minutes or who make 5 errors are assigned a time of 300 seconds (Lezak et al., 2012). Heaton et al. (2004) provide normative data the TMT, which is stratified by ethnicity, age, gender, and education. Total T-scores for Part A and Part B will be used for the present study.

The TMT correlates moderately well with other measures of attentional abilities such as visual search and visual-spatial sequencing or scanning, as well as speeded processing (i.e. SDMT and a variant of the PASAT; Royan, Tombaugh, Rees, & Francis, 2004). Additionally, TMT performance is strongly correlated with tests of executive control, in particular cognitive flexibility (Strauss et al., 2006). For example, a factor analysis (O'Donnell, McGregor, Dabrowski, Oestreicher, & Romero, 1994) showed that Part B loaded on a *focused mental processing speed* factor along with the PASAT. WAIS FSIQ has been reported to correlate with Part A at .37 and Part B at .50 (Steinberg, Bieliauskas, Smith, & Ivnik, 2005). Parts A and B correlate moderately well with each other (r=.31-.60), suggesting that they measure similar although somewhat different functions (Strauss et al., 2006).

Reported test-retest reliability is quite variable, with most reliability coefficients ranging from .60 to .90 (Lezak et al., 2012). Dikmen, Heaton, Grant, and Temkin (1999) found test-retest reliability coefficients of .79 for Part A and .89 for Part B in a group of healthy adults. However, reliability is generally less strong in clinical groups. Interrater reliability has been reported as .94 for Part A and .90 for Part B (Strauss et al., 2006).

Age and education have been shown to have a significant effect on performance, where poorer test scores are found with advancing age and lower levels of education. However, age appears to affect only the time score, not accuracy (Backman et al, 2004). Major depression has been found to negatively affect performance, especially on Part B (Naismith et al., 2003).

It has been found to be sensitive to a variety of disorders, including HIV infection, heterogeneous neurological damage, and closed head injury (Strauss et al.,

2006). However, the speed variables used to determine an individual's score demonstrate poor sensitivity, and many patients with mild brain dysfunction will not have difficulty with this test (Cicerone & Azulay, 2002; Lezak et al., 2012). Regardless, it is one of the five most frequently used neuropsychological measures, ranking as the top measure of attention and the fourth measure of executive function (Rabin, Barr, & Burton, 2005).

Digit Span

The Digit Span subtest of the Wechsler Adult Intelligence Test-Fourth Edition (WAIS-IV; Wechsler, 2008a) is used to measure basic auditory attention and working memory. The test is given in three trials, Digit Span Forward, Digit Span Backward, and Digit Span Sequencing. Each trial requires participants to repeat increasing sets of numbers either forward, reverse, or in sequence. The raw score for each trial is the number of digits correctly recalled, which is then converted into a scaled score based on normative data stratified by age. Additionally, the raw scores for all three trials are added together to create a total score, which is also converted into a scaled score based on age-adjusted normative data (Wechsler, 2008b). Scaled scores for Digit Span Forward and Digit Span Backward will be used in the present study.

Internal consistency is high for Digit Span Total score (r=.93) as well as each of the trials (Digit Span Forward, r=.81; Digit Span Backward, r=.82). Test-retest reliability is good as well (Total score, r=.83; Digit Span Forward, r=.77; Digit Span Backward, r=.71).

As expected, each trial score is highly correlated with Digit Span Total score, at similar levels (Digit Span Forward, r=.79; Digit Span Backward, r=.83). Digit Span

Total score is moderately correlated with other WAIS-IV tests of working memory (Arithmetic, *r*=.60; Letter-Number Sequencing, *r*=.69) and the RBANS Attention composite (*r*=.65). However, it is poorly correlated with RBANS Visuospatial/Constructional (*r*=.42) and Language (*r*=.27) composites. Additionally, Digit Span Total score demonstrates weak correlations with WAIS-IV tests of processing speed (Cancellation, *r*=.34; Coding, *r*=.45; Symbol Search, *r*=.40) as well as with the CVLT-II (Trials 1-5, *r*=.36; Trial 1, *r*=.29; Trial 5, *r*=.33; Long-Delay Free Recall, *r*=.33; Wechsler, 2008b).

Digit Span as a whole is relatively vulnerable to brain damage (Groth-Marnat, 2009); however, Digit Span Forward tends to be only minimally affected by many brain disorders, while Digit Span Backward is highly sensitive to many different types of brain damage, including frontal lobe lesions and dementing processes (Lezak et al., 2012).

Coding

The Coding subtest of the Wechsler Adult Intelligence Test-Fourth Edition (WAIS-IV; Wechsler, 2008a) is a substitution task that measures divided attention, visual scanning, and motor processing speed. The examinee is required to pair specific numeric digits with geometric figures as presented in a reference key, and the number of correctly written digits after 120 seconds is counted as the total raw score. This raw score is converted into a scaled score based on demographically-adjusted normative data (Wechsler, 2008b).

Internal consistency reliability of the Coding subtest is excellent (r=.86) as is test-retest reliability (r=.83). Coding is similar in format to SDMT (Smith, 1982) with

correlations between the two reported as high as .91 (Morgan & Wheelock, 1992). Coding correlates higher with tests of processing speed (e.g., WAIS-IV Symbol Search, *r*=.65) and attention (RBANS Attention composite, *r*=.56) than with more direct measures of visuospatial (RBANS Visuospatial/Constructional composite, *r*=.32) or verbal ability (RBANS Language composite, *r*=.23). Additionally, Coding demonstrated weak correlations with CVLT-II variables (Trials 1-5, *r*=.39; Trial 1, *r*=.23; Trial 5, *r*=.38; Long-Delay Free Recall, *r*=.32; Wechsler, 2008b).

Coding is one of the most sensitive of the WAIS-IV subtests, and impaired performance has been shown in patients with dementia, rapidly-growing tumors, chronic alcoholism, and hypertension (Lezak et al., 2012).

Color Word Interference

The Color Word Interference Test, a subtest of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001), is used to assess response inhibition, impulse control, selective attention, and cognitive flexibility. This test includes four conditions. In the first, names of colors are printed in black ink and the participant is asked to read the words as quickly as possible within a given time limit. In the second condition, the participant is asked to name the ink color in which Xs are printed. In the third condition, names of colors are printed in a different color ink, and the participant is asked to name the ink color. In the fourth condition, names of colors are again printed in a different color ink, and the participant is asked to read the color word in some cases and name the color ink in others, designated by being enclosed in boxes. Raw scores are determined based on the time to complete each of the four trials (in

seconds) and converted to scaled scores corrected for age. Scaled scores for Condition 3 (Inhibition) will be used for the present study.

Internal consistency of Color Word Interference is good (*r*=.72-.86 depending on age group) as is test-retest reliability (Condition 3, *r*=.75; Condition 4, *r*=.65). The test demonstrated poor correlation with the CVLT-II, providing evidence for discriminant validity. Moreover, Conditions 3 and 4 are intercorrelated at .63, suggesting that they tap similar but slightly different abilities (Delis et al., 2001). Correlations between the TMT and Color Word Interference range from .62 to .76 (Strauss et al., 2006).

Performance on Stroop tasks, specifically on the inhibition trials, has been associated with lateral prefrontal cortex and anterior cingulate function in fMRI studies (Kerns et al., 2004), and is often considered an indicator of executive functioning. However, it is unclear to what extent impairment on the Stroop test reflects executive, attentional, and working memory functioning, or more generalized processing speed and efficiency (Strauss et al., 2006). The importance of processing speed to Stroop performance was investigated by Denney and Lynch (2009). Their comparison of 248 MS patients with 178 controls found that the greatest differences between groups were accounted for by generalized slowing in MS patients. Kramer, Reed, Mungas, Weiner, and Chui (2002) found that patients with subcortical ischemic vascular disease performed as well as controls on the color naming condition but significantly slower on the interference condition of the Stroop. Increased interference has been found in a variety of other patient groups thought to have executive disturbance, including HIV infection (Lezak et al., 2012).

Paced Auditory Serial Addition Test (PASAT)

The PASAT (Gronwall, 1977) is a measure of divided attention, auditory information processing speed, working memory, and mental flexibility. Single digits are presented every 3 seconds and the participant is required to add each new digit to the one presented immediately prior to it. The PASAT is presented on audiocassette tape or compact disk to control the rate of stimulus presentation. The number of correct responses and errors are recorded, and Total T-scores for correct responses are computed from demographically-based normative data.

Chronbach's alpha is very high in adults (r = .90; Crawford, Obansawin, & Allan, 1998), and test retest correlations following short retest intervals (7-10 days) are excellent (r > .90; McCaffrey et al., 1995). The PASAT is moderately correlated with other measures of attention such as Digit Span, Auditory Consonant Trigrams, d2 Test, Trail Making Test (especially Part B), and the Stroop test (Strauss et al., 2006). It is also moderately correlated with reaction time tests (Schachinger, Cox, Linder, Brody, & Keller, 2003). However, it also appears to measure unique aspects of attentional functioning not measured by other paradigms. For instance, in one factor-analytic study, PASAT loaded on a factor separate from other attentional measures such as Digit Span, Trail Making Test, and Stroop (Fos, Greve, South, Mathias, & Benefield, 2000). The PASAT has demonstrated high split-half reliability and evidence for convergent and divergent validity with good sensitivity for deficits in the areas of auditory information processing speed and flexibility (Fischer, Rudick, Cutter, & Reingold, 1999). It is moderately correlated with IQ and moderately to highly correlated with mathematical ability (r= .41-.68; Strauss et al., 2006).

While the PASAT was originally thought to measure processing speed, it is now recognized as a measure of several cognitive domains because it requires the use of multiple functions, namely divided attention, sustained attention, and working memory because of the requirement to switch between two ongoing tasks over several trials (Tombaugh, 2006). Kalmar, Bryant, Tulsky, and DeLuca (2004) commented that, because of its demanding processing speed component, the PASAT may be more sensitive to impairment of subcortical brain systems and white matter tracks than tasks that assess only working memory (e.g. Letter-Number Sequencing from the WAIS). Although chemotherapy-related cognitive dysfunction is not clearly understood, deficits are hypothesized to occur as a result of changes in subcortical white matter tracks (Deprez et al., 2011). As such, it follows that the PASAT may be more sensitive than other attention/concentration measures to impairment after chemotherapy because of the additional demand on processing speed.

Performance has also been shown to be affected by cognitive slowing associated with moderate hypoglycemia, chronic fatigue syndrome, chronic pain, systemic lupus erythematosus, and mild concussion. In particular, the PASAT is useful in identifying subtle attentional deficits, more so than other standard measures of attention (Lezak et al., 2012). Moreover, neuroimaging studies suggest that frontal and parietal areas are activated by the PASAT (Lazeron, Rombouts, de Sonneville, Barkhof & Scheltens, 2003).

The International Cognition and Cancer Task Force recently developed a working group to help make recommendations as to which neuropsychological tests to routinely include in the assessment of chemotherapy-related cognitive dysfunction. The

PASAT was suggested based on clinician experience and subjective patient complaints (Wefel et al., 2011). This, in conjunction with its frequent use and demonstrated sensitivity in MS populations, suggests that further research on its utility in chemotherapy-related cognitive dysfunction may be warranted.

FAS

The FAS test will be used to measure verbal fluency in this study. This measure evaluates the spontaneous production of words under restricted search conditions (Strauss et al., 2006). Normative data exist for the Total score based on age and education level, as well as gender and ethnicity (Heaton et al., 2004). For the purposes of the present study, demographically-adjusted Total T-scores for total words on FAS will be utilized.

FAS (also referred to as phonemic fluency) requires the examinee to orally produce as many words as possible that begin with the letter *F* in 60 seconds. The task is then repeated for the letters *A* and *S*. A total score is calculated summing the number of correct words produced across the 3 trials. Additionally, the number of losses of set (words that are proper nouns or begin with an incorrect letter) and perseverations are totaled. Internal consistency reliability among *F*, *A*, and *S* conditions, as measured by coefficient alpha using the total number of words generated for each letter, is high (r = .83; Tombaugh, Kozak, & Rees, 1999). Test-retest reliability is also high (above .70), as is interrater reliability (r=.99; Ross, 2003).

This measure appears sensitive to the effects of nonspecific generalized slowing of processing (Lezak et al., 2012). Impaired verbal fluency is seen in left temporal lobe epilepsy, MS, dementia, schizophrenia, and mild traumatic brain injury, particularly

frontal lobe damage or diffuse brain injury. Phonemic fluency has been shown to be sensitive to frontal lobe dysfunction (Lezak et al., 2012; Strauss et al., 2006). A recent meta-analytic study found that semantic and phonemic fluency tasks make demands on frontal structures, but that semantic fluency tasks make additional demands on temporal structures (Henry & Crawford, 2004). Additionally, working memory performance and processing speed are both correlated with performance on fluency measures (Rosen & Engle, 1997; Strauss et al., 2006).

California Verbal Learning Test- Second Edition, Standard Form (CVLT-II)

The CVLT-II (Delis et al., 2000) is a well-validated measure of verbal learning and memory. It has been shown to be sensitive to learning and memory (frontal and temporal lobe) dysfunction across neuromedical and psychiatric populations. It involves the verbal presentation of 16 words from 4 semantic categories across five learning trials, followed by presentation of a different 16-item distracter list (List B). Afterwards, immediate and 20-minute delayed free and cued recall trials are administered, as well as delayed recognition testing for the initial word list.

The examinee's responses are entered into a computer program which provides raw and standardized scores controlling for age and education for 93 normed variables (Strauss et al., 2006). Variables of interest for the present study include: List A Trial 1, List A Trial 5, Long-delay Free Recall, and Recognition Discriminability z-scores; and Total Learning T-scores. These variables were chosen based on a factor analysis (Donders, 2008) which suggested four latent constructs including Attention Span, Learning Efficiency, Delayed Memory, and Inaccurate Memory. The variable that had

the highest factor loading on each construct was chosen for the present study. Additionally, Total Learning will be included as it is commonly used in clinical practice.

Internal consistency for the CVLT-II is adequate across the delayed and 5 immediate recall trials for both normative and mixed clinical samples (Strauss et al., 2006). Specifically, split-half reliabilities were high for both normative (r = .94) and clinical (r = .96) samples. Chronbach's alphas for the cued recall trials are high for both samples (normative, r = .82; clinical, r = .83). Test-retest reliability for Total Recall across trials 1-5, Short- and Long-Delayed Free Recall, and Total Recognition Discriminability are high. The CVLT-II correlates well with the original CVLT and is moderately correlated with IQ (r=.48 between WAIS-IV FSIQ and Trials 1-5 Correct; Wechsler, 2008b).

In addition to providing data about learning curves, memory recall, and recognition, qualitative information such as error types and learning strategies can also be obtained from the CVLT-II (Freeman & Broshek, 2002). However, reliability coefficients tend to be low for these process-oriented variables, suggesting that caution must be used in interpretation (Strauss et al., 2006). The CVLT-II can also provide information regarding mechanisms of memory failure. For example, a selective deficit on delayed memory variables in the context of normal performance on variables associated with attention (e.g. List A Trial 1) might suggest a specific deficit in consolidated verbal memory as opposed to difficulties with attention or executive functioning (Donders, 2008, p. 129).

Self-Report

Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond & Snaith, 1983) is a 14-item self-report screening measure of depression and anxiety symptoms in medical populations. Two subscale scores are calculated: Anxiety (HADS-A) and Depression (HADS-D). Each item can be answered on a four-point scale, yielding a total score for each subtest that ranges from 0-21. A cutoff score of 8 was used for each subtest. For the HADS-D subscale, this cutoff results in an approximate sensitivity of 0.66 and sensitivity of 0.83. For the HADS-A subtest, mean sensitivity is 0.72 and mean specificity is 0.81 (Bjelland, Dahl, Huag, & Neckelmann, 2002). Scores for each subscale will be used for the present study.

Correlation between the subscales is reported between .49 and .63. Internal consistency is high, with a Coefficient alpha of .78-.93 for HADS-A and .82-.90 for HADS-D. HADS-D is highly correlated with the BDI (r=.83), and HADS-A with the State-Trait Anxiety Inventory (r=.81; Mykletun, Stordal, & Dahl, 2001).

Functional Assessment of Cancer Therapy-General (FACT-G)

The FACT-G (Cella et al., 1993) is a 27-item self-administered measure of QoL in cancer patients within the domains of physical well-being (PWB), functional well-being (FWB), social well-being (SWB), and emotional well-being (EWB). Items utilize a Likert-type scale from 0 to 4, yielding a total score that ranges from 0 to 108, with higher scores signifying better functioning. The total FACT-G score is computed by summing the scores for the four subscales and will be used for the present study.

Correlation with the Functional Living Index-Cancer (Schipper, Clinch, McMurray, & Levitt, 1984), a quality of life measure designed specifically for use with cancer patients, was high (r=.79), supporting convergent validity. The FACT-G is able to differentiate patients according to stage of disease. Test-retest reliability is high (r=.92), as is Cronbach's alpha (r=.89; Cella et al., 1993).

Normative data is available for two reference groups: a sample of the general U.S. adult population (N=1400) and a sample of adult patients with cancer (N= 1075), both of which are stratified by gender (Brucker, Yost, Cashy, Webster, & Cella, 2005).

Functional Assessment of Cancer Therapy-Fatigue Scale (FACT-F)

The FACT-F (Yellen et al., 1997) is a 13-item scale that can be added to the FACT-G to measure fatigue-related symptoms. Possible scores range from 0-52, with higher scores signifying less fatigue. A cutoff score of 36 is recommended to provide a sensitivity of 80% and a specificity of 71% (Alexander, Minton, & Stone, 2009, p 1197). The total score will be used in the present study.

The FACT-F demonstrates high correlations with the POMS fatigue subscale (r=-.74) and the Piper Fatigue Scale (r=-.75; Piper et al., 1998). It is able to differentiate patients according to hemoglobin level, an objective measure relating to anemia (which often results in fatigue). Internal consistency (r=.93) and test-retest reliability (r=.90) are excellent. (Yellen et al., 1997) It is widely used in clinical studies for fatigue intervention in cancer patients (Minton, Stone, Richardson, Sharpe, & Hotopf, 2009).

Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog)

The FACT-Cog (Wagner, Sweet, Butt, Lai, & Cella, 2009) is a brief self-report measure of cognitive function for patients who have received chemotherapy treatment for cancer and is designed as a complementary module of the FACT-G scale. It is comprised of 4 scales: Perceived cognitive impairment (CogPCI); Impact on quality of life (CogQOL); Comments from others (CogOth); and Perceived cognitive abilities (CogPCA). The highest possible score is 16 for the CogQOL and CogOth subscales; 28 for the CogPCA subscale; and 72 for the CogPCI subscale. Higher scores indicate better QOL/cognitive functioning. Total scores for each of the four subscales will be used in the present study. Normative data is available for two reference groups: cancer patients (N=20) and healthy controls (N=51) (Vardy et al., 2006).

Cronbach's alpha is high for all scales, ranging from .73 (CogPCA) to .95 (CogPCI). Test-retest reliability is also high, ranging from .79 (CogOth) to .86 (CogQOL). Correlations between the FACT-Cog subscales and the Cognitive Difficulties Scale, a self-report measure of perceived cognitive impairment (Derouesne et al., 1993), range from -.51 (CogPCA) to -.84 (CogPCI). Divergent validity is demonstrated through low correlations with the RBANS Total Percentile (CogPCI, r=.05; CogQOL, r=-.07; CogOth, r=-.08; and CogPCA, r=.13). The FACT-Cog subscales demonstrate moderate correlations with the HADS Anxiety scale (r=-.26 for CogPCA to r= -.52 for CogQOL), HADS Depression Scale (r=-.29 for CogOth to r=-.63 for CogQOL), and FACT-F (r=.45 for CogOth to r=.81 for CogQOL; Wagner, 2008). All reported correlations are based on scores obtained 6 months post-chemotherapy treatment.

APPENDIX B
Additional Analyses

Comparison of Different Criteria for Impairment

Because there is no clear consensus on the most appropriate definition of "impairment" in chemotherapy-related cognitive impairment, we analyzed the frequency of impairment on each neuropsychological test at several different cut-offs (≤ 1.5 *SD* and ≤ 1 *SD*). Table 1 shows the frequency of impairment and indicates whether each is significantly different than would be expected in a normal population.

Table 1. *Descriptive Statistics for Neuropsychological Measures at Different Criteria for Impairment (N=72)*

Variable	Mean (*SD*)	Median	Range	Impaired at ≤ 1.5 *SD*		Impaired at ≤ 1 *SD*	
				N (%)	*p***	*N* (%)	*p***
FAS†	45.7 (9.1)	46	23 - 66	10 (13.9)	**0.01**	19 (26.4)	**0.01**
Category Fluency†*	46.9 (11.1)	50	9 - 63	7 (9.7)	0.22	15 (20.8)	0.17
WAIS-IV Digit Span							
Forward§	10.3 (2.7)	10	5 - 19	1 (1.4)	0.06	11 (15.3)	0.50
Backward§	10.0 (2.2)	10	5 - 16	1 (1.4)	0.06	10 (13.9)	0.37
Sequencing§	10.9 (2.4)	11	5 - 18	1 (1.4)	0.06	3 (4.2)	**0.01**
Total§	10.5 (2.4)	11	6 - 19	0 (0)	**0.02**	4 (5.6)	**0.01**
D-KEFS Color Word Interference Test							
Color Naming§	10.6 (2.9)	11	1 - 16	4 (5.6)	0.44	8 (11.1)	0.17
Word Reading§	10.5 (2.4)	11	5 - 15	1 (1.4)	0.06	9 (12.5)	0.26
Inhibition§	10.6 (3.0)	11	1 - 17	5 (6.9)	0.50	10 (13.9)	0.37
Inhibition/Switching§	10.8 (2.76)	11	3 - 16	3 (4.2)	0.27	9 (12.5)	0.26
Paced Auditory Serial Addition Test†	43.1 (13.1)	45	9 - 60	16 (22.2)	**<0.001**	25 (34.7)	**<0.001**
WAIS-IV Coding§	12.2 (2.5)	12	6 - 17	0 (0.0)	**0.02**	3 (4.2)	**0.01**
Trail Making Test							
Part A†	49.7 (9.5)	50	19 - 71	5 (6.9)	0.50	12 (16.7)	0.50
Part B†	51.2 (10.1)	54	13 - 71	5 (6.9)	0.50	8 (11.1)	0.17
CVLT-II							
Total Learning†	53.3 (9.73)	55	30 - 71	7 (9.7)	0.44	4 (5.6)	0.10
Trial 1‡	0.03 (1.00)	0	-2.0 - 2.0	7 (9.7)	0.22	13 (18.1)	0.38
Short Delay Free Recall‡	-0.03 (0.98)	0	-3.0 - 2.0	8 (11.1)	0.10	15 (20.8)	0.17
Short Delay Cued Recall‡	-0.16 (1.03)	0	-3.5 - 1.5	10 (13.9)	**0.01**	17 (23.6)	0.06
Long Delay Free Recall‡	-0.20 (1.02)	0	-3.0 - 1.5	12 (16.7)	**<0.001**	18 (25.0)	**0.03**
Long Delay Cued Recall‡	-0.21 (0.97)	0	-3.0 - 1.5	10 (13.9)	**0.01**	19 (26.4)	**0.01**
Discriminability (*d'*)‡	0.24 (1.24)	0.5	-3.0 - 2.0	22 (30.6)	**<0.001**	22 (30.6)	0.10

Note. p-values ≤ .05 are in boldface. §Means reported as Scaled scores; †Means reported as T-scores; ‡Means reported as z-scores. *N = 69; **One-Sample Proportions Test; significant p-values indicate that the rate of impairment in this sample is significantly different from the frequency of 6.7% (1.5 SD cutoff) or 16% (1 SD cutoff) expected in a normal population.

Associations between Neuropsychological Tests and Self-Report Measures

Associations between neuropsychological tests and self-report measures were determined with Pearson product-moment correlations and are described in Table 2 below.

Table 2. *Correlations between Neuropsychological and Self-Report Measures*

	Self-Report Measures						
	Mood	QoL		Cognitive Functioning			
Neuropsychological Measures	HADS Total	FACT-G Total	FACT-F	FACT-Cog PCI	FACT-Cog Oth	FACT-Cog PCA	FACT-Cog QOL
FAS							
Total Sample	0.01	0.08	-0.13	-0.01	0.07	0.01	-0.11
Impaired	-0.06	0.24	0.03	-0.18	0.23	-0.22	-0.07
Not Impaired	0.10	-0.01	-0.18	0.21	0.10	0.26	0.10
Category Fluency							
Total Sample	0.03	0.03	-0.21	-0.12	0.09	-0.04	-0.08
Impaired	0.18	-0.08	-0.24	-0.21	-0.18	-0.19	-0.16
Not Impaired	-0.15	0.15	-0.11	0.01	0.40*	0.16	0.13
WAIS-IV Digit Span Total							
Total Sample	-0.04	0.02	-0.04	0.03	0.11	0.09	-0.08
Impaired	-0.24	0.09	0.02	-0.09	0.37*	0.12	0.20
Not Impaired	0.10	<0.001	<0.001	0.14	0.06	0.12	-0.06
D-KEFS Color Word Interference (Inhibition Trial)							
Total Sample	-0.21	0.16	0.12	0.13	0.07	0.18	-0.06
Impaired	-0.13	0.01	-0.06	0.21	0.06	0.08	-0.03
Not Impaired	-0.33*	0.31*	0.41**	0.16	0.14	0.36*	0.07

Note. $^{*}p < .05$; $^{**}p < .01$.

Table 2 (Continued). *Correlations between Neuropsychological and Self-Report Measures*

	Self-Report Measures						
	Mood	QoL		Cognitive Functioning			
Neuropsychological Measures	HADS Total	FACT-G Total	FACT-F	FACT-Cog PCI	FACT-Cog Oth	FACT-Cog PCA	FACT-Cog QOL
PASAT							
Total Sample	-0.01	0.04	-0.15	0.04	0.25*	0.08	-0.13
Impaired	<0.001	0.06	-0.34	-0.20	0.29	0.01	-0.19
Not Impaired	-0.01	0.04	0.20	0.44**	0.51**	0.30	0.19
WAIS-IV Coding							
Total Sample	-0.04	0.04	-0.19	-0.07	0.08	-0.01	-0.20
Impaired	-0.27	0.24	0.03	0.08	0.26	0.06	0.16
Not Impaired	0.18	-0.10	-0.31*	-0.14	0.06	-0.02	-0.27
TMT-A							
Total Sample	-0.09	0.15	-0.03	0.07	0.02	0.05	-0.25*
Impaired	-0.45*	0.39*	0.39*	0.41*	0.34	0.29	-0.02
Not Impaired	0.28	-0.01	-0.28	-0.12	-0.11	-0.08	-0.27
TMT-B							
Total Sample	-0.06	0.08	-0.14	0.06	0.09	0.11	-0.11
Impaired	-0.07	0.12	-0.04	0.20	0.17	0.13	-0.07
Not Impaired	-0.04	0.06	-0.19	<0.001	0.10	0.15	-0.02
CVLT-II Total Learning							
Total Sample	-0.03	0.07	-0.14	-0.17	0.02	-0.12	-0.15
Impaired	0.13	-0.11	-0.35	-0.33	-0.13	-0.32	-0.18
Not Impaired	-0.18	0.22	0.08	-0.03	0.13	0.04	-0.09

Note. $^{*}p < .05$; $^{**}p < .01$.

Endorsement of General Cognitive Complaints

As part of the questionnaire packet that each participant was asked to complete, three general questions regarding perceived cognitive changes (since completion of chemotherapy) were asked. Table 3 shows the frequency with which each of those questions was endorsed in the sample.

Table 3. *Frequency of Endorsement of General Cognitive Complaints (N = 72)*

	N (% Yes)
"Do you have problems with attention (greater than before your cancer treatment)?"	37 (51.4)
"Do you have problems with memory (greater than before your cancer treatment)?"	50 (69.4)
"Do you think you have chemo-brain?"	47 (65.3)

Self-Report Measures of Well-Being by Cognitive Complaint Status

Participants were divided into two groups based on their endorsement of cognitive complaints. Those who endorsed one or more of the three questions noted above (see Table 3) were designated as the "Cognitive Complaint" group ($N = 53$); those that did not endorse any of the three questions were designated as the "No Cognitive Complaint" group ($N = 19$). The groups were compared on self-report measures of mood, QoL, and cognitive function. No significant differences between the groups were found on any of these measures (see Table 4).

Table 4. *Frequency (N, %) of Clinically Significant Self-Report Scores by Cognitive Complaint Status*

	Cognitive Complaint (N = 53)	No Cognitive Complaint (N = 19)	χ^2	p^*
Mood				
HADS[§a]				
Anxiety	18 (34.0)	3 (15.8)	2.21	0.14
Depression	9 (17.0)	1 (5.3)	1.58	0.21
QoL				
FACT-G Total[†]	5 (9.4)	0 (0.0)	1.90	0.17
FACT-F[§b]	18 (34.0)	7 (36.8)	0.05	0.82
Cognitive Function				
FACT-Cog[§c]				
Perceived Cognitive Impairment	7 (13.2)	0 (0.0)	2.74	0.10
Comments from Others	5 (9.4)	0 (0.0)	1.90	0.17
Perceived Cognitive Abilities	4 (7.5)	0 (0.0)	1.50	0.22
Impact on Quality of Life	7 (13.2)	0 (0.0)	2.74	0.10

Note. [a]Cutoff score = 8, with higher scores indicating higher levels of anxiety or depression. [b]Cutoff score = 36, with higher scores indicating lower levels of fatigue. [c]Sample mean and SD were used to determine frequency of significant scores. Lower scores indicate greater cognitive complaints. [*]Kruskal Wallis Test

Neuropsychological Test Performance by Cognitive Complaint Status

Neuropsychological test performance was also examined in those with and without cognitive complaints. In terms of mean scores, the only significant difference was found on the Color Word Interference Test (Inhibition Trial), with the "Cognitive Complaint" group scoring slightly but significantly lower on this measure than the "No Cognitive Complaint" group (M = 10.1 and 11.8, respectively; p = .03). The only test that was more frequently impaired in the "Cognitive Complaint" group was the PASAT (χ^2[1] = 4.24; p = .04).

Table 5. *Neuropsychological Performance by Cognitive Complaint Status*

	Cognitive Complaint (N = 53)		No Cognitive Complaint (N = 19)		Independent Samples T-test		Kruskal Wallis Test	
Variable	Mean (SD)	Impaired (N, %)	Mean (SD)	Impaired (N, %)	*t*	*p*	χ^2	*p*
FAS Total[†]	45.5 (9.1)	7 (13.2)	46.3 (9.0)	3 (15.8)	0.31	0.76	0.08	0.78
Category Fluency Total[†]	46.1 (12.3)	7 (13.2)	49.3 (6.7)	0 (0.0)	1.08	0.29	2.74	0.10
WAIS-IV Digit Span								
Forward[§]	10.4 (2.7)	1 (1.9)	10.0 (2.5)	0 (0.0)	-0.63	0.53	0.36	0.55
Backward[§]	10.1 (2.1)	1 (1.9)	9.6 (2.4)	0 (0.0)	-0.79	0.43	0.36	0.55
D-KEFS Color Word Interference Test (Inhibition Trial) [§]	10.1 (3.1)	5 (9.4)	11.8 (2.3)	0 (0.0)	2.24	**0.03**	1.90	0.17
PASAT Total[†]	41.6 (14.3)	15 (28.3)	47.3 (8.3)	1 (5.3)	1.63	0.11	4.24	**0.04**
WAIS-IV Coding[§]	12.3 (2.5)	0 (0.0)	11.9 (2.5)	0 (0.0)	-0.66	0.51	0.00	1.00
Trail Making Test								
Part A[†]	49.5 (9.7)	4 (7.5)	50.5 (9.0)	1 (5.3)	0.42	0.67	0.11	0.74
Part B[†]	50.9 (10.9)	4 (7.5)	52.0 (7.7)	1 (5.3)	0.40	0.69	0.11	0.74

Note. p-values ≤ .05 are in boldface. [§]Means reported as scaled scores; [†]Means reported as T-scores.

Neuropsychological Performance by Fatigue Level

In order to examine the effects of reported level of fatigue, participants were divided into two groups based on their score on the FACT-F and compared on neuropsychological test performance. Those with a clinically significant score (≥ 36) were designated as the "High Fatigue" group ($N = 25$); those who did not endorse clinically significant symptoms of fatigue (a score < 36) were designated as the "Low Fatigue" group ($N = 47$). In terms of mean scores, the only significant difference was found on the Digit Span Backward subtest of the WAIS-IV; however, the High Fatigue group actually performed *better* than the Low Fatigue group on this test overall, although the difference is small ($M = 10.8$ and 9.6, respectively; $p = .03$). This test was also more frequently impaired in the High Fatigue group ($\chi^2[1] = 3.84$; $p = .05$). Notably, FAS was more frequently impaired in the Low Fatigue group ($\chi^2[1] = 3.77$; $p = .05$). Overall, results do not suggest a significant effect of fatigue on performance or rate of impairment on these neuropsychological tests.

Table 6. *Neuropsychological Performance by Fatigue Level*

	High Fatigue (*N* = 25)		Low Fatigue (*N* = 47)		Independent Samples T-test		Kruskal Wallis Test	
Variable	Mean (SD)	Impaired (N, %)	Mean (SD)	Impaired (N, %)	*t*	*p*	χ^2	*p*
FAS Total[†]	48.4 (8.8)	2 (8.0)	44.3 (8.9)	8 (17.0)	-1.90	0.06	3.77	**0.05**
Category Fluency Total[†]	49.5 (6.8)	0 (0.0)	45.7 (12.5)	7 (14.9)	-1.38	0.17	0.61	0.44
WAIS-IV Digit Span								
Forward[§]	10.2 (3.2)	0 (0.0)	10.3 (2.4)	1 (2.1)	0.18	0.86	0.18	0.68
Backward[§]	10.8 (2.9)	1 (4.0)	9.6 (1.6)	0 (0.0)	-2.29	**0.03**	3.84	**0.05**
D-KEFS Color Word Interference Test (Inhibition Trial) [§]	10.2 (2.8)	1 (4.0)	10.8 (3.1)	4 (8.5)	0.77	0.45	1.67	0.20
PASAT Total[†]	46.7 (11.1)	2 (8.0)	41.2 (13.8)	14 (29.8)	-1.70	0.09	2.63	0.11
WAIS-IV Coding[§]	12.8 (2.7)	0 (0.0)	11.9 (2.4)	0 (0.0)	-1.33	0.19	1.96	0.16
Trail Making Test								
Part A[†]	50.6 (10.8)	1 (4.0)	49.3 (8.7)	4 (8.5)	-0.56	0.58	0.85	0.36
Part B[†]	52.9 (7.5)	0 (0.0)	50.3 (11.2)	5 (10.6)	-1.05	0.30	0.33	0.57

Note. p-values ≤ .05 are in boldface. [§]Means reported as scaled scores; [†]Means reported as T-scores.

Comparison of Impairment Rates on Selected Neuropsychological Tests

It was posited that rates of impairment would be higher on a measure of complex sustained attention and processing speed (PASAT) than on measures of simple attention (Digit Span Forward and TMT-A). To analyze this, Cochran's Q test, a non-parametric statistical test designed to analyze whether there is a relationship between paired dichotomous, categorical variables, was used (Elliot & Woodward, 2007). Table 6 indicates that participants who were categorized as impaired overall (using the criteria of two or more scores at or below -1.5 *SD* from the mean) differed in the frequency of impairment on certain tests (PASAT, TMT-A, and Digit Span Forward). Because Cochran's Q test was significant, follow-up pairwise analyses were conducted using McNemar's tests and showed that PASAT was more frequently impaired than TMT-A ($p < .01$) or Digit Span Forward ($p < .001$) in participants who were classified as impaired.

Table 7. *Frequency of Impaired Scores on Selected Tests in Impaired Group*

	N (%)	Q	*p**
PASAT	16 (22.2)		
TMT-A	5 (6.9)		
WAIS-IV Digit Span Forward	1 (1.4)		
		22.6	
			<0.001

*Cochran's Q Test

The Role of Premorbid IQ in Self-Reported Well-Being

To investigate whether differences would be seen on self-report measures of mood, quality of life, and cognitive function between individuals with cognitive

impairment and those without, independent-samples t-tests were performed. No significant differences were found (see Table 6 in Paper 2). However, given that estimated premorbid IQ (WTAR score) was significantly different between the groups, a between-groups analysis of covariance was conducted to compare the effect of impairment status on each of several measures of self-reported mood, quality of life, and cognitive functioning. After controlling for estimated premorbid IQ, there were significant differences between the groups on self-report measures of fatigue, perceived cognitive abilities, and impact on quality of life (see Table 5). Surprisingly, the non-impaired group rated themselves lower on these measures than the impaired group.

Table 8. *Group Differences (M, SD) on Self-Report Measures after Controlling for Premorbid IQ*

	Impaired (*N* = 13)	Non-Impaired (*N* = 59)	*F*	*p*
Mood				
HADS[§a]				
Anxiety	5.5 (5.8)	5.2 (3.8)	0.25	0.62
Depression	3.9 (4.6)	3.0 (3.2)	0.64	0.43
QoL				
FACT-G Total[†]	52.3 (11.1)	54.0 (8.1)	0.75	0.39
FACT-F[§b]	42.0 (12.4)	37.9 (11.7)	6.10	**0.02**
Cognitive Function				
FACT-Cog[§c]				
Perceived Cognitive Impairment	52.8 (15.7)	46.2 (16.4)	3.20	0.08
Comments from Others	14.8 (2.4)	15.0 (2.2)	2.71	0.11
Perceived Cognitive Abilities	19.8 (4.6)	18.0 (5.8)	3.87	**0.05**
Impact on Quality of Life	14.2 (2.2)	12.3 (3.4)	6.87	**0.01**

Note. p-values ≤ .05 are in boldface. [a]Cutoff score = 8, with higher scores indicating higher levels of anxiety or depression. [b]Cutoff score = 36, with higher scores indicating lower levels of fatigue. [c]Sample mean and *SD* were used to determine significance.

Exploratory Aim: Predictors of Memory Performance

An exploratory hypothesis posited that performance on neuropsychological tests of attention/concentration would account for a significant amount of variance in CVLT-II performance. To evaluate this hypothesis, a linear regression analysis was conducted with CVLT-II total score as the criterion variable and each of nine attention/executive function measures (WAIS-IV Digit Span Forward, WAIS-IV Digit Span Backward, TMT-A, TMT-B, PASAT, WAIS-IV Coding, FAS, Category Fluency, and D-KEFS Color Word Interference Inhibition). Table 6 shows that results of a standard linear regression analysis indicate a relationship between CVLT-II performance and these particular tests of attention/executive function. The model accounted for 23% of the variance in CVLT-II scores: adjusted $R^2 = 0.23$, $F(1, 72) = 3.41$, $p = .002$. In a stepwise linear regression analysis (data not shown), only TMT-B significantly predicted CLVT-II scores: $\beta = 4.28$, $t(72) = 4.16$, $p < .001$. TMT-B accounted for 19% of the variance in CVLT-II scores: adjusted $R^2 = .19$, $F(1, 72) = 17.30$, $p < .001$.

Table 9. *Neuropsychological Predictors of CVLT-II Total Score (N = 72)*

	Unstandardized Coefficients		Standardized Coefficients	
Variable	β	Std. Error	β	*p*
FAS	-0.23	0.21	-0.22	0.26
Category Fluency	0.25	0.13	0.28	0.05
WAIS-IV Digit Span Forward	-0.28	0.14	-0.25	0.05
WAIS-IV Digit Span Backward	0.25	0.20	0.19	0.21
D-KEFS Color Word Interference (Inhibition Trial)	0.20	0.12	0.21	0.09
PASAT	-0.11	0.08	-0.15	0.20
WAIS-IV Coding	-0.15	0.17	-0.13	0.40
TMT-A	-0.14	0.16	-0.13	0.40
TMT-B	0.52	0.16	0.54	0.00
F			3.41	0.00
Adjusted R^2			0.23	

An additional exploratory analysis was conducted using self-report measures of mood, quality of life, and cognitive function as predictors of memory performance. A linear regression analysis was conducted using CVLT-II total score as the criterion variable and the following self-report measures as predictor variables: HADS-A, HADS-D, FACT-G total score, FACT-F, FACT-Cog PCI, FACT-Cog Oth, FACT-Cog PCA, and FACT-Cog QOL. Table B7 shows that results of a standard linear regression analysis indicate no significant linear relationship between CVLT-II performance and these measures of self-reported mood, quality of life, or cognitive function. The model accounted for 3% of the variance in CVLT-II scores: adjusted $R^2 = 0.03$, $F(1, 72) = 1.29$, $p = .27$.

Table 10. *Self-Report Predictors of CVLT-II Total Score (N = 72)*

Variable	β
Mood	
HADS	
Anxiety	-0.58
Depression	0.86
QoL	
FACT-G Total	0.43
FACT-F	-0.21
Cognitive Function	
FACT-Cog	
Perceived Cognitive Impairment	-0.14
Comments from Others	0.51
Perceived Cognitive Abilities	0.23
Impact on Quality of Life	-0.39
Adjusted R^2	0.03
F	1.29

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