

EXECUTIVE FUNCTIONING IN WOMEN WITH BREAST CANCER:
A LONGITUDINAL EXAMINATION OF INTRAINDIVIDUAL VARIABILITY
IN REACTION TIME

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Abstract

Cognitive symptoms are commonly reported by women diagnosed with breast cancer and have a negative impact on daily life. These cognitive changes are influenced by factors such as treatment (e.g., chemotherapy, hormone therapy), mood disruption, and even the cancer itself. In general, cognitive changes are subtle and affect multiple cognitive domains, although there is evidence that executive functioning may be particularly sensitive to the effects of breast cancer and its treatments. Most research in neuropsychology, including that with cancer populations, assesses mean performance level, which does not capture within-person variability. Intraindividual variability (IIV) is a different metric from measures of central tendency that examines fluctuations in task performance that are relatively transient and occur rapidly over short periods of time. IIV may provide novel information about cognitive functioning in cancer-related cognitive impairment. This dissertation first presents a systematic review of four specific cognitive subcomponents of executive function in breast cancer survivors: inhibition, set-shifting, working memory, and planning/decision making. Inhibition appears to be the subcomponent least affected by chemotherapy. Findings are mixed for set-shifting, working memory, and planning/decision making in part due to the heterogeneity in study methodologies. Next, two studies are reported which examine IIV in performance on a Stroop reaction time (RT) task as an indicator of cognitive functioning in women with breast cancer before and after chemotherapy compared to healthy controls assessed at similar time points. At baseline testing before surgery and neoadjuvant chemotherapy, breast cancer patients were more variable than healthy controls as task complexity increased (e.g., congruent vs. incongruent task conditions). Change scores from baseline

to 1-month postchemotherapy were similar between patients and controls on all Stroop measures. From baseline to 9 months postchemotherapy, however, patients did not improve as much as healthy controls did and IIV was more sensitive than mean RT in detecting group differences. Self-reported cognitive symptoms increased from baseline to 9 months postchemotherapy, and change in symptoms associated with language and communication were positively correlated with change in variability. Taken together, the findings demonstrate that IIV is an important characteristic of cognitive performance in breast cancer patients.

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Chapter 1: General Introduction

Overview of Cognitive Performance in Women with Breast Cancer

Breast cancer is the most common cancer diagnosis among Canadian women (Canadian Breast Cancer Foundation, 2015). In recent years, advances in breast cancer detection and treatment (e.g., surgical care, chemo-, radiation, and hormone therapies) have led to significantly improved survival rates (Park, Anderson, & Gail, 2015; Trudeau et al., 2005). Along with a focus on breast cancer survivorship comes an increased recognition that many women experience subtle impairments in cognitive performance. Although commonly referred to as “*chemo brain*” or “*chemo fog*,” it is now recognized that the neurotoxic effects of chemotherapy do not exclusively account for cognitive symptoms. There is growing evidence that cognitive dysfunction may also be related to the cancer itself, other cancer treatments (e.g., surgery, endocrine therapy), genetic factors (e.g., APOE ϵ 4 allele), fatigue, and psychological distress (e.g., depression, anxiety; for reviews see Ahles, 2012; Seruga, Zhang, Bernstein, & Tannock, 2008). Thus, cancer-related cognitive impairment is a more accurate term to describe this phenomenon. The prevalence of cognitive decline ranges from 19 to 78% in women with breast cancer (Wefel & Schagen, 2012). Commonly affected cognitive domains include learning and memory, processing speed, and executive functioning (Wefel & Schagen, 2012).

Neuropsychological Studies of Cancer-Related Cognitive Impairment

Early studies in this area had cross-sectional designs (Ahles et al., 2002; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Schagen et al., 2002; 1999; van Dam et al., 1998; Wieneke & Dienst, 1995). These studies compared breast cancer patients who

received chemotherapy to comparison groups (e.g., patients who did not receive chemotherapy, healthy controls, or normative data) and demonstrated variable findings with respect to the frequency and severity of impairment and the cognitive domains impaired after chemotherapy. Nevertheless, the collective evidence from these studies did suggest that a significant proportion of women experience cognitive deficits within two years after receiving chemotherapy. More recent cross-sectional studies also show late effects of chemotherapy in breast cancer survivors at 5 to 20 years posttreatment follow-up (de Ruiter et al., 2011; Kesler, Kent, & O'Hara, 2011; Koppelmans et al., 2012; Nguyen et al., 2013; Scherwath et al., 2006).

An important limitation of the cross-sectional studies is the failure to account for possible pretreatment differences between breast cancer patients and comparison groups. Thus, it is unclear whether the cognitive deficits observed in women with breast cancer result from chemotherapy exposure and/or are related to disease or patient factors. In fact, results from prospective studies indicate that approximately 20 to 30% of women diagnosed with breast cancer demonstrate impaired cognitive function prior to initiation of chemotherapy treatment (Bender et al., 2006; Hermelink et al., 2007; Jansen, Cooper, Dodd, & Miaskowski, 2011; Quesnel, Savard, & Ivers, 2009; Wefel, Saleeba, Buzdar, & Meyers, 2010). Pretreatment impairment appears to persist even after factors such as depression, anxiety and fatigue are accounted for (Bender et al., 2006; Hermelink et al., 2007; Jansen et al., 2011). Other studies have shown that cancer-related posttraumatic stress is related to pretreatment impairment (Hermelink et al., 2015), and older age and lower cognitive reserve (Ahles et al., 2010) are risk factors for cognitive decline after chemotherapy. Together, findings suggest that the source of underlying pretreatment

cognitive impairment is likely multifaceted, and includes the effects of cancer itself, psychological distress, and other individual differences such as age or cognitive reserve.

To date, prospective longitudinal studies of cognition in women with breast cancer have demonstrated inconsistent patterns of results. Although many studies show evidence of cognitive decline over the course of treatment (Ahles et al., 2010; Bender et al., 2006; Collins, MacKenzie, Stewart, Bielajew, & Verma, 2009; Hermelink et al., 2007; 2008; Hurria et al., 2006; Jansen et al., 2011; Quesnel et al., 2009; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005; Stewart et al., 2008; Vearncombe et al., 2009; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a), others report no significant decline (Debess, Riis, Engebjerg, & Ewertz, 2010; Jenkins et al., 2006; Mehlsen, Pedersen, Jensen, & Zachariae, 2009; Schagen et al., 2006; Tager et al., 2009). In general, the effects of impairment obtained from longitudinal studies are weaker than those reported in cross-sectional studies when pretreatment level of performance is accounted for, supporting the view that changes in cognition are subtle (Bender et al., 2006; Shilling et al., 2005; Stewart et al., 2008; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a).

In terms of the time course of cognitive dysfunction after chemotherapy, some prospective studies report improved cognitive functioning among some patients at 1-year posttreatment, indicating that recovery does occur (Ahles et al., 2010; Hermelink et al., 2007; Jansen et al., 2011; Jenkins et al., 2006; Shilling et al., 2005; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a). However, there is also evidence of persistent or delayed onset of cognitive decline after completion of chemotherapy treatment in other patients (Collins, MacKenzie, Tasca, Scherling, & Smith, 2014; Wefel et al., 2010).

The cognitive domains frequently affected include learning and memory, attention and concentration, executive function, and processing speed (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Hodgson, Hutchinson, Wilson, & Nettelbeck, 2013; Wefel & Schagen, 2012), which are also the domains most often studied (Ono et al., 2015). However, deficits in motor function, visuospatial ability, and language are also reported (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Jansen et al., 2011; Jim et al., 2012). Such patterns of impairment have led some researchers to suggest that cognitive dysfunction associated with chemotherapy is diffuse and nonspecific (Falleti et al., 2005) and others to claim a preferential dysfunction of frontal-subcortical networks (Dietrich, Monje, Wefel, & Meyers, 2008; Wefel & Schagen, 2012).

The inconsistent findings are likely partly a result of substantial heterogeneity in study design and research methods. There are differences among neuropsychological studies in terms of: (a) patient sample characteristics, such as individual differences (e.g., age, education) and treatment regimens, which may include varying chemotherapy agents, dosages and schedules and the inclusion of other adjuvant treatments (e.g., hormone therapy); (b) neuropsychological tests used, which may have differing levels of sensitivity to detect subtle cognitive changes; (c) the comparator, such as healthy controls, disease-specific controls, or normative data; (d) criteria for defining and classifying cognitive impairment (e.g., 1 SD or 2 SDs below the mean) or reliable change (e.g., reliable change indices or standardized regression-based approaches); and (e) statistical analyses used, such as whether impairment is defined at the group or individual level and, in the case of longitudinal studies, whether and how the analyses control for practice effects associated with repeated testing.

Relationship Between Neuropsychological Performance and Self-Reported Cognitive Functioning in Women with Breast Cancer

The prevalence of self-reported cognitive impairment ranges from 21 to 90% (Pullens, De Vries, & Roukema, 2010) in breast cancer survivors, with symptoms reported as many as 21 years following initial diagnosis (Koppelmans et al., 2012). Although the prevalence of cognitive impairment is similar between self-reported cognitive functioning and objective neuropsychological findings, there is a lack of correlation between the two assessment methods in women with breast cancer (Hermelink et al., 2010; Jansen et al., 2011; Jenkins et al., 2006; Shilling & Jenkins, 2007). A similar dissociation between self-report and objective data are seen in other populations, including patients with HIV (Moore et al., 1997), traumatic brain injury (Schiehser et al., 2011), and normal older adults (Benito-Leon, Mitchell, Vega, & Bermejo-Pareja, 2010). Instead, it appears that self-reported cognitive symptoms have stronger associations with psychological factors such as anxiety (Hermelink et al., 2007; van Dam et al., 1998), depression (Hermelink et al., 2007; 2010; van Dam et al., 1998), negative affect (Hermelink et al., 2010), general psychological distress (Jenkins et al., 2006; Shilling & Jenkins, 2007) and fatigue (Castellon et al., 2004; Servaes, Verhagen, & Bleijenberg, 2002), which suggest that self-reported cognitive symptoms and objective testing measure different phenomena (Pullens et al., 2010). It is also important to note that neuropsychological testing is typically conducted in a quiet, structured, and examiner-directed environment, which for most people capture their optimal level of functioning. Thus, patients may experience greater cognitive difficulties in more natural home, work, or community settings (Pullens et al., 2010).

Another potential explanation for the discrepant self-report and objective findings is the ability of patients to compensate for changes in cognitive function by recruiting greater neural resources during task performance. For instance, Ferguson, McDonald, Saykin, and Ahles (2007) reported a broader extent of neural activation on an n-back working memory task and higher levels of self-reported cognitive problems for a woman treated with chemotherapy compared to her healthy identical twin, although their levels of performance did not differ. Potential compensatory processes were also reported in a longitudinal fMRI study that used the n-back task with varying cognitive load on working memory (McDonald, Conroy, Ahles, West, & Saykin, 2012). This study found that although performance on the n-back task did not differ between chemotherapy and nonchemotherapy patient groups at any time points, there were alterations in activation patterns apparent at all three time points during low and high memory loads. Such findings suggest that mean performance level may not accurately reflect endogenous changes in the brain related to chemotherapy (e.g., neural activation patterns).

Overview of Intraindividual Variability in Performance

Within the breast cancer and cognition literature, the focus has been on differences or changes in mean performance level. When there is low performance variability, then mean performance levels may sufficiently characterize behaviour. However, as variability increases due to a general endogenous influence (e.g., reduced neurological integrity), performance as indexed by a single assessment can yield flawed estimates of group differences (Hultsch, Strauss, Hunter, & MacDonald, 2008). Thus, there is increased recognition that emphasis on mean level performance may be an oversimplification of behaviour that may lead to false inferences (Nesselroade, 2002).

Intraindividual variability (IIV) is a term used to describe within-person fluctuations in performance across RT trials within a given task (Hultsch et al., 2008; Nesselroade, 1991). This type of within-person variability differs from dispersion, which refers to variability across different tasks. Increased IIV in performance has been repeatedly associated with a number of neurological and neurodevelopmental conditions, including traumatic brain injury (Stuss, Murphy, Binns, & Alexander, 2003), dementia (Burton, Strauss, Hultsch, Moll, & Hunter, 2006; Murtha, Cismaru, Waechter, & Chertkow, 2002), mild cognitive impairment (Christensen et al., 2005; Dixon et al., 2007), Parkinson's disease (Burton et al., 2006; de Frias, Dixon, & Camicioli, 2012), multiple sclerosis (Bodling, Denney, & Lynch, 2012), and attention deficit hyperactivity disorder (Williams, Strauss, Hultsch, Hunter, & Tannock, 2007). Furthermore, studies demonstrate a relationship between IIV and severity of neurological dysfunction, such that increased variability is associated with greater severity of neurological disturbance. In contrast, individuals with non-neurological diseases such as arthritis do not show increased IIV compared to healthy controls (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Strauss, MacDonald, Hunter, Moll, & Hultsch, 2002). These findings suggest that IIV is informative in discriminating between neurologically intact and neurologically impaired individuals.

Age-related Changes in Intraindividual Variability

IIV is seen as a fundamental phenomenon of aging and has been largely studied within this context. The magnitude of IIV observed among healthy individuals has been found to fluctuate according to a U-shaped function across the lifespan from age 6 to 100 years, with greater variability in performance observed in childhood/adolescence and

older adulthood relative to young adulthood and middle age (Williams, Hultsch, Strauss, Hunter, & Tannock, 2005). Similarly, a number of studies show that IIV increases as people age and appears to depend on task complexity (Bielak, Cherbuin, Bunce, & Anstey, 2014; Deary & Der, 2005). For example, an 8-year longitudinal study comparing IIV in young (20-24 years), middle (40-44 years), and older (60-64 years) adults found that IIV was stable for those in their 20s and 40s on a simple reaction time (RT) task (Bielak et al., 2014). However, IIV increased for those in their 60s over the course of the study. On complex RT tasks, both the middle and older adult groups showed greater variability than the young group over three assessment points with the older group demonstrating a larger difference. Thus, developmental change in IIV did not occur until older age for the simple RT tasks, but was observed in middle adulthood for the more complex task.

Increased IIV has been associated with deleterious age-related outcomes. Virtually all published studies demonstrate positive associations between older age and IIV across both fluid (e.g., executive function, processing speed) and crystallized (e.g., semantic memory, vocabulary) cognitive abilities (Hultsch et al., 2008; Rabbitt, Osman, Moore, & Stollery, 2001). Bunce, MacDonald, and Hultsch (2004) showed that increased IIV in older adults is not due to slower motor processing, but rather is caused by increased attentional demands. In addition, experimental manipulations to elevate IIV levels in younger adults to that of older adults by degrading the visual stimuli were unsuccessful (MacDonald, Hultsch, & Bunce, 2006). These findings suggest that increased IIV in older adults is not due to sensory loss such as motor slowing or perceptual difficulties that may accompany normative aging but rather is attributable to

decreased attentional resources.

Prospective longitudinal studies have also shown developmental changes in IIV and cognitive performance. For example, increases in IIV across a 6-year period were associated with corresponding 6-year declines in other cognitive domains of working and episodic memory (MacDonald, Hultsch, & Dixon, 2003). Similarly, significant inverse relationships were found between IIV and performance on cognitive tasks (Lövdén, Li, Shing, & Lindenberger, 2007), with stronger relationships between IIV and fluid measures that required greater cognitive load than more crystallized measures (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010b).

IIV provides information beyond that of mean-level performance (e.g., mean RT) despite the finding that these measures are often highly correlated (i.e., a wider response range tends to be associated with increases in both the mean and standard deviation because performance across trials is typically positively skewed). Although some studies find negligible predictive differences between the two measures in relation to cognitive outcomes (Christensen et al., 2005), other studies show that IIV contributes predictive information that is unique from mean-level performance (Li, Aggen, Nesselroade, & Baltes, 2001a; MacDonald, Nyberg, Sandblom, Fischer, & Bäckman, 2008b). In a particularly compelling investigation, increased IIV preceded and predicted subsequent decline in cognition, whereas mean-level performance did not (Lövdén et al., 2007). Altogether the findings indicate that, in addition to mean-level performance, IIV represents an important marker of cognitive integrity.

Although the majority of research has focused on IIV as maladaptive in that it is associated with negative outcomes, variability may also serve as an indicator of resilience

and be associated with positive outcomes (Allaire & Marsiske, 2005). The issue of task characteristics is important because IIV in RT tasks that measure attention appear to follow a different pattern than IIV in other cognitive domains. For instance, increased IIV observed on learning tasks is proposed to be adaptive because the optimal method to perform a task is unknown and thus requires an individual to experiment with various strategies with room for growth and improvement (Allaire & Marsiske, 2005). In contrast, IIV in attentional tasks where response strategies are constrained is more likely to yield a maladaptive index of variability (Hultsch et al., 2002; Rabbitt et al., 2001). Phase of skill acquisition is another important consideration. Li, Huxhold, and Schmiedek (2004) proposed distinct functions of variability from initial learning to skill acquisition (e.g., reaching asymptotic performance level). Thus, IIV associated with initial acquisition of abilities may be considered adaptive, and IIV after asymptotic performance may reflect maladaptive functioning (MacDonald, Li, & Bäckman, 2009).

Conceptualizations of Intraindividual Variability

IIV has been hypothesized to represent momentary lapses of attention (Bunce, Warr, & Cochrane, 1993) or fluctuations in executive control processes (West, Murphy, Armilio, Craik, & Stuss, 2002). For example, whereas healthy older adults tend to exhibit significant correlations between IIV and cognitive performance regardless of task load, associations for younger adults are more likely to be observed only on more difficult tasks requiring frontally based executive processes (Hultsch, MacDonald, & Dixon, 2002). These findings suggest that limited attentional resources are available for older adults relative to younger adults, with increased IIV as a behavioural manifestation of more frequent lapses in attention or fluctuations in executive control. Such observed

patterns converge with functional brain imaging studies that indicate involvement of frontal neural networks. In healthy older adults, white matter hyperintensities in the frontal lobe have been correlated with increased IIV (Bunce et al., 2007); in middle-aged adults, frontal white matter hyperintensities were correlated with increased IIV in women, whereas temporal white matter hyperintensities were correlated with IIV in men (Bunce et al., 2010). Increased IIV has also been associated with smaller corpus callosum volume in patients with mild cognitive impairment, particularly in the anterior region (Anstey et al., 2007). Patients with focal frontal lobe lesions (with the exception of ventral medial/orbitofrontal region) have also shown greater IIV than those with nonfrontal lesions and controls (Stuss et al., 2003). Similarly, people diagnosed with frontotemporal dementia are more variable on speeded tasks than those diagnosed with Alzheimer's disease of similar disease severity (Murtha et al., 2002).

The most widely used operationalization of IIV is the intraindividual standard deviation (ISD). ISD scores computed using raw scores have been criticized for containing both systematic within-person variability (e.g., practice effects, fatigue) and systematic between-group differences (e.g., group differences in overall mean performance are often correlated with differences in raw SD values). To address these issues, regression-based approaches are used to "purify" the data with respect to systematic trends in performance (Hultsch et al., 2008). Resulting residualized ISD scores have been found to increase as a function of age and cognitive status at a magnitude similar to raw ISDs (Dykiert, Der, Starr, & Deary, 2012). Another approach to understand the source of elevated variability involves restricting calculation of variability to the fast and slow tails of the RT distribution. This approach follows the hypothesis that

increases in IIV result from attentional or executive control lapses in the slow end of the RT distribution (Hultsch et al., 2002; Salthouse, 1993). This approach is an alternative to fitting the RT data to the ex-Gaussian distribution, which permits the analysis of the tau parameter representing the right tail of the RT distribution but is more computationally complex.

Relevance of Intraindividual Variability for Women with Breast Cancer

IIV appears to be an important characteristic of individual performance that represents a sensitive behavioural marker of neurobiological compromise (Li, Lindenberger, & Sikström, 2001b). The link between IIV and neurological functioning is potentially relevant for women treated for breast cancer because injury to the central nervous system resulting from neurotoxic effects of chemotherapy may underlie at least some cognitive symptoms. In the first study to investigate IIV in women diagnosed with breast cancer, Bernstein, Catton, and Tannock (2014) evaluated patients and healthy controls on a simple sustained Go-No Go attention task. Group differences were found under certain task conditions, such that patients with breast cancer were more variable than controls at short interstimulus intervals and less variable at longer intervals, which suggested greater difficulty on the shorter interval that involved increased cognitive load. IIV in that study was conceptualized using the coefficient of variation (CoV), which accounts for mean group differences but does not account for potential confounds of age or practice on RT. Nevertheless, the study findings provided a proof of concept that IIV is relevant for the study of cognitive dysfunction related to breast cancer and its treatments.

Study Aims and Overview

The main purpose of this dissertation is to better understand executive functioning in women with breast cancer with an emphasis on exploring IIV in women before and after chemotherapy. First, a systematic review of published studies is presented (Chapter 2). Studies were grouped according to four predefined subdivisions of executive functioning (Miyake, Emerson, & Friedman, 2000; Miyake & Friedman, 2012): (a) response inhibition, (b) set-shifting, (c) working memory, and (d) planning/decision making. The review chapter is followed by suggestions for future directions, including the use of methods beyond central measures of tendency--namely IIV--to evaluate performance of women treated for breast cancer.

Chapter 3 reports an original study that examined pretreatment IIV in women diagnosed with breast cancer and healthy controls on a Stroop RT task. The Stroop task requires response inhibition and provides measures of increasing cognitive difficulty (e.g., congruent and incongruent task conditions). A secondary aim of the study was to examine whether demographic, clinical, and self-report variables are related to pretreatment IIV.

Chapter 4 presents a second study, which examined changes from baseline IIV among women treated with chemotherapy at 1-month and 9-month posttreatment compared to healthy controls assessed at similar intervals. Additional analyses examined change in self-reported cognition over the same assessment periods and correlations of self-reported cognitive symptoms with change in objective performance. The task paradigm includes task conditions that involve increasing cognitive load which allows for the examination of IIV associated with simple attention, as well as potential increases in

IIV associated with increases in cognitive demand (Hultsch et al., 2000). IIV results are also discussed in relation to mean-level performance (i.e., mean RT) to determine whether IIV provides unique information regarding cognitive performance in women treated for breast cancer.

Chapter 2: Do Women Treated For Breast Cancer Have Impaired Executive Functioning? A Systematic Review

Publication Status

The following chapter is based on a manuscript in preparation for publication:

Yao, C., Bernstein, L. J., & Rich, J. B. Executive functioning impairment in women treated for breast cancer with chemotherapy: A systematic review.

Abstract

Women treated for breast cancer may experience cognitive difficulties following chemotherapy. Impaired performance on tasks examining executive functioning is commonly observed, yet it isn't clear whether some subcomponents of executive functioning are more vulnerable to impairment than others. A comprehensive systematic review of articles that reported quantitative information on executive functioning among breast cancer survivors who had been treated with chemotherapy was performed. Studies were identified using three electronic databases (MEDLINE, PsycINFO, and Web of Science) and a manual search of relevant reference lists. The methodological quality of included studies was assessed using a checklist of predefined criteria. Of 1227 identified articles, a total of 36 were included for review. Study findings were categorized into four subcomponents of executive functioning: inhibition, set-shifting, working memory, and planning/decision-making. Inhibition appears relatively spared from the effects of chemotherapy, whereas findings were inconsistent for set-shifting, working memory, and planning/decision making. Methodological heterogeneity contributed to the mixed findings. Examining subcomponents of executive functioning is recommended to better characterize the nature of executive dysfunction in women treated with chemotherapy.

Future studies should include executive functioning tasks of varying complexity, use of individual and composite measures, and alternative indices to capture performance, such as within-person variability.

Introduction

Many women with breast cancer experience subtle impairments in cognitive performance associated with chemotherapy. Although many prospective studies demonstrate that cognitive dysfunction improves within one year after the completion of chemotherapy (Collins et al., 2009; Jansen et al., 2011; Reid-Arndt, Hsieh, & Perry, 2010), some cognitive deficits persist (Collins et al., 2014; Wefel et al., 2010). Cross-sectional studies have documented long-term cognitive deficits up to 21 years from initial diagnosis (de Ruiter et al., 2011; Koppelmans et al., 2012; Nguyen et al., 2013), and these deficits can have an adverse impact on quality of life (Reid-Arndt et al., 2010). Executive functioning is commonly investigated in these studies. Despite reports of deficits on tasks of executive functioning following chemotherapy among women with breast cancer (Chen et al., 2013; Hermelink et al., 2007; Jim et al., 2009; Nguyen et al., 2013), some studies demonstrate normal performance (Ahles et al., 2010; Castellon et al., 2004; Jenkins et al., 2006; Mehlsen et al., 2009; Vearncombe et al., 2009). The inconsistent findings may be related to differences in study characteristics, such as the breast cancer population under study (age, stage of tumor, menopausal status), type of comparison cohort (healthy controls, other cancers, untreated patients, normative data), time since diagnosis or treatment, type of treatment (e.g., chemotherapy alone vs. in combination with hormonal or radiation, chemotherapy dose), and study design (cross-sectional or longitudinal; Ahles, 2012; Collins, MacKenzie, & Kyeremanteng, 2013a; Edelstein &

Bernstein, 2014). Another reason for the inconsistent findings may be related to the complexity of the executive functioning construct itself.

Executive functioning includes a set of cognitive processes involved in goal-directed behavior and adaptation to novel situations and is often linked to the prefrontal cortex. The extent to which executive functioning represents a unitary concept reflecting activation of one underlying neural network or separate, dissociable concepts is an area of considerable debate (Duncan & Owen, 2000; Jurado & Rosselli, 2007; Stuss, 2011).

Another confounding factor is the issue of task impurity, which arises because many tests of executive functioning also require nonexecutive processes for task completion (Miyake & Friedman, 2012). For example, performance on the Trail Making Test, Part B, a measure of set-shifting, additionally draws upon psychomotor speed, visual scanning, and sequencing. Although executive functioning has been difficult to define and measure (Jurado & Rosselli, 2007), an accepted schema that reflects the cognitive and biological underpinnings of executive functioning is the unity and diversity framework (Miyake et al., 2000; Miyake & Friedman, 2012). This framework suggests that different executive functions tap a common underlying ability and are generally correlated (i.e., unity) but are also dissociable (i.e., diversity). Four separable subcomponents that may be useful for classifying executive functioning tasks include: (a) *inhibition*: deliberate overriding of a dominant or prepotent response; (b) *set-shifting*: switching between tasks or mental sets; (c) *working memory*: monitoring incoming information and rapid addition or deletion of working memory contents; and (d) *planning and decision making* (Friedman et al., 2008; Miyake & Friedman, 2012).

Within the breast cancer literature, various neuropsychological and experimental tasks have been used to assess executive functioning across studies. Some studies rely on a single measure, whereas others include multiple measures or use a composite measure to operationalize executive functioning. Previous meta-analyses and reviews have been published examining the magnitude and pattern of executive impairment in breast cancer patients treated with chemotherapy; however, these studies typically average across all executive functioning measures to yield an aggregate score (Anderson-Hanley et al., 2003; Falletti et al., 2005; Ono et al., 2015). In the present review, we compare performance across different tasks of executive abilities to determine whether any subcomponents of executive functioning are more sensitive than others to dysfunction following chemotherapy.

Methods

Search Strategy

A systematic literature search was conducted using the following electronic databases: MEDLINE (1966–2016), PsycINFO (1872– 2016), and Web of Science (1945–2016). The key search terms used were “breast cancer” AND cogni* AND (“executive function*” OR frontal OR prefrontal OR neuro* OR assessment). In addition, reference lists from included papers were manually searched to help ensure that no relevant studies were missed through the electronic databases.

Study Selection

The review was limited to studies using women with breast cancer and published in English. Studies were included if they reported on at least one standardized neuropsychological test or objective experimental measure of executive functioning.

Initial screening for inclusion was based on titles of all identified papers, followed by abstract and full-text screening. When multiple studies shared an overlapping patient sample, only the highest quality study (as detailed below) was included (Khan, Kunz, Kleijnen, & Antes, 2003; Pullens et al., 2010).

Methodological Quality Assessment

Two raters (CY and a research assistant) independently assessed the quality of each study using a standardized set of 17 predefined criteria (Table 1) adapted from Pullens and colleagues (2010). Studies earned 0 or 1 point for each criterion in the checklist. A score of 0 was assigned if insufficient information was provided for rating a given criterion. Discrepancies between raters were discussed among all authors to reach consensus. Studies scoring 70% or more of the maximum score (≥ 12 points) were categorized as *high quality*. Studies scoring between 50% and 70% (9 -11 points) were categorized as *moderate quality*, and studies with ≤ 8 points were considered *low quality*. Level of agreement between raters was analyzed using the intraclass correlation coefficient (ICC; Bartko, 1966; 1966).

Results

Search Strategy and Quality Assessment

The search strategy identified 1227 articles. Figure 1 provides a flowchart of the article selection process. After removing duplicates, excluding articles based on title, abstract, and full-text screening, and adding articles identified manually, a total of 36 studies were eligible for inclusion in the final review. The included studies were published between 1995 and 2016, with half of the studies published in 2010 or later.

Table 1. Checklist to Assess Methodological Quality of Included Articles (Modified from Pullens et al., 2010)

Criteria
<p><i>Study Population</i></p> <ul style="list-style-type: none"> A. Patient signed an informed consent form before study participation B. A description is present of at least two sociodemographic data (e.g., age, race, employment status, educational status, etc). C. Medical data are described (e.g., tumor stage at diagnosis, treatment, etc.) D. Inclusion and/or exclusion criteria are formulated E. Participation and response rates for patient groups have to be more than 75% F. Information is presented about patient/disease characteristics of nonresponders or reasons for not participating <p><i>Study Design</i></p> <ul style="list-style-type: none"> G. Sample size is at least 50 patients (arbitrarily chosen) H. The process of data collection is described (e.g., neuropsychological assessments, self-report measurements, interview) I. More than one neuropsychological measure to assess executive functioning is described J. A baseline measurement is obtained before treatment K. There are multiple assessment points L. Mean or median and range or standard deviation of time before/since diagnosis/treatment or test interval between measurement occasions is given M. Data collection is prospectively gathered N. Drop out rate is less than 20% O. The study controlled for at least two of the following factors in the results for executive functioning: depressive symptoms, fatigue, anxiety, stress, menopausal status, influence of hormonal therapy, educational level, or age <p><i>Results</i></p> <ul style="list-style-type: none"> P. The results for executive functioning are compared between two or more groups (e.g., healthy population, different treatment groups, comparison with time, etc.) Q. An appropriate statistical test was used

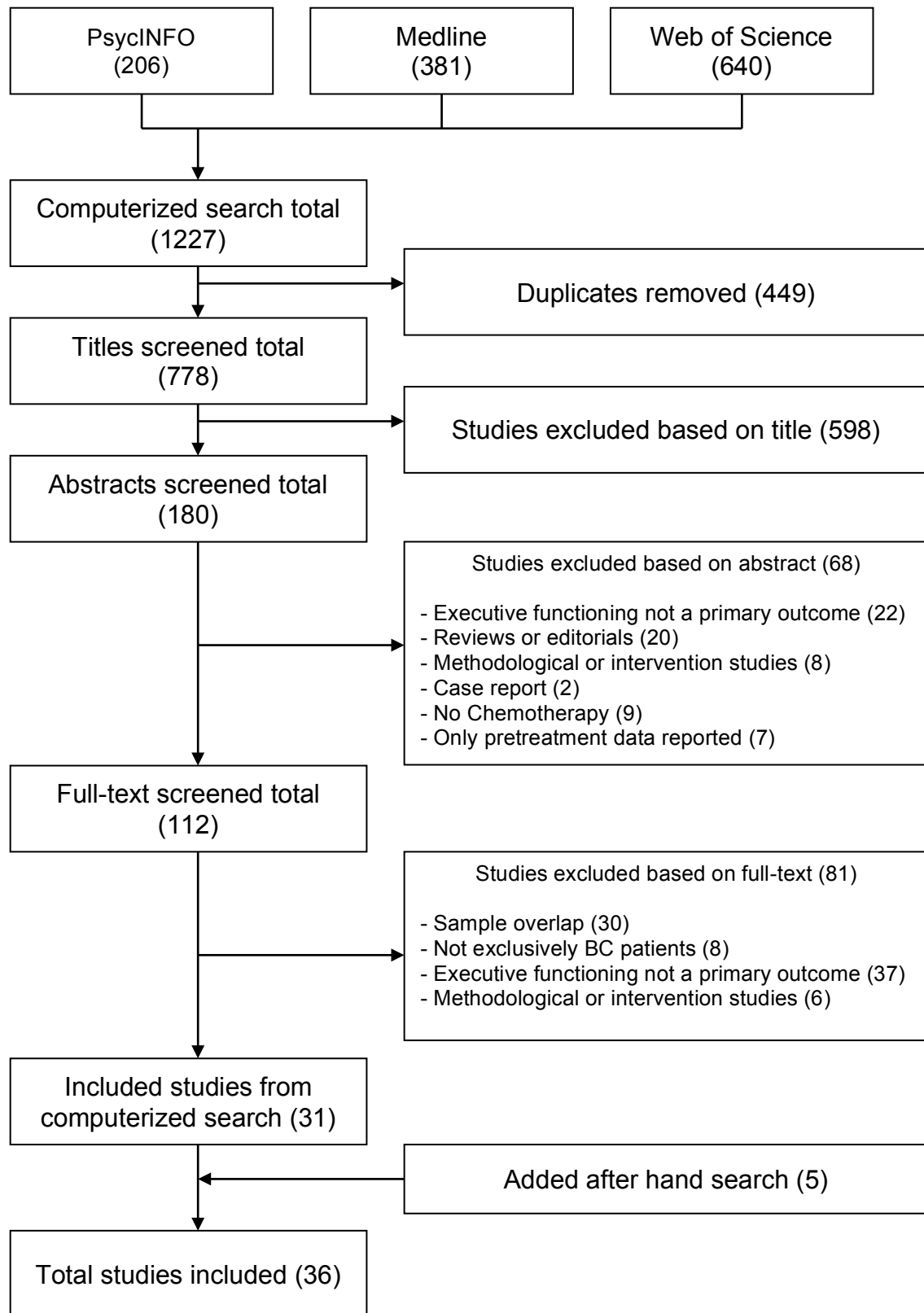


Figure 1. Study Search Flowchart

Inter-rater agreement of methodological quality assessment was high ($ICC = .80$). On a 17-point scale, the average score was 11.95 ($SD = 2.36$, range = 8 to 16).

Executive Functioning Subdivisions

The cognitive tasks that were used to assess executive functioning are described in Table 2. The results are presented according to Miyake and Friedman's (2012) unity and diversity framework of executive functioning. The outcome data were assigned to a subcomponent by using generally accepted descriptions (Lezak, Howieson, Bigler, & Tranel, 2012) or author report. Characteristics of the included studies are provided in Table 3. The findings from each study are summarized in Table 4.

Inhibition

Inhibition was assessed in 13 studies using the Stroop task (time to completion or age/education-corrected standardized scores). Only one high quality cross-sectional study found that patients treated with chemotherapy were slower compared to those who did not undergo chemotherapy or healthy controls at 1-month follow-up (Chen et al., 2013). The other 12 studies (five cross-sectional, seven longitudinal) did not show impaired performance in patients at short-term (up to 1 year after treatment; Debess et al., 2010; Deprez et al., 2011; Hurria et al., 2006; 2014; Jansen et al., 2011; Jenkins et al., 2006; Mehlsen et al., 2009; Reid-Arndt et al., 2010; Vearncombe et al., 2009) or long-term follow-up (up to 21 years after treatment; Castellon et al., 2004; Koppelmans et al., 2012; Schagen et al., 1999; van Dam et al., 1998). One low-quality cross-sectional study used a Flanker test (de Ruiter et al., 2011), and found patients treated with chemotherapy made more errors than patients who did not receive chemotherapy at 9 years posttreatment.

Together, the studies published to date suggest that inhibition is not impaired in patients after chemotherapy.

Set-Shifting

Twenty-five studies have assessed set-shifting. Women treated with chemotherapy were impaired on the Trail Making Test, Part B (TMT-B) in four moderate- to high-quality studies (2 cross-sectional and 2 longitudinal; Chen et al., 2013; 2013; Mar Fan et al., 2005; Schagen et al., 1999; Wefel et al., 2010), whereas they performed similarly to control groups in 17 other investigations of similar methodological quality (Bender et al., 2006; Biglia et al., 2011; Castellon, Silverman, & Ganz, 2005; Donovan et al., 2005; Hermelink et al., 2007; Hurria et al., 2006; Jim et al., 2009; Mehlsen et al., 2009; Nguyen et al., 2013; Quesnel et al., 2009; Reid-Arndt et al., 2010; Ruzich, Ryan, Owen, Delahunty, & Stuart-Harris, 2007; Scherwath et al., 2006; Tager et al., 2009; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a; Wefel, Lenzi, Theriault, Buzdar, Cruickshank, & Meyers, 2004b; Wieneke & Dienst, 1995). Group differences were found 1 to 6 months and 1 to 2 years after treatment, but not when assessments were undertaken up to 5 to 10 years after treatment (Castellon et al., 2005; Nguyen et al., 2013; Scherwath et al., 2006).

Three studies assessed set-shifting using the Wisconsin Card Sorting Test (WCST). Two cross-sectional studies of moderate quality showed impaired performance in breast cancer survivors 5 to 10 years after chemotherapy (e.g., fewer categories completed, greater number of errors, increased time to completion; Kesler et al., 2011; Nguyen et al., 2013), although one of them found that patients were impaired relative to healthy controls but not to patients who did not receive chemotherapy (Nguyen et al.,

2013). In one 6-month longitudinal study of moderate quality, patients showed improvement over assessments (Ruzich et al., 2007). However, no comparison groups were included in the study, so practice effects common to this test were not accounted for across four measurement occasions (Basso, Bornstein, & Lang, 1999; Ferland, Ramsay, Engeland, & O'Hara, 1998).

Among the seven studies using other variants of set-shifting tasks, two high-quality longitudinal studies found decline within 1 month after chemotherapy on a trail-making type test (Debess et al., 2010) and on a test of verbal fluency involving category switching (Hermelink et al., 2007). In contrast, five studies of high to moderate quality did not find impairments from immediately postchemotherapy up to 10 years later using D-KEFS Sorting Test (Ahles et al., 2010; Vearncombe et al., 2009), Booklet Category Test (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a; Wieneke & Dienst, 1995) and a computerized test of concept shifting (Nguyen et al., 2013).

Together, the studies using set-shifting tasks do not corroborate consistent chemotherapy-related impairments. There were methodological differences between studies with respect to the particular tests used to assess set-shifting, outcome measures (e.g., total correct vs. standardized score), and comparison group (e.g., healthy controls vs. normative data), which make direct comparison challenging and contribute to the inconsistent findings.

Working Memory

Twenty-four studies evaluated working memory using individual neuropsychological tests and working memory composites. Using Digit Span Backward (DSB), four cross-sectional studies of 13 studies that used this task, ranging from low to

high quality, observed reduced span and fewer total trials completed in women treated with chemotherapy compared to no chemotherapy and healthy control groups up to 2-year follow-up (Chen et al., 2013; Deprez et al., 2012; Jung & Cimprich, 2014; Schagen et al., 1999). The remaining studies (3 cross-sectional; 6 longitudinal) ranging from moderate to high quality found similar performance in patients and control groups up to 2 years posttreatment (Bender et al., 2006; Deprez et al., 2011; Hermelink et al., 2007; Mehlsen et al., 2009; Quesnel et al., 2009; Scherwath et al., 2006; Tager et al., 2009; van Dam et al., 1998; Vearncombe et al., 2009).

Working memory was also assessed using Letter-Number Sequencing (LNS). LNS performance was impaired in women treated with chemotherapy at 4-month follow-up in a moderate-quality cross-sectional study (Deprez et al., 2012). In another moderate-quality cross-sectional study, chemotherapy-treated patients performed worse than healthy controls 10 years posttreatment, although they did not differ from nonchemotherapy-treated patients (Nguyen et al., 2013). In three other longitudinal studies of moderate to high quality, performance was unimpaired at short-term follow-up (Mehlsen et al., 2009; Ruzich et al., 2007; Tager et al., 2009), although the effects of task repetition were not consistently controlled due to lack of control groups in one of these studies (Ruzich et al., 2007).

On the Arithmetic test, women treated with chemotherapy did not differ from comparison groups when assessed immediately postchemotherapy up to 10 years later in one cross-sectional (Nguyen et al., 2013) and three longitudinal studies (Ruzich et al., 2007; Tager et al., 2009; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a). Two of these

studies did not include control groups (Ruzich et al., 2007; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a).

One moderate-quality cross-sectional study that used the Paced Auditory Serial Addition Test (PASAT) found impaired performance in patients 6 months postchemotherapy treatment relative to normative data (Wieneke & Dienst, 1995). Two other studies of high or moderate quality found no group differences on PASAT performance in relation to comparison groups up to 5 years after diagnosis (Ahles et al., 2010; Castellon et al., 2004).

Other variants of the working memory tasks (e.g., n-back) used in three moderate- to high-quality longitudinal studies did not find group differences in change at 1-month (Askren et al., 2014; McDonald et al., 2012) and 1-year postchemotherapy (Dumas et al., 2013).

Finally, two high-quality longitudinal studies generated working memory composite scores based on five to seven tests (e.g., Digit Span, LNS, PASAT, Arithmetic, Spatial Span, Consonant Trigrams, Controlled Oral Word Association test, CNS-VS Flexibility Index, CNS-VS Working Memory Index). Composite scores were calculated by averaging standardized scores determined by principal components analysis (Collins et al., 2014) or using standard regression-based change scores based on the performance of healthy controls (Collins et al., 2009). Both of these studies found significant working memory impairments in chemotherapy-treated patients assessed immediately posttreatment. Furthermore, over the course of treatment, working memory worsened with each additional chemotherapy cycle given (Collins et al., 2014).

As with the other subcomponents, there is methodological heterogeneity which likely contributes to inconsistent findings in this subcomponent of executive functioning.

Planning/Decision Making

Three studies investigated planning/decision making. Using the Iowa Gambling Task (IGT) and Game of Dice Task (GDT), one high-quality cross-sectional study (Chen et al., 2013) showed that patients treated with chemotherapy showed a selective deficit when information on probabilities was ambiguous (IGT) at 6-month follow-up. Assessing planning using the Tower of London (ToL), a low-quality cross-sectional study found breast cancer patients treated with chemotherapy made more errors on the ToL task at 10-year follow-up than did a group of patients not exposed to chemotherapy (de Ruiter et al., 2011). In contrast, a moderate-quality longitudinal study reported that ToL performance did not change when tested during and 6 months after chemotherapy (Ruzich et al., 2007); however, practice effects were not accounted for. There is inconsistent evidence of impaired decision-making ability and planning/problem. Impairment was observed in cross-sectional but not longitudinal studies.

Table 2. Task Descriptions of Executive Functioning Measures

Executive Functioning Subdivision	Task	Task Requirements
<i>Inhibition:</i> ability to suppress a response based on a set of predefined rules.	<i>Stroop task</i> (Golden & Freshwater, 2002; Gualtieri & Johnson, 2006; Hammes, 1978; Houx, Jolles, & Vreeling, 1993; Mitrushina, Boone, & D'Elia, 1999; Stroop, 1935)	Say the ink color of written words while inhibiting the automatic response, which is to read the word (e.g., responding “blue” when viewing the word <i>red</i> written in blue ink).
	<i>Flanker task</i> (Eriksen & Schultz, 1979)	Respond to a target letter and refrain from responding to the target letter when flanked by distracting letters.
<i>Set-Shifting:</i> ability to switch between tasks, operations or mental sets in response to changing goals or environmental demands.	<i>Trail Making Test – Part B</i> (Reitan, 1958); <i>Concept Shifting Test</i> (Vink & Jolles, 1985)	Order a series of numbers and letters in alternating sequence (e.g., 1-A-2-B-3-C) as quickly and accurately as possible.
	<i>Color Trails Test – Trial 2</i> (D'Elia, Satz, Uchiyama, & White, 1996)	Connect colored number targets in numerical order in an alternating color as quickly as possible
	<i>Wisconsin Card Sorting Test</i> (Heaton, 2004; Heaton, Chelune, Talley, Kay, & Curtiss, 1993)	Sort a deck of cards in relation to four key cards while alternating sorting strategies (e.g., color, shape, number) in response to feedback from the examiner or computer
	<i>D-KEFS Sorting Test</i> (Delis, Kaplan, & Kramer, 2001)	Sort six cards into two groups, according to as many rules as possible, and then are given the opportunity to identify the rules from cards sorted by the examiner.
	<i>Booklet Category Test</i> (DeFilippis, McCampbell, & Rogers, 1979)	Determine the underlying organizational principle of sets of stimuli using feedback from the examiner.
	<i>Intradimensional/Extradimensional Shift Task</i> (Sahakian & Owen, 1992)	Shift attention between intra- and extradimensional stages (e.g., shapes overlaid with lines) based on feedback
	<i>Regensburg Word Fluency</i>	Alternate between saying words from two

	<i>with category change</i> (Aschenbrenner, Tucha, & Lange, 2000)	different semantic categories.
<i>Working Memory:</i> involves the ability to hold and manipulate information in mind for a short period of time.	<i>Digit Span Backward, WAIS</i> (Wechsler, 1955; 1981; 1997)	Verbally repeat a string of numbers in reverse order.
	<i>Letter Number Sequencing, WAIS</i> (Wechsler, 1997)	Reorder random alphanumeric sequences presented orally
	<i>Arithmetic, WAIS</i> (Wechsler, 1981; 1997)	Mentally solve mathematical word problems as quickly as possible.
	<i>Paced Auditory Serial Addition Test</i> (Fischer, Jak, Kniker, Rudick, & Cutter, 2001; Gronwell, 1977; Rao, Leo, Bernardin, & Unverzagt, 1991)	Serial addition of pairs of randomly presented numbers from 1 to 9, such that each number is added to the one that immediately preceded it (i.e., the numbers 4, 3, 5, 9, 2 yield responses of 7, 8, 14, 11).
	<i>n-back task</i> (McAllister et al., 1999)	Participants are shown a series of letters or shapes one at a time and determine whether the current item was presented 0-, 1-, 2- or 3-back in the sequence.
<i>Planning/Decision Making:</i> involves mental processes such as planning, rule acquisition, initiating appropriate responses, and selecting relevant information.	<i>Iowa Gambling Task</i> (Bechara, Damasio, & Anderson, 1994)	Choose cards from four decks to maximize gains using feedback from previous choices to learn the rules for gains/losses of each deck.
	<i>Game of Dice Task</i> (Brand et al., 2002)	Maximize gains by tossing a die with explicit rules for gains/losses and stable probabilities (two risky and two non-risky options)
	<i>Tower of London</i> (Shallice, 1982; van den Heuvel et al., 2003)	Determine the minimum number of steps required to reach a target configuration of colored beads placed on vertical rods.

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

Table 3. Study Characteristics of Included Studies

Author (Year)	Participants						Measurement Interval
	ChT patients		No ChT patients		Healthy Controls		
	Age M (SD)	n	Age M (SD)	n	Age M (SD)	n	
Cross-sectional Studies							
<i>High Quality</i>							
Chen (2013)	43.7 (7.7)	63	44.3 (8.9)	62	42.0 (9.7)	61	1 month post ChT
Donovan (2005)	52.3 (8.1)	60	-	-	57.7 (9.1)	83	6 months post ChT
Koppelmans (2012)	64.1 (6.4)	196	-	-	57.9 (5.4)	1,509	21 years after diagnosis
<i>Moderate Quality</i>							
Castellon (2004)	46.8 (6.3)	36	48.3 (4.0)	17	49.2 (6.0)	19	2-5 years after diagnosis
Deprez (2011)	45.4 (4.5)	14	42.9 (6.15)	10	45.1 (4.0)	15	4 months post ChT
Jim (2009)	50 (9)	97	58 (9)	90	Matched to ChT: 53 (8) Matched to no ChT: 59 (9)	97 90	6 months post ChT
Kesler (2011)	56.2 (7.8)	25	58.1 (6.5)	19	55.6 (9.4)	18	5 years since ChT
Nguyen (2013)	72.0 (4.9)	27	76.7 (5.4)	30	72.6 (5.5)	30	10+ years since ChT
Schagen (1999)	47.1 (6.5)	39	46.1 (5.2)	34	-	-	2 years post ChT
Scherwath (2006)	Std ChT: 51.8 (8.6); Hi ChT: 53.3 (7.1)	23 24	54.6 (8.0)	29	-	-	5 years post ChT
Van Dam (1998)	Std ChT: 48.1 (6.8); Hi ChT: 45.5 (6.2)	36 34	46.1 (5.2)	34	-	-	2 years post ChT
Wieneke (1995)	42.0 (6.7)	28	-	-	-	-	6 months post ChT
<i>Low Quality</i>							
De Ruiter (2012)	56.5 (5.1)	17	58.2 (5.8)	15	-	-	9.5 years post ChT
Jung (2014)	46 (8)	32	-	-	48 (8)	32	2 months post ChT
Longitudinal Studies							
<i>High Quality</i>							
Ahles (2010)	51.7 (7.1)	60	56.6 (8.3)	72	52.9 (10.0)	45	Baseline, 1 month, 6 month, 18 months post ChT
Askren (2014)	50 (10)	28	53 (9)	37	50 (9)	32	Baseline, 1 month post ChT
Bender (2006)	ChT: 40.1 (6.5) ChT/HT: 44.1 (3.5)	19 15	44.5 (4.2)	12	-	-	Baseline, immediately post ChT, 1-year later

Author (Year)	Participants						Measurement Interval
	ChT patients		No ChT patients		Healthy Controls		
	Age M (SD)	n	Age M (SD)	n	Age M (SD)	n	
Collins (2014)	51.8 (7.8)	56	-	-	51.3 (7.7)	56	Baseline, after each ChT cycle, 1-year post ChT
Debess (2010)	47.2	75	49.7	19	48.1	208	Baseline, 1-month post ChT
Deprez (2012)	43.7 (6.1)	34	43.1 (5.7)	16	43.8 (4.9)	19	Baseline, 3-4 months post ChT
Hermelink (2007)	48.6 (9.7)	101	-	-	-	-	Baseline; immediately post ChT
Jansen (2011)	ChT: 50.9 (2.2)	22	-	-	-	-	Baseline, immediately post ChT,
	ChT/HT: 50.7 (1.6)	49					6 months post ChT
Jenkins (2006)	51.5 (9.6)	85	58.9 (7.3)	43	51.9 (8.9)	49	Baseline, immediately post ChT,
							1-year post ChT
Quesnel (2009)	50.3 (7.2)	41	57.7 (4.9)	40	Matched to ChT: 47.9 (7.4)	22	Baseline, immediately post ChT,
					Matched to no ChT: 55.0 (7.1)	23	3 month follow-up
Tager (2010)	60.3 (5.6)	30	61.1 (6.2)	31			Baseline, immediately post ChT,
							6-months follow-up
Vearncombe (2009)	49.4 (7.9)	136	54.0 (8.2)	21	-	-	Baseline, immediately post ChT
Wefel (2010)	48.8 (8.1)	42	-	-	-	-	Baseline, During ChT (acute),
							immediately after ChT (acute), 1-
							year post ChT (late)
Wefel (2004)	45.4 (6.7)	18	-	-	-	-	Baseline, immediately post ChT,
							1-year post ChT
Moderate Quality							
Biglia (2012)	51.0 (7.8)	40	-	-	-	-	Baseline, immediately post-ChT
Dumas (2013)	57.10 (8.6)	9	-	-	-	-	Baseline, 1-month post ChT, 1-
							year follow-up
Hurria (2006)	71 (5)	28	-	-	-	-	Baseline, 6-months post ChT
Mar Fan (2005)	Median age: 48	104	-	-	Median age: 47	102	Immediately post ChT, 1-year, 2-
							year follow-up
McDonald (2012)	52.9 (8.6)	16	52.7 (7.2)	12	50.5 (6.0)	15	Baseline, 1-month post-ChT, 1-
							year later
Mehlsen (2009)	48.6 (8.0)	36	Cardiac group: 50.4 (9.1)	14	39.3 (11.7)	17	Baseline, 1-month post ChT
Reid-Arndt (2010)	53.4 (9.6)	39	-	-	-	-	1-month post-ChT, 6-month and

Author (Year)	Participants						Measurement Interval
	ChT patients		No ChT patients		Healthy Controls		
	Age M (SD)	n	Age M (SD)	n	Age M (SD)	n	
Ruzich (2007)	Median age: 53	35	-	-	-	-	1-year follow-up Baseline, mid ChT, post ChT, 6-month post ChT

Note. BC=Breast Cancer; ChT= chemotherapy; COWA= Controlled Oral Word Association; D-KEFS=Delis-Kaplan Executive Function System; DSB= Digit Span Backward; EF=Executive Functioning; LNS= Letter-Number Sequencing; HT=Hormone Therapy; PASAT= Paced Auditory Serial Addition Test; RT= Radiotherapy; RWT= Regensburger Word Fluency Test; sig.=significant; SX= Surgery; TMT-B= Trail Making Test – Part B; ToL=Tower of London; TX= treatment; WCST= Wisconsin Card Sorting Test.

Table 4. Results of Included Studies

Author (Year)	Study Design	Measure	Results ^a
A. INHIBITION			
High Quality			
Chen (2013)	C	Stroop	ChT < Non-ChT, HC
Koppelmans (2012)	C	Stroop	ns
Debess (2010)	L	Stroop	ns
Jansen (2011)	L	Stroop	ns
Jenkins (2006)	L	Stroop	ns
Vearncombe (2009)	L	Stroop	ns
Moderate Quality			
Castellon (2004)	C	Stroop	ns
Deprez (2011)	C	Stroop	ns
Schagen (1999)	C	Stroop	ns
Van Dam (1998)	C	Stroop	ns
Hurria (2006)	L	Stroop	ns
Mehlsen (2009)	L	Stroop	ns
Reid-Arndt (2010)	L	Stroop	ns
Low Quality			
De Ruiter (2012)	C	Flanker test	ChT < Non-ChT
B. SET-SHIFTING			
High Quality			
Chen (2013)	C	TMT-B	ChT < Non-ChT, HC
Donovan (2005)	C	TMT-B	ns
Ahles (2010)	L	D-KEFS Sorting Test	ns
Bender (2006)	L	TMT-B	ns
Debess (2010)	L	Concept Shifting Test	1 mos F/U: ChT < Non-ChT
Hermelink (2007)	L	TMT-B, RWT Lexical Search with Change of Category	ns
		RWT Semantic Search with Change of Category	Last TX cycle F/U: ChT < normative data
Quesnel (2009)	L	TMT-B	ns
Tager (2010)	L	TMT-B	ns
Vearncombe (2009)	L	D-KEFS Sorting Test	ns
Wefel (2010)	L	TMT-B	1 mos & 1 yr F/U: ChT < normative data
Wefel (2004)	L	TMT-B, BCT	ns
Moderate Quality			
Castellon (2004)	C	TMT-B	ns
Jim (2009)	C	TMT-B	ns
Kesler (2011)	C	WCST	ChT < Non-ChT, HC
Nguyen (2013)	C	TMT-B, IED Shift task	ns
		WCST	ChT, Non-ChT < HC
Schagen (1999)	C	TMT-B	ChT < non-ChT
Scherwath (2006)	C	TMT-B	ns
Van Dam (1998)	C	TMT-B	ns
Wieneke (1995)	C	TMT-B, BCT	ns
Biglia (2012)	L	TMT-B	ns
Hurria (2006)	L	TMT-B	ns
Mar Fan (2005)	L	TMT-B	1 & 2 yr F/U: ChT < HC
Mehlsen (2009)	L	TMT-B	ns
Reid-Arndt (2010)	L	TMT-B	ns

Author (Year)	Study Design	Measure	Results ^a
Ruzich (2007)	L	TMT-B, WCST	ns
C. WORKING MEMORY			
High Quality			
Chen (2013)	C	DSB	ChT < Non-ChT, HC
Ahles (2010)	L	PASAT	ns
Askren (2014)	L	VWMT	ns
Bender (2006)	L	DSB	ns
Collins (2014)	L	WM composite	Last TX cycle F/U: ChT < HC
Collins (2009)	L	WM composite	1 mos F/U: ChT < Non-ChT
Deprez (2012)	L	DSB	4 mos F/U: ChT < Non-ChT, HC
		LNS	4 mos F/U: ChT < Non-ChT, HC
Hermelink (2007)	L	DSB	ns
Jenkins (2006)	L	DSB, LNS	ns
Quesnel (2009)	L	DSB	ns
Tager (2010)	L	DSB, LNS, Arithmetic	ns
Wefel (2004)	L	Arithmetic	ns
Moderate Quality			
Castellon (2004)	C	PASAT	ns
Deprez (2011)	C	DSB	ns
Nguyen (2013)	C	LNS	ChT, Non-ChT < HC
		Arithmetic	ns
Schagen (1999)	C	DSB	ChT < Non-ChT
Scherwath (2006)	C	DSB	ns
Van Dam (1998)	C	DSB	ns
Wieneke (1995)	C	PASAT	ChT < normative data
Dumas (2013)	L	n-back test	ns
McDonald (2012)	L	n-back test	ns
Mehlsen (2009)	L	Arithmetic, DSB, LNS	ns
Ruzich (2007)	L	Arithmetic, LNS	ns
Low Quality			
Jung (2014)	C	DSB	ChT < HC
D. PLANNING/DECISION-MAKING			
High Quality			
Chen (2013)	C	IGT	ChT < Non-ChT, HC
		GDT	ns
Moderate Quality			
Ruzich (2007)	L	ToL	ns
Low Quality			
De Ruiter (2012)	C	ToL	ChT < Non-ChT

Note: ^aResults are presented as impaired functioning.

BCT=Booklet Category Test; ChT=chemotherapy patients; C=cross-sectional; D-KEFS=Delis-Kaplan Executive Function System; DSB=Digit Span Backward; F/U=follow-up; GDT=Game of Dice Task; HC=healthy controls; IED=Intra/Extradimensional; IGT=Iowa Gambling Test; L=longitudinal; LNS=Letter-Number Sequencing; mos= months; non-ChT= non-chemotherapy patients; ns= not significant; PASAT=Paced Auditory Serial Addition Test; RWT=Regensburger Word Fluency Test; TMT-B=Trail Making Test – Part B; ToL=Tower of London; TX=treatment; VWMT=Verbal Working Memory Task; WCST=Wisconsin Card Sorting Test; WM=working memory; yr=year.

Discussion

The present review illustrates that a broad range of executive functions has been assessed among women with breast cancer using a variety of neuropsychological and experimental measures across studies. Most studies examined subcomponents of executive functioning using individual measures, although some combined several tasks into a composite measure of working memory. The primary objective of this systematic review was to examine subcomponents of executive functioning in women treated with chemotherapy for breast cancer. Substantial methodological heterogeneity made it difficult to draw definitive conclusions regarding whether some aspects of executive functioning are more vulnerable to impairment than others. Inhibition, which was primarily assessed using the Stroop task, appears to be least prone to impairment after chemotherapy. The other subcomponents of set-shifting, working memory, and planning/decision making were inconsistently impaired in patients. In general, deficits were more likely to be reported in cross-sectional studies, which is consistent with smaller effect sizes found in longitudinal studies reported in meta-analyses examining executive functioning (Anderson-Hanley et al., 2003; Ono et al., 2015). Uncontrolled practice effects for some tasks in particular (e.g., WCST, ToL) may contribute to the failure to detect chemotherapy-related impairment in longitudinal studies with multiple assessment points. Although sample size was accounted for in the methodological quality assessment, many studies did have relatively small sample sizes. Thus, studies may be underpowered to detect subtle effects of chemotherapy on executive functioning.

Results indicate that inhibition is relatively spared in women treated with chemotherapy. Factor analyses of executive functioning suggest that there is no

inhibition-specific factor (Friedman et al., 2008; Miyake & Friedman, 2012). Rather, inhibition tasks appear to load on a common executive factor (e.g., maintaining an active goal and managing that goal when there is interference) which is separable from shifting and working memory. It is possible that inhibition was least sensitive to the effects of chemotherapy because it was narrowly assessed using the Stroop task, which may not represent inhibition as a broader construct. Nigg (2002) also argues that there are eight different types of inhibition including interference control, cognitive inhibition, behavioral inhibition, oculomotor inhibition, motivational inhibition, and automatic inhibition of attention. Within this framework, the Stroop task measures only one aspect of inhibition: interference control or prevention of interference due to stimulus competition.

An explanation of why deficits in executive functioning were not consistently detected concerns the sensitivity of the tasks, given the subtle nature of chemotherapy-related cognitive dysfunction (Anderson-Hanley et al., 2003; Falsetti et al., 2005). Many of the neuropsychological measures of executive functioning discussed above (e.g., TMT-B) are primarily used clinically with individuals who have sustained head injuries or other damage to prefrontal cortex. Such tests may lack the sensitivity to detect subtle impairments in executive functions in women treated with chemotherapy. It may also explain why impairments appear to be more evident on tasks of increased complexity (e.g., ToL, IGT). There is emerging evidence that within-person variability in reaction time tasks may be a sensitive indicator of cognitive function and useful for providing further insights into executive dysfunction in women with breast cancer beyond that of mean-level performance (Bernstein et al., 2014).

A closer examination of the subcomponents of executive functioning has important clinical implications. For instance, executive functioning as a multicomponent construct may reveal a specific profile of executive dysfunction characteristic of chemotherapy-related impairment. In addition, subcomponents of executive functioning may be related to other quality of life outcomes in breast cancer survivors, such as mood and daily functioning. Based on the findings from this review, the following recommendations for the assessment of executive functioning in the breast cancer literature are suggested. With respect to study design, it is important to control for task repetition in longitudinal studies using control groups, as many neuropsychological tests are prone to practice effects. Consideration should be given to the specific subcomponent of executive functioning under investigation, which can facilitate the selection of appropriate tasks that specifically tap into those functions. Inclusion of tasks that assess at least two different subcomponents is recommended to study executive functioning, and it may also be beneficial to include tasks of varying complexity to determine whether increased cognitive load affects performance.

It is important to recognize that within the context of the unity and diversity framework (Miyake & Friedman, 2012), the cognitive components of executive functioning are dissociable and thus using a single measure of executive ability may not fully describe executive functioning. The use of multiple measures for each executive function which can be examined individually and as a composite may increase the reliability of the executive functioning construct. Composite measures also have an advantage of greater power to detect change (Crane et al., 2008). Given the issue of task impurity associated with many executive functioning measures, the use of multiple

measures allows for aggregation by statistical methods (e.g., latent variable analysis) to extract commonalities across tasks and provide a better measure of the intended process than any one task alone (Gibbons et al., 2012; Miyake et al., 2000). Working memory composites which used five to seven tests appear to be sensitive to detecting change in performance associated with chemotherapy treatment that did not emerge when assessed by any single test of working memory (Collins et al., 2009; 2014). Thus, it is recommended that at least two tasks are included for each subcomponent of executive functioning.

Finally, although neuroimaging findings were not the focus of this review, there is evidence of changes in white and gray matter integrity (de Ruiter et al., 2011) and altered frontal-subcortical activity, which may underlie poor executive functioning performance (Kesler et al., 2011). In particular, changes in task-related brain activation in women treated with chemotherapy were noted on set-shifting, planning/decision making, and working memory measures despite normal behavioural performance on these tasks (Kesler et al., 2011; McDonald et al., 2012). Given these data and discrepant findings of chemotherapy-related impairment using traditional measures of central tendency, alternative methods to examine executive functioning performance should be considered, including within-person variability in performance.

This review included a rigorous process to ensure collection of all relevant studies and did not exclude any studies on the grounds of low quality. Importantly, we evaluated studies in terms of methodological quality using an adaptation of predefined criteria (Pullens et al., 2010). Although our assignment of individual neuropsychological tests to areas of executive functioning was based on conventional distinctions in clinical

neuropsychology, there is no gold standard to classify individual tasks, as many executive functioning tasks overlap subcomponents.

In conclusion, this systematic review of the literature revealed that women treated with chemotherapy appear relatively less vulnerable to experiencing impairment on tasks measuring inhibition, whereas findings were mixed for the other subcomponents of set-shifting, working memory, and planning/decision making. Findings from planning/decision making were based on a small number of studies, thus replications using these tasks are needed. Future directions for examining subcomponents of executive functioning might include clearly defining the executive process under investigation and selecting appropriate tasks and indices to better characterize the nature of executive dysfunction.

Summary

In Chapter 2, recommendations were formulated based on the results of the systematic review for studying executive functioning in women with breast cancer. In keeping with the above recommendations, a computerized Stroop task was selected to examine IIV in women diagnosed with breast cancer before (Chapter 3) and after (Chapter 4) chemotherapy. Although inhibition was the subcomponent of executive functioning that appeared to be the least sensitive to chemotherapy, a closer examination using IIV derived from a computerized version of the Stroop task was hypothesized to yield additional performance information. Specifically, the Stroop task consists of two conditions of varying complexity, which allows examination of the effects of increased cognitive load on performance.

In Chapter 3, IIV in women diagnosed with breast cancer is examined in accordance with recommendations from the systematic review to include other potentially sensitive measures to complement mean performance level. Because IIV is posited to reflect lapses in attention and executive control failures (Bunce et al., 1993; West et al., 2002), IIV across the entire RT distribution is examined (e.g., all trials, fastest trials, slowest trials). The relative sensitivity of IIV in distinguishing patients with breast cancer from healthy controls compared to mean performance indicators is also examined.

Chapter 3: Pretreatment Differences in Intraindividual Variability in Reaction Time between Women Diagnosed with Breast Cancer and Healthy Controls

Publication Status

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Abstract

Chemotherapy has adverse effects on cognitive performance in women treated for breast cancer, but less is known about the period before chemotherapy. Studies have focused on mean level of performance, yet there is increasing recognition that variability in performance within an individual is also an important behavioral indicator of cognitive functioning and underlying neural integrity. Intraindividual variability (IIV) was examined prior to chemotherapy and surgery in women diagnosed with breast cancer ($n = 31$), and a healthy control group matched on age and education ($n = 25$). IIV was calculated across trials of a computerized Stroop task, including an examination of the slowest and fastest trials of reaction time (RT) responses. The groups were equivalent on overall accuracy and speed, and participants in both groups were less accurate and slower on incongruent trials compared with congruent trials. However, women with breast cancer became more variable with increased task difficulty relative to healthy controls. Among the slowest RT responses, women with breast cancer were significantly more

variable than healthy controls on incongruent trials. This suggests that a specific variability-producing process (e.g., attentional lapses) occurs in task conditions that require executive control (e.g., incongruent trials). Results are consistent with other evidence of executive dysfunction among women treated for breast cancer. These findings highlight the importance of pretreatment assessment and show that variability in performance provides information about cognition that measures of central tendency do not.

Introduction

An accumulating body of research demonstrates that chemotherapy has adverse effects on cognitive performance in women treated for early breast cancer. Less is known about cognitive functioning in the period prior to chemotherapy. Findings from prospective longitudinal studies indicate that a subset of women (approximately 20 to 30%) diagnosed with breast cancer demonstrate cognitive impairment after surgery and prior to chemotherapy on neuropsychological tests (Bender et al., 2006; Hermelink et al., 2007; Jansen et al., 2011; Quesnel et al., 2009; Wefel et al., 2010). Hermelink et al. (2007) assessed women diagnosed with breast cancer before both surgery and chemotherapy, and reported that 27% of the sample ($n = 101$) performed poorer than expected compared with published normative data for neuropsychological tests. This suggests that impairments can be observed prior to any therapy, such as surgery and/or exposure to general anesthesia and chemotherapy. Additionally, pretreatment cognitive performance was not associated with depression, anxiety, or fatigue (Bender et al., 2006; Hermelink et al., 2007), and impairment persists after statistically controlling for these factors (Jansen et al., 2011). Recent evidence suggests that other influences including

tumor-related factors and comorbidities (Mandelblatt et al., 2014), as well as post-traumatic stress symptoms (Hermelink et al., 2015) may be related to cognitive impairment before any adjuvant treatment. These findings suggest that pretreatment impairment may be attributed to a number of factors, such as adverse biological response to the cancer itself (e.g., cytokine activity), stress response to having a cancer diagnosis (e.g., “battle brain” rather than chemobrain), or pre-existing cognitive vulnerability.

Functional MRI (fMRI) studies of brain activity when engaged in tasks of working memory and response inhibition reveal differences between women who were in the period between breast cancer surgery and chemotherapy and healthy controls (Cimprich et al., 2010; McDonald et al., 2012; Scherling, Collins, MacKenzie, Bielajew, & Smith, 2011; 2012). Notably, although task performance was equivalent between patients and controls, the patients showed increased activation in the frontal cortex relative to controls, (McDonald et al., 2012; Scherling et al., 2012). Thus, neural activity as revealed by fMRI does not necessarily correspond to behavioral task performance. Greater cortical activation observed in patients may represent compensatory processes for neural dysfunction necessary to achieve performance that is comparable to healthy controls. Overall, these studies highlight the importance of characterizing pretreatment cognition in women with breast cancer, and indicate that examination of task performance does not provide a complete understanding of underlying neural dysfunction.

There is increasing recognition that within-person variability in performance is an important behavioral indicator of cognitive function and underlying central nervous system integrity. Intraindividual variability (IIV) reflects fluctuations in task performance

that occur over short periods of time (Hultsch et al., 2008; Nesselroade, 1991). Numerous studies demonstrate that increased IIV in reaction time (RT) is associated with other behavioral and functional indices including lower general intellectual level (Jensen, 1992; Rabbitt et al., 2001; Strauss et al., 2002), poorer functional capacity in instrumental activities of daily living (Burton, Strauss, Hultsch, & Hunter, 2009), and closer proximity to death (MacDonald, Hultsch, & Dixon, 2008a). Increased IIV in RT also represents a risk factor for declines in cognitive status, including mild cognitive impairment and dementia (e.g., Dixon et al., 2007; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Murtha, Cismaru, Waechter, & Chertkow, 2002). Furthermore, studies demonstrate a relationship between IIV and severity of neurological dysfunction, such that greater variability is associated with increasing severity of dementia (Murtha et al., 2002), and multiple areas of impairment in people with mild cognitive impairment (Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007). In contrast, individuals with diseases that are not typically linked with neurological symptoms such as arthritis do not show increased IIV compared to healthy controls (Hultsch et al., 2000; Strauss et al., 2002). The link between IIV and neurological function is relevant for women diagnosed with breast cancer given the alterations observed in fMRI studies, which may underlie cognitive symptoms. In addition, greater IIV in RT may indicate presence of frontal lobe pathology (Stuss et al., 2003), a finding that is relevant to the study of women with breast cancer as the frontal cortex appears particularly susceptible to the effects of breast cancer and its treatments (for a review see: Anderson-Hanley et al., 2003; 2003).

IIV was evaluated as a potentially useful marker of cognitive dysfunction in women treated for breast cancer (Bernstein et al., 2014). Women with breast cancer

treated with chemotherapy and healthy controls were assessed on a simple sustained Go-No Go attention task, and found group differences under certain conditions. Women with breast cancer were more variable than controls at short interstimulus intervals and less variable at longer intervals, suggesting greater sensitivity to stimulus presentation rate. IIV in that study was conceptualized using the coefficient of variation (CoV), which accounts for mean group differences but does not account for potential confounds of age or practice on RT. That study provided proof of concept that examination of IIV in women diagnosed with breast cancer might be informative for characterizing cognitive dysfunction.

Based on evidence that inhibitory control in women treated for cancer differs from healthy controls (Bernstein et al., 2014), as well as fMRI findings reviewed above of increased pretreatment activation in the frontal cortex, I hypothesized that pretreatment fluctuations in inhibitory control in women diagnosed with breast cancer might be expected. Inhibitory control as required in the Stroop task is thought to result from attentional/executive control processes that maintain the goals of a task across time and control competing pathways, and rely on the prefrontal cortex. Decreased efficiency of these processes have been associated with increased IIV, which may be a behavioural manifestation of more frequent attentional lapses (Bunce, Warr, & Cochrane, 1993) or fluctuations in executive control (Bunce et al., 1993; West et al., 2002) that result in lapses of intention (Heilman & Watson, 2012). The Stroop task has been shown to be sensitive in distinguishing between normative and pathological aging (Duchek et al., 2009) and has task conditions that place varying demands on attentional/executive control processes.

The primary goal of the present study was to examine IIV in women with breast cancer before chemotherapy or surgical intervention. A secondary aim was to explore possible mechanisms underlying IIV by examining its relationship to demographic, clinical and self-report variables.

Method

This study is part of an on-going longitudinal investigation of women with breast cancer conducted at Princess Margaret Cancer Centre in Toronto, Canada. Only those aspects of the method that are relevant to the current study are detailed here.

Participants

Participants included women with newly diagnosed breast cancer scheduled to be treated with neoadjuvant chemotherapy prior to surgery, most of whom had locally advanced breast cancer ($n = 31$). A group of healthy women ($n = 25$) matched on age and education also participated in the study. All participants were between the ages of 25 and 65 and fluent in English. Exclusion criteria included impaired color vision, health conditions known to be associated with elevated serum levels of cytokines or other inflammatory markers (e.g., cardiovascular disease, diabetes, autoimmune systemic disease), previous history of other cancer, chemotherapy, psychiatric or neurological conditions known to be associated with cognitive deficits (e.g., schizophrenia, dementia, stroke), significant history of substance abuse, or current use of psychotropic medication.

Women attending medical oncology clinics (prior to any cancer treatment) were screened for possible inclusion in the study by a clinical trials coordinator. Potentially eligible candidates were introduced to the study by their oncologist. If their eligibility was confirmed and they gave written informed consent, demographic information was

collected first, and then participants completed the objective measures followed by the self-report measures described below. Women were compensated \$25/hour for their time and/or transportation costs for each study visit. This study was approved by the University Health Network Research Ethics Board.

Measures

Stroop RT task. This task was presented using E-Prime 1.2 software (Psychology Software Tools, 2006) on a laptop computer. An external Serial Response Box (Psychology Software Tools) was configured with four buttons representing red, blue, green, and yellow from left to right and allowed one millisecond accurate RT recording. The task was administered individually in a hospital testing room. A single word was displayed on the computer screen in one of the four colors (red, blue, green, or yellow) against a black background in each trial. Participants responded as quickly and accurately as possible by pressing the key on the external response box that corresponded to the color of the word. Stroop task instructions are presented in Appendix A.

The task included three phases: color-to-key acquisition, practice, and test phases. Each block began with a message instructing the participant to press any button to begin the block of trials. The word appeared after a 1-second delay and remained on the screen until a response was made. The color-to-key acquisition phase was designed to establish strong mapping between stimulus color and the corresponding response keys. Each of the four colors was presented 10 times in random order in the form of “XXXX” in a single block of 40 trials. The practice and test phases consisted of both congruent and incongruent trials. On congruent trials, the words were written in the color corresponding to the meaning of the word (e.g., “RED” written in red). On incongruent trials, the words

were displayed in a color that did not match the meaning (e.g., “BLUE” written in red). Practice trials were presented in one block of 24 trials, and test trials were presented in four blocks of 96 trials with 48 congruent trials and 48 incongruent trials randomly intermixed in each block. Between blocks of trials, participants could take a break before initiating the next block of trials by pressing any response button. Response times were recorded as the time between the onset of the stimulus on the screen and the response recorded by the computer. The dependent measures were accuracy and reaction time responses calculated separately for congruent and incongruent test trials.

Self-reported measures. To investigate other potential pretreatment differences, participants completed self-report questionnaires evaluating mood, fatigue, and cognitive symptoms.

Mood. The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-reported measure designed to assess depression and anxiety symptoms in patients with medical conditions (Zigmond & Snaith, 1983), and has been shown to be valid and reliable for use in people with cancer (Moorey et al., 1991). It contains two 7-item subscales assessing frequency of depression and anxiety over the previous week. Higher scores indicate more distress (maximum score for each scale is 21). HADS questionnaire is presented in Appendix B.

Fatigue. The Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) is a validated 13-item measure of fatigue in cancer patients (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). Participants rate the frequency of fatigue-related symptoms (five items) or activity-related consequences of fatigue (eight items) over the past week on a 5-point scale. Eleven of the items are negatively worded (e.g., “I feel

weak all over”). The two positively worded items (e.g., “I have energy”) are reverse scored. Higher scores reflect more fatigue. FACIT-F questionnaire is presented in Appendix C.

Cognitive function. The Functional Assessment of Cancer Therapy Cognitive Scale – Version 3 (FACT-Cog 3) is a 37-item measure designed to evaluate self-reported cognitive impairment in cancer patients (Wagner, Sweet, Butt, Lai, & Cella, 2009). The FACT-Cog 3 assesses cognitive impairment (20 items), comments from others (4 items), cognitive ability (9 items), and impact on quality of life (4 items). Participants rate the frequency with which each statement has occurred over the past week on a 5-point scale. Positively worded items were reverse scored so that higher total scores reflect more cognitive problems. FACT-Cog 3 is presented in Appendix D.

Data Preparation

RT data were prepared prior to calculation of IIV measures to be consistent with previous approaches (Hultsch et al., 2000; 2008). Significant group differences in mean level of performance are often positively associated with differences in SD values. Thus, IIV may be large in women with breast cancer because their mean RT is larger than healthy controls. In addition, systematic changes across trials may also be present (e.g., practice, learning effects). Therefore, it is recommended that these systematic effects be removed from RT data prior to calculating measures of IIV (Hultsch et al., 2000; 2002). The distribution of raw latency scores was first examined at the level of individual trials. Outliers with extremely slow or fast responses that might reflect error (e.g., accidental key press, task interruption) were excluded. A lower bound for valid responses was set at 150 ms based on minimal RTs suggested by prior research on four-choice RT measures

(Strauss et al., 2007). An initial upper bound was determined based on examination of frequencies of RTs (i.e., 4,000 ms), and extreme outliers were excluded relative to the rest of the sample. A subsequent upper bound was based on computing the mean and standard deviation separately for each group and task condition (congruent and incongruent) and dropping any trials exceeding the mean by three or more standard deviations. The percentage of trials excluded across the entire Persons by Trials data matrix was 2.04%. The procedure of excluding outlying data points represents a conservative approach to examining IIV as this method underestimates variability somewhat.

Intraindividual standard deviation (ISD) scores. IIV was indexed by computing the ISD scores across correct response latency trials of congruent and incongruent conditions of the Stroop task (Hultsch et al., 2000; 2008). To control for age and group as well as systematic changes associated with practice, a regression procedure was used to adapt the RT data prior to calculating ISDs. Using a Person by Trial matrix, data were corrected for the effects of age, group, trial and their higher order interactions to yield adjusted residual scores:

$$y = a + (age)b + (group)c + (trial)d + (age \times group)e + (age \times trial)f + (group \times trial)g + (age \times group \times trial)h + e$$

This process (Hultsch et al., 2000; 2008) yields scores that can be subsequently converted to T-scores to facilitate interpretation. Larger scores indicate relatively uneven performance across trials, whereas smaller ISD scores reflect a more consistent performance.

Slowest/fastest ISD scores. Adapting methodology from the literature on age-related differences in RT distributions (Hultsch et al., 2002; Salthouse, 1993), further analyses were conducted to differentiate variability within the slowest RT trials from all responses. If increased IIV in RT reflects attentional lapses resulting from reduced attention/executive efficiency, then long RTs and a positive skew in the RT distribution should be observed. Thus, group differences should occur only in the slowest RT trials and even after controlling for variability in the fast trials. ISDs corrected for effects of age, group, and trial were calculated for the trials that fell within the 20th (slowest) and 80th (fastest) percentile of the RT distribution.

Statistical Analyses

RT data preparation was performed with IBM SPSS Statistics 22.0. All subsequent statistical analyses used SAS 9.4. Independent samples *t*-tests and Fisher's exact tests were used to assess differences between groups at baseline. To assess interactions of task condition and group, separate mixed effects model analyses were computed for each Stroop performance variable (i.e., accuracy, mean RT and ISD for all, fast, and slow trials). Alpha levels of $p < .05$ were set as the threshold to indicate statistical significance. A final set of analyses used Pearson correlations to compare Stroop performance variables, self-report measures, demographic (i.e., age and education), and clinical characteristics (i.e., days since diagnosis). To account for multiple comparisons, a threshold of $p < .001$ was used for the resulting correlations.

Results

Participant Characteristics

Table 5 summarizes demographic, clinical, and self-report characteristics of women with breast cancer and healthy controls. Total HADS scores and HADS Anxiety subscale scores were higher for women with breast cancer ($ps < .01$). More women with breast cancer expressed clinically significant levels of anxiety (i.e., score > 7) compared to controls (see Table 1). There were no significant differences in age, education, HADS Depression subscale, FACIT-Fatigue, or FACT-Cog 3 scores between groups.

Table 5. Participant Demographic, Clinical, and Self-report Characteristics

Variable	Patients ($n = 31$) <i>M (SD)</i>	Controls ($n = 25$) <i>M (SD)</i>	<i>p</i>
Age, years	46.1 (8.7)	46.1 (11.0)	.98
Education, years	15.3 (2.1)	15.8 (2.1)	.38
Breast cancer stage			
I	$n = 1$	—	—
II	$n = 5$	—	—
III	$n = 24$	—	—
IV	$n = 1$	—	—
Days since diagnosis	32.5 (23.9)	—	—
HADS Total	12.7 (7.4)	7.8 (6.5)	.01
HADS Depression subscale	4.2 (3.9)	2.6 (3.0)	.10
Normal	$n = 26$	$n = 22$.72 ^a
Mild	$n = 1$	$n = 2$	
Moderate	$n = 3$	$n = 1$	
Severe	$n = 1$	$n = 0$	
HADS Anxiety subscale	8.5 (4.8)	5.1 (3.9)	.007
Normal	$n = 13$	$n = 20$.01 ^a
Mild	$n = 7$	$n = 3$	
Moderate	$n = 8$	$n = 1$	
Severe	$n = 3$	$n = 1$	
FACIT – Fatigue	12.5 (9.8)	9.7 (8.7)	.26
FACT – Cog 3	40.2 (26.5) ^b	29.3 (17.7)	.08

Note. HADS=Hospital Anxiety and Depression Scale; FACT=Functional Assessment of Cancer Treatment; FACIT=Functional Assessment of Chronic Illness Therapy Fatigue.

^a Fisher exact test compared frequency of normal and clinically significant levels of affective distress.

^b $n = 30$ due to incompleteness of FACT- Cog 3.

Table 6. Participant Performance Variables on the Stroop Task

Variable	Stroop Congruent Trials			Stroop Incongruent Trials			Group-Task Condition Interaction		
	Patients (<i>n</i> =31)	Controls (<i>n</i> =25)	<i>p</i> ^a	Patients (<i>n</i> =31)	Controls (<i>n</i> =25)	<i>p</i> ^a	<i>F</i>	<i>p</i>	η^2
Accuracy ^b , %	99.28 (0.74)	98.96 (1.31)	.26	97.56 (2.04)	96.67 (3.84)	.30	.61	.44	.007
Mean RT ^b , <i>ms</i>	808.17 (171.14)	752.27 (107.89)	.14	966.31 (228.11)	885.03 (147.34)	.11	1.71	.20	.006
Mean RT – fastest, <i>ms</i>	574.62 (119.00)	535.53 (86.21)	.17	580.59 (132.93)	534.64 (87.85)	.13	1.43	.24	.03
Mean RT ^b – slowest, <i>ms</i>	1251.99 (263.09)	1172.75 (175.30)	.20	1333.27 (319.64)	1225.58 (190.16)	.12	2.83	.10	.02
ISD ^b	7.46 (1.99)	6.96 (1.36)	.29	9.78 (2.60)	8.87 (1.67)	.12	1.44	.24	.007
ISD - fastest	2.20 (0.84)	1.98 (0.53)	.24	2.23 (0.90)	2.03 (0.62)	.35	.02	.88	.00
ISD ^b - slowest	5.19 (1.52)	5.41 (1.34)	.58	8.16 (1.79)	7.03 (1.40)	.01	7.82	.007	.05

Note. Values in parentheses are standard deviations; RT=Reaction Time; ISD=Intraindividual Standard Deviation.

^a Paired *t* test *p*-value.

^b Significant main effect of task condition at *ps* < .001.

Stroop Mean Level Performance

Differences as a function of condition (congruent vs. incongruent) and group (women with breast cancer vs. healthy controls) were examined using 2 (group) by 2 (condition) mixed-model ANOVAs on accuracy and mean RT: all, fastest, and slowest trials (Table 6). Both breast cancer and healthy control groups performed at a very high level on the Stroop task (mean accuracy > 96%). There was a significant main effect of condition on accuracy and mean RT for all and slowest trials, such that participants were less accurate and slower on the incongruent trials compared to congruent trials. No significant group effects or group by condition interactions were observed on Stroop accuracy or mean RT scores.

Stroop IIV Performance

A mixed-model ANOVA revealed a significant interaction between groups and performance on congruent vs. incongruent trials of the Stroop task ($p < .01$; see Table 6). Independent samples t -tests showed that women with breast cancer were significantly more variable than healthy controls on the slowest trials in the incongruent condition ($p < .01$). Responses of women with breast cancer became more variable with increased task difficulty, whereas variability did not change as much with task difficulty in healthy controls. The interaction remained significant even after controlling for group differences in speed of performance (i.e., mean RT of the slowest trials), $F(1, 52) = 5.30, p = .03, \eta^2 = .03$. No significant interaction effects were observed between groups and performance on the fastest trials and across all trials.¹ Figure 2 displays RTs from the slow portion of the distribution for each participant with the incongruent condition. Using procedure

¹ Data analyses were performed on the final block of the Stroop task (i.e., last 96 trials), which served as a proxy for successful acquisition of key/color mapping and effort by the end of the task. The pattern of results for the last 96 trials was identical to results based on all trials.

recommended by Hultsch et al. (2002), a one-way analysis of covariance (ANCOVA) was conducted to examine group differences in the slowest trials in the incongruent condition while controlling for the effects of the fastest trials. The magnitude of the group effect observed in the uncontrolled analysis was retained, $F(1, 53) = 5.82, p = .01, \eta^2 = .09$.

Potential Covariates

Table 7 shows the correlations between demographic, clinical, self-report characteristics and select Stroop performance variables for all participants. Across all participants, FACT-Cog 3 scores were not significantly correlated with congruent or incongruent trials on accuracy, mean RT (all, fastest, and slowest trials), or ISD (all, fastest, and slowest trials), although they were significantly related to HADS Depression, HADS Anxiety, and FACIT-Fatigue scores ($ps < .001$). That is, women who reported a greater number of depressive, anxiety, and fatigue symptoms also reported more cognitive problems. Age was correlated with mean RT and accuracy; older women were slower across conditions but more accurate on congruent trials. Otherwise, education, days since diagnosis, HADS Anxiety, HADS Depression or FACIT-Fatigue scores were unrelated to Stroop performance.

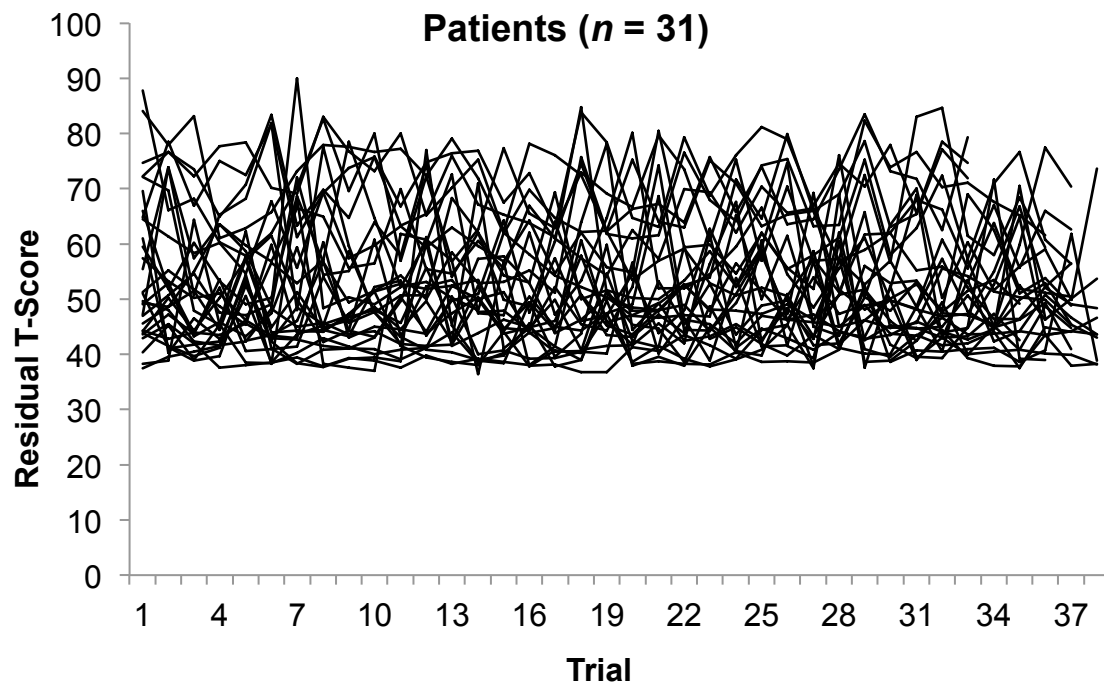
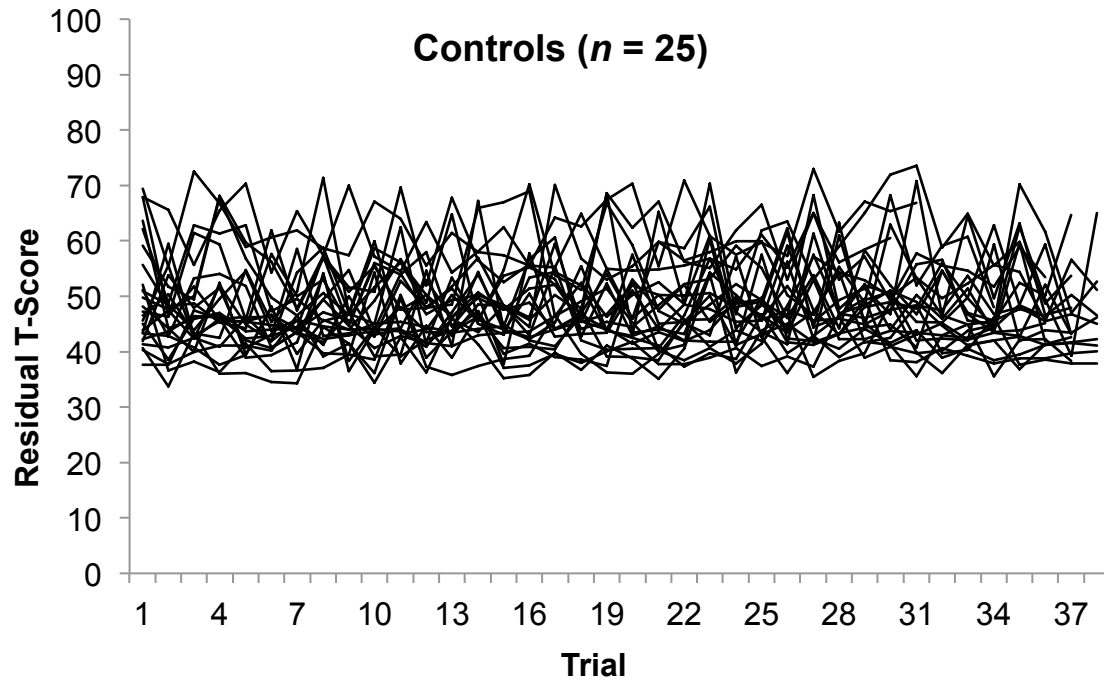


Figure 2. Stroop Residual T-Scores of the Slowest RT Responses across Incongruent Trial Items for Each Participant in Patient and Healthy Control Group

Table 7. Pearson Correlations of Demographic, Clinical, Self-Reported Measures, and Stroop Performance Variables For Patients and Controls (n = 56)

	Age	Education	Days Since Diagnosis ^a	FACT-Cog 3	HADS-A	HADS-D	FACIT-F	Accuracy (Con.)	Accuracy (Incon.)	Mean RT (Con.)	Mean RT (Incon.)	ISD-Slowest (Con.)	ISD-Slowest (Incon.)
Age	1.00												
Education	0.27	1.00											
Days Since Diagnosis ^a	-0.01	-0.30	1.00										
FACT-Cog 3	0.01	0.23	-0.25	1.00									
HADS-A	-0.15	0.23	-0.19	0.50*	1.00								
HADS-D	-0.08	0.09	-0.22	0.49*	0.59*	1.00							
FACIT-F	-0.25	0.11	-0.29	0.52*	0.43*	0.71*	1.00						
Accuracy (Con.)	0.44*	-0.05	-0.13	0.14	0.06	0.15	0.06	1.00					
Accuracy (Incon.)	0.05	0.22	0.08	-0.002	0.25	0.29	0.16	0.40*	1.00				
Mean RT (Con.)	0.43*	-0.29	-0.02	0.09	-0.07	0.006	-0.11	0.42*	-0.02	1.00			
Mean RT (Incon.)	0.42*	-0.23	-0.03	0.06	-0.11	-0.06	-0.12	0.44*	-0.10	0.95*	1.00		
ISD-slowest (Con.)	-0.08	0.03	-0.12	-0.03	-0.16	-0.07	0.06	0.01	0.05	-0.30	-0.32*	1.00	
ISD-slowest (Incon.)	-0.13	0.24	-0.12	0.23	0.11	0.02	0.17	-0.01	-0.06	0.20	0.20	0.28	1.00

Note. ^a Analyses performed on patient group only ($n = 31$); * $p < .001$; Con. = congruent condition; Incon. = incongruent condition; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; FACT=Functional Assessment of Cancer Treatment; HADS-A=Hospital Anxiety and Depression Scale-Anxiety Subscale; HADS-D=Hospital Anxiety and Depression Scale-Depression Subscale; ISD = intraindividual standard deviation.; RT = reaction time.

Discussion

The primary objective of this study was to examine IIV in RT on an inhibitory control task in women with breast cancer prior to any treatment. There were no differences between groups on overall accuracy, mean RT or variability; however, patients demonstrated greater variability in their performance compared to healthy controls as the difficulty of the task increased and greater executive control was required. Consistent with other studies that have examined IIV and various health and neurological conditions (Burton et al., 2006; de Frias et al., 2012; Fuentes, Hunter, Strauss, & Hultsch, 2001; Hultsch et al., 2000), our results suggest that IIV is more sensitive than a measure of central tendency (mean RT) for detecting differences in cognitive performance between patients and healthy controls. Specific to the breast cancer population, the current data are also in keeping with our prior study in which examination of IIV revealed that on a test of sustained attention requiring inhibitory control, patients had greater IIV at faster stimulus presentation rate, suggesting that they are more variable with increased cognitive load (Bernstein et al., 2014). Thus, IIV appears to provide an important behavioral measure of function even at pretreatment assessment.

Results show that group differences varied across the RT distribution, such that women with breast cancer were more variable in the slow portion of the RT distribution on incongruent trials of the task, but variability was equivalent between groups on the congruent trials and in the fast portion of the RT distribution. IIV appears to result from a specific variability-driving process, such as attentional lapses, present only at the slow end of the RT distribution under conditions that require increased inhibitory control. Our results are consistent with reports within the aging literature that demonstrate IIV in RT

changes across task conditions that require increased executive control. For example, performance variability is greater for older adults compared to younger adults under task conditions requiring active recruitment of executive processes (West et al., 2002), probably because decreased attentional resources associated with aging results in more fluctuations in executive control. These fluctuations produce longer RTs, increase the variability of an individual's performance, and lead to greater positive skew in the RT distribution of older adults. Such findings have been described as failures of attention or intention within the IIV and cognitive aging literature. Although attention and intention may be subserved by different neural networks (with greater involvement of the parietal lobes for attention and of the frontal lobes for intention), they nevertheless share reciprocal connections (Heilman & Watson, 2012) and are likely overlapping constructs. The findings obtained from the Stroop task used in this study primarily reflect lapses of attention, which resulted in higher IIV in the slowest trials in the incongruent trial for the breast cancer group despite highly accurate overall performance across all participants.

If IIV is a marker of neural integrity, then our results indicate that the biological or psychological response to breast cancer diagnosis may have adverse effects on brain function. Results show that women with breast cancer reported more anxiety compared to controls but anxiety was not related to mean RT or ISD measures. Hermelink et al. (2007; 2015) suggested that cognitive impairment seen prior to neoadjuvant treatment may be related to stress-response symptoms that do not necessarily coincide with symptoms of depression and/or anxiety. Persistent stress-response symptoms may have adverse effects on neurological functioning and behavior in high cognitive-demand circumstances. The finding of differences between patients and controls prior to treatment is important to

better understand the long-term cognitive impairment associated with breast cancer and its treatment; any pretreatment deficits may be compounded by the neurotoxic effects of chemotherapy.

The source of performance variability has been attributed to both neurobiological (e.g., disruptions or damage to neural networks) and behavioral (e.g., fluctuations in affective state) factors (Montgomery, 1995). Previous research suggests that affective influences are more likely to impact IIV that is measured across longer time periods (e.g., hours, days or weeks). In contrast, changes in neural integrity are more likely to affect IIV that is measured over shorter intervals, such as the present trial-to-trial RT data (Hultsch et al., 2000; Strauss et al., 2002). Given the substantial psychological distress associated with breast cancer diagnosis and treatment, IIV may also be a useful measure in that it is primarily sensitive to neurological changes rather than affective states.

A methodological strength of this study is the computation of IIV that controls for the systematic effects of age, group, and practice that could impact mean RT. In addition, the slowest and fastest RT responses were examined to address potential variability-driving mechanisms. Another strength of this study is recruitment of women with breast cancer who were scheduled to undergo neoadjuvant chemotherapy followed by surgical treatment, which provided an opportunity to examine pretreatment cognitive performance. In contrast, most studies of breast cancer patients prior to chemotherapy are conducted after surgery (e.g., mastectomy, lumpectomy; Cimprich et al., 2010; McDonald et al., 2012; Scherling et al., 2011; 2012).

Limitations of our study include an inability to rule out pre-existing cognitive vulnerabilities that might contribute to pretreatment group differences (e.g., stress

response). Secondly, the standardized effects were small and in the range of $\eta^2 = .03$ to $.09$, although they are comparable to those reported in other studies examining executive function in comparison to controls (see: Anderson-Hanley et al., 2003; 2003; Ono et al., 2015). Statistical power was low in this study due to a relatively small sample size and small effects, which may explain there was no group effect in IIV across all trials or no influence of potential covariates (e.g., age, education, days since diagnosis, other self-report indices). However, there was sufficient power to detect IIV differences at the group level in the slowest RT responses, consistent with *a priori* hypotheses. The present study is also limited by the examination of a single measure of intraindividual variability. Although performance on the congruent condition of the Stroop task was contrasted with the incongruent condition, the inclusion of tasks assessing other domains (e.g., semantic or lexical decision) would strengthen the view that executive functioning is selectively impaired in women newly diagnosed with breast cancer. Lastly, although our patients and controls were equivalent in education level, both groups were composed of well-educated women, which limit the generalizability of the results to populations with a fuller range of educational attainment.

In future studies, it will be important to replicate these findings in a larger and more diverse sample. It will also be important to examine IIV and change in cognitive function following adjuvant treatments, which will be examined in the following chapter. Additional task manipulations to investigate other aspects of executive function (e.g., working memory, task switching) would be useful in providing additional information on the nature of cognitive impairment. An important question is whether pretreatment IIV can predict cognitive functioning after breast cancer treatment. Such information might

help identify those at risk and inform treatment options for those individuals. Further elucidation of the mechanisms that drive differences in IIV should be examined as well. If differences in IIV are due to a persistent stress-based response, then the inclusion of objective measures of stress (e.g., basal cortisol levels, cortisol reactivity to stress) will contribute to better understanding of pretreatment cognitive impairment. Additionally, if pretreatment cognitive impairment results from a biological response to the cancer itself, then examining associations to cancer stage would be important, which was not possible to examine because of homogeneity in the sample.

The present study provides evidence that untreated women with breast cancer have greater IIV when performing cognitive tasks that require inhibitory control than do healthy controls. In particular, conditions demanding increased load on the executive system produced greater variability in patients than healthy controls, even after controlling for affective distress. Our results highlight the importance of examining IIV in addition to measures of central tendency to better understand the subtle nature of cognitive impairment in women with breast cancer. It would be worth exploring if IIV is a reliable indicator of cognitive change due to breast cancer and its treatments in other tasks. If it is, then this measure of variability holds promise as a predictor of cognitive change. Furthermore, the results have methodological implications for the design and analysis of future studies, namely to include pretreatment assessment, tasks that vary in executive control demands, measures of variability, and larger and more diverse patient populations.

Summary

Chapter 3 provided evidence that untreated women with breast cancer have greater IIV when performing cognitive tasks that require inhibitory control than do healthy controls. In particular, conditions demanding increased load on the executive system produced greater variability in patients than healthy controls, even after controlling for factors such as practice, learning effects, and group-level differences in mean performance. IIV in performance was not related to age, education, days since diagnosis, self-reported cognitive symptoms, or affective distress. Furthermore, IIV revealed differences between women with breast cancer and healthy controls that mean performance level measures did not.

Thus far, evidence suggests that IIV is an important indicator of cognitive function. Because many cognitive symptoms in women with breast cancer have been attributed to the effects of chemotherapy, the following chapter examines IIV in Stroop performance by observing the same cohort of women after neoadjuvant chemotherapy. Additional analyses examine changes in self-reported cognition across two self-report questionnaires and their relationship to change in objective Stroop performance.

Chapter 4: Intraindividual Variability in Reaction Time Before and After Neoadjuvant Chemotherapy in Women Diagnosed with Breast Cancer

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Abstract

Women treated with chemotherapy for breast cancer experience subtle cognitive deficits. Research has focused on mean performance level, yet recent work suggests that within-person variability in reaction time (RT) performance may underlie cognitive symptoms. We examined intraindividual variability (IIV) in women diagnosed with breast cancer and treated with neoadjuvant chemotherapy. Women with breast cancer ($n = 28$) were assessed at baseline before neoadjuvant chemotherapy (T1), approximately 1 month after chemotherapy but prior to surgery (T2), and after surgery about 9 months post chemotherapy (T3). Healthy women of similar age and education ($n = 20$) were assessed at comparable time intervals. Using standardized regression-based approach, we examined changes in mean performance level and IIV on a Stroop task and self-report measures of cognitive function from T1 to T2 and T1 to T3. At T1, women with breast cancer were more variable than controls as task complexity increased. Change scores from T1 to T2 were similar between groups on all Stroop performance measures. From T1 to T3, healthy controls improved more than women with breast cancer. IIV was more sensitive than mean RT in capturing group differences. Additional analyses showed

increased cognitive symptoms reported by women with breast cancer from T1 to T3. Specifically, change in language symptoms was positively correlated with change in variability. Women with breast cancer have declines in attention and inhibitory control relative to pretreatment performance. Future studies should include measures of variability, as they are an important, sensitive indicator of change in cognitive function.

Introduction

The previous study demonstrated pretreatment differences of greater IIV in women diagnosed with breast cancer compared to healthy controls as task difficulty increased and attentional control was required. These results show that IIV is a sensitive marker of pre-existing differences between women with breast cancer and healthy individuals. It is important to understand whether there are changes in variability following breast cancer treatment, as women treated with chemotherapy commonly report cognitive difficulties (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Pullens et al., 2010).

Cancer-related cognitive impairment is multifaceted and can be influenced by factors such as the disease itself, stress and mood disturbances, and other adjuvant therapies. Prospective longitudinal studies reveal that a proportion of women diagnosed with breast cancer may demonstrate impaired neuropsychological test performance before receiving chemotherapy (Hermelink et al., 2007; Jansen et al., 2011). Most longitudinal studies show that cognitive deficits emerge during (Collins, MacKenzie, Tasca, Scherling, & Smith, 2013b) and immediately following chemotherapy (Brezden et al., 2000; Hermelink, 2010; Stewart et al., 2008; Tchen et al., 2003) and tend to resolve over time (Collins et al., 2014; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a),

although some indicate persistent, progressive, or delayed onset of deficits one year post chemotherapy (Collins et al., 2014; Wefel et al., 2010). In general, effects obtained from longitudinal studies when pretreatment level of performance is accounted for are weaker than those reported in cross-sectional studies, which underscores the subtlety of changes in cognition associated with breast cancer and its treatments (Bender et al., 2006; Shilling et al., 2005; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004a).

Research in neuropsychological assessment has traditionally overlooked within-person variability in performance. Instead, cognitive abilities are typically measured by mean performance level and treated as trait-like dimensions of individual functioning. However, intraindividual variability (IIV) or trial-to-trial fluctuations in reaction time (RT) tasks are of sufficient magnitude to be theoretically and practically important (Eizenman, Nesselroade, Featherman, & Rowe, 1997; Hultsch et al., 2000; Strauss et al., 2002). For example, higher levels of IIV have been associated with age-related decline and poorer performance across multiple cognitive domains (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010a; 2010b; MacDonald et al., 2003). Moreover, IIV offers predictive utility for cognitive status in older adults (de Frias et al., 2012; Dixon et al., 2007; Hultsch et al., 2000).

IIV appears to be useful in the detection of subtle cognitive deficits associated with breast cancer and its treatment. For example, breast cancer survivors treated with chemotherapy 1 year earlier were more variable compared with healthy controls under specific task conditions on a measure of simple sustained attention involving short inter-stimulus intervals (Bernstein et al., 2014). Increased IIV has been attributed to more frequent attentional lapses (Bunce et al., 1993) or fluctuations in cognitive control (West

et al., 2002). Thus, the elevated IIV observed among women treated for breast cancer may reflect disruptions in allocation of attention or cognitive control.

The current study was designed to examine IIV and mean performance level on the same Stroop RT task longitudinally in women newly diagnosed with breast cancer and in healthy controls. Our primary aim was to determine if performance on those measures differs over time between groups. A secondary aim was to examine self-reported cognitive function at the same time points in relation to objective measures of cognition.

Methods

Participants

The same sample of women diagnosed with breast cancer and scheduled to receive neoadjuvant chemotherapy and healthy controls were followed after pretreatment assessment. We recruited 28 women with breast cancer and 20 healthy controls to the study. Attrition rates ranged from 4-12% and did not differ between patient and control group ($p = .31$). One patient died and three controls did not continue in the study.² Table 8 presents demographic and clinical characteristics of each group. Age and education were equivalent across groups.

For a full description of the participants including exclusion criteria, see Chapter 3 Methods section.

² A technical problem with the Serial Response Box resulted in missing data from two patients and two controls not attributable to participant drop out. To maximize the number of participants included in the analyses, those who missed a single assessment due to problems with task apparatus were included in the study. The pattern of results did not differ between women who missed one assessment and those who completed all three assessments.

Table 8. Demographic and Clinical Characteristics of Patient and Control Groups

Characteristic	Patients (<i>n</i> = 28)	Controls (<i>n</i> = 20)	<i>p</i>	<i>d</i>
Age at baseline, <i>years</i>	45.3 (8.5)	45.7 (11.3)	.90	.04
Education, <i>years</i>	15.4 (2.2)	15.6 (2.3)	.75	.09
Stage of disease				
I	<i>n</i> = 1			
II	<i>n</i> = 5			
III	<i>n</i> = 21			
IV	<i>n</i> = 1			
Type of Chemotherapy				
AC-P	<i>n</i> = 4			
FEC	<i>n</i> = 20			
AC-D/T	<i>n</i> = 1			
TCH	<i>n</i> = 1			
Docetaxel	<i>n</i> = 1			
Unknown	<i>n</i> = 1			
	T2	T3		
No. of patients who had started on hormone therapy prior to T2 or T3 assessment	0 (0%)	19 (76%)		

Note. Values in parentheses are standard deviations.

AC-P = Doxorubicin, cyclophosphamide, paclitaxel; FEC-D = Fluorouracil, epirubicin, cyclophosphamide, docetaxel, trastuzumab; AC-D/T = Doxorubicin, cyclophosphamide, docetaxel; TCH = Docetaxel, carboplatin, trastuzumab; T2 = Time 2; T3 = Time 3.

Procedure

All participants completed a baseline assessment, which included a computerized RT Stroop task and self-report questionnaires to assess symptoms of depression, anxiety, fatigue, and cognitive dysfunction. Baseline (T1) was completed before surgery and chemotherapy for women diagnosed with breast cancer. Further assessment was undertaken approximately 1 month after chemotherapy but prior to surgery (T2), and again after surgery and 9 months post chemotherapy (T3). The healthy control group was also tested three times at comparable intervals.

Measures

RT task. The same Stroop RT task used in the previous study was also employed here (see Chapter 3 Methods for a full description of the task).

Self-report measures. Participants completed the same self-report questionnaires evaluating mood, fatigue, and cognitive symptoms as previously reported in Chapter 3 (see Methods section details). In addition to the FACT-Cog 3, participants completed an additional measure of self-reported cognition. The Patient's Assessment of Own Functioning Inventory (PAOFI) includes 33 items which measure cognitive functions in everyday life (Chelune, Heaton, & Lehman, 1986), and has been found to be useful in identifying domain-specific cognitive symptoms in women with breast cancer (Bender et al., 2006; Ganz et al., 2013). The inventory consists of four subscales: memory (10 items), language and communication (9 items), sensorimotor skills (5 items), and higher-level cognition (9 items). Each item response was given on a 6-point scale. Subscale scores and a total summed score were calculated, with higher scores indicating greater everyday cognitive difficulties. To examine clinical significance, participants were categorized as having "high complaints" if their score was > 1 SD above the mean of the healthy controls (Ganz et al., 2013). PAOFI questionnaire is presented in Appendix E. A decrease of 10.6 points in the total FACT-Cog 3 score is considered clinically significant change (Cheung et al., 2014).

RT Data Preparation

An established procedure (Hultsch et al., 2000; 2008) was used to prepare the RT data prior to calculation of variability measures described previously in Chapter 3. IIV was indexed by computing the intraindividual standard deviation (ISD) scores across

correct response latency trials of congruent and incongruent conditions, which was also described in the previous study. To summarize, ISD scores were calculated for each task condition (congruent and incongruent) across (a) all RT trials and (b) the fastest and slowest RT trials (within the 20th and 80th percentile of the RT distribution), which were then converted to T-scores to facilitate interpretation. The examination of the fastest and slowest RT trials provides information about the source of variability.

Statistical Analyses

A planned sample size of 31 patients and 31 controls was selected to provide 80% power (Type I error of 5% and two-sided tests) to detect medium effect sizes based on previous studies (Anderson-Hanley et al., 2003). It was estimated that 26 patients and 26 controls would be available for assessment at 1-year follow-up based on retention rates reported in other studies (Collins et al., 2009; Jenkins et al., 2006).

To assess individual change in Stroop performance (e.g., accuracy, mean RT and IIV) and self-reported cognition (e.g., PAOFI, FACT-Cog 3) across the two assessment intervals (T1-T2 and T1-T3), we used a standardized regression-based (SRB) approach, which has been employed in other longitudinal neurocognitive studies in cancer populations (Collins et al., 2009; Stewart et al., 2008). This approach, recommended for the study of cancer-related cognitive change (Duff, 2012; Ouimet, Stewart, Collins, Schindler, & Bielajew, 2009), has several advantages, including accounting for factors that may affect outcomes, such as demographic and mood-related variables and regression to the mean (Sawrie, Marson, Boothe, & Harrell, 1999). Using SRB methodology on both Stroop and self-report measures of cognitive function provides a common metric to facilitate comparison across assessment tools (Martin, Griffith,

Sawrie, Knowlton, & Faught, 2006; McSweeney, Naugle, Chelune, & Lüders, 1993).

Candidate variables including age and education, as well as *change* in HADS Depression and Anxiety scores and *change* in FACIT-F scores were included in the model in a stepwise fashion using $p = .05$ as the criterion for entrance and $p = .10$ as criterion for removal. Data from the control group were used to construct the regression equation predicting retest scores (i.e., T2 or T3) from baseline (T1) scores. SRB change scores for each participant were computed by subtracting the predicted from the observed retest score on each measure and dividing by the standard error of the estimate in the control group. These change scores represent the extent to which the observed change on each measure deviated from that expected on the basis of practice and measurement error alone.

Independent sample *t*-tests were used to assess group differences in baseline and change scores across T1-T2 and T1-T3. Mixed ANOVAS were also used to test the interactions between task condition and group on Stroop performance variables. To increase comparability between the current study and previous research, classification of women who declined or did not decline (remained stable or improved) was calculated such that any SRB change score exceeding ± 1.96 represented statistically significant change. Pearson correlations measured the associations between change in Stroop performance measures and change in self-report cognitive measures. Because of the multiple planned analyses, the statistical significance cutoff was set a priori at $p < .01$ for all analyses.

Results

Participant Characteristics

Means and standard deviations of Stroop performance and self-report measures at each of the three assessments are presented in Table 9. Analysis of the baseline (T1) data showed that patients were more variable in the incongruent condition of the slowest RT trials compared to controls, $t(46) = -2.92, p < .01, d = 0.88$. Patients tended to report more anxiety, $t(46) = -2.13, p = .04, d = 0.64$. Groups did not significantly differ in other baseline Stroop performance variables (i.e., accuracy on congruent and incongruent trials, mean RT, ISD scores), self-reported cognition (i.e., PAOFI and FACT-Cog 3), or symptoms of depression or fatigue.

Stroop RT Task

The percentage of RT trials excluded was small; T1 = 2.0%; T2 = 1.5%; T3 = 1.4%. Groups showed similar changes from T1-T2 accuracy, mean reaction time, and ISD for both congruent and incongruent conditions (Table 10).³ There were no significant group by task condition interactions involving T1-T2 change scores. From T1 to T3, there were significant group effects in ISD change scores for both congruent and incongruent task conditions; patients did not improve as much as controls did at T3 (Table 10).⁴ Analysis of change scores of the fastest and slowest RT trials revealed a relative decline in patients compared to controls on the slowest trials indexed by ISD and mean RT (congruent task condition only). T1-T3 change was otherwise similar between

³ Age predicted T2 test scores on congruent and incongruent IIV of the fastest trials ($ps = .01$). Change in depression symptoms predicted T2 scores on PAOFI Memory ($p = .03$), PAOFI Higher Level Cognition ($p = .003$), and FACT-Cog Total ($p = .02$).

⁴ Age predicted T3 scores on incongruent accuracy and congruent ISD of the slowest trials ($ps = .02$). Change in depression symptoms predicted T3 scores on: PAOFI Sensorimotor ($p = .002$), PAOFI Higher Level Cognition ($p = .05$), PAOFI Total ($p = .02$), and FACT-Cog Total ($p < .001$).

groups on accuracy and mean RT across all trials. There were no significant group by task condition interactions.⁵

Self-Report Cognition

Change scores from T1 to T2 on the PAOFI did not significantly differ between patients relative to controls (Tables 10 and 11). Patients reported significantly more cognitive symptoms at T3 than T1 on the PAOFI Sensorimotor subscale and total score, but did not significantly differ on the other PAOFI subscales. On the FACT-Cog 3, there were no significant group differences in change scores from T1 to T2 or T1 to T3. Analysis of clinically meaningful change on FACT-Cog 3 scores revealed no significant differences between patients and controls from T1 to T2 (44% vs. 29%, respectively, $\chi^2 = .85, p = .36$), or T1 to T3 (56% vs. 26%, respectively, $\chi^2 = 3.81, p = .05$).

Intercorrelations Between Change in Stroop RT Task and Self-Reported Cognition

Changes in self-reported cognitive function from T1 to T2 were not significantly related to changes in objective Stroop performance measures in patients (r s ranged from -.02 to .31) or controls (r s ranged from -.002 to .45). From T1 to T3, change in PAOFI language score was significantly positively correlated with ISD change scores in patients for congruent ($r = .52$) and incongruent conditions ($r = .50$; Table 12). Change scores on other PAOFI subscales and FACT-Cog 3 were not significantly correlated with change in variability on either congruent or incongruent Stroop conditions (r s ranged from -.001 to .45). In controls, there were no significant correlations between self-report cognitive symptoms and objective performance (r s ranged from -.01 to .50; Table 13).

⁵ In order to test whether results are due to learning difficulties with button/color mapping, we performed data analyses on the final block of the Stroop task (i.e., last 96 trials) at baseline, which served as a proxy for successful acquisition of button/color mapping and effort by the end of the task. The pattern of results for the last 96 trials was identical to results based on all trials.

Table 9. Means and Standard Deviations for Patient and Healthy Control Groups on Cognitive and Self-Report Measures

Variables	Time 1		Time 2		Time 3	
	Patients (<i>n</i> = 28)	Control (<i>n</i> = 20)	Patients (<i>n</i> = 18)	Control (<i>n</i> = 17)	Patients (<i>n</i> = 25)	Control (<i>n</i> = 16)
Accuracy, %						
Congruent	99.3 (0.7)	98.9 (1.4)	99.5 (0.7)	98.7 (1.6)	98.9 (1.2)	98.1 (2.2)
Incongruent	97.7 (1.8)	96.8 (3.9)	97.0 (5.2)	97.7 (2.6)	98.3 (2.3)	97.3 (3.0)
Mean RT, <i>ms</i>						
Congruent	797.7 (164.7)	741.3 (116.3)	763.2 (164.9)	729.1 (120.0)	784.6 (179.0)	694.5 (93.9)
Incongruent	956.3 (220.6)	872.7 (157.2)	910.2 (232.2)	857.6 (152.3)	925.3 (231.8)	806.1 (123.7)
Mean RT – fastest, <i>ms</i>						
Congruent	571.3 (120.4)	530.7 (91.9)	549.8 (126.6)	521.0 (90.0)	553.8 (138.9)	500.8 (83.9)
Incongruent	574.6 (133.6)	531.4 (93.3)	553.7 (136.5)	518.9 (85.6)	555.3 (155.6)	504.2 (91.5)
Mean RT – slowest, <i>ms</i>						
Congruent	1238.9 (250.7)	1151.1 (185.1)	1191.0 (209.6)	1154.1 (204.9)	1238.4 (264.0)	1051.4 (139.7)
Incongruent	1319.9 (301.6)	1199.9 (196.4)	1268.8 (284.1)	1192.9 (218.9)	1300.0 (316.3)	1111.7 (153.3)
ISD						
Congruent	7.3 (1.8)	6.7 (1.3)	7.5 (1.1)	7.2 (1.9)	7.8 (1.8)	6.2 (1.2)
Incongruent	9.7 (2.4)	8.6 (1.6)	9.7 (2.0)	9.2 (1.9)	9.8 (2.5)	7.9 (1.5)
ISD – fastest						
Congruent	2.2 (0.9)	1.9 (0.5)	2.0 (0.7)	1.8 (0.5)	2.0 (0.8)	1.8 (0.5)
Incongruent	2.2 (0.9)	2.0 (0.7)	1.9 (0.8)	1.9 (0.6)	1.9 (0.7)	1.7 (0.4)
ISD – slowest						
Congruent	5.2 (1.5)	5.3 (1.5)	6.07 (2.0)	6.4 (1.4)	6.2 (1.9)	4.7 (0.8)
Incongruent	8.2 (1.8)	6.8 (1.4)	8.3 (1.9)	7.6 (1.3)	8.2 (1.7)	6.1 (1.2)

PAOFI Total “High Complaints”	28.2 (15.3) <i>n</i> = 6 (21%)	27.0 (15.9) <i>n</i> = 3 (15%)	36.9 (24.7) <i>n</i> = 6 (33%)	25.4 (18.0) <i>n</i> = 4 (24%)	39.8 (21.8) <i>n</i> = 11 (44%)	25.5 (18.9) <i>n</i> = 11 (44%)
PAOFI Subscales						
Memory	12.7 (9.2)	9.7 (5.7)	15.1 (10.3)	9.5 (7.8)	15.9 (9.1)	10.0 (7.4)
Language	7.9 (4.6)	8.6 (6.3)	10.5 (6.8)	8.8 (5.6)	11.5 (7.1)	9.2 (7.5)
Sensorimotor	1.7 (2.0)	2.5 (3.0)	4.1 (4.8)	3.0 (3.0)	4.7 (4.9)	1.9 (1.9)
Higher Level	5.9 (5.3)	6.2 (6.1)	5.6 (6.0)	4.1 (6.0)	7.7 (6.1)	4.5 (5.7)
FACT-Cog 3 Total	41.0 (27.4)	27.5 (18.9)	51.2 (30.7)	33.1 (24.6)	53.0 (29.9)	31.3 (26.0)
HADS						
Total	12.8 (7.8)	8.3 (7.0)	10.8 (6.9)	7.8 (7.7)	11.1 (7.4)	7.8 (6.4)
Depression	4.3 (4.0)	2.8 (3.3)	5.3 (3.8)	2.4 (3.8)	4.5 (3.3)	1.9 (1.9)
Normal	<i>n</i> = 24 (86%)	<i>n</i> = 17 (85%)	<i>n</i> = 12 (67%)	<i>n</i> = 14 (82%)	<i>n</i> = 20 (80%)	<i>n</i> = 16 (100%)
Mild	<i>n</i> = 0 (0%)	<i>n</i> = 2 (10%)	<i>n</i> = 5 (28%)	<i>n</i> = 2 (12%)	<i>n</i> = 5 (20%)	<i>n</i> = 0 (0%)
Moderate	<i>n</i> = 3 (11%)	<i>n</i> = 1 (5%)	<i>n</i> = 1 (5%)	<i>n</i> = 1 (6%)	<i>n</i> = 0 (0%)	<i>n</i> = 0 (0%)
Severe	<i>n</i> = 1 (3%)	<i>n</i> = 0 (0%)	<i>n</i> = 0 (0%)	<i>n</i> = 0 (0%)	<i>n</i> = 0 (0%)	<i>n</i> = 0 (0%)
Anxiety	8.4 (5.0)	5.6 (4.0)	5.6 (3.5)	5.4 (4.7)	5.8 (4.8)	5.8 (4.8)
Normal	<i>n</i> = 12 (43%)	<i>n</i> = 16 (80%)	<i>n</i> = 12 (67%)	<i>n</i> = 11 (65%)	<i>n</i> = 13 (52%)	<i>n</i> = 11 (69%)
Mild	<i>n</i> = 6 (21%)	<i>n</i> = 2 (10%)	<i>n</i> = 4 (22%)	<i>n</i> = 4 (23%)	<i>n</i> = 5 (20%)	<i>n</i> = 3 (19%)
Moderate	<i>n</i> = 7 (25%)	<i>n</i> = 1 (5%)	<i>n</i> = 2 (11%)	<i>n</i> = 1 (6%)	<i>n</i> = 7 (28%)	<i>n</i> = 1 (6%)
Severe	<i>n</i> = 3 (11%)	<i>n</i> = 1 (5%)	<i>n</i> = 0 (0%)	<i>n</i> = 1 (6%)	<i>n</i> = 0 (0%)	<i>n</i> = 1 (6%)
FACIT - Fatigue	13.1 (10.0)	9.0 (9.3)	23.0 (12.6)	10.6 (12.7)	16.2 (8.4)	9.6 (8.6)

Note. Values in parentheses are standard deviations unless otherwise indicated.

ChT = chemotherapy; FACT-Cog 3 = Functional Assessment of Cancer Therapy – Cognitive Function; FACIT = Functional Assessment of Chronic Illness Therapy Fatigue; HADS=Hospital Anxiety and Depression Scale; ISD = Intraindividual Standard Deviation; PAOFI = Patient’s Assessment of Own Functioning Inventory; RT = Reaction Time.

Table 10. One-Way Analysis of Variance (ANOVA) of SRB Scores on Cognitive and Self-Report Measures By Group

Variables	Time 1 – Time 2					Time 1 – Time 3				
	Patients Mean (SD)	Controls Mean (SD)	<i>t</i>	<i>p</i>	<i>d</i>	Patients Mean (SD)	Control Mean (SD)	<i>t</i>	<i>p</i>	<i>d</i>
Accuracy, %										
Congruent	0.31 (0.73)	-0.00 (0.97)	-1.07	.29	.37	-0.05 (0.78)	-0.00 (0.97)	.17	.86	.05
Incongruent	-0.39 (2.10)	0.00 (0.97)	.72	.48	.25	0.17 (1.32)	-0.00 (0.93)	-.46	.65	.15
Mean RT, <i>ms</i>										
Congruent	0.17 (1.40)	-0.00 (0.97)	-.42	.68	.15	0.68 (1.26)	0.00 (0.97)	-1.83	.08	.59
Incongruent	0.22 (1.44)	-0.00 (0.97)	-.53	.60	.18	0.55 (1.02)	0.00 (0.97)	-1.73	.09	.55
Mean RT – fastest, <i>ms</i>										
Congruent	-0.09 (1.96)	-0.00 (0.97)	.17	.87	.06	0.32 (1.51)	-0.00 (0.97)	-.76	.45	.24
Incongruent	0.08 (1.68)	0.00 (0.97)	.17	.87	.06	0.05 (1.44)	-0.00 (0.97)	-.11	.91	.04
Mean RT – slowest, <i>ms</i>										
Congruent	-0.03 (0.91)	0.00 (0.97)	.08	.93	.03	1.20 (1.27)	-0.00 (0.97)	-3.22	.003	1.03
Incongruent	0.09 (1.58)	0.00 (0.97)	-.21	.84	.07	0.86 (1.22)	-0.00 (0.97)	-2.39	.02	.77
ISD										
Congruent	0.14 (1.07)	0.00 (0.97)	-.41	.69	.14	1.14 (1.11)	0.00 (0.97)	-3.39	.002	1.09
Incongruent	-0.08 (1.51)	0.00 (0.97)	.19	.85	.07	0.92 (1.23)	-0.00 (0.97)	-2.55	.01	.82
ISD – fastest										
Congruent	0.54 (1.14)	0.00 (0.94)	-1.52	.14	.53	-0.07 (0.96)	0.00 (0.96)	0.23	.82	.07
Incongruent	0.09 (1.35)	0.00 (0.94)	-.23	.82	.08	0.22 (1.81)	0.00 (0.97)	-0.45	.66	.14
ISD – slowest										
Congruent	-0.18 (1.38)	0.00 (0.97)	.45	.65	.16	1.97 (2.17)	-0.00 (0.93)	-3.98	.0003	1.34
Incongruent	0.52 (1.34)	0.00 (0.97)	-.13	.90	.05	1.53 (1.42)	-0.00 (0.93)	-3.78	.0005	1.21

PAOFI										
Total	1.11 (1.88)	0.00 (0.97)	-2.12	.05	.90	0.98 (1.03)	-0.00 (0.93)	-3.03	.004	.97
Memory	0.28 (1.40)	-0.00 (0.94)	-.67	.50	.23	0.75 (1.14)	-0.00 (0.97)	-2.14	.04	.69
Language	0.89 (1.53)	-0.00 (0.97)	-2.02	.05	.70	0.87 (1.14)	0.00 (0.97)	-2.49	.02	.82
Sensorimotor	0.46 (1.66)	0.00 (0.97)	-.96	.35	.33	2.51 (3.32)	0.00 (0.93)	-3.44	.002	1.10
Higher Level	0.92 (2.04)	-0.00 (0.94)	-1.64	.04	.72	0.73 (1.11)	-0.00 (0.93)	-2.16	.04	.69

FACT-Cog 3

Total	0.30 (2.12)	0.00 (0.94)	-.52	.61	.22	0.14 (1.59)	0.00 (0.93)	-.36	.72	.12
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Note. FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive Function; ISD = Intraindividual Standard Deviation; PAOFI = Patient's Assessment of Own Functioning Inventory; RT = Reaction Time; SRB = Standardized Regression-Based

Table 11. Number of Patients and Controls with Significant Decline Based on SRB Change Scores

Number (%)	Time 1 – Time 2 ^a			Time 1 – Time 3 ^b		
Variables	Patients	Controls	<i>p</i> -value (odds ratio)	Patients	Controls	<i>p</i> -value (odds ratio)
Accuracy						
Congruent	0/18 (6%)	0/17 (0%)	1.00 (UND)	0/25 (0%)	0/16 (0%)	1.00 (UND)
Incongruent	0/18 (6%)	0/17 (6%)	1.00 (UND)	1/25 (4%)	1/16 (6%)	.85 (.63)
Mean RT						
Congruent	2/18 (11%)	0/17 (0%)	.26 (UND)	5/25 (20%)	1/16 (6%)	.23 (3.75)
Incongruent	3/18 (17%)	1/17 (6%)	.32 (3.20)	2/25 (8%)	0/16 (0%)	.37 (UND)
ISD						
Congruent	1/18 (6%)	0/17 (0%)	.51 (UND)	6/25 (24%)	1/16 (6%)	.15 (4.74)
Incongruent	1/18 (6%)	1/17 (6%)	.77 (0.94)	5/25 (20%)	1/16 (6%)	.23 (3.75)
PAOFI						
Total	4/16 (25%)	0/17 (0%)	.04 (UND)	2/23 (9%)	1/16 (6%)	.64 (1.43)
Memory	2/16 (13%)	1/17 (6%)	.48 (2.29)	5/23 (22%)	1/16 (6%)	.20 (4.2)
Language	4/16 (25%)	0/17 (0%)	.04 (UND)	4/23 (17%)	1/16 (6%)	.30 (3.16)
Sensorimotor	1/16 (6%)	1/17 (6%)	.77 (1.07)	11/23 (48%)	0/16 (0%)	<.001 (UND)
Higher Level	5/16 (31%)	0/17 (0%)	.02 (UND)	4/23 (17%)	1/16 (6%)	.30 (3.16)
FACT-Cog 3						
Total	3/17 (18%)	0/17 (0%)	.11 (UND)	3/24 (13%)	1/16 (6%)	.47 (2.14)

Note. ^a *n* = 16 on PAOFI and *n* = 17 on FACT-Cog 3 due to incompleteness of these measures.

^b *n* = 23 on PAOFI and *n* = 24 on FACT-Cog 3 due to incompleteness of these measures.

FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive Function; ISD = Intraindividual Standard Deviation; PAOFI = Patient's Assessment of Own Functioning Inventory; RT = Reaction Time; SRB = Standardized Regression Based

Table 12. Pearson Correlations of Cognitive and Self-Report Change between T1-T3 for Patients (n = 25)

	Accuracy Congruent	Accuracy Incongruent	Mean RT Congruent	Mean RT Incongruent	ISD Congruent	ISD Incongruent	PAOFI Total	PAOFI Memory	PAOFI Language	PAOFI Sensori- motor	PAOFI Higher- Order	FACT- Cog 3 Total
Accuracy Congruent	1.00	-										
Accuracy Incongruent	0.55 (.004)	1.00										
Mean RT Congruent	0.22 (0.29)	-0.09 (.65)	1.00									
Mean RT Incongruent	0.23 (.27)	-0.04 (.85)	0.86 (<.001)	1.00								
ISD Congruent	0.09 (.67)	-0.25 (.23)	0.45 (.02)	0.42 (.04)	1.00							
ISD Incongruent	-0.17 (.41)	-0.55 (.004)	0.27 (.19)	0.41 (.04)	0.73 (<.001)	1.00						
PAOFI Total	-0.08 (.73)	-0.006 (.98)	0.04 (.85)	0.17 (.44)	0.44 (.04)	0.42 (.05)	1.00					
PAOFI Memory	0.06 (.79)	-0.10 (.66)	0.01 (.98)	0.20 (.35)	0.36 (.09)	0.45 (.03)	0.82 (<.001)	1.00				
PAOFI Language	-0.26 (.24)	-0.09 (.68)	-0.001 (.99)	0.11 (.62)	0.52 (.01)	0.50 (.01)	0.79 (<.001)	0.52 (.01)	1.00			
PAOFI Sensorimotor	0.18 (.40)	-0.06 (.79)	0.36 (.09)	0.32 (.13)	0.40 (.06)	0.43 (.04)	0.52 (<.001)	0.54 (<.001)	0.25 (.26)	1.00		
PAOFI Higher-Order	-0.13 (.55)	0.18 (.41)	-0.02 (.94)	-0.05 (.83)	0.09 (.67)	-0.07 (.74)	0.64 (<.001)	0.28 (.20)	0.41 (.06)	0.12 (.59)	1.00	
FACT-Cog 3	-0.02 (.91)	-0.25 (.23)	-0.08 (.72)	0.26 (.23)	0.19 (.37)	0.31 (.14)	0.70 (<.001)	0.64 (.001)	0.41 (.06)	0.48 (.02)	0.48 (.02)	1.00

Note. *p*-values in parentheses; FACT – Cog =Functional Assessment of Cancer Treatment – Cognitive Function; ISD = Individual Standard Deviation; PAOFI = Patient’s Assessment of Own Functioning Inventory; RT = Reaction Time.

Table 13. Pearson Correlations of Cognitive and Self-Report Change between T1-T3 for Healthy Controls (n = 16)

	Accuracy Congruent	Accuracy Incongruent	Mean RT Congruent	Mean RT Incongruent	ISD Congruent	ISD Incongruent	PAOFI Total	PAOFI Memory	PAOFI Language	PAOFI Sensori- motor	PAOFI Higher- Order	FACT- Cog 3 Total
Accuracy Congruent	1.00	-										
Accuracy Incongruent	0.06 (.82)	1.00										
Mean RT Congruent	0.20 (.45)	0.08 (.77)	1.00									
Mean RT Incongruent	0.25 (.35)	0.27 (.32)	0.88 (<.001)	1.00								
ISD Congruent	0.28 (.29)	0.38 (.14)	0.56 (.02)	0.63 (.008)	1.00							
ISD Incongruent	0.18 (.51)	0.47 (.06)	0.36 (.18)	0.66 (.006)	0.69 (.003)	1.00						
PAOFI Total	-0.15 (.58)	-0.08 (.76)	0.01 (.96)	0.13 (.64)	-0.15 (.59)	0.11 (.68)	1.00					
PAOFI Memory	-0.06 (.82)	-0.01 (.96)	0.02 (.93)	0.17 (.52)	-0.12 (.65)	0.18 (.50)	0.97 (<.001)	1.00				
PAOFI Language	-0.06 (.82)	-0.06 (.81)	0.01 (.96)	0.12 (.66)	-0.20 (.47)	0.04 (.88)	0.90 (<.001)	0.83 (<.001)	1.00			
PAOFI Sensorimotor	0.03 (.89)	-0.11 (.68)	0.50 (.05)	0.39 (.14)	0.18 (.51)	0.20 (.45)	0.37 (.16)	0.34 (.19)	0.29 (.27)	1.00		
PAOFI Higher-Order	-0.37 (.16)	-0.13 (.63)	-0.25 (.36)	-0.14 (.60)	-0.18 (.49)	-0.02 (.95)	0.80 (<.001)	0.74 (.001)	0.59 (.02)	-0.06 (.82)	1.00	
FACT-Cog 3 Total	-0.22 (.41)	-0.22 (.41)	-0.08 (.76)	0.005 (.99)	-0.40 (.12)	-0.23 (.39)	0.75 (<.001)	0.68 (.003)	0.74 (<.001)	0.19 (.48)	0.64 (.002)	1.00

Note. *p*-values in parentheses; FACT – Cog =Functional Assessment of Cancer Treatment – Cognitive Function; ISD = Individual Standard Deviation; PAOFI = Patient's Assessment of Own Functioning Inventory; RT = Reaction Time.

Discussion

The main results of the present study indicate that, at the third assessment (occurring 9 months postchemotherapy), women treated for breast cancer have greater variability in Stroop RT relative to healthy controls, which is evidence of cognitive dysfunction. This finding is consistent with previous research reporting a decreased ability to benefit from practice in women treated for breast cancer (Collins et al., 2014; Stewart et al., 2008) and supports a multifaceted causation of cancer-related cognitive change, which includes the influences of cancer itself, surgery/anesthesia, hormone therapy, and chemotherapy. No significant group differences were found in change from baseline to T2, after chemotherapy. The analysis also showed IIV to be more sensitive than mean RT for capturing differences in change across all trials of the Stroop task.

Congruent Stroop trials are affected by fundamental brain processes (e.g., perception and sensorimotor speed), whereas incongruent trials additionally require higher order cognition (e.g., inhibitory control). Given the subtle nature of cancer-related cognitive deficits, we might expect a greater group difference in the incongruent conditions, as we previously found in women before they had received surgery or chemotherapy (Chapter 3). However, present results show that patients did not have disproportionate difficulty on the more demanding task condition following treatment. Our findings of increased variability among patients in the slowest RT trials suggest a reduced ability to stay consistently focused on the specific goals of the task, which may then manifest in more frequent lapses in attention and increased variability (Bunce et al., 1993; West et al., 2002). A similar pattern of increased variability in the slow end of the RT distribution has been seen in both normative and pathological aging (Duchek et al.,

2009; Hultsch et al., 2002). This common mechanism of change in variability supports the hypothesis that biological processes underlying aging and cancer-related factors (e.g., impact of disease and treatment) are linked and that cancer treatments may accelerate the aging process (Ahles, Root, & Ryan, 2012; Maccormick, 2006)

Change scores on PAOFI Total from T1 to T3 differed between groups due to increased reporting of cognitive symptoms among the patients. A significant proportion of patients also reported increased sensorimotor problems from T1 to T3, which may be related to chemotherapy-induced peripheral neuropathy that could potentially interfere with the manual responses required on the RT task. However, women with breast cancer did not make significantly more errors nor were they significantly slower than healthy controls, which would be expected if they experienced difficulty using the response keypad.

Increased symptoms on the PAOFI Language subscale from T1 to T3 were significantly related to increased IIV in the same period. This association might be related to initiation of hormone therapy in the majority of women with breast cancer by T3, given the demonstrated positive relationship between estradiol levels and verbal fluency and verbal memory (Kampen & Sherwin, 1994; Maki, Rich, & Rosenbaum, 2002). There were no significant effects showing associations on PAOFI total and other subscales and variability.

A potential limitation of the study is fluctuation of the number of participants across the assessment points. To address this, we analyzed the data using only participants who completed all three assessments and found the same pattern of results, namely a reduced ability to benefit from repeated testing among patients from T1 to T3.

Due to small sample size, we were unable to examine performance differences between women who did or did not receive hormone therapy at T3. Another limitation is the inclusion of only one measure of IIV. Although we examined performance at different levels of task difficulty (e.g., congruent and incongruent conditions), the inclusion of tasks assessing other domains (e.g., semantic or lexical decision) would provide greater insights into the pattern of cancer-related cognitive dysfunction.

Strengths of this study include its prospective longitudinal study design, which permits comparisons to baseline performance before both surgery and chemotherapy, and the high participant retention rate (88-96%). A closely matched healthy control group allowed for full estimate of practice effects. We accounted for the potential confounding effects of age, group differences in mean RT, and practice effects in IIV. Finally, groups were not significantly different on accuracy across assessment points, which suggest that the control group did not demonstrate a speed/accuracy trade-off that could extraneously result in a faster performance.

In conclusion, healthy individuals show performance gains from repeated assessments, whereas women with breast cancer treated with neoadjuvant chemotherapy did not demonstrate expected benefits of practice. IIV is a sensitive and meaningful indicator of cognitive performance, which may be particularly relevant for women with breast cancer because of the subtle effects of cancer treatment on cognitive function.

Chapter 5: General Discussion

The purpose of the dissertation was to examine executive functioning in women with breast cancer using IIV measures of cognitive performance. The key findings from the studies are summarized below, followed by a discussion of theoretical implications of the results. Finally, limitations of the present studies and future avenues for research examining IIV in women with breast cancer are suggested.

Summary of Studies

The systematic review (Chapter 2) provided an overview of performance on neuropsychological and experimental tests of four subcomponents of executive functioning in women treated with chemotherapy. Inhibition seemed to be relatively unaffected in breast cancer survivors, whereas the findings were largely inconsistent for tasks assessing set-shifting, working memory, or planning/decision making. The substantial heterogeneity in study methods (e.g., clinical samples, study design, statistical procedures) used to define impairment and assess group differences contributed to the mixed results. Recommendations for future research included careful operationalization of executive functioning and selection of appropriate tasks as well as alternative methods to examine performance. In particular, the inclusion of tasks of varying complexity and measures of within-person variability were hypothesized to yield unique information about cognitive functioning in women diagnosed and treated for breast cancer.

The remainder of this dissertation was a report of IIV in Stroop RT performance among women diagnosed with breast cancer compared to healthy controls at baseline (Chapter 3) and follow-up after neoadjuvant chemotherapy and other adjuvant treatments (e.g., surgery, hormone therapy; Chapter 4). Assessment before and after neoadjuvant

chemotherapy provided an opportunity to examine the effects of chemotherapy without the confounding effects of surgery and anesthesia. A Stroop RT task that included two conditions of varying complexity was used at all assessments. Women diagnosed with breast cancer were more variable prior to receiving neoadjuvant chemotherapy (i.e., at baseline) compared to healthy controls only on the more difficult, incongruent condition of the task.

Change in overall IIV from baseline to 1-month postchemotherapy did not differ between breast cancer patients and controls. However, change from baseline to 9-months postchemotherapy revealed a relative deficit in patients, as they did not improve on either task condition as much as healthy controls did. Self-reported cognitive symptoms also increased from baseline to 9-months postchemotherapy in patients relative to controls. In patients, there was a significant positive correlation between change in self-reported language difficulties and change in variability at 9-months postchemotherapy. However in controls, there were no significant correlations between change in self-reported symptoms and change in Stroop performance. Both at baseline and across assessments, IIV was a more sensitive measure of group differences than was mean RT.

These results suggest that there are cognitive deficits related to breast cancer itself and associated treatments (e.g., surgery/anesthesia, chemotherapy, hormone therapy). Overall, findings contribute to the current understanding of the behavioural relationship between IIV and cognitive functioning in women with breast cancer. Findings also add to the IIV literature suggesting that variability is a sensitive measure that is able to detect subtle differences and changes in women with breast cancer (Bernstein et al., 2014).

Longitudinal Change in IIV in Women with Breast Cancer

A prospective longitudinal design is recommended to document performance trends across time and to account for baseline level of functioning (Wefel, Vardy, Ahles, & Schagen, 2011). The data reported here add to the accumulating literature that demonstrates pretreatment cognitive deficits in breast cancer patients relative to comparison groups. The deficit was present only in the slowest trials of the RT distribution from the Stroop task and when indexed by IIV, which is hypothesized to be a more sensitive measure of neural integrity than mean RT (Lövdén et al., 2007). It is unclear from the data whether increased pretreatment variability in women diagnosed with breast cancer is due to the cancer itself or other unidentified factors such as, posttraumatic stress. However, pretreatment variability was not significantly correlated with age, education, days since diagnosis, depression, anxiety, fatigue, or self-reported cognition.

In contrast to many longitudinal studies that show cognitive impairment in women during (Collins et al., 2013b) and immediately after (Debess et al., 2010; Hermelink et al., 2007; Vearncombe et al., 2009) chemotherapy, the present data did not reveal any significant effects of neoadjuvant chemotherapy 1 month posttreatment. At 9 months postchemotherapy, however, women with breast cancer did not show decreased variability from baseline to the extent that healthy women did. By this assessment point, women with breast cancer had received additional treatments (e.g., surgery/anesthesia, hormone therapy) that could have negative effects on cognitive functioning. The results should be considered tentative due to the small sample size. It will be important for future studies to follow patients longer term, given cross-sectional findings of cognitive

impairment 5 to 9 years postchemotherapy on functional imaging studies (de Ruiter et al., 2011; Kesler et al., 2011) and 10 to 20 years postchemotherapy on neuropsychological testing (Koppelmans et al., 2012; Nguyen et al., 2013).

Relationship between Self-Reported Cognition and Objective Performance

Previous studies show that self-reported cognitive symptoms do not correlate with performance on objective neuropsychological tests (Pullens et al., 2010), whereas symptoms do correlate with measures of depression, anxiety, and posttraumatic stress associated with the breast cancer diagnosis (Hermelink et al., 2015; Shilling & Jenkins, 2007; van Dam et al., 1998). The dissociation between self-report and objective cognition has been accounted for by various explanations including that testing conducted in a structured environment lacks the ecological validity of daily functioning (Bender et al., 2008; Downie, Mar Fan, Houédé-Tchen, Yi, & Tannock, 2006; Shilling & Jenkins, 2007) or patient's ability to compensate for subtle neural dysfunction that is evident in fMRI studies but not on neuropsychological test performance (Ferguson et al., 2007; McDonald et al., 2012; Silverman et al., 2006). It is likely that both types of assessment are important for characterizing cognitive impairment after breast cancer treatment, as they may reflect different but overlapping constructs.

One of the aims of this dissertation was to investigate whether IIV, hypothesized as a unique and sensitive measure to detect cognitive impairment related to breast cancer and treatment, is related to self-reported differences between patients and healthy controls. Consistent with previous studies, we found no significant association between change in self-reported cognition and change in objective performance from baseline to 1 month postchemotherapy. In the baseline to 9-month postchemotherapy period, change in

self-reported language symptoms was positively correlated with change in variability among patients but not healthy individuals. The timeframe of reference may be particularly important in studying the relationship between self-reported cognition and objective performance. For example, Collins, Paquet, Dominelli, White, and MacKenzie, (2015) proposed that participants likely rate their current level of functioning in relation to their baseline level in self-reports, which automatically references a change in function. However, most objective scores are typically based on a single assessment point. Recently, a study found that change in psychomotor speed was associated with higher language complaints on the PAOFI 6 months after starting hormone treatment (Ganz et al., 2014). The present findings of associations between subjective appraisals and objective performance using change scores support the hypothesis that timeframe of reference may be an important methodological consideration.

Further Considerations of IIV

Results from this dissertation suggest that IIV is a sensitive indicator of cognitive functioning that provides information that is unique from mean level performance (i.e., accuracy and mean RT). At baseline, breast cancer patients were shown to have difficulty on the more complex condition (incongruent trials) in the slowest trials only when measured using variability and not by accuracy or mean RT. In terms of baseline to 9-month postchemotherapy change, women with breast cancer showed relative increases in both congruent and incongruent IIV across the entire RT distribution compared to healthy individuals, whereas significant RT differences were seen only in the slowest trials of RT and not across the entire distribution. Thus, IIV captured information about cognitive functioning in women with breast cancer that would have been unobserved if only mean

performance level was examined. This underscores the utility of including measures of variability when evaluating cognition in women with breast cancer.

Another consideration for IIV is the influence of task complexity on performance variability. Studies have shown that increased IIV is associated with tasks that involve greater cognitive demands (Hultsch et al., 2000; West et al., 2002). Consistent with these findings, women newly diagnosed with breast cancer demonstrated increased IIV on the Stroop condition that required greater attentional control compared to the condition of simple attention. The Stroop task involved 384 trials and required approximately 12 to 15 minutes to complete. Thus, in this regard, IIV on this task may also be related to sustained attention. However, examination of the last block of trials (i.e., last 96 trials) yielded similar results to that of the entire 384 trials, which suggested that observed group differences were not due to poor sustained attention or increased fatigue over the course of the test. As discussed in Chapter 3, these findings suggest that the elevated IIV in patients might reflect fluctuations in executive control or lapses in attention. In both interpretations, the concept of IIV reflects frontally mediated processes which include maintaining attention and executive control.

After neoadjuvant chemotherapy, women with breast cancer relative to healthy individuals showed increased IIV in congruent and incongruent Stroop task conditions across the entire RT distribution and specifically in the slowest trials. This finding suggests that variability represents a general characteristic of overall performance and not just for the most difficult condition, which emphasizes the effect of chemotherapy beyond pretreatment differences in performance. The results are consistent with other studies that show IIV is a general characteristic of performance in individuals with mild

cognitive impairment (Christensen et al., 2005; Dixon et al., 2007; Duchek et al., 2009).

The increase in IIV is also consistent within an attentional control framework on a simple and complex task. Specifically, the major goal of the cognitive system is to flexibly adjust itself to current task demands and stay tuned to these demands across time. As attentional control systems becomes compromised due to the negative effects of breast cancer treatment, these systems are no longer consistently tuned across time to the specific goals of the task that are both simple and more complex in nature.

Limitations and Directions for Future Research

Whereas there are several strengths of the studies comprising this dissertation, including the prospective longitudinal study design and operationalization of IIV, there are some limitations that warrant further consideration. One limitation is that not every person was assessed at every time point, which reduced power to detect differences between women with breast cancer and healthy controls in the baseline to 1-month postchemotherapy assessment period. Besides the issue of small sample size, participants were relatively homogenous. Female participants were predominantly middle-aged and well-educated, which limits generalizability of the findings to a broader breast cancer population. Another limitation is the increased possibility of Type I error due to the numerous statistical comparisons that are reported. To reduce the likelihood of Type I error, a more conservative $p < .01$ was used to correct for multiple comparisons. These limitations present opportunities for future research to replicate and extend the findings of this dissertation in a larger and more diverse sample.

Further research is needed to examine IIV derived from tasks assessing other cognitive domains to determine whether executive functioning is selectively impaired in

women or if the pattern of deficits is global and nonspecific. In this dissertation, IIV was conceptualized as an indicator of vulnerability and assessed with a task requiring attentional control. As described in Chapter 1, IIV has also been hypothesized to be adaptive under certain task conditions (Allaire & Marsiske, 2005; Garrett, MacDonald, & Craik, 2012). In contrast to most RT tasks that are strategy-constrained, complex cognitive tasks that incorporate learning and multiple response strategies would likely yield an adaptive index of variability (Allaire & Marsiske, 2005). Future studies should evaluate IIV as an indicator of adaptability or resiliency in women with breast cancer given that many longitudinal studies show improvement in cognitive functioning approximately one year after chemotherapy (Collins et al., 2009; Jansen et al., 2011).

The present results established group differences in IIV between women with breast cancer and healthy controls at baseline and change after neoadjuvant chemotherapy. It will be important to extend the findings by examining possible links between increases in IIV, performance on neuropsychological tests, and neural correlates. If increased IIV is a behavioural marker of reduced neural integrity, then we may expect a corresponding decrease in performance on cognitive tasks, particularly more complex ones. Comparison of IIV measures with standardized neuropsychological tests might assist with understanding how IIV can complement standardized testing, which may have clinical implications for assessments of women with breast cancer and contribute toward defining diagnostic criteria for “chemo brain,” which still do not exist. In addition, understanding the neural underpinnings of IIV in breast cancer patients can inform the mechanisms underlying increased variability and lead to better understanding of breast cancer-related cognitive dysfunction.

As in the cognitive aging literature, IIV may be a prospective marker of important outcomes in women with breast cancer. Given the findings of increased pretreatment IIV in women with breast cancer, it would be interesting to determine whether IIV predicts cognitive decline after chemotherapy and other adjuvant treatment. Early identification of women at risk for treatment-related cognitive impairment is important for developing potential prevention or treatment options (e.g., cognitive intervention or rehabilitation programs) and improving long-term quality of life. This focus is particularly important in the context of increased breast cancer survivorship; however, substantial research is needed to bridge the gap between cognitive literature and clinical practice.

Conclusions

Women diagnosed with breast cancer exhibit increased IIV compared to healthy controls before and after chemotherapy on tasks of varying demands on attentional resources. The studies presented here further our understanding of differences and changes in cognitive performance related to breast cancer and its treatments. Furthermore, findings demonstrate that IIV is an important characteristic that describes cognitive functioning in the breast cancer population. IIV holds promise for improving our understanding of complex processes and is a theoretically important aspect of functioning not captured by central tendency.

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Appendix A: Stroop Reaction Time Task Instructions

Colour-To-Key Mapping Acquisition Trials

In this task you will press 1 of 4 buttons to indicate the color of the letters or word that appears on the screen. The colors are red, blue, green, and yellow. Before beginning the test trials you will have a chance to practice the color-to-button mapping so that you know which button corresponds to which color.

I [Research Assistant] will show you how to position your hands over the response box buttons.

I [Research Assistant] will also review which button corresponds to red, blue, green, and yellow.

Please take a few minutes right now to get familiar with the button/color mapping.

After you feel you know them pretty well, you should begin practice trials. I [Research Assistant] will go over these with you and give you feedback.

<Colour-To-Key Mapping Acquisition Trials begins.>

Practice Trials

Now you will practice the Stroop task. For each trial, press the key to indicate the color that the word appears in. Be careful not to respond to the word that is presented.

<Practice Trials begins.>

Test Trials

Now you will perform 4 blocks of 96 trials. Remember to always respond to the color of the font. Do not 'read' what the word says; indicate the color that the word appears in. Respond as quickly as you can without making mistakes.

Indicate the color that the word appears in.

Respond as quickly as you can without making mistakes.

<Test Block 1 begins.>

Take a break. Press any button to continue to the next block of trials.

<Test Block 2-4 begins.>

This is the end of the task. Thank you for your participation.

Appendix B: Hospital Anxiety and Depression Scale (HADS)

Instructions: Read each item and place a tick in the box opposite the reply that comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response. Tick only one box in each section.

I feel tense or wound up:

- ☐ Most of the time
- ☐ A lot of the time
- ☐ Time to time
- ☐ Not at all

I feel as if I am slowed down:

- ☐ Nearly all the time
- ☐ Very often
- ☐ Sometimes
- ☐ Not at all

I still enjoy the things I used to enjoy:

- ☐ Definitely as much
- ☐ Not quite so much
- ☐ Only a little
- ☐ Hardly at all

I get a sort of a frightened feeling like butterflies in the stomach:

- ☐ Not at all
- ☐ Occasionally
- ☐ Quite often
- ☐ Very often

I get a sort of frightened feeling as if something awful is about to happen:

- ☐ Very definitely and quite badly
- ☐ Yes, but not too badly
- ☐ A little, but it doesn't worry me
- ☐ Not at all

I have lost interest in my appearance:

- ☐ Definitely
- ☐ I don't take so much care as I should
- ☐ I may not take quite as much care
- ☐ I take just as much care as ever

I can laugh and see the funny side of things:

- ☐ As much as I always could
- ☐ Not quite as much now
- ☐ Definitely not so much now
- ☐ Not at all

I feel restless as if I have to be on the move:

- ☐ Very much indeed
- ☐ Quite a lot
- ☐ Not very much
- ☐ Not at all

Worrying thoughts go through my mind:

- ☐ A great deal of the time
- ☐ A lot of the time
- ☐ From time to time but not too often
- ☐ Only occasionally

I look forward with enjoyment to things:

- ☐ As much as I ever did
- ☐ Rather less than I used to
- ☐ Definitely Less than I used to
- ☐ Hardly at all

I feel cheerful:

- ☐ Not at all
- ☐ Not often
- ☐ Sometimes
- ☐ Most of the time

I get sudden feelings of panic:

- ☐ Very often indeed
- ☐ Quite often
- ☐ Not very often
- ☐ Not at all

I can sit at ease and feel relaxed

- ☐ Definitely
- ☐ Usually
- ☐ Not often
- ☐ Not at all

I can enjoy a good book or radio or TV program:

- ☐ Often
- ☐ Sometimes
- ☐ Not often
- ☐ Very seldom

☐

Appendix C: FACIT-F

Instructions: By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

	Not at all	A little bit	Some- what	Quite a bit	Very much
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless (“washed out”)	0	1	2	3	4
I feel tired	0	1	2	3	4
I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
I have energy	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat	0	1	2	3	4
I need help doing my usual activities	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
I have to limit my social activity because I am tired	0	1	2	3	4

Appendix D: FACT-Cognitive Function Version 3

Instructions: Below is a list of statements that other people with your condition have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>Perceived Cognitive Impairments</u>	Never	About once a week	Two to times a week	Nearly every day	Several times a day
I have had trouble forming thoughts	0	1	2	3	4
My thinking has been slow	0	1	2	3	4
I have had trouble concentrating	0	1	2	3	4
I have had trouble finding my way to a familiar place	0	1	2	3	4
I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
I have had trouble finding the right word(s) to express myself	0	1	2	3	4
I have used the wrong word when I referred to an object	0	1	2	3	4
I have had trouble saying what I mean in conversations with others	0	1	2	3	4
I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
I have forgotten names of people soon after being introduced	0	1	2	3	4

My reactions in everyday situations have been slow	0	1	2	3	4
I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
My thinking has been slower than usual	0	1	2	3	4
I have had to work harder than usual to express myself clearly	0	1	2	3	4
I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

<u>Comments From Others</u>	Never	About once a week	Two to times a week	Nearly every day	Several times a day
Other people have told me I seemed to have trouble <u>remembering information</u>	0	1	2	3	4
Other people have told me I seemed to have trouble <u>speaking clearly</u>	0	1	2	3	4
Other people have told me I seemed to have trouble <u>thinking clearly</u>	0	1	2	3	4
Other people have told me I seemed <u>confused</u>	0	1	2	3	4

<u>Perceived Cognitive Abilities</u>	Not at all	A little bit	Some-what	Quite a bit	Very Much
I have been able to concentrate	0	1	2	3	4
I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4

I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
My mind is as sharp as it has always been	0	1	2	3	4
My memory is as good as it has always been	0	1	2	3	4
I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Appendix E: Patient's Assessment of Own Functioning Inventory (PAOFI)

Instructions: Please answer each of the following questions by placing a check next to the response, which most accurately describes the way you have been recently.

Memory:

1. How often do you forget something that has been told to you within the last day or two?
 - ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
2. How often do you forget events which have occurred in the last day or two?
 - ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
3. How often do you forget people who you met in the last day or two?
 - ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
4. How often do you forget things that you knew a year or more ago?
 - ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
5. How often do you forget people whom you knew/met a year or two ago?
 - ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently

- ☐ Almost never
6. How often do you lose track of time, or do things either earlier or later than they are usually done or supposed to be done?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
7. How often do you fail to finish something you start because you forgot that you were doing it? (Include such things as forgetting to put out cigarettes, turn off stove, etc.)
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
8. How often do you fail to complete a task that you start because you have forgotten how to do one or more aspects of it?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
9. How often do you lose things or have trouble remembering where they are?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
10. How often do you forget things that you are supposed to do or have agreed to do (such as putting gas in the car, paying bills, taking care of errands, etc.)?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never

Language and Communication:

11. How often do you have difficulties understanding what is said to you?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
12. How often do you have difficulties recognizing or identifying printed words?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
13. How often do you have difficulty understanding reading material which at one time you could have understood?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
14. Is it easier to have people show you things than it is to have them tell you about things?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
15. When you speak, are your words indistinct or improperly pronounced?
- ☐ Almost always
 - ☐ Very often
 - ☐ Fairly often
 - ☐ Once in a while
 - ☐ Very infrequently
 - ☐ Almost never
16. How often do you have difficulty thinking of the names of things?
- ☐ Almost always

- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

17. How often do you have difficulty thinking of the words (other than names) for what you want to say?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

18. When you write things, how often do you have difficulty forming the letters correctly?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

19. Do you have difficulty spelling, or make more errors in spelling than you used to?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

Sensorimotor:

20. How often do you have difficulty performing tasks with your right hand (including such things as writing, dressing, carrying, lifting, sports, cooking, etc.)?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

21. How often do you have difficulty performing tasks with your left hand?

- ☐ Almost always
- ☐ Very often

- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

22. How often do you have difficulty feeling things with your right hand?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

23. How often do you have difficulty feeling things with your left hand?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

24. Lately do you have more difficulty than you used to in seeing all of what you are looking at, or all of what is in front of you (in other words, are some areas of your vision less clear or less distinct than others)?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

Higher Level Cognitive and Intellectual Functions:

25. How often do your thoughts seem confused or illogical?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

26. How often do you become distracted from what you are doing or saying by insignificant things which at one time you would have been able to ignore?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often

- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

27. How often do you become confused about (or make a mistake about) where you are?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

28. How often do you have difficulty finding your way about?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

29. How often do you have more difficulty now than you used to in calculating or working with numbers (including managing finances, paying bills, etc.)?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

30. Do you have more difficulty now than you used to in planning or organizing activities (i.e., deciding what to do and how it should be done)?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

31. Do you have more difficulty now than you used to in solving problems that come up around the house, or at your job, etc.? (In other words, when something new has to be accomplished, or some new difficulty comes up, do you have more trouble figuring out what should be done and how to do it)?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while

- ☐ Very infrequently
- ☐ Almost never

32. Do you have more difficulty than you used to in following directions to get somewhere?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never

33. Do you have difficulty than you used to in following instructions concerning how to do things?

- ☐ Almost always
- ☐ Very often
- ☐ Fairly often
- ☐ Once in a while
- ☐ Very infrequently
- ☐ Almost never