The Effects of Chemotherapy on Cognition in Women with Breast Cancer

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Abstract

Advances in cancer treatment have led to increasing numbers of survivors left to struggle with the long-term adverse effects of disease and treatment. Many possible effects have been described including anxiety, depression, as well as physical side effects and consequences of cancer treatment. One particular adverse effect that is frequently reported but often overlooked in clinical practice is disturbances of cognitive functioning. Cancer-related cognitive impairment (CRCI) is a growing area of research with important clinical implications for current patients and survivors. Despite a huge increase in this research endeavour in the last 20 years, many important questions remain unanswered due, in large part, to methodological limitations of many of the studies. The overall goal of this dissertation is to critically examine previous CRCI research from a methodological perspective. It will explore limitations and confounds in this research and provide suggestions for improving future work. This dissertation is comprised of three manuscripts, a critical literature review and two original papers, addressing specific research questions. The first original paper addresses the disparity between the results of objective (performance-based) and subjective (self-report) measures of cognition that is typically observed in samples of cancer patients, using multilevel modeling to explore the hypothesis that this is due to failure to address measures of change over time. Despite negative findings, the methodological approach taken to this research question provided greater evidence for this subjective-objective disparity as well as methodological suggestions for future studies. The second original paper explores the sensitivity and validity of a computerized cognitive test for measuring CRCI to determine if it might be an appropriate alternative to traditional, resource-intensive neuropsychological testing. This study found that, although the computerized measure of cognitive functioning was not sensitive enough to detect changes at the individual level or

within specific domains, it was sensitive to changes in cognitive functioning at the group level suggesting its usefulness as a screening tool in research settings. By addressing methodological limitations of research to date and, specifically, the two issues identified above, this dissertation aims to a) make recommendations to help improve the quality of future research, b) validate the cognitive complaints of cancer patients, and c) improve access to cognitive assessments leading to increased detection and treatment of cognitive side effects and improvement in quality of life of cancer survivors.

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Ethical Standards

The data used for this dissertation were collected as a part of a previous research study. Approval for the original study was obtained from the Ottawa Hospital Research Ethics Board (see Appendix A). Approval for use of the data for the current dissertation was obtained from the University of Ottawa Research Ethics Board (see Appendix B).

Statement of Co-Authorship

This dissertation and included manuscripts were written with the guidance of Dr. Barbara Collins. The data used for the included manuscripts was previously collected by Joyce MacKenzie and Dr. Barbara Collins. As primary author on the manuscripts, I was responsible for the formulation of the research questions, selection of statistical analyses, and preparation of the manuscripts. Dr. Collins provided ongoing guidance throughout the dissertation development and execution. Joyce MacKenzie provided valuable assistance with preparation of the first manuscript for publication. Dr. Dwayne Schindler and Dr. Daniel Coulombe provided assistance and consultation for the statistical analyses for the second manuscript. Dr. Andra Smith provided valuable feedback regarding the second and third manuscripts.

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General Introduction

Breast cancer is the most common cancer among adult women, accounting for almost 26% of all new cancer diagnoses in 2016 and with 158,430 cases within Canada in the last 10 years (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2016). Advances in breast cancer detection and treatment, including surgical interventions and adjuvant chemotherapy, have increased survival over the past decades such that the 5-year relative survival rate for women diagnosed with breast cancer in Canada between 2006 and 2008 was 87% (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2016). As a result of this increased survivorship, greater numbers of women now live with the long-term side effects of cancer and cancer treatments. Cognitive impairments, such as memory disturbances and difficulties with executive functioning (e.g., processing speed and cognitive flexibility), are among the persistent adverse effects reported by patients both during and following chemotherapy treatment. Traditionally, these cognitive complaints were thought to be expressions of psychological distress related to the cancer diagnosis and treatment. Research over the past 3 decades, however, has yielded objective evidence of the adverse effect of adjuvant chemotherapy on cognitive functioning in approximately 17 to 78% of patients (Hodgson, Hutchinson, Wilson, & Nettelbeck, 2013; Jim et al., 2012; review by Phillips & Bernhard, 2003; Wefel & Schagen, 2012), and of neurobiological underpinnings for these cognitive changes (Brown et al., 1995; Brown et al., 1998; Deprez et al., 2012; de Ruiter et al., 2011; Kesler, Kent, & O'Hara, 2011; McDonald et al., 2010; Seigers & Fardell, 2011; Silverman et al., 2007; Stemmer, Stears, Burton, Jones, & Simon, 1994; Winocur et al., 2012). Despite the increased evidence for cancer-related cognitive impairment (CRCI), questions regarding the subtleties of this phenomenon remain unanswered or highly debated within the research community. This dissertation contends that the

lack of agreement and answers is due, in large part, to the methodological limitations of current research studies. Thus, the overall goal of this dissertation is to critically examine previous CRCI research, methodology, and limitations, and to attempt to address some of these limitations using more sophisticated methodology and powerful statistical techniques. In doing so, this dissertation will provide methodological guidelines for future research in an effort to help clarify ongoing questions surrounding CRCI.

CRCI and Quality of Life

The rationale for research into CRCI is a direct outcome of patient reports of subjective changes in cognitive functioning after exposure to chemotherapeutic drugs. In fact, breast cancer patients coined the terms "chemofog" and "chemobrain" to describe their experiences. During and after treatment for breast cancer, women undergo significant changes and side effects that impact quality of life both in the short term and long term. The effects of cancer and treatment include physical aspects such as lumpectomy or mastectomy, nausea, fatigue, weight gain, hair loss, sexual dysfunction, etc.; psychological aspects such as depression, anxiety, changes in self-esteem, changes in body image, etc.; and cognitive aspects such as those identified by patients as "chemofog" or "chemobrain". As a result of these side effects, decreased social engagement, economic stress, and decreased quality of life are further outcomes of cancer and treatment. (Boykoff, Moieni, & Subramanian, 2009; Fitch, Armstrong, & Tsang, 2008; Howard-Anderson, Ganz, Bower, & Stanton, 2012; review by Myers, 2013; Shilling & Jenkins, 2007; Von Ah, Habermann, Carpenter, & Schneider, 2013). Understanding the impact of cancer and treatment is critical for patient care and serves as a driving force behind CRCI research. Without patient reports of CRCI and its impact on daily functioning and quality of life, research into this phenomenon would have never begun and cognitive complaints would continue to be dismissed

as psychological distress.

Several qualitative studies over the past decade have examined patient experience with respect to CRCI. These studies have generally revealed consistent findings in terms of cognitive experiences after exposure to chemotherapy and their impact on functioning and quality of life. For example, the most commonly reported cognitive disturbances across studies include changes in short-term memory, and attention and concentration. Other areas affected and commonly reported include comprehension, word-finding difficulties, processing speed, and executive functioning (Fitch et al., 2008; review by Myers, 2013; Shilling & Jenkins, 2007; Von Ah et al., 2013). When describing their experiences, patients often describe misplacing items, forgetting names and numbers, forgetting appointments, having to re-read things, feeling less "sharp", activities taking longer to complete than before, and difficulty multitasking (Boykoff et al., 2009; Fitch et al., 2008; review by Myers, 2013; Shilling & Jenkins, 2007; Von Ah et al., 2013). For almost all patients, these cognitive changes have significant impacts in their lives. Some individuals describe difficulties engaging in previously enjoyed leisure activities such as reading, writing, or watching films. Many individuals describe changes to social functioning, such that family and friends notice difficulties and respond with dismissal, frustration, or fear, which leads to increased distress and withdrawal among patients (Boykoff et al., 2009; Fitch et al., 2008; review by Myers, 2013; Von Ah et al., 2013). Finally, for many individuals, CRCI becomes a significant factor impacting return to work. In fact, a survey conducted by the Canadian Breast Cancer Network in 2010 found that 8% of women reported that CRCI was a contributing factor in their perceived ability to return to work and therefore in their actual likelihood of returning to work during or after treatment (Dunbrack, 2010). In qualitative research examining patient experiences, cognitive difficulties at work were associated with job loss, being passed over for

promotions, taking on less responsibilities, and early retirement (Boykoff et al., 2009; Fitch et al., 2008; review by Myers, 2013; Von Ah et al., 2013). These return to work decisions and difficulties have significant consequences including potentially negative impacts on economic status, sense of identity, and sense of contribution to both family and society. The qualitative studies examining patient reports highlight the widespread impact of CRCI. In addition to daily distress, it is clear that CRCI impacts social interactions, employment, and overall quality of life. Although CRCI may not affect all women who receive adjuvant chemotherapy treatment, it is clear that this phenomenon has significant functional implications and can adversely affect many aspects of life for cancer survivors who do experience cognitive changes.

Breast Cancer Treatment

Chemotherapy is a commonly used treatment for a variety of cancers, including breast cancer. Chemotherapeutic drugs commonly used for the treatment of breast cancer are broadly classified into three categories: alkylating drugs, antimetabolites, and natural products (i.e., products derived from natural sources such as bacteria) (Canadian Cancer Society, 2017). Alkylating drugs include the common drugs cyclophosphamide and carboplatin. Their mechanism of action is via disruption of cellular replication (Chu & DeVita, 2015; Siddik, 2002). Antimetabolites include the common agent 5-fluorouracil and work by substituting the building blocks of DNA and RNA, thus interfering with cellular growth (Chu & DeVita, 2015). Natural products include anthracyclines, such as doxorubicin and epirubicin, and taxanes. Anthracyclines work by inducing double strand DNA breaks and free radical damage on cells, and taxanes interfere with cellular mitosis, thus preventing cell proliferation (Chu & DeVita, 2015; Kesley & Blayney, 2016). While each of these classes of drugs work to target cancer cells independently, common chemotherapy regimens employ a combination of these common drug

classes in an effort to optimize cancer cell death.

Research in CRCI has traditionally focused on the role of chemotherapy in cognitive impairment and has demonstrated negative effects of chemotherapeutic agents on cognitive functioning and neurological functioning, in both human and animal studies (Ahles, 2012; Collins, Mackenzie, Tasca, Scherling, & Smith, 2012; Deprez et al., 2011; Deprez et al., 2012; Kesler & Blayney, 2016; Seigers & Fardell, 2011; Seigers, Schagen, Van Tellingen, & Dietrich, 2013; Vardy & Tannock, 2007). It is, however, becoming increasingly clear that CRCI is a multifactorial phenomenon likely impacted by all aspects of cancer treatment, including surgery, radiation therapy, hormone therapy, and chemotherapy.

Post-operative cognitive dysfunction is a well-recognized phenomenon previously thought to be transient in nature (Newman, Stygall, Hirani, Shaefi, & Maze, 2007; Rundshagen, 2014; Steinmetz, Christensen, Lund, Lohse, & Rasmussen, 2009). More recent research within this field has revealed some evidence of possible long-term cognitive consequences of anesthesia exposure, although there is currently a lack of consensus regarding the true duration of post-operative cognitive dysfunction (Newman et al., 2007; Rundshagen, 2014; Steinmetz et al., 2009). Given that a large proportion of women with breast cancer undergo lumpectomy or mastectomy, the effects of surgery is a potential contributing factor to CRCI.

Radiation therapy is another commonly used treatment in breast cancer administered following surgery and used to target any remaining cancer cells (Canadian Cancer Society, 2017). Research into the effects of radiation therapy on cognition have found similar effects as chemotherapy thus implicating radiation therapy as a further contributing factor of CRCI (Janelsins, Kesler, Ahles, & Morrow, 2014; Quesnel, Savard, & Ivers, 2009).

Given the frequency of estrogen-receptor positive breast cancers, hormone therapy to

inhibit the production of estrogen is a common adjuvant treatment used following surgery, radiation therapy, and chemotherapy (Canadian Cancer Society, 2017). While some neuropsychological and neuroimaging research implicates hormone therapy in CRCI (Bender et al., 2006; Castellon et al., 2004; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009; Eberling et al., 2004; Shilling, Jenkins, Fallowfield, & Howell, 2003), other research has found no effects of hormone treatment (Fan et al., 2005; Jenkins et al., 2006). Despite ongoing inconsistencies in this field of research, the effects of hormone therapy have been implicated in CRCI and remain a possible factor in the CRCI phenomenon.

Given the many types and combinations of cancer treatments, each of which have been independently associated with cognitive changes, it is clear that CRCI is a complex problem which likely involves an intricate interaction of several factors.

Early Research on CRCI

Research into the field of CRCI began in the mid-1990s. Most research to date has been conducted with breast cancer patients, likely reflecting a number of factors including prevalence of the disease, survivorship, and the fact that women with breast cancer first reported this phenomenon.

Early research evidence supported the idea that breast cancer patients who had received adjuvant chemotherapy were at greater risk of cognitive impairment than patients without chemotherapy treatment (Ahles et al., 2002; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Castellon et al., 2004; Tchen et al., 2003; van Dam et al., 1998; Wefel et al., 2004a; Wieneke & Dienst, 1995). One of the earliest systematic studies of CRCI was that of Wieneke and Dienst in 1995. They found that 75% of their sample of breast cancer patients who had completed chemotherapy showed moderate impairment on one or more cognitive measures when

compared to published norms from healthy individuals. They further noted that performance of the chemotherapy group as a whole was significantly beneath estimated premorbid function in most cognitive domains. This cognitive impairment was not related to depression or type of chemotherapy but was correlated with the length of chemotherapy treatment suggesting a dose-response relationship. A subsequent study by van Dam et al. in 1998 further explored this dose-response relationship by comparing cognitive functioning of high-risk breast cancer patients who had been randomly assigned to receive high-dose or standard-dose chemotherapy, to early-stage breast cancer patients receiving no chemotherapy (this was justified at the time as there was equipoise concerning the benefit of high-dose chemotherapy in this population). The study revealed a significant difference among the groups in terms of risk of cognitive impairment, with 32% of the high-dose group showing cognitive impairment compared to 17% of the standard-dose group and 9% of the control group. These results were interpreted as strong evidence for the neurotoxicity of systemic chemotherapy and implied a causal relationship between chemotherapy and cognitive disturbances.

Following these early studies, a number of similar studies appeared in the literature. Most, but not all, supported the idea that breast cancer patients who had received adjuvant chemotherapy were at greater risk of cognitive impairment than patients who had not received chemotherapy and healthy women without breast cancer (Ahles et al., 2002; Brezden et al., 2000; Castellon et al., 2004; Tchen et al., 2003; Wefel et al., 2004a). While these early studies were pivotal in drawing attention to this problem, they were inconsistent with regard to effect size (which varied from small to large) and, indeed, as to whether an effect was found at all, casting doubt on the etiology of CRCI. It has since become evident that this inconsistency stemmed largely from methodological issues, such as the use of mainly cross-sectional study designs

rather than longitudinal designs, failure to control for confounding variables, and the use of inadequate statistical techniques (O'Farrell, MacKenzie, & Collins, 2013). Subsequent meta-analyses have indicated that cancer-related cognitive changes are generally quite subtle (Hodgson et al., 2013; Jim et al., 2012; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006) suggesting that more powerful and appropriate statistical techniques in addition to careful consideration of study methodology are critical if we are to obtain a true picture of the effects of chemotherapy on cognitive functioning (Ouimet, Stewart, Collins, Schindler, & Bielajew, 2009).

Methodological Issues in CRCI Research

   Longitudinal vs. cross-sectional study design. Most of the early studies of CRCI used cross-sectional study designs rather than repeated-measures, longitudinal designs. Although these studies provided preliminary evidence for CRCI, they were seriously limited by the lack of baseline measurements. Without such measurements, it was impossible to determine whether the cognitive impairments measured were caused by cancer treatment (as was typically assumed) or were pre-existing (Cimprich et al., 2010; Schilder et al., 2010; Wefel et al., 2004a). Furthermore, without baseline measurements, it was possible that these studies underestimated the prevalence of cognitive impairment by failing to capture subtle losses in higher functioning individuals whose scores may have declined but still fell within normal limits (Wefel et al., 2004a). Recognition of these limitations of cross-sectional studies resulted in a call for prospective longitudinal approaches with baseline measurements and multiple data points to determine how an individual's objective performance changed over the course of treatment. Increasingly, longitudinal studies began to appear which provided stronger evidence of the role of treatment in CRCI (Ahles et al., 2010; Bender et al., 2006; Hurria, Somlo, & Ahles, 2006; Jansen, Cooper, Dodd, & Miaskowski, 2011; Minisini et al., 2008; 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, 2004b; Wefel et al., 2010). Within longitudinal designs, however, careful consideration regarding study design and statistical analysis is required.

Control groups. Many previous studies used only a healthy control group (Brezden, Phillips, Bunston, & Tannock, 2000; Tchen et al., 2003; Wieneke & Dienst, 1995) thus failing to take into consideration effects of the disease itself or host effects, characteristics of the individual that might predispose him or her to both cancer and cognitive decline. Others employed only disease control groups to account for disease and host factors, but the controls were often receiving other forms of treatment with the potential to affect cognition (e.g., anti-hormonal therapies) which threatened to confound results (Bender et al., 2007; Castellon et al., 2004; Eberling et al., 2004; Falleti et al., 2005; Jenkins et al., 2004; Palmer et al., 2008; Phillips et al., 2011; Schilder et al., 2010; Shilling et al., 2003). Some longitudinal studies failed to use control groups altogether (Hermelink et al., 2010; Jansen, Cooper, Dodd, & Miaskowski, 2011), on the assumption that each participant serves as their own control for disease and host effects. The use of a control group, either healthy or disease, is critical in longitudinal study designs to control for practice effects of repeated testing and is recommended by the International Cognition and Cancer Task Force (ICCTF) (Wefel, Vardy, Ahles, & Schagen, 2011).

Statistical analysis. Many longitudinal CRCI studies to date have used linear regression analyses to objectively analyze their repeated measures data. Provided that there are sufficient repeated measurements, multilevel modeling (MLM) is a preferable statistical approach to traditional ordinary least squares approaches for evaluating changes at the group level, as it is more robust with respect to violations of assumptions and can better support datasets with

missing data (Wefel et al., 2011). Missing data is common when using longitudinal designs as a result of multiple assessment points. For example, in the current dissertation, the sample of breast cancer participants underwent neuropsychological testing after every cycle of chemotherapy but, depending on the treatment regimen, some women received 5 cycles of chemotherapy while others received 6 or 7 cycles. When using this type of model, MLM is essential to obtaining results without having to eliminate participants based on missing assessments. Unlike repeated-measures ANOVA, which deletes the entire case when there are data points missing, MLM uses all available data in estimating effects using a process of maximum likelihood estimation.

Given that methodological issues are found across all CRCI research, we chose two particular research questions to address while examining how methodological choices and statistical analysis may impact study outcome. Our research questions addressed 1) the subjective-objective disparity in current CRCI research and 2) the usefulness and appropriateness of a brief computerized test for detecting CRCI.

Subjective-Objective Disparity in CRCI Research

Two basic approaches are taken to the assessment of CRCI: subjective and objective. Subjective measurement involves self-reporting of cognitive function/complaints, usually by means of a structured questionnaire or rating scale, whereas objective measurement involves having participants undergo performance-based tests of cognitive abilities. Previous research has generally failed to find significant correlations between these two types of measures. Most studies have found that subjective reports tend to correlate more strongly with measures of psychological distress than with objective performance, reinforcing the idea that "chemobrain" or "chemo fog" is more of a psychological than a neurological disturbance and casting doubt on

any causative role of chemotherapy (Biglia, et al., 2012; Cheung, Tan, & Chan, 2012; Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Iconomou, Mega, Koutras, Iconomou, & Kalofonos, 2004; Jansen, Cooper, Dodd, & Miaskowski, 2011; Pullens, De Vries, & Roukema, 2010). Many of the studies examining the subjective-objective relationship have, however, suffered from serious limitations in study design and data analysis. While a number of studies have made use of more appropriate longitudinal designs to examine how objective measures and subjective reports of CRCI differ before and after chemotherapy, limitations can still be identified in these studies that have likely impacted the current findings in this area of CRCI research. For example, some studies (such as Hermelink et al., 2010 and Jansen et al., 2011) have failed to include a control group to account for practice effects associated with repeated neuropsychological testing. This tends to result in underestimation of the objective impairments thus making subjective complaints appear inflated in comparison. Furthermore, most longitudinal designs to date have failed to assess how subjective and objective measures of cognitive functioning co-vary across time, that is to say, whether the measures follow a similar trajectory over time. Previous longitudinal studies have assessed each time point individually using simple correlations rather than assessing the changes in each measure across time to determine their covariation. As a result of these simplistic and possibly insufficient statistical techniques used to analyze longitudinal data, the relationship between subjective and objective measures in previous studies may have been underestimated.

The Usefulness of a Computerized Cognitive Test for Detecting CRCI

Although many breast cancer patients complain of cognitive disturbances during and following chemotherapy, very few receive assessment or treatment for these symptoms. In current clinical practice and research, the gold standard for the assessment of cognitive

functioning involves employing a battery of paper-and-pencil neuropsychological tests that requires lengthy administration and interpretation by a trained neuropsychologist (Wefel et al., 2011). The requirement of a trained neuropsychologist makes neuropsychological testing a very costly and restricted undertaking and, as a result, it is mostly employed for primary neurocognitive disorders, such as acquired brain injury and dementia, and rarely for cancer patients other than those with primary CNS tumours. A number of other factors limit the usefulness of traditional neuropsychological testing in clinical and research settings with breast cancer patients reporting CRCI. Because traditional neuropsychological tests were developed to primarily assess these more severe cognitive disorders, the sensitivity of such tests may not be adequate to appropriately measure the more subtle cognitive changes experienced by cancer patients. Additionally, these tests may lack ecological validity, that is, they may not measure the cognitive problems that are experienced in the day-to-day tasks of cancer patients and survivors (Jansen, Miaskowski, Dodd, & Dowling, 2007; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Matsuda et al., 2005; Nelson & Suls, 2013; Vardy & Tannock, 2007). For example, a common complaint among cancer patients is the failure to remember to do something at some point in the future but traditional neuropsychological tests do not address such "prospective memory" failures (Lezak, 2004; Paquet et al., 2013).

Computerized neuropsychological testing has begun to be employed in clinics (sports clinics, in particular) and in research of cognitive disorders ranging in severity from mild (e.g. concussion and mild cognitive impairment) to more severe (e.g. multiple sclerosis), as well as psychological disorders such as depression (Collie & Maruff, 2003; Iverson, Brooks, & Young, 2009; Snyder et al., 2011; Wilken et al., 2003). These computerized tests are generally far more practical to administer and have several advantages over traditional neuropsychological tests.

They can be self-administered either on-site or through web-based programs and take between 15 and 45 minutes, and they are designed for repeat administration and thus are less prone to practice effects (Cheung et al., 2012; Phillips et al., 2010). A meta-evaluation examining computerized tests with cancer patients also found that these tests generally have strong psychometric properties (Cheung et al., 2012).

Computerized tests have already been employed in CRCI research and have been found to be sufficiently sensitive to detect the subtle cognitive changes following cancer treatment (Castellon et al., 2004; Vardy et al., 2006). Computerized tests have also been used in a large-scale randomized drug trial of anti-estrogen adjuvant therapy (Phillips et al., 2010) and in intervention studies examining the effects of cognitive rehabilitation in women with CRCI (Ercoli et al., 2013). Given the practical benefits of computerized testing, it may lend itself well to both clinical and research assessments of CRCI.

Purpose and Research Questions

The purpose of this dissertation is to examine and address some of the methodological limitations in previous CRCI research. This work will explore the way in which methodological choices can influence study outcomes and interpretation. This dissertation uses data from a previous study done by the thesis supervisor, Dr. Barbara Collins (Collins et al., 2012), which employed a controlled, prospective, longitudinal design in which 60 breast cancer patients were assessed prior to commencing chemotherapy and again after each cycle of chemotherapy to provide a picture of cognitive changes *throughout* treatment. To explore different methodological approaches and in an effort to clarify and advance the current CRCI literature, the current dissertation capitalizes on the multiple measurement points in the data and the use of a control group to examine two specific research questions important to the study of CRCI. The

first research question addresses how *changes over time* in subjective accounts of cognitive decline relate to contemporaneous *changes* in objective measures of cognitive decline in an effort to clarify the current discrepancies in the literature. We submit that clarification of this issue may promote patient care if we were to find that a patient's subjective reports are a true indication of cognitive decline and not just a product of anxiety or depression associated with cancer and cancer treatment, as has traditionally been believed. The second research question examines the validity of a computerized cognitive test in comparison to a more traditional battery of paper-and-pencil neuropsychological tests to determine its usefulness in clinical and research settings. By conducting a head-to-head comparison of the paper-and-pencil test battery and a brief computerized test, we hope to determine whether computerized cognitive testing may be a practical substitute. If so, this would allow for monitoring of cognitive function in patients across treatments to identify neuropsychological issues that may need to be addressed *as* they occur (rather than post-treatment) as well as charting patient recovery after treatment. On the research front, computerized cognitive testing could be applied within drug trials as a way of efficiently monitoring adverse cognitive side effects of investigational drugs. Our project will be examining the computerized test CNS Vital Signs (CNS-VS). To date, the CNS-VS has been validated for use in different cancer populations and has been used in studies of breast cancer patients; however, no studies have specifically examined the appropriateness and sensitivity of the CNS-VS computerized test for use with breast cancer patients (Calvio, Peugeot, Bruns, Todd, & Feuerstein, 2010; Peters et al., 2013).

This dissertation is presented in manuscript format starting with a manuscript of a critical review of CRCI research, and followed by manuscripts pertaining to the two specific research questions.

Hypotheses

With respect to the first research question about the objective-subjective disparity, we hypothesize that the trajectory of change over time (i.e., the slope) of the objective and the subjective cognitive measure will be highly and positively correlated. Higher scores on both the objective and subjective measures indicate better cognitive functioning therefore we predict that scores on both measures will decrease together over time indicating a similar decrease in cognitive functioning whether measured objectively or subjectively.

With respect to the second research question about the validity of CNS-VS for use with breast cancer patients, we again expect highly significant covariation in the trajectory over time (i.e., the slopes) in total scores from the computerized cognitive test and the traditional neuropsychological battery. Higher scores on both the computerized and paper-based cognitive tests indicate better cognitive functioning; therefore we predict that scores on both tests will decrease similarly over time.

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Clearing the Air: A Review of Our Current Understanding of "Chemo Fog"

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Abstract

An increasing number of cancer survivors has led to a greater interest in the long-term side effects of cancer treatments and their impact on quality of life. In particular, cognitive impairments have been frequently reported by cancer survivors as an adverse effect which they attribute to the neurotoxicity of chemotherapy and have dubbed "chemobrain" or "chemo fog". Research within the past 15-20 years has explored the many factors thought to contribute to cancer related cognitive decline in an attempt to determine a potential cause. In spite of many confounding factors, there is growing evidence that the neurotoxicity of chemotherapy does contribute to cognitive changes. This review examines the evolution of "chemo fog" research with a look at methodological issues, the status of our current understanding, and suggestions for future research.

Introduction

Advances in cancer treatments have led to increased survival rates and a growing number of individuals who are living with the long-term side effects of cancer therapies. Cognitive decline is one of the most frequently reported adverse effects among cancer survivors (Boykoff, Moieni, & Subramanian, 2009). Patients generally attribute these cognitive disturbances to toxic effects of chemotherapy, as implied by their use of terms such as "chemo fog" and "chemobrain." However, in the early years of the adjuvant chemotherapy era, such symptoms were generally dismissed by the medical community as psychological rather than neurological. Although it was recognized that many chemotherapeutic agents could be acutely neurotoxic when delivered directly to the central nervous system, it was believed that most of these agents could not penetrate the blood–brain barrier and thus were unlikely to cause neurotoxicity when administered systemically in the adjuvant setting.

Most studies of the cognitive effects of adjuvant systemic chemotherapy have been conducted primarily in breast cancer (BC) patients. These studies began to appear in the literature in the latter half of the 1990s (Wieneke & Dienst, 1995; van Dam et al., 1998), shortly following the establishment of adjuvant chemotherapy as the new standard of care for treatment of most breast tumors. The study of chemotherapy-related cognitive impairment (CRCI) has largely focused on patients with BC for several reasons, primarily its high prevalence and generally good prognosis, such that many BC survivors expect to resume active, cognitively demanding lives following treatment. These early efforts were generally small, local, retrospective, cross-sectional studies and, although they were important in validating the cognitive complaints of cancer patients and impelling the research endeavor, uncontrolled confounding factors prevented isolation of the specific effects of chemotherapy on cognition.

One of the most troublesome confounding factors was this issue of psychological distress—cancer patients, particularly those patients requiring chemotherapy, are at elevated risk of anxiety and depression, both of which can undermine cognitive function. Other confounding factors include fatigue and effects of anesthetic and surgery. One particularly important confounder is the effect of medications and treatments given in conjunction with cytostatic drugs that may, in and of themselves, affect cognition. Among these are palliative medications designed to mitigate the side effects of chemotherapy, including anti-nauseants, anti-emetics, and anti-inflammatories, as well as other adjuvant treatments. In some two thirds of BC patients, their tumors express estrogen and/or progesterone receptors and grow in the presence of these hormones (Early Breast Cancer Trialists' Collaborative Group, 2005). An important adjunctive treatment for these tumors is long-term (5 years or more) anti-estrogen therapy (with or without cytostatic drugs). It is well established that estrogen acts in the brain to influence cognition (Maki & Hogervorst, 2003; Sherwin, 2012), and there is growing evidence to suggest that the hormonal therapies, which work either by blocking estrogen receptors or by preventing estrogen synthesis, have a detrimental effect on cognitive functioning (Bender et al., 2006; Bender et al., 2007; Castellon et al., 2004; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009a; Eberling, Wu, Tong-Turnbeaugh, & Jagust, 2004; Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004; Palmer, Trotter, Joy, & Carlson, 2008; Phillips et al., 2011; Schilder et al., 2010; Shilling, Jenkins, Fallowfield, & Howell, 2003).

Careful attention to study design and methodology is required to address these many confounding factors. Therefore, key researchers in this field formed the International Cognition and Cancer Task Force (ICCTF) (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008) in 2006 to establish guidelines for harmonizing study methodologies, thereby promoting more comparable

findings among studies (Wefel, Vardy, Ahles, & Schagen, 2011). As a result, we are now able to provide at least partial answers to some of the most frequently asked questions concerning CRCI. This article will review current methodological issues and recommendations and the status of our knowledge with regard to these frequently asked questions.

Methodological Considerations

Cross-Sectional Versus Longitudinal Designs

One of the major limitations to the early studies on CRCI was that they were retrospective and cross-sectional in design and thus could not distinguish chemotherapy-induced cognitive changes from pretreatment cognitive disturbances related to host or disease factors. These studies were prey to both overestimation and underestimation of CRCI. Overestimation was a particular risk in studies that used a healthy control group because, as later prospective studies demonstrated, up to 35% of BC patients showed pretreatment cognitive impairment which would have been misattributed to chemotherapy in these cross-sectional designs (Cimprich et al., 2010; Schilder et al., 2010; Wefel et al., 2004). On the other hand, cross-sectional designs failed to detect pretreatment-to-posttreatment cognitive decline in up to 46 % of individuals who, because of high premorbid function, still scored within the normal range on posttreatment cognitive testing (Wefel et al., 2004). In most cases, the ICCTF recommends prospective longitudinal studies (Wefel et al., 2011).

Control Groups

An important methodological consideration is the nature of the control group used. In retrospective, cross-sectional studies in which patients are assessed at a single point in time after completing chemotherapy, a disease control group is essential to account for a number of factors besides treatment that may influence cognition, such as constitutional and genetic risk factors for

cancer, psychological distress associated with a cancer diagnosis, and biological changes associated with the disease itself (as noted already, cancer patients are at increased risk of cognitive disturbance before any exposure to adjuvant therapy). A disadvantage to the disease control group is the fact that those patients who are not receiving chemotherapy may be receiving alternative treatments, such as anti-estrogen therapy, that may, in themselves, affect cognition (Bender et al., 2006; Bender et al., 2007; Castellon et al., 2004; Eberling et al., 2004; Falleti et al., 2005; Jenkins et al., 2004; Palmer et al., 2008; Phillips et al., 2011; Schilder et al., 2009; Shilling et al., 2003).

In prospective within-subject designs, repeated measurement of the same subject before and after treatment serves to control for stable host and disease factors. One important disadvantage of this approach is that practice effects associated with repeated testing of an individual can mask subtle adverse effects of treatment. Investigators attempt to mitigate this by using parallel alternative forms of tests but practice effects encompass far more than just content-based savings (e.g., reduced anxiety, an established strategy) and, thus, it is still important to include a control group to measure and account for these effects. In fact, without a control group, it may even appear that cancer patients' cognition improves after chemotherapy (Wefel et al., 2004). The ICCTF recommends inclusion of both a disease control group and a healthy control group even in prospective longitudinal studies (in the event that the practice effect may be different in cancer patients from that in healthy individuals) (Wefel et al., 2011). However, we have empirically addressed the issue of control groups. We obtained the same results with our longitudinal data whether we used a disease control group, a healthy control group, or published norms (unpublished observations).

Approach to Data Analysis

The effect sizes in this field are typically quite modest and, thus, the data analytic techniques used can significantly influence the conclusions drawn from a particular study. One key difference among studies is whether data are analyzed at the aggregate level (e.g., comparing group means) or at the level of individual impairment or decline (comparing the frequency of impairment or decline across groups). In that CRCI affects only a subgroup of patients, these subtle effects can be easily obscured in comparing group means. Several studies have failed to find group differences in mean cognitive function but have found significant differences in the frequency of cognitive impairment or decline between the chemotherapy and control groups (Wefel et al., 2004; Stewart et al., 2008). However, as elegantly demonstrated by Shilling et al. (2006) and Schilder et al. (2010), the use of different definitions of impairment (e.g., the extent of negative change in a given score as well as how many scores showing decline would constitute impairment) greatly influences estimates of risk. The ICCTF generally recommends that, in order to be considered impaired, the standardized scores on a given measure should be −1.5 or lower and that the number of such scores required to consider a given participant cognitively impaired should be determined in accordance with the probability of obtaining such a result by chance given the size of the test battery (Wefel et al., 2011).

When data are analyzed at the aggregate level, longitudinal modeling techniques are recommended over analysis of variance or t tests, in that they allow for differing numbers and spacing of assessments across respondents and are more robust to violation of assumptions (Wefel et al., 2011). Different statistical approaches have been taken to evaluate decline at the individual level. The ICCTF recommends approaches that account for practice effects, such as the reliable change index with practice effects model or regression-based change models (Wefel et al., 2011). We have argued in favor of the latter because it allows the inclusion of important

covariates (Ouimet, Stewart, Collins, Schindler, & Bielajew, 2009). Differences among studies in the choice of covariates used in the analysis may also contribute to inconsistency in results. Most studies have included, as a minimum, measures of mood and fatigue, and this would seem advisable.

Cognitive Measures Used

Another critical issue concerns whether cognition is assessed subjectively, by means of a self-report questionnaire, or objectively, by means of performance-based neuropsychological testing. In most cases, subjective measures of cognitive impairment correlate poorly, if at all, with objective measures, indicating a need to include both (Biglia et al., 2012; Cheung, Tan, & Chan, 2012; Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Jansen, Cooper, Dodd, & Miaskowski, 2011; Pullens, De Vries, & Roukema, 2010). Among neuropsychological studies, the size and composition of the test battery differs widely. The selection of tests can contribute to overestimation or underestimation of true cognitive impairment (Shilling, Jenkins, & Trapala, 2006). Many neuropsychological tests may not be sensitive enough to detect the subtle changes associated with chemotherapy or may fail to target the affected cognitive domains. For example, basic mental status screening tests are probably not sensitive enough for this purpose (Iconomou, Mega, Koutras, Iconomou, & Kalofonos, 2004). The number of neuropsychological measures used may also be a critical determinant of study outcome as the likelihood of finding an impaired score or abnormal decline in a score will generally increase in keeping with the size of the test battery (Ingraham & Aiken, 1996). The ICCTF has recommended a core battery of neuropsychological measures that are well validated, sensitive to the types of deficits observed in cancer patients, and appropriate for multinational use (Wefel et al., 2011).

What Do We Know Now?

Is There an Association Between Chemotherapy Exposure and Cognitive Disturbance?

Despite considerable variability in methodology and findings, most of the studies done in this area over the past 20 years support the idea that chemotherapy-exposed BC patients are at increased risk of cognitive dysfunction. Wefel and Schagen (2012) recently tabulated results of studies conducted in BC patients between 1995 and 2012 and found that 78% of cross-sectional studies (n = 23) and 69% of prospective longitudinal studies (n = 26) found evidence in support of CRCI.

Is the Cognitive Disturbance Caused by Chemotherapy-Related Neurotoxicity?

It is now quite clear that many factors contribute to cognitive disturbances in cancer patients, including anxiety, depression, hormonal fluctuations, fatigue, other treatments, and the disease itself. Recent prospective studies find cognitive dysfunction in a substantial portion of cancer patients even prior to starting adjuvant therapy (Cimprich et al., 2010; Schilder et al., 2010). MRI measures of brain structure and function have also shown pretreatment differences between cancer patients and healthy controls (Cimprich et al., 2010; Scherling, Collins, MacKenzie, Bielajew, & Smith, 2011; Scherling, Collins, MacKenzie, Bielajew, & Smith, 2012a; Scherling, Collins et al., 2012b) which cannot be fully accounted for by depression, anxiety, fatigue, or surgical factors, suggesting that they may be due to the disease itself. In recognition of this, it has been suggested that terms such as "chemofog" and "chemobrain" be replaced with a more encompassing term such as "cancer- or cancer-therapy- related cognitive change" (Hurria, Somlo, & Ahles, 2007). At the same time, there is also mounting evidence that chemotherapy exposure is a significant contributing factor to cognitive symptoms in cancer survivors.

As recently as 8–10 years ago, a BC patient complaining of cognitive disturbances during chemotherapy was likely to be prescribed an antidepressant. This belief that cognitive disturbances were psychogenic was supported by the fact that most studies found poor, if any, correlation between patients' subjective reports of cognitive disturbance and objective measures of cognitive performance (Biglia et al., 2012; Cheung et al., 2012; Hutchinson et al., 2012; Jansen et al., 2011; Pullens et al., 2010). Subjective complaints were found to correlate more strongly with measures of emotional state, reinforcing this idea that what a patient referred to as chemo fog was a psychological reaction to stress. However, recent findings suggest that the poor correlation between subjective and objective cognitive measures may have to do with fundamental differences in measurement parameters (Hutchinson et al., 2012). It seems likely that patients' self-assessments capture perceived decline from premorbid function, whereas, in most cases, the neuropsychological scores do not (typically, static scores are used in these correlations). In analyzing our own data, we found that an objective pretreatment–posttreatment measure of cognitive change did correlate with subjective reports, whereas a one-time posttreatment objective measure did not (unpublished observations). Deprez et al. (2012) also found a significant correlation between objective and subjective measures when using a cognitive change score. It has also been suggested that subjective and objective measures often tap different cognitive domains and that this may contribute to their poor correlation. In relating subjective complaints to neuropsychological test scores, Deprez et al. also focused on specific, relevant, and compatible cognitive domains. Other investigators who have taken this more focused approach (Bender et al., 2006; Ganz, 2012) have also found significant subjective–objective correlations. Moreover, although cognitive complaints do tend to correlate with emotional functioning, most studies find that this cannot fully account for the objective

neuropsychological abnormalities (Biglia et al., 2012; Collins, MacKenzie, Tasca, Scherling, & Smith, 2013; Hedayati, Alinaghizadeh, Schedin, Nyman, & Albertsson, 2012; Stewart et al., 2008; Wefel & Schagen, 2012; Wieneke & Dienst, 1995). Clearly, there is more to the story than psychological distress.

Increasingly sophisticated clinical studies, supplemented by animal and brain imaging research, are producing objective evidence that chemotherapy is neurotoxic and can contribute to cognitive disturbances. An early study by van Dam et al. (1998) hinted at this, by suggesting a dose–response relationship. They compared cognitive function in high-risk BC patients who had been randomly assigned to receive high-dose or standard-dose chemotherapy and in early-stage BC patients receiving no systemic adjuvant treatment. This study, conducted an average of 2 years after completion of chemotherapy, revealed a significant difference among the groups in risk of cognitive impairment, with 32% of the high-dose group showing cognitive impairment compared with 17% of the standard-dose group and 9% of the control group. In a follow-up to that study, these investigators also showed that their high-dose group was significantly more likely to show late electrophysiological abnormalities (Kreukels et al. 2005; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001) than the control patients, with the risks in the standard-dose group falling somewhere in between. This group has corroborated their findings in a prospective randomized controlled study which showed that BC patients receiving high-dose therapy were at a significantly elevated risk of cognitive decline, whereas the standard-dose group was not (Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006). Other cross-sectional studies have identified duration of treatment and number of chemotherapy cycles as risk factors for cognitive disturbance (Ahles et al., 2002; Jansen et al., 2011; Wieneke & Dienst, 1995). Magnetic resonance spectroscopy studies in BC patients have shown white matter

abnormalities following high-dose chemotherapy that were not detectable following lower-dose induction chemotherapy (Brown et al., 1995; Brown et al., 1998; Stemmer, Stears, Burton, Jones, & Simon, 1994).

We capitalized on this notion of "dose–response" relationship as an approach to establishing causality in our latest prospective longitudinal study (Collins, MacKenzie, Tasca, Scherling, & Smith, 2013). We assessed BC patients after each cycle of chemotherapy and observed a linear decline in cognitive function even after controlling for baseline performance, practice effects, and changes in mood and fatigue. We submit that this clear dose–response relationship strongly suggests that chemotherapy is indeed a cause of cognitive disturbance.

Compelling evidence of chemotherapy neurotoxicity also comes from animal studies, which allow tighter control of the factors that confound clinical research. These studies have shown persistent performance decrements in animal models of learning and memory following exposure to chemotherapeutic agents, as well as decreased neurogenesis and cellular proliferation and increased cellular death within areas of the brain such as the hippocampus and the subventricular zone (Seigers & Fardell, 2011; Winocur et al., 2012).

Further causal evidence for the neurotoxicity of chemotherapy comes from structural and functional neuroimaging studies, which show differences in cerebral blood flow (de Ruiter et al., 2011; Kesler, Kent, & O'Hara, 2011; Silverman et al., 2007) and in the volume of white and grey matter in chemotherapy-treated BC patients compared with controls (Abraham et al., 2008; Brown et al., 1995; Brown et al., 1998; Deprez et al., 2011; Deprez et al., 2012; de Ruiter et al., 2012; Ferguson, McDonald, Saykin, & Ahles, 2007; Inagaki et al., 2007; Koppelmans et al., 2012b; Stemmer et al., 1994). A landmark neuroimaging study was that of McDonald et al. (2010) as it was the first controlled prospective MRI study in the field. They found significant

decreases in gray matter density in bilateral frontal, temporal, and cerebellar regions as well as the right thalamus in BC patients shortly following completion of chemotherapy that were not evident in either a disease or healthy control group. These changes could not be accounted for in terms of postsurgical effects, disease stage, psychiatric symptoms, psychotropic medication, or hormonal treatment status, suggesting that they were due to the effects of chemotherapy. New techniques such as diffusion tensor imaging (DTI) are contributing to a better understanding of the nature and scope of the underlying structural changes and suggest that white matter may be particularly vulnerable to the neurotoxic effects of chemotherapy and that changes in white matter function may persist for years after completion of treatment (de Ruiter et al., 2012).

Functional MRI (fMRI) and positron emission tomography (PET) studies have also been conducted in cancer patients. These studies show patterns of brain activation in response to a cognitive challenge and provide a "window on the working brain." Abnormalities have been observed in a number of brain areas in response to a variety of activation tasks. For example, increased activation in the prefrontal cortex and the cerebellum has been observed in patients during a working memory task (Silverman et al., 2007). Increased activation has been interpreted as an indication that the brain is having to compensate for insult by recruiting a wider neural network than would normally be required to support the task. These aberrations in neural activation patterns can be observed in the absence of differences in performance on the cognitive activation tasks and may account for patient complaints of cognitive decline in the absence of actual performance decrements (i.e., they may experience their cognitive processing as less efficient and more tiring). Regional decreases in brain activation have also been observed, and are construed as evidence that the damage to the brain has surpassed its capacity to compensate.

Neuroimaging studies in this field are restricted by the same methodological flaws that

characterized the early neuropsychological studies, including the failure to conduct pretreatment baseline assessment. Studies by our group revealed significant pretreatment differences in white and grey matter volume (whole brain and regional) between patients and controls (Scherling et al., 2012b), as well as in brain activation patterns on fMRI (Scherling et al., 2011; Scherling et al., 2012a), emphasizing the importance of prospective longitudinal designs. We have published one of the first prospective longitudinal fMRI studies in BC patients (Zunini et al., 2012), which showed abnormal changes in the activation pattern in chemotherapy-treated patients and thus lends further support to the idea that chemotherapy affects neural function.

Functional imaging studies, although holding great promise, are in their infancy and the significance of the findings is difficult to interpret. For example, both increases and decreases in brain activation are construed as evidence of brain dysfunction, and high numbers of comparisons are conducted in small samples, raising concerns about inflated type I error rates. Improvement of this situation will require that studies become more focused and hypothesis-driven.

The recent study of Deprez et al. (2012) constitutes a significant advance in the imaging literature and a model for future studies. It is one of the first studies to examine relationships between changes in neuropsychological and neuroimaging measures in a well-controlled prospective design. Thirty-five BC patients who received chemotherapy, as well as a group of cancer patients not treated with chemotherapy and a healthy control group, were repeatedly assessed with a comprehensive neuropsychological battery and DTI. The results showed significant decline in white matter integrity in multiple tracts involved in cognition, significant decreases on neuropsychological tests of attention and memory, and significant correlations between the neuropsychological and imaging results in the chemotherapy group. This cross-

validation from the neuropsychological and imaging investigations is much more compelling than either finding in isolation.

What Is the Frequency/Rate of Occurrence of CRCI?

There is general consensus among researchers that only a subgroup of BC patients develop CRCI; however, the estimated rate of impairment ranges from 17 to 78% (Wefel & Schagen, 2012). Clearly, this variation has to do with the aforementioned methodological differences. In a recent longitudinal study conducted by our group that met the recommendations of the ICCTF (Collins et al., 2013), we found that approximately one third of patients showed cognitive decline over the course of their chemotherapy. This is in close agreement with a previous longitudinal study conducted by our group (Stewart et al., 2008) and with figures reported by Jansen et al. (2008).

What Cognitive Domains Are Impaired?

All cognitive and psychomotor domains have been implicated in one study or another (Ahles et al., 2010; Collins et al., 2013; Jansen et al., 2011; Kyale et al., 2010; Quesnel, Savard, & Ivers, 2009; Tager et al., 2010; Vearncombe et al., 2009). Disagreement among studies as to the most vulnerable cognitive domains is primarily due to the multifactorial nature of neuropsychological tests and the relatively arbitrary assignment of a given test to a particular cognitive domain. In our recent longitudinal study (Collins et al., 2013), we assigned tests to cognitive domains on empirical grounds by means of principal components analysis. This resulted in four cognitive factors which seemed to correspond to processing speed, working memory, visual memory, and verbal memory. We obtained a large effect size for working memory and processing speed, and significant but small effect sizes for the domains of visual memory and verbal memory. This fits well with patients' self-reports of diminished cognitive

efficiency and difficulties with multitasking. It is also consistent with results of recent imaging (Abraham et al., 2008; Deprez et al., 2011; Deprez et al., 2012) and animal (Seigers & Fardell, 2011) studies showing that the toxic effects of chemotherapy may affect white matter. Alternatively, working memory and processing speed scores may have been more sensitive because they were time-dependent and because very subtle cognitive deficits may be better captured by speed than by accuracy of response. For this reason, computerized testing is attracting increasing interest from researchers in this field because it allows for accurate measurement of response time in milliseconds.

It could well be that chemotherapy-related neurotoxicity results in a generalized decrease in mental processing speed and capacity rather than focal cognitive deficit and that this may be manifested in preexisting areas of weakness that will differ from one individual to another. This could partly account for why studies are more likely to find significant effects if impairment is analyzed at the individual level independently of a specific cognitive domain.

What Is the Severity and Duration of CRCI?

Meta-analyses of BC studies (Falleti et al., 2005; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Jansen, Miaskowski, Dodd, & Dowling, 2007; Jim et al., 2012; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006) consistently yield small to moderate effect sizes (−0.2 to −0.5 range), indicating a subtle negative effect of chemotherapy on cognitive functioning. Anderson-Hanley et al. (2003) found larger effect sizes (approaching 1.0 in the domains of executive function and verbal memory), but their analysis included studies of various cancer populations and covered a broader range of disease severity.

Retrospective, cross-sectional studies have found evidence of impaired cognitive functioning in BC patients as long as 21 years after treatment (de Ruiter et al., 2011;

Kopplemans et al., 2012a), and irregularities in brain structure and function have also been reported in long-term BC survivors 4–21 years after treatment. Functional differences include altered activation patterns on fMRI (de Ruiter et al., 2011) and PET (Silverman et al., 2007) and lower amplitude and increased latency of the P3 component in electrophysiological studies (Kreukels et al., 2005; Kreukels et al., 2006; Kreukels, van Dam, Ridderinkhof, Boogerd, & Schagen, 2008a; Kreukels et al., 2008b). Structural studies using various MRI techniques (voxel-based morphometry, spectroscopy, DTI) show reductions in brain volume (de Ruiter et al., 2012; Koppelmans et al., 2012), axonal injury, and decreased white matter integrity (de Ruiter et al., 2012).

More recent prospective longitudinal studies with mid-range to long-range follow-up (9 months to 4 years) generally find that CRCI remits after termination of chemotherapy (Ahles et al. 2010; Collins, MacKenzie, Stewart, Bielajew, & Verma, 2009b; Jansen et al., 2011; Weis, Poppelreuter, & Bartsch, 2009). However, there appears to be a small subgroup showing more intractable cognitive dysfunction (Weis et al., 2009), and one recent prospective longitudinal study (Wefel, Saleeba, Buzdar, & Meyers, 2010) indicated the occurrence of new, delayed cognitive decline in 29% of patients following treatment completion (we question if this might be partly due to postchemotherapy commencement of hormonal therapy). Recent epidemiological studies have looked at whether or not chemotherapy exposure is a risk factor for the later development of dementia. Heflin et al. (2005) found that, among 486 monozygotic geriatric twin pairs discordant for cancer, long-term cancer survivors were twice as likely to be diagnosed with dementia as their unaffected sibling. In very large cohorts of elderly BC survivors, Heck et al. (2008) found a significantly higher risk of dementia in women treated with chemotherapy than in those patients not exposed to chemotherapy, whereas Baxter et al. (2009)

reported that past chemotherapy was not associated with a greater risk of developing dementia and Du et al. (2010) found that dementia risk was significantly lower in patients who had received chemotherapy in the past. We simply do not know yet whether or not chemotherapy exposure increases the risk of dementia later in life.

What Is the Impact of CRCI in Everyday Life?

In an online survey conducted in 2010 by the Canadian Breast Cancer Network to determine the economic impact of BC, it was determined that chemotherapy had important economic implications for survivors. Among some 450 respondents—women with a BC diagnosis in the previous 5 years—8% reported that "chemobrain" was a significant barrier to returning to work. Those women who had received chemotherapy had the greatest reduction in household income, had taken more time off work (as had their family members), were more likely to have had to quit their jobs, and had a greater perception that the financial burden imposed by their illness would impact their long-term health. Chemotherapy exposure also emerged as a significant predictor of work changes after cancer in a population-based study with a more heterogeneous cancer population (Mols, Thong, Vreugdenhil, & van de Poll-Franse, 2009). Smaller cohort studies of BC patients that included neuropsychological testing have reported an association between cognitive functioning and work-related outcomes (perceived ability to work and actual likelihood of return to work) (Nieuwenhuijsen, de Boer, Spelten, Sprangers, & Verbeek, 2009; Wefel et al., 2004). Reid-Arndt et al. (2009) reported an association between executive functioning deficits and decreased productivity, community involvement, and social role functioning in BC patients 1 month after chemotherapy. In sum, evidence is beginning to accrue that, although CRCI may be subtle, it has important functional implications and can adversely affect quality of life for cancer survivors.

What Are the Risk Factors for CRCI?

In their recent prospective longitudinal study, Ahles et al. (2010) found that older age and lower cognitive reserve were risk factors for short-term treatment-related reductions in processing speed, and that additional treatment with hormonal therapy was a risk factor for more persistent decline in verbal ability. The results of our initial study were compatible with this, likewise indicating that lower educational level (considered an index of cognitive reserve) was a risk factor for short-term decline (Stewart et al., 2008) and that patients who went on to receive hormonal therapy after chemotherapy were more likely to show persistent decline at the 1-year follow-up (Collins et al., 2009b). Wefel et al. (2010) found that the delayed decline observed in almost one third of their participants was related to baseline performance, further hinting at neural reserve as a risk factor for long-term deficits. At the same time, other studies have failed to find any correlation between CRCI and age or cognitive reserve (at least as reflected in education) (Wefel & Schagen, 2012). There may also be genetic risk factors for CRCI. Ahles et al. (2003) found that, among long-term survivors of BC and lymphoma treated with chemotherapy, those who carried an ε4 allele of the apolipoprotein E gene (which is a genetic risk factor for other cognitive disorders, including Alzheimer's disease) scored lower on cognitive tests than those without an ε4 allele. However, to our knowledge, these results have not been replicated. Higher dose of chemotherapy, whether we are talking about dose intensity (van Dam et al., 1998) or cumulative dose (Collins et al., 2013; Wieneke & Dienst, 1995) is a well-established risk factor. Most prospective studies find no association between cognitive and menopausal status, although Jenkins et al. (2006) reported that BC patients who experienced a chemotherapy-induced menopause were more likely to show cognitive decline over the course of treatment than those who did not. As noted, most studies fail to find a correlation between

cognitive change and psychological factors, such as depression, anxiety, and fatigue (Jansen et al., 2011; Wefel & Schagen, 2012). The differential risk associated with specific chemotherapeutic agents and regimens is not well characterized as yet. This awaits larger multisite studies with sufficient sample sizes to provide adequate power for this type of subgroup analysis.

Conclusions and Future Directions

Although complaints of "chemo fog" have existed since the institution of systemic adjuvant chemotherapy, it is only in the last 15–20 years, with increasing use of adjuvant chemotherapy and a growing cohort of cancer survivors with a focus on quality of life, that we have seen serious systematic study of this problem. It has proved to be a rather elusive phenomenon—it seems that only a subgroup of patients are affected and the cognitive changes are generally subtle. As a result, methodological variations from study to study can greatly influence whether or not cognitive changes are detected. Furthermore, there are a host of other factors that can influence cognition in cancer patients—anxiety, mood disturbance, other medications, and biological responses to the disease itself—and confound the study of CRCI. In spite of this, with increasing collaboration among researchers and resulting refinement and harmonization of study methods, the "fog" surrounding chemo fog is beginning to clear.

The preponderance of studies shows that cancer patients are at increased risk of mild cognitive impairment. In many instances, abnormalities can be detected even prior to commencement of systemic adjuvant treatment, suggesting that factors other than chemotherapy contribute to these cognitive changes. However, a prospective study that controlled for practice effects indicated that about one third of BC patients, the most widely studied population, show significant cognitive decline over the course of treatment. Although many of these women still

score within normal limits on neuropsychological testing after chemotherapy, there is now some evidence to suggest that the decline is sufficient to affect quality of life (e.g., return to work) for some individuals. Given the impossibility of doing randomized controlled trials in this field, the type and duration of treatment are inextricably confounded with host and disease characteristics, making it very difficult to establish whether chemotherapy is truly a causative factor. However, data from animal studies and from imaging studies, along with evidence of a dose–response relationship between chemotherapy and cognitive disturbance, strongly indicate that systemic chemotherapy can be neurotoxic and that its effects on the central nervous system do contribute to the cognitive changes. Psychological distress—long thought to be responsible for the cognitive changes in cancer patients—does not prove to be significantly related to the neuropsychological changes. Longitudinal studies that extend beyond the end of treatment suggest that, in most cases, CRCI abates over time (Collins et al., 2009b; Schagen et al., 2002). However, both cross-sectional and longitudinal studies indicate that there may be a small subgroup of patients who experience more chronic, perhaps even permanent, cognitive changes. The risk factors for this are still not well understood but may include chemotherapy dose and neural reserve. At this time, there is no evidence to suggest that chemotherapy exposure increases the risk of developing dementia later in life.

An understanding of the potential cognitive side effects of cancer treatment is critical to making informed decisions about treatment, particularly for patients with a good prognosis for whom adjuvant chemotherapy minimally reduces the risk of disease-free survival. It is, moreover, important that we screen for CRCI in our patients so that we can provide education, support, reassurance, and intervention for those patients who are affected. Future studies should aim to provide a better understanding of the relative neurotoxicity of specific chemotherapeutic

agents and regimens used in the adjuvant setting as well as host factors which place a given individual at risk of developing cognitive side effects, as such information can be used to personalize treatment recommendations. Further study of the mechanisms of neurotoxicity is also a priority for future research, as this will guide the development of neuroprotective and preventive strategies. Ultimately, we will seek to develop new chemotherapeutic drugs with minimal neurotoxicity and, towards this aim, we should consider routinely including cognitive testing as a secondary outcome in chemotherapy drug trials.

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Objective–subjective disparity in cancer-related cognitive impairment: does the use of change measures help reconcile the difference?

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Abstract

Objective: Studies to date have found little correlation between subjective and objective measures of cognitive function in cancer patients, making it difficult to interpret the significance of their cognitive complaints. The purpose of this study was to determine if a stronger correlation would be obtained using measures of cognitive change rather than static scores.

Methods: Sixty women with early stage breast cancer underwent repeated cognitive assessment over the course of chemotherapy with a neuropsychological test battery (objective measure) and with the FACT-Cog (subjective measure). Their results were compared to 60 healthy women matched on age and education and assessed at similar intervals. We used multilevel modeling, with FACT-Cog as the dependent measure and ordinary least squares slopes of a neuropsychological summary score as the independent variable, to evaluate the co-variation between the subjective and objective measures over time

Results: Measures of both objective and subjective cognitive function declined over the course of chemotherapy in the breast cancer patients but there was no significant relationship between them, even when using change measures. Change in objective cognitive function was not related to change in anxiety or fatigue scores but the decline in perceived cognitive function was associated with greater anxiety and fatigue.

Conclusions: The discrepancy in objective and subjective measures of cognition in breast cancer patients cannot be accounted for in terms of a failure to use change measures. Although the results are negative, we contend that this is the more appropriate methodology for analyzing cancer-related changes in cognition.

Background

Cognitive dysfunction is a commonly reported adverse effect of cancer and its treatment among breast cancer patients (Jean-Pierre et al., 2011; Pullens, De Vries, & Roukema, 2010). Research over the past 3 decades has substantiated these reports, providing objective evidence of significant, long-term impacts of cancer, and chemotherapy treatment on cognitive and neural functioning (Wefel, Kesler, Noll, & Schagen, 2015; Wefel & Schagen, 2012). This same research, however, has generally failed to find any correlation between patients' subjective complaints and objective measures of cognitive performance. Most studies find that self-report measures correlate more strongly with psychological factors such as depression and anxiety than with objective neuropsychological measures (Debess, Riis, Engebierg, & Ewertz, 2010; Green, Pakenham, & Gardiner, 2005; Hermelink et al., 2010; Hermelink et al., 2007; Jenkins et al., 2006; Mehnert et al., 2007; Pullens et al., 2010) which casts some doubt on the validity of patients' complaints.

Different investigators have suggested that the failure to find a subjective–objective relationship might be because of limitations in study design and data analysis (Ganz et al., 2013; Hutchinson, Hosking, Kichendasse, Mattiske, & Wilson, 2012; Pullens et al., 2010; Shilling & Jenkins, 2007). For example, some studies (such as Hermelink et al., 2010 and Jansen, Cooper, Dodd, & Miaskowski, 2011) failed to include a control group and thus did not take account of practice effects associated with repeated neuropsychological testing. The lack of control group tends to result in underestimation of the objective impairments thus making subjective complaints appear inflated in comparison. Another methodological concern is that the traditional neuropsychological tests commonly used in these studies may not tap the areas of cognitive compromise that the patients experience in their day-to-day lives, and that they are referencing in

their subjective complaints; in other words, that objective and subjective instruments are not measuring the same construct (Pullens et al., 2010).

We contend that a third methodological issue is the failure to assess how subjective and objective cognitive measures co-vary across time. Most longitudinal studies have used simple bivariate correlation to assess the relationship between subjective and objective measures at a given time point rather than assessing the changes in each measure across time to determine their co-variation. The relationship between subjective and objective measures may be underestimated with such a simplistic approach.

It is important that we accurately interpret cognitive complaints in cancer patients if we are to effectively prevent and treat them. Towards this end, we must seek to better understand the discrepancy between subjective and objective measures of cognitive dysfunction. In the current analyses, we used previously published longitudinal data (Collins, MacKenzie, Tasca, Scherling, & Smith, 2013) to more adequately address the relationship between perceived cognitive function and cognitive performance by using multilevel modeling (MLM) to examine how these variables change together over time. In this instance, where we have multiple repeated measures for each participant, MLM is a superior statistical approach to traditional ordinary least squares (OLS) methods for evaluating changes at the group level. This is because it is more robust with respect to violations of assumptions and can better support datasets with missing data (Singer & Willett, 2003), a common occurrence in longitudinal studies with multiple assessment points.

Methods

This is a secondary analysis of data collected between September 2008 and April 2010 as part of a past study addressing cognitive changes in breast cancer patients during and following chemotherapy. Full details as to study methodology, and results from primary analyses, have

been previously published (Collins et al., 2013).

Participants

Patients were recruited from the Ottawa Hospital Regional Cancer Centre with the help of their treating oncologists. The final sample consisted of 60 women with early stage breast cancer who underwent mastectomy or lumpectomy and received various regimens of adjuvant chemotherapy. This was a pairwise comparison design study such that every patient had her own corresponding non-cancer control matched on sex-, age-, and education, and assessed at roughly equivalent inter-test intervals. The control participants were either nominated by the breast cancer patient or recruited through advertisement. All participants were 65 years of age or younger to reduce the risk of age-related cognitive disorders. Participants had to be fluent in English with at least a grade-8 level of education. Participants were excluded if: (a) they had received adjuvant anti-estrogen therapy prior to completing chemotherapy, (b) they had a previous history of cancer, chemotherapy, radiotherapy, serious psychiatric or neurological illness, or substance abuse, or (c) if they developed any inter-current cancer or illness affecting cognition during the study. The study was approved by the Ottawa Hospital Research Ethics Board and informed consent was obtained from all participants.

Procedure

Women were tested shortly before commencing chemotherapy (baseline, T0) and after every chemotherapy cycle (T1–T6). The number of chemotherapy cycles ranged from 4 to 8, depending on the chemotherapy regimen, and so the final treatment phase testing session for any given patient may have been T4, T5, or T6 (patients who received 8 chemotherapy cycles were re-tested after every second cycle). Testing between chemotherapy cycles was performed shortly before the next cycle commenced (usually within a week) to allow sufficient time for acute side

effects of treatment to subside. The inter-test interval varied depending on the participant's

particular chemotherapy regimen (number of cycles and interval between cycles), and

complications of treatment in some cases (such that a study visit or a chemotherapy cycle itself

was delayed or skipped), and ranged from 12 to 58 days. Control participants were tested at the

same time intervals as their matched breast cancer participant (the maximum difference between

group means in test–retest interval was 2 days). Post-treatment testing sessions lasted 1–1.5 h;

the baseline assessment lasted somewhat longer (2–2.5 h) because of the inclusion of the social

and medical history. A battery of standardized neuropsychological tests and a computerized

cognitive test battery were administered to the patients and the controls at every testing session

(including baseline), along with questionnaires addressing perceived cognition, mood, fatigue,

and physical symptoms. Except for T0, participants were given questionnaires at each study visit

for the next test session, with instructions to complete them within 24 h of their next study visit.

If the participant did not bring the completed questionnaires, they were done at the study visit

upon completion of the objective neuropsychological testing.

Measures

      Objective cognitive function. Cognition was objectively assessed with a conventional

neuropsychological battery comprised of pencil-and-paper tests, as well as CNS-Vital Signs

(CNS-VS) (Gualtieri & Johnson, 2006), a computerized test. The tests administered and the

variable(s) used from each test are listed by cognitive domain in Table 1. Alternate versions were

used on different sessions where available. Psychometric properties of all the neuropsychological

tests have previously been established and these tests have been deemed reliable and valid

(Army, 1944; Benedict, 1997; Brandt & Benedict, 2001; Brown, 1958; Delis, Kaplan, & Kramer,

2001; Fischer, Jak, Kniker, Rudick, & Cutter, 2001; Gualtieri & Johnson, 2006; Lezak,

Howieson, Bigler, & Tranel, 2012; Strauss, Sherman, & Spreen, 2006; Wechsler, 1997).

An objective cognitive summary score (COGSUM) was calculated by standardizing the raw score for each participant on each cognitive measure (from computerized and non-computerized tests, see Table 1) at each time point (using the mean and standard deviation on that variable in the control group) and then averaging these standardized scores. Higher COGSUM scores are associated with better functioning. Domain-specific cognitive summary scores were also calculated as some researchers, such as Ganz et al. (2013), have found some relationship between subjective and objective scores when using more domain-specific cognitive measures. Given that most neuropsychological tests are multi-factorial, and are assigned to various cognitive domains by different clinicians and researchers, we used principle components analysis (PCA) on baseline (T0) neuropsychological scores, pooled for chemotherapy and control groups, to empirically derive our domains. The results of this PCA revealed four clear clusters of tests, which roughly corresponded to the domains of verbal memory, visual memory, working memory, and processing speed. There were some anomalies in this classification of tests as compared to conventional conceptual assignment of particular neuropsychological tests to cognitive domains. However, these anomalies were not particularly difficult to reconcile. For example, the fact that the CNS-VS Working Memory Index loaded on what we refer to as the Visual Memory domain score rather than our Working Memory domain score likely reflected the fact that the CNS-VS Working Memory Index is largely based on a visual n-back task. Summary scores were obtained for the PCA-derived domains by averaging the standardized scores on tests within each cluster at each time point (i.e., we did not use a factor score per se and assignment of tests to domain was held constant across all test sessions according to the PCA done on baseline scores).

Subjective cognitive function. Subjective cognitive function was assessed using Version 3 of the Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog) (Wagner, Sweet, Butt, Lai, & Cella, 2009). The FACT-Cog is a 37-item self-report measure of subjective cognitive functioning and quality of life as it relates to cognitive impairments. Each item is rated on a 5-point Likert scale from 0 (never, not at all) to 4 (several times a day, very much), with higher overall scores indicating better functioning. Subscales from the FACT-Cog include Perceived Cognitive Impairments (PCI), comprised of negatively worded items, Perceived Cognitive Abilities (PCA), comprised of positively worded items, Comments from Others (to assess how the respondent feels others perceive her cognitive ability), and Impact on Quality of Life. Psychometric characterization of the PCI and PCA scales indicates that they measure distinct constructs (Lai et al., 2009) and scoring instructions for the FACT-Cog indicate that subscale scores are not to be combined. We therefore used the PCI score as our subjective cognitive measure. The FACT-Cog items assess various domains of cognitive functioning including memory, attention and concentration, and language. It has been validated for use with cancer patients (Jacobs et al., 2007; Wagner et al., 2009).

Psychological function. Psychological function was assessed using the Profile of Mood States (POMS) (McNair, Lorr, & Droppleman, 1992). The POMS is a 65-item self-report questionnaire designed to assess 6 dimensions of mood: tension–anxiety, depression–dejection, anger– hostility, vigor–activity, fatigue–inertia, and confusion– bewilderment. The items are mood adjectives, which the participant rates on a 5-point Likert scale from 0 (not at all) to 4 (extremely) based on how well the adjective describes how they have been feeling in the past week. The anxiety scale and the fatigue scale were used in the current analyses. The psychological distress experienced by cancer patients includes both anxiety and depressive

symptoms. However, because the POMS anxiety and depression scores were highly correlated in the breast cancer patients (correlation exceeded 0.8 at most time points), we included only the anxiety score to avoid multi-collinearity. The anxiety scale was chosen because it correlated more strongly than depression with the FACT-Cog PCI.

Statistical Analysis

Data were screened and cleaned for missing data and normality. To retain as much data as possible, outliers were Winsorized (Tabachnik & Fidell, 2013). There were relatively few missing data in this data set (the maximum amount of data replaced for any given individual was <2%). Where an individual skipped an item on a questionnaire, scores were prorated. When participants missed entire test sessions, or failed to complete one or more questionnaires at a given session, missing data were not replaced as MLM will estimate reliable parameters using maximum likelihood estimation (one of the strengths of this method). As scores on all neuropsychological tests were required in order to calculate COGSUM, missing neuropsychological scores were replaced in cases where neuropsychological testing was undertaken but not all measures were completed. The missing scores were replaced by the average of scores on the same neuropsychological measure at the surrounding time points, where possible. When an average of surrounding time points was not possible, scores were either replaced with the average from all time points for that participant or with the group mean for that time point (if no other time point scores were available). Even after Winsorizing, POMS Anxiety and Fatigue were positively skewed and FACT-Cog PCI was negatively skewed. These distributions were corrected with square-root transformation (applied for all test sessions) (Tabachnik & Fidell, 2013).

Bivariate correlation was used to assess the relationship between COGSUM and FACT-

Cog in the patient group at T6 (i.e., post-chemotherapy). Univariate MLM was used to model the co-variation of subjective and objective measures of cognitive functioning over time. Standardizing COGSUM and FACT-Cog scores to controls at each respective time point served to account for any practice effects from repeated test administration and to set the slope of the control group over time to zero (as the mean for the control group at each time point is de facto zero). Thus, only the chemotherapy group data were used for analyses. The two-level model was set up with participants at level two and session (i.e. chemotherapy cycle T0-T6 uncentered) at level one. In analyses involving COGSUM and FACT-Cog, the subjective cognitive measure was designated as the dependent variable and the objective cognitive measure was treated as an independent variable.

OLS slopes derived from simple two-variable growth models served as the independent variables in more complex models designed to evaluate whether the slopes of these variables were related to changes in FACT-Cog over time (i.e., across testing sessions, with accumulating chemotherapy dosage). OLS values were obtained by setting a linear model with the independent variable of interest as the dependent variable and session as the sole predictor at level one. This model was run for each independent variable of interest and a slope of that variable across sessions was obtained for each participant. These slope values, reflecting change over time, were then used as independent variables for subsequent analyses.

A simple model examining the effect of COGSUM slope on FACT-Cog was evaluated first, then other predictors of interest—POMS Anxiety slope, POMS Fatigue slope, and age— were added to the model as independent variables to determine their contribution to variability in the slope of COGSUM over time. We next analyzed if the relationship between subjective and objective cognitive measures differed by cognitive domain by replacing COGSUM as a predictor

with one or all of the domain-specific cognitive summary OLS scores. All level two variables were grand mean centered.

Data cleaning and summary score calculations were conducted using SPSS (v. 22). MLM analyses were conducted using HLM software (v. 7.01). Type I error rate was set at 0.05.

Results

Sample Characteristics

Table 2 lists demographic and treatment characteristics of the chemotherapy and control groups. Given the matching of individuals, there were no differences in age or education level. The chemotherapy group ranged in age from 34 to 65 years, and the healthy controls from 31 to 65 years and approximately three-quarters of each group had some post-secondary education. Age was analyzed in the base model with session as the sole predictor at level 1. No significant effect of age was found on FACT-Cog PCI and it was therefore excluded from subsequent analyses in order to limit the number of parameters being estimated. Table 3 lists the means and standard deviations of data at all time points for variables used in MLM analyses.

Change in Objective and Subjective Cognitive Measures Over Time

COGSUM declined significantly over time in the breast cancer patients compared to controls, as evident in a significant negative slope (β_{10} = -0.049, p < 0.001; Figure 1). FACT-Cog also decreased significantly across chemotherapy sessions in the patients (β_{10} = -0.047, p < 0.001; Figure 1).

Change in Anxiety and Fatigue Over Time

Changes in POMS scores were evaluated independently to determine their trajectory over the course of chemotherapy. POMS Anxiety scores decreased over time (β_{10} = -0.076, p < 0.001; Figure 2); POMS Fatigue scores increased (β_{10} = 0.165, p < 0.001; Figure 2).

Relationship Between POMS Scores and Objective and Subjective Cognitive Measures

Neither POMS Anxiety slopes ($\beta_{11} = 0.017$, p = 0.638) nor POMS Fatigue slopes ($\beta_{11} = 0.008$, p = 0.728) were associated with change in COGSUM over the course of chemotherapy. Increases over time in both POMS Fatigue scores and POMS Anxiety scores were associated with decline in FACT-Cog PCI scores (Fatigue: $\beta_{11} = -0.099$, p = 0.017; Anxiety: $\beta_{11} = -0.121$, p = 0.041).

Relationship Between FACT-Cog PCI and COGSUM

The bivariate correlation between post-treatment FACT-Cog PCI and COGSUM scores (i.e., at T6) was nonsignificant (r = 0.056; p = 0.710). Using MLM, we found no significant effect of COGSUM slopes on change in FACT-Cog PCI whether we assessed the relationship independent of other variables ($\beta_{11}=0.100$, p=0.631) or whether we included POMS Anxiety slopes and POMS Fatigue slopes in the model. In the latter model, none of the factors emerged as significant predictors of change in FACT-Cog PCI (COGSUM: $\beta_{11} = 0.135$, p = 0.514; Fatigue: $\beta_{12} = -0.078$, p = 0.115; Anxiety: $\beta_{13} = -0.073$, p = 0.304).

Relationship Between FACT-Cog PCI and Cognitive Domain Scores

None of the cognitive domain slopes significantly predicted change in FACT-Cog PCI over the course of chemotherapy (refer to Figure 3 for change in domain scores over time).

<div align="center">

Conclusions

</div>

There is a curious lack of correlation between subjective and objective measures of cognitive function in many clinical conditions; cancer-related cognitive impairment is no exception (Debess, Riis, Engebierg, & Ewertz, 2010; Green, Pakenham, & Gardiner, 2005; Hermelink et al., 2010; Hermelink et al., 2007; Jenkins et al., 2006; Mehnert et al., 2007; Pullens

et al., 2010). Like most other investigators, we failed to find a relationship between subjective and objective measures of cognitive function using bivariate correlation of post-treatment scores. However, in the current study, we went beyond static correlation, using MLM to examine how the changes in subjective and objective measures of cognition co-varied over time (i.e., to examine the correlation in their slopes over time rather than the correlation of scores at one particular time point). We contend that static correlation and co-variation approaches could yield quite different results. For example, it has been shown that there is a significant relationship between self-perceived cognitive function and the personality trait of negative affectivity (Hermelink et al., 2010). We would therefore expect that individuals with greater negative affectivity would score lower on cognitive self-report measures than those with more positive affectivity; however, this does not necessarily imply that change in self-reported cognitive dysfunction would be predicted by a trait measure (which is presumed to be stable). By using change scores (i.e., slope scores) rather than static post-treatment scores, we focus less on individual differences in reporting tendencies and focus more on change in perceived cognitive functioning across treatment and the extent to which perceived change correlates with objective change.

Hermelink et al. (2010) attempted to address this same issue by using pre- to post-chemotherapy difference scores on objective and subjective cognitive measures as independent and dependent variables, respectively, in linear mixed regression analyses. However, the lack of a control group to account for expected practice effects on the neuropsychological tests may have masked a subtle but significant decline in the objective measures and, thereby, distorted the objective–subjective relationship.

In keeping with mounting evidence that cancer and chemotherapy are associated with

objective cognitive disturbance (Wefel et al,. 2015; Wefel & Schagen, 2012), our sample of breast cancer patients showed significant decline in objective cognitive performance over the course of chemotherapy after adjusting for positive practice effects observed in healthy controls. Significant cognitive decline was also reflected in subjective ratings of cognitive function that were standardized to the control group. Contrary to our hypothesis, however, we did not find that change in objective cognitive scores (whether domain-specific or general) significantly correlated with change in subjective reports of functioning.

Given these negative findings, alternative explanations for this objective–subjective discrepancy must be explored. One of the most common explanations is that subjective complaints are driven by psychological distress or fatigue, whereas neuropsychological test scores reflect underlying neurological dysfunction. We examined the relationships among neuropsychological scores, ratings of perceived cognitive function, and measures of anxiety and fatigue in the current data. In keeping with other reports, we found that anxiety and fatigue were related to subjective cognitive reports but not to objective cognitive performance (Pullens et al., 2010), although mean anxiety score actually decreased over the course of chemotherapy in our sample.

The relationship between subjective cognitive function and fatigue has been construed as favoring a psychogenic rather than neurogenic basis for cognitive impairment in cancer patients. However, this assumes a directional relationship that is not warranted by correlational studies. Recent imaging studies indicate that exposure to chemotherapeutic agents results in structural and functional changes in the brain which may be a cause, rather than an effect, of cancer-related fatigue. Functional imaging studies conducted in cancer patients have shown abnormal patterns of neural activation in response to a cognitive task (de Ruiter & Schagen, 2013; Ferguson,

McDonald, Saykin, & Ahles, 2007; Scherling & Smith, 2013). In many instances, activation is actually increased, suggesting that the brain is having to recruit a wider neural network to support the task than would normally be the case (de Ruiter & Schagen, 2013; Ferguson et al., 2007; Scherling & Smith, 2013). This increase in activation may give rise to a subjective experience that cognitive processing is more effortful and tiring. In other words, according to this conceptualization, a decrease in neural and cognitive processing resources may be the cause, rather than the result, of fatigue. The findings of Ganz et al. (2013) that perceived cognitive function in breast cancer patients was related to ratings of mental but not physical fatigue lend some credence to this conceptualization. It is similarly plausible that anxiety is a result rather than a cause of cognitive symptoms, arising when cognitive resources decline to the extent that they are inadequate to meet cognitive demands.

Interestingly, these changes in brain activation seen on neuroimaging in cancer patients are usually observed in the context of normal performance on the cognitive activation tasks (de Ruiter & Schagen, 2013; Ferguson et al., 2007; Scherling & Smith, 2013) suggesting that the individual is able to compensate behaviourally for the reduction in processing resources. However, the greater mental effort required may be reflected in self-assessment, thereby contributing to the discrepancy in objective and subjective cognitive measures.

The disparity between objective and subjective measures of cancer-related cognitive impairment has also been attributed to a number of other methodological limitations (Downie, Fan, Houédé-Tchen, Yi, & Tannock, 2006; Ganz et al., 2013; Hutchinson et al., 2012; Paquet et al., 2013; Pullens et al., 2010; Shilling & Jenkins, 2007; Wefel et al., 2015). Some of these limitations apply to the current study. One concern is incompatibility in the content and the context of objective and subjective measures. Subjective reports may be reflecting changes in

cognitive domains other than those assessed by traditional neuropsychological tests. Furthermore, whereas neuropsychological testing is very time-limited and is carried out in highly structured and controlled environments, subjective reports sample a much longer time span and are thus more likely to capture periodic disturbances, or symptoms that arise in uncontrolled, distracting environments or during periods of stress or fatigue.

This is the latest in a series of papers by our group addressing methodological issues in studies of cancer-related cognitive impairment (Collins, MacKenzie, & Kyeremanteng, 2013; Collins, Paquet, Dominelli, White, & MacKenzie, 2015; Ouimet, Stewart, Collins, Schindler, & Bielajew, 2009). We feel that the careful attention to methodology illustrated by this paper is perhaps its greatest contribution to the literature. We recommend that the current approach, which employs a prospective, longitudinal study design, a control group to account for practice effects, and sensitive statistical analyses of change in variables over time, be adopted in future studies. Future studies would further benefit from more sensitive and ecologically valid objective measures of cognitive functioning. Research is beginning to examine the role of virtual reality-based neuropsychological testing which may hold promise for future studies of chemotherapy-related cognitive impairment (Parsons, 2015). Measures of variability in performance across 'real life' conditions such as distraction, multi-tasking demands, fatigue, and stress may also prove more sensitive than optimal scores on traditional neuropsychological tests to the subtle cognitive disturbances associated with cancer and cancer treatments. Refinements such as these may move us forward in our attempt to unravel the complex phenomenon of cancer-related cognitive impairment and to ensure that affected patients receive appropriate support and treatment.

Table 1

Cognitive test battery organized by cognitive domain

Tests (by Cognitive Domain)	Variable(s) Analyzed
PROCESSING SPEED	
Digit-Symbol Coding, WAIS-III Symbol Search, WAIS-III Trail Making Test A (Trails A) Trail Making Test B (Trails B) CNS-VS Processing Speed Index CNS-VS Reaction Time Index	Number correct in 120 seconds Number correct in 120 seconds Time to complete in seconds Time to complete in seconds
WORKING MEMORY	
Digit Span, WAIS-III Letter-Number-Sequencing, WAIS-III Paced Auditory Serial Addition Task (PASAT) Auditory Consonant Trigrams Test (CCCs) Controlled Oral Word Association Test (COWA)	Total raw score Total raw score Total number correct on 3.0 second condition Total number of letters correct across 0, 9 & 18 second intervals Sum of correct words across all 3 letters
VERBAL MEMORY	
Hopkins Verbal Learning Test-Revised (HVLT-R) CNS-VS Verbal Memory Index	1. Total raw score on 3 learning trials 2. Number correct on delayed free recall
VISUAL MEMORY	
Brief Visuospatial Memory Test-Revised (BVMT-R) CNS-VS Visual Memory Index CNS VS Working Memory Index	1. Total raw score on 3 learning trials 2. Number correct on delayed free recall

WAIS-III = Wechsler Adult Intelligence Scale-III
CNS-VS = CNS Vital Signs

Table 2

Demographic and treatment characteristics of the sample

	Group		
Characteristic	**Patients**	**Controls**	**p-value**
Age at Baseline - Mean (SD)	52.35 (7.93)	51.97 (7.86)	0.79
Education - Frequency (%)			
< High School (HS)	2 (3%)	3 (5%)	0.40
HS	12 (20%)	10 (17%)	
Some post-HS/community college	22 (37%)	21 (35%)	
Undergraduate degree	15 (25%)	14 (23%)	
Graduate degree	9 (15%)	12 (20%)	
Chemotherapy Regimen - Frequency (%)			
FEC-T (with Herceptin in 6 cases)	42 (70%)		
FEC	5 (8%)		
CT (with Herceptin in 1 case)	7 (12%)		
AC-T	3 (5%)		
AC	2 (3%)		
Other	1 (2%)		
Number of Chemotherapy Cycles – Frequency (%)			
4	9 (15%)		
5	2 (3%)		
6	46 (77%)		
8*	3 (5%)		

SD = standard deviation, FEC = 5-fluourouracil, epirubicin, cyclophosphamide, FEC-T = FEC plus taxotere, CT = cyclophosphamide plus taxotere, AC = adriamycin and cyclophosphamide, AC-T = AC plus paclitaxel, Other = carboplatin, taxotere, Avastin and Herceptin
*Patients who received 8 chemotherapy cycles were re-tested after every second cycle.
Sample characteristics have been previously published (Collins et al., 2013).

Table 3

Means and standard deviations (in parentheses) at all time points for variables used in MLM analyses

Test Session Measure	T0	T1	T2	T3	T4	T5	T6
COGSUM	-0.094 (0.579)	-0.201 (0.641)	-0.194 (0.600)	-0.273 (0.703)	-0.333 (0.720)	-0.335 (0.619)	-0.341 (0.642)
Processing Speed	-0.155 (0.873)	-0.269 (0.841)	-0.171 (0.898)	-0.244 (0.953)	-0.383 (1.029)	-0.402 (0.915)	-0.361 (0.928)
Working Memory	-0.156 (0.735)	-0.236 (0.690)	-0.283 (0.745)	-0.330 (0.733)	-0.381 (0.853)	-0.445 (0.697)	-0.498 (0.776)
Verbal Memory	0.014 (0.789)	-0.055 (1.034)	-0.244 (0.935)	-0.259 (0.998)	-0.261 (0.983)	-0.178 (1.040)	-0.274 (1.008)
Visual Memory	0.018 (0.794)	-0.053 (0.808)	-0.160 (0.837)	-0.230 (1.027)	-0.253 (0.968)	-0.111 (0.847)	-0.069 (0.866)
FACT-Cog PCI	-0.157 (1.567)	-0.516 (1.688)	-0.748 (1.768)	-0.805 (1.777)	-0.690 (1.768)	-0.998 (2.225)	-0.639 (1.691)
POMS Anxiety	10.683 (7.012)	8.186 (6.277)	6.950 (5.806)	7.817 (6.326)	8.310 (7.233)	7.875 (5.811)	6.565 (5.799)
POMS Fatigue	6.029 (4.509)	7.133 (5.374)	7.200 (5.626)	9.050 (6.606)	10.983 (7.447)	11.333 (7.791)	9.935 (6.990)

COGSUM values and domain-specific summary scores represent average of Z-scores (referenced to control group mean and standard deviation at same time point).

T0 refers to pre-treatment baseline testing; T1 – T6 refer to testing sessions following first to sixth chemotherapy treatment.

FACT-Cog PCI = Perceived Cognitive Impairment score on Functional Assessment of Cancer Therapy Cognitive Scale, Version 3. FACT-Cog PCI values represent Z-scores referenced to control group mean and standard deviation at same time point.

POMS = Profile of Mood States.

Means and standard deviations on all individual tests at all time points for breast cancer patients and controls have been previously published (Collins et al., 2013).
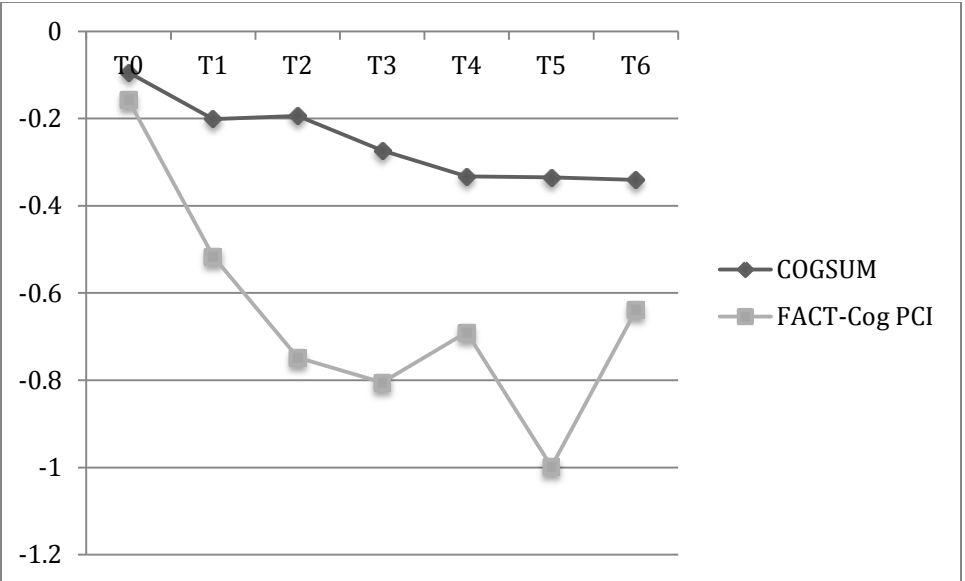
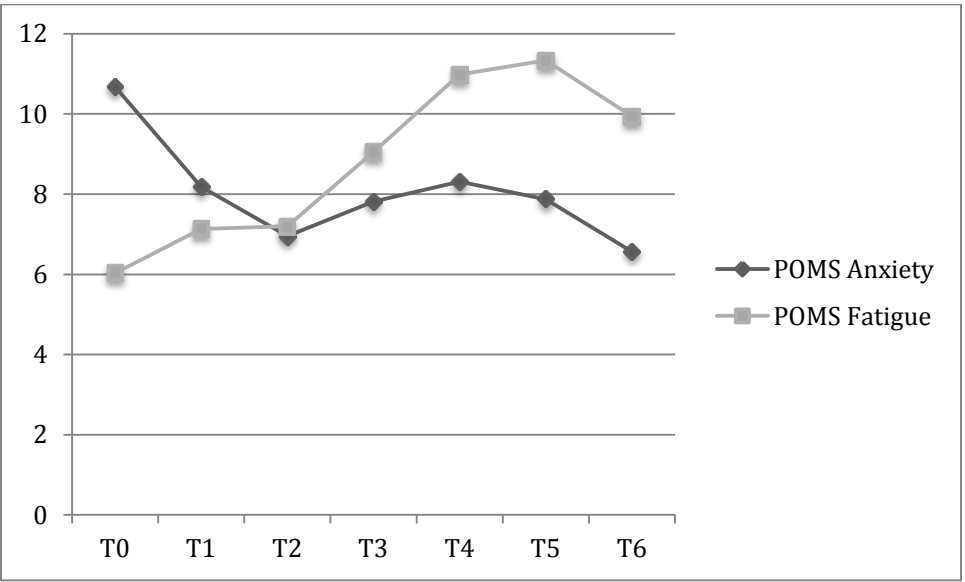*Figure 1*. Means of COGSUM and FACT-Cog PCI at all time points
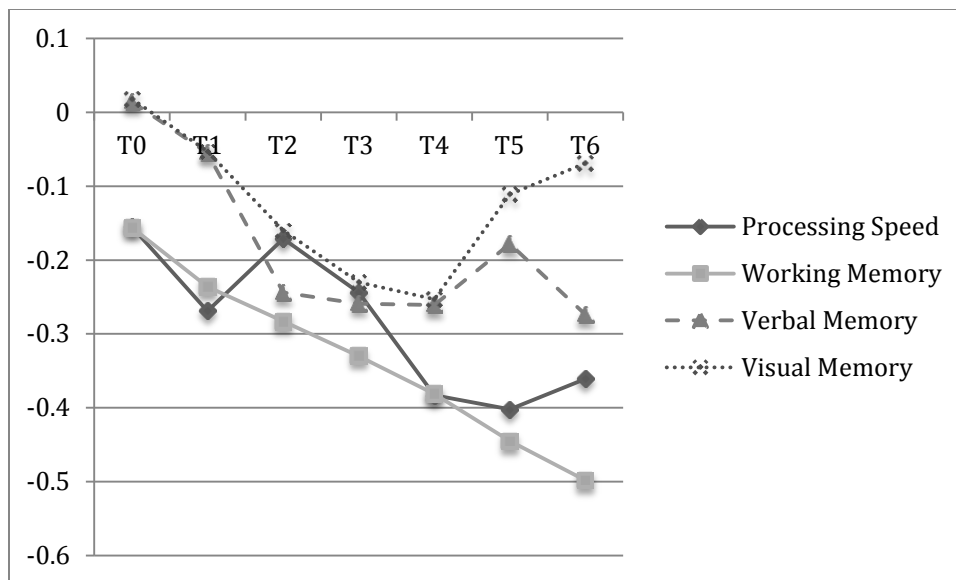

Figure 2. Means of POMS scores at all time points

Figure 3. Means of cognitive domain scores at all time points

Appendix

Model 1: Full two-level multilevel model to assess change over time in FACT-Cog, COGSUM, POMS Anxiety, and POMS Fatigue

Level 1: $Y_{ti} = \pi_{0i} + \pi_{1i}(time_{ti}) + e_{ti}$
Level 2: $\pi_{0i} = \beta_{00} + r_{0i}$
             $\pi_{1i} = \beta_{10} + r_{1i}$

Model 2: Full two-level multilevel model to assess effect of COGSUM OLS slopes on FACT-Cog

Level 1: $Y_{ti} = \pi_{0i} + \pi_{1i}(time_{ti}) + e_{ti}$
Level 2: $\pi_{0i} = \beta_{00} + \beta_{01}(OLS\ COGSUM_i) + r_{0i}$
             $\pi_{1i} = \beta_{10} + \beta_{11}(OLS\ COGSUM_i) + r_{1i}$

Model 3: Full two-level multilevel model to assess effect of POMS (Anxiety and Fatigue) OLS slopes on FACT-Cog

Level 1: $Y_{ti} = \pi_{0i} + \pi_{1i}(time_{ti}) + e_{ti}$
Level 2: $\pi_{0i} = \beta_{00} + \beta_{01}(OLS\ POMS_i) + r_{0i}$
             $\pi_{1i} = \beta_{10} + \beta_{11}(OLS\ POMS_i) + r_{1i}$

Model 4: Full two-level multilevel model to assess the effect of POMS Anxiety and Fatigue OLS slopes on cognitive summary scores.

Level 1: $Y_{ti} = \pi_{0i} + \pi_{1i}(time) + e_{ti}$
Level 2: $\pi_{0i} = \beta_{00} + \beta_{01}(OLS\ COGSUM_i) + \beta_{02}(OLS\ POMS\ Anxiety_i) + \beta_{03}(OLS\ POMS\ Fatigue_i) + r_{0i}$
             $\pi_{1i} = \beta_{10} + \beta_{11}(OLS\ COGSUM_i) + \beta_{12}(OLS\ POMS\ Anxiety_i) + \beta_{13}(OLS\ POMS\ Fatigue_i) + r_{0i}$

Note: Time was uncentered. All predictors at level two were grand mean centred. In all models, Level 1 refers to modeling repeated measurements across time within the individual; Level 2 refers to modeling between-individual intercepts and slopes (population estimates); Y_{ti} refers to the dependent variable Y at time "t" for individual "i"; individual and mean (population estimated) intercepts are represented by π_{0i} and β_{00} respectively; e_{ti} and $r_{.i}$ indicate within and between individual residuals respectively; all other parameters represent individual (π) and population estimated (β) slopes. In Models 2- 4, OLS slopes are used to indicate change over time in COGSUM and in POMS anxiety and fatigue scores as derived from a linear growth model.

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Comparison of the sensitivity of a traditional neuropsychological battery and a brief computerized battery (CNS-VS) in detecting chemotherapy-related cognitive decline in breast cancer patients

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Abstract

Objective: Cognitive complaints are common among cancer patients but the time and resources required for traditional neuropsychological testing are barriers to accessing assessment and treatment. We sought to determine if a brief computerized battery would be able to detect subtle cognitive changes in breast cancer patients undergoing chemotherapy.

Methods: Data for the current analyses were collected as part of a prospective, longitudinal study in which 60 breast cancer patients were assessed throughout chemotherapy and 60 healthy matched controls were assessed at equivalent intervals. A battery of neuropsychological tests, as well as CNS Vital Signs, a computerized cognitive test battery, were administered at each test session. A cognitive summary score (COGSUM) was derived from the respective paper and computer batteries. Hierarchical linear modeling was used to compare changes in the paper and computerized cognitive summary scores over time. The two batteries were also compared in terms of their ability to identify "decliners".

Results: Both Paper COGSUM and Computer COGSUM declined significantly over time. Group was found to have a significant effect on the slope for both Paper COGSUM and Computer COGSUM, with the patients showing greater decline over time than the controls. Paper COGSUM and Computer COGSUM slopes were significantly correlated in the full sample but not when analyzed by group. The paper battery identified more decliners in the breast cancer group than the control group but the computerized battery did not. There was limited overlap in the classification of individual "decliners" and "non-decliners" derived from the two test batteries.

Conclusions: Our results suggest that CNS-VS is not sufficiently sensitive to chemotherapy-related cognitive change in individual breast cancer patients, nor is it sensitive

enough to detect changes within specific cognitive domains. Despite these limitations, the CNS-

VS is sensitive to subtle cancer-related cognitive changes at the aggregate group level and may

be a useful alternative to traditional paper-and-pencil neuropsychological testing for research

applications, including clinical drug trials.

Background

Many cancer patients complain of cognitive disturbances. Most patients attribute these changes to neurotoxic effects of chemotherapy, as reflected in their use of terms such as "chemobrain" and "chemo fog" (Jean-Pierre et al., 2011; Pullens, De Vries, & Roukema, 2010). Although these cognitive symptoms can have a significant impact on day-to-day function and quality of life, and are now regarded as an important survivorship issue, it is rare that patients receive targeted assessment and intervention for such problems. In current clinical and research practice, the gold standard for cognitive assessment is a comprehensive battery of paper-and-pencil neuropsychological tests (Wefel, Vardy, Ahles, & Schagen, 2011). Administration is costly and time-consuming, and interpretation requires a trained neuropsychologist. Access to neuropsychological services is extremely limited within the public health-care system. The main question that we address in this paper is whether a brief, computerized cognitive testing battery, with potential for self-administration and automatic scoring, would be capable of detecting subtle cancer-related cognitive changes and, hence, serve as a practical and accessible substitute for traditional neuropsychological testing.

Computerized neuropsychological testing is being increasingly employed in a variety of settings, such as sports clinics and research, for a variety of disorders ranging in severity from mild (e.g. concussion and mild cognitive impairment) to severe (Collie & Maruff, 2003; Iverson, Brooks, & Young, 2009; Snyder et al., 2011). Most of these computerized tests take between 15 and 45 minutes to administer and many can be self-administered through web-based programs, making testing accessible and efficient. An evaluation of 43 studies using computerized tests with cancer patients (Cheung, Tan, & Chan, 2012) found promising psychometric properties and strong advantages of computerized tests, such as the ability to overcome some of the cultural

limitations of paper-and-pencil testing. It is conceivable that computerized tests, by virtue of their ability to precisely measure response time as well as accuracy, could actually be more sensitive to subtle cognitive disturbance than more traditional measures. Traditional neuropsychological tests have generally been validated in clinical populations with relatively severe cognitive deficits, such as traumatic brain injury, tumour, stroke, or dementia, and may not be sufficiently sensitive to detect more subtle neurocognitive disorders, such as those associated with systemic treatment for cancers outside the central nervous system (Jim et al., 2012; Hodgson, Hutchinson, Wilson, & Nettelbeck, 2013, Jean-Pierre et al., 2011; Wefel & Schagen, 2012).

The current study compares a computerized cognitive test, CNS Vital Signs (CNS-VS) (Gualtieri & Johnson, 2006; Gualtieri & Johnson, 2008), to traditional paper-and-pencil neuropsychological tests in terms of the ability to detect changes in breast cancer patients undergoing chemotherapy. CNS-VS has previously been used with cancer populations as a measure of cognitive functioning, although its validity in these populations has not been directly examined (Calvio, Peugeot, Bruns, Todd, & Feuerstein, 2010; Crowgey, et al., 2014). By conducting a head-to-head comparison, we hope to determine whether computerized testing is an appropriate alternative for clinical and research screening in breast cancer patients.

Methods

This is a secondary analysis of previously collected data. The original study, examining cognitive changes in breast cancer patients undergoing chemotherapy, has been previously published (Collins, MacKenzie, Tasca, Scherling, & Smith, 2013).

Participants

Participants were recruited from the Ottawa Hospital Regional Cancer Centre. The patient

sample consisted of 60 women who underwent mastectomy or lumpectomy and received various

regimens of adjuvant chemotherapy for early stage breast cancer. Controls were matched in a

pairwise manner on sex, age, and education, and assessed at similar inter-test intervals. All

participants were 65 years of age or younger, were fluent in English and had at least a grade-8

level of education. Exclusion criteria included: 1) history of previous cancer, chemotherapy, or

radiotherapy; 2) neoadjuvant chemotherapy for current breast cancer; 3) history of serious

psychiatric, substance abuse or neurological disorder (past or present); and 4) inter-current

cancer or illness affecting cognition while participating in the study. Ethics approval was

obtained from the Ottawa Hospital Research Ethics Board and all participants provided informed

consent.

Procedure

Testing occurred at baseline, before chemotherapy commenced (T0), and after every

chemotherapy cycle (T1-T6). The number of chemotherapy cycles varied from one patient to the

next, depending on her treatment regimen, and ranged between 4 and 8 (those who received 8

chemotherapy cycles were re-tested after every second cycle). Inter-test interval (12 to 58 days)

depended on chemotherapy schedule and complications that might delay or prevent treatment.

Whenever possible, testing was performed shortly before the next chemotherapy cycle (one week

or less) to minimize the impact of acute side effects of treatment. Controls were tested on the

same schedule as the breast cancer participants to whom they were matched (within 2 days).

Measures

Cognitive assessment included a traditional neuropsychological battery of pencil-and-

paper tests and CNS-VS, the computerized test. The tests, and variable(s) from them, are listed

by cognitive domain in Tables 1 and 2. When available, alternate versions of tests were used at

different testing sessions. CNS-VS has a large bank of items for each test which are presented in random order from one administration to the next allowing for an almost infinite number of alternate versions.

CNS-VS includes putative measures of processing speed, working memory, verbal memory, visual memory, and executive function that have been modeled after traditional neuropsychological tests. Scores from the individual tests are combined to derive a number of domain scale scores which have been shown to have good test-retest reliability (r ranging from 0.65 to 0.87) and have been validated in various clinical populations, including attention deficit hyperactivity disorder, mild cognitive impairment, dementia, post-concussion syndrome, and traumatic brain injury, both severe and mild (Gualtieri & Johnson, 2006; Gualtieri & Johnson, 2008; Lanting, Iverson, & Lange, 2012).

A cognitive summary score from the traditional tests, Paper COGSUM, was calculated by standardizing the raw score for each participant on each cognitive measure (see Table 1) at each time point (using the mean and standard deviation on that variable in the control group) and then averaging these standardized scores. The same procedure was followed with the standardized domain scores from the CNS-VS (see Table 2) to calculate Computer COGSUM. Standardizing summary scores to controls was done to account for practice effects from repeated testing. Higher COGSUM scores are associated with better functioning.

We also analyzed domain scores from both the paper and computerized tests. We used principle components analysis (PCA) on baseline (T0) paper-and-pencil test scores of all participants to empirically derive our domains. The results of this PCA revealed 3 clusters of tests, which corresponded to the domains of memory, processing speed, and working memory. We did not use a factor score *per se;* rather, summary scores were obtained for the PCA-derived

domains by averaging the standardized scores on tests within each cluster at each time point. The CNS-VS scale yields domain scores (the scale scores). To allow comparison with the paper-and-pencil tests, these were reduced from 6 to 3 by combining visual and verbal memory into a single memory factor, processing speed and reaction time into a single processing speed factor, and working memory and flexibility into a single working memory factor. Lists of the tests used for domain score calculations can be found in Tables 1 and 2.

Statistical Analysis

Procedures for data cleaning and screening are described in detail in a previous paper (O'Farrell, Smith, & Collins, 2016). Bivariate correlations between Paper COGSUM and Computer COGSUM values were evaluated at each time-point in both the aggregate group and in each separate group.

Trajectory of change in Paper COGSUM and Computer COGSUM over sessions was analyzed using two-level hierarchical linear modeling (HLM). The two-level model was set up with participants at level 2 and session (i.e. chemotherapy cycle T0-T6 uncentered) at level 1. Paper COGSUM and Computer COGSUM were run as the dependent variable in separate analyses. Group was then added as a level-2 variable.

Ordinary least squares (OLS) slopes for both Paper COGSUM and Computer COGSUM were derived from simple two-variable growth models and used to analyze correlation in change over time. OLS values for each individual on Paper COGSUM were obtained by running a linear model with Paper COGSUM as the dependent variable and session as a predictor at level 1. Likewise, OLS values for Computer COGSUM were obtained by running the same linear model except with Computer COGSUM as the dependent variable. This same procedure was followed with the domain scores from the respective batteries. Bivariate correlation analysis of the slope

values for Paper COGSUM and Computer COGSUM was conducted to determine correlation between change over time in the two test batteries.

"Decliners" were identified as those participants whose OLS slope value (standardized to the mean and standard deviation of the control group) fell at or below -1.5. The number of decliners identified using Paper COGSUM and Computer COGSUM was compared using Fisher's Exact Test. The number and identity of decliners as determined by the respective test batteries was compared to determine sensitivity and specificity of CNS-VS relative to traditional paper-and-pencil tests.

Data cleaning, summary score calculations, bivariate correlations, and decliner identification were conducted using SPSS (v. 22). HLM analyses were conducted using HLM software (v. 7.01). Type I error rate was set at 0.05.

Results

Table 3 lists demographic and treatment details of the breast cancer and control groups. There were no differences in age or education level. The breast cancer group ranged in age from 34 to 65 years, and the healthy controls from 31 to 65 years; approximately three-quarters of each group had some post-secondary education. Table 4 lists the means and standard deviations of the COGSUM summary scores at all time points for the groups, separately and combined.

Group Level Analyses - Comparison of Paper COGSUM and Computer COGSUM

Bivariate correlations between Paper COGSUM and Computer COGSUM ranged from 0.6 to 0.8 at all time-points (T0 to T6) and were all significant at the 0.01 level whether groups were analyzed together or separately. Both COGSUM measures declined significantly over time in the full sample, as evident in a significant negative slope for Paper COGSUM (β_{10} = -0.028, p < 0.001) and Computer COGSUM (β_{10} = -0.016, p = 0.019) (Figure 1). Group was found to have a

significant effect on the slope for both Paper COGSUM (β_{11} = -0.048, p < 0.001) and Computer

COGSUM (β_{11} = -0.035, p = 0.010), with the breast cancer group showing greater decline than

the controls (Figure 2). The bivariate correlation between Paper COGSUM and Computer

COGSUM slopes was significant when both groups were analyzed together (r = 0.22, p = 0.017),

but not when analyzed separately (breast cancer group: r = 0.148, p = 0.258; control group: r =

0.130, p = 0.320).

Domain Analysis

There was modest but significant decline over time in all of the paper-based cognitive

domain scores in the full sample (Memory: β_{10} = -0.029, p = 0.001; Processing Speed: β_{10} = -

0.019, p = 0.018; Working Memory: β_{10} = -0.038, p < 0.001). The changes in computer-based

cognitive domains were also negative but were all nonsignificant (Memory: β_{10} = -0.017, p =

0.190; Processing Speed: β_{10} = -0.012, p = 0.139; Working Memory: β_{10} = -0.022, p = 0.065).

Group was found to have a significant effect on the slopes of all paper domains (Memory: β_{11} = -

0.045, p = 0.009; Processing Speed: β_{11} = -0.053, p < 0.001; Working Memory: β_{11} = -0.059, p <

0.001). Group was found to have a significant effect on the working memory domain of the

computer test (β_{11} = -0.050, p = 0.036) but not on memory or processing speed (β_{11} = -0.033, p =

0.193; β_{11} = -0.025, p = 0.123, respectively).

Individual Level Analyses – Identifying "Decliners"

The paper battery identified significantly more decliners in the breast cancer group than the

control group (17 chemotherapy patients vs. 6 controls; χ^2 = 6.508, p = 0.019) while the

computer battery did not (9 chemotherapy patients vs. 4 controls; χ^2 = 2.157, p = 0.239). The

paper and computer batteries had very little overlap in terms of which breast cancer participants

were identified as "decliners". While the computer battery was found to have good specificity at

84%, it had very low sensitivity at 13%. The positive predictive value for the computerized test was 33% while the negative predictive value was 61%.

Conclusions

Whereas reports of troubling cognitive changes are frequent among breast cancer patients following chemotherapy, it is rare that they receive targeted assessment and treatment for these problems. This gap is due to the cost- and time-intensive nature of neuropsychological testing and the limited resources available in the public health-care system. The current analyses examined whether a shorter computerized test of cognitive functioning that does not require a trained neuropsychologist or psychometrist would be able to detect the subtle cognitive decline experienced by breast cancer patients following chemotherapy. More specifically, we examined the validity, sensitivity, and specificity of CNS-VS in breast cancer patients to determine whether it could serve as a feasible substitute in clinical and research settings.

All single time-point correlations between the computerized summary score and the paper summary score were highly significant, indicating approximately 50% shared variance, whether the groups were analyzed separately or together. This suggests that both the computerized battery and the paper battery are measuring a similar phenomenon overall and lends construct validity to the CNS-VS.

We found that the CNS-VS was able to detect mild chemotherapy-related cognitive decline at the group level of analysis. When we examined the breast cancer patients and healthy controls combined (n=120), we found that the slope (reflecting change in score over time) in the computerized summary score was significantly correlated to the slope in the paper summary score. This correlation was no longer significant when the groups were analyzed separately. While this likely reflects loss of power due to the smaller sample size and reduced range in

scores, it also suggests that the batteries differ somewhat in terms of the size and nature of the changes that they detect.

We also compared the batteries in terms of domain scores. Whereas, all of the paper-based cognitive domain scores declined significantly over time, in no case was the change in the computer-based domain scores significant, even in the combined sample. This suggests that CNS-VS may not be appropriate for the measurement of domain-specific change or for characterization of the cognitive profile. This conclusion is in keeping with results from another recent study (Gualtieri & Hervey, 2015) showing that the CNS-VS was able to detect overall mental ability and severity of cognitive dysfunction but was not a valid measure of more specific cognitive domains. The fact that group was significant for all of the paper-based domain scores (such that the breast cancer group was driving the decline), but only for the working memory domain of the computerized test, further attests to questionable validity of the domain-specific computerized measures.

We next examined the ability of the paper-based cognitive battery and the computerized cognitive battery to identify individual participants as "decliners" versus "non-decliners". We found that the paper-based battery, but not the computer battery, was able to identify change at the individual level. This suggests that the computerized battery may not be suitable for tracking individual change in cognitive functioning over time. This was further supported by the lack of correspondence in the identification of "decliners" vs. "non-decliners" between the CNS-VS and the traditional paper-and-pencil test battery. Although the CNS-VS had good specificity in our breast cancer sample, at 84%, it had low sensitivity at only 13% indicating that the CNS-VS was unable to detect a large proportion of women who were experiencing cognitive changes.

In keeping with a number of other studies (De Marco & Broschek, 2016; Gualtieri & Hervey, 2015; Lanting et al., 2012; Lenchan, Summers, Saunders, Summers, & Vickers, 2016; Witt, Alpherts, & Helmstaedter, 2013), we found little agreement between CNS-VS and more traditional neuropsychological measures with respect to domain-specific cognitive decline. Discrepancies between the paper and computerized batteries at the level of domain scores suggest that the CNS-VS domains may not be measuring the same specific constructs as traditional neuropsychological tests. Although the tasks on the CNS-VS were designed to be analogous to traditional neuropsychological measures, this does not guarantee concurrent validity. As pointed by Gualtieri and Hervey (2015), computerized measures may be much more heavily influenced by processing speed, such that speed may actually predominate over the more substantive construct of interest. This idea is further supported by our finding that the CNS-VS identified a different subgroup of individuals as "decliners" compared to the traditional neuropsychological battery of tests. It is possible that the CNS-VS is identifying primarily changes in processing speed over the course of chemotherapy whereas the traditional batteries are identifying changes in multiple constructs, including but not limited to processing speed.

Taken together, these results suggest that CNS-VS is not sufficiently sensitive to chemotherapy-related cognitive loss or change in individual breast cancer patients, or to specific cognitive strengths and weaknesses, to warrant clinical application in this population. As stipulated in guidelines set forth by the American National Academy of Clinical Neuropsychology and the National Academy of Neuropsychology (Bauer et al., 2012), more research and development of computerized cognitive testing is required before it can replace traditional neuropsychological testing for the purposes of characterizing the profile of cognitive

strengths and weaknesses as required for localizing brain dysfunction, establishing diagnosis, individualizing rehabilitation programs, and determining appropriate accommodations. However, given our findings that the CNS-VS was able to detect subtle cognitive change at the aggregate group level, it may be a practical alternative to traditional neuropsychological testing in research settings, for screening global cognitive changes in groups to determine the adverse cognitive side effects of investigational drugs, for example.

Table 1

Paper test battery organized by cognitive domain

DOMAIN	TESTS	VARIABLE
Memory	Hopkins Verbal Learning Test-Revised	(Total number correct on 3 learning trials + number correct on delayed free recall)/2
	Brief Visuospatial Memory Test-Revised	(Total number correct on 3 learning trials + number correct on delayed free recall)/2
Processing Speed	Digit-Symbol Coding	Number correct in 120 secs
	Symbol Search	Number correct in 120 secs less errors
	Trail Making Test A	Time to complete
	Trail Making Test B	Time to complete
Working Memory	Digit Span	Total raw score
	Letter-Number-Sequencing	Total raw score
	Paced Auditory Serial Addition Task	Number correct on 3.0 sec condition
	Auditory Consonant Trigrams Test	Sum of letters correctly recalled on 0", 9" & 18" intervals

Table 2

Computerized test battery organized by cognitive domain

DOMAIN	TESTS	VARIABLE
Memory	Verbal Memory: 15 words appear successively on screen followed by an immediate and delayed Y/N recognition trial	Correct hits plus correct passes on both immediate and delayed trials
	Visual Memory: 15 geometric designs appear successively on screen followed by an immediate and delayed Y/N recognition trial	Correct hits plus correct passes on both immediate and delayed trials
Processing Speed	Symbol Digit Coding: Respondent fills in numbers to match with symbols according to a key at the top of the screen over a 2-minute interval	Number correct responses less number incorrect responses

	Stroop Test: Colour names presented in different colours one at a time
	    Complex condition: Respond when word and colour match
	    Stroop condition: Respond when word and colour DO NOT match
		Mean reaction time for correct responses on Complex and Stroop conditions

Working Memory	Shifting Attention Test: Subject matches a stimulus to a target stimulus according to randomly changing rules	Difference between number of correct responses and the number of errors
	Stroop Test: Stroop condition	Difference between number of correct responses and the number of errors
	4-Part Continuous Performance Test, Part 4: Respondent must respond when the figure on the screen is the same shape and colour as the figure that appeared two screens earlier	Difference between number of correct responses and the number of errors

Table 3

Demographic and treatment characteristics of the sample

Characteristic	Group		p-value
	Patients	Controls	
Age at Baseline - Mean (SD)	52.35 (7.93)	51.97 (7.86)	0.79
Education - Frequency (%)			
< High School (HS)	2 (3%)	3 (5%)	0.40
HS	12 (20%)	10 (17%)	
Some post-HS/community college	22 (37%)	21 (35%)	
Undergraduate degree	15 (25%)	14 (23%)	
Graduate degree	9 (15%)	12 (20%)	
Chemotherapy Regimen - Frequency (%)			
FEC-T (with Herceptin in 6 cases)	42 (70%)		
FEC	5 (8%)		
CT (with Herceptin in 1 case)	7 (12%)		
AC-T	3 (5%)		
AC	2 (3%)		
Other	1 (2%)		
Number of Chemotherapy Cycles – Frequency (%)			
4	9 (15%)		
5	2 (3%)		
6	46 (77%)		
8*	3 (5%)		

SD = standard deviation, FEC = 5-fluourouracil, epirubicin, cyclophosphamide, FEC-T = FEC plus taxotere, CT = cyclophosphamide plus taxotere, AC = adriamycin and cyclophosphamide, AC-T = AC plus paclitaxel, Other = carboplatin, taxotere, Avastin and Herceptin
*Patients who received 8 chemotherapy cycles were re-tested after every second cycle.
Sample characteristics have been previously published (O'Farrell et al., 2016).

Table 4

Means and standard deviations (in parentheses) for Paper COGSUM and Computer COGSUM for both groups and combined sample at all time points

Test Session	Paper COGSUM			Computer COGSUM		
	Patients	**Controls**	**Combined**	**Patients**	**Controls**	**Combined**
T0	-0.101 (0.586)	0.004 (0.519)	-0.049 (0.554)	-0.085 (0.681)	0.000 (0.586)	-0.042 (0.634)
T1	-0.169 (0.599)	0.000 (0.551)	-0.084 (0.579)	-0.212 (0.757)	0.000 (0.578)	-0.106 (0.679)
T2	-0.187 (0.622)	0.000 (0.521)	-0.094 (0.579)	-0.202 (0.679)	0.002 (0.492)	-0.100 (0.599)
T3	-0.265 (0.633)	0.000 (0.523)	-0.132 (0.593)	-0.223 (0.816)	0.000 (0.573)	-0.112 (0.711)
T4	-0.295 (0.624)	0.000 (0.502)	-0.148 (0.583)	-0.351 (0.847)	0.000 (0.511)	-0.175 (0.718)
T5	-0.339 (0.611)	0.000 (0.511)	-0.170 (0.586)	-0.296 (0.759)	0.000 (0.575)	-0.148 (0.686)
T6	-0.391 (0.633)	0.000 (0.521)	-0.196 (0.609)	-0.202 (0.744)	0.000 (0.579)	-0.101 (0.671)

COGSUM values represent average of Z-scores (referenced to control group mean and standard deviation at same time point).

T0 refers to pre-treatment baseline testing; T1 – T6 refer to testing sessions following first to sixth chemotherapy treatment.

Means and standard deviations on all individual tests at all time points for breast cancer patients and controls have been previously published (Collins et al., 2013).
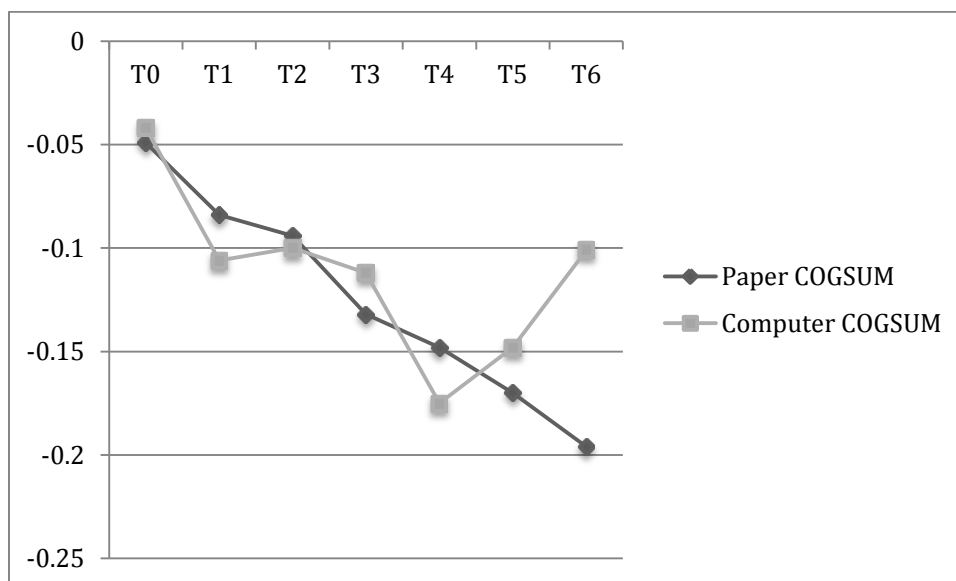
Figure 1. Mean paper and computer COGSUM values for combined sample (breast cancer patients and controls) at each time point
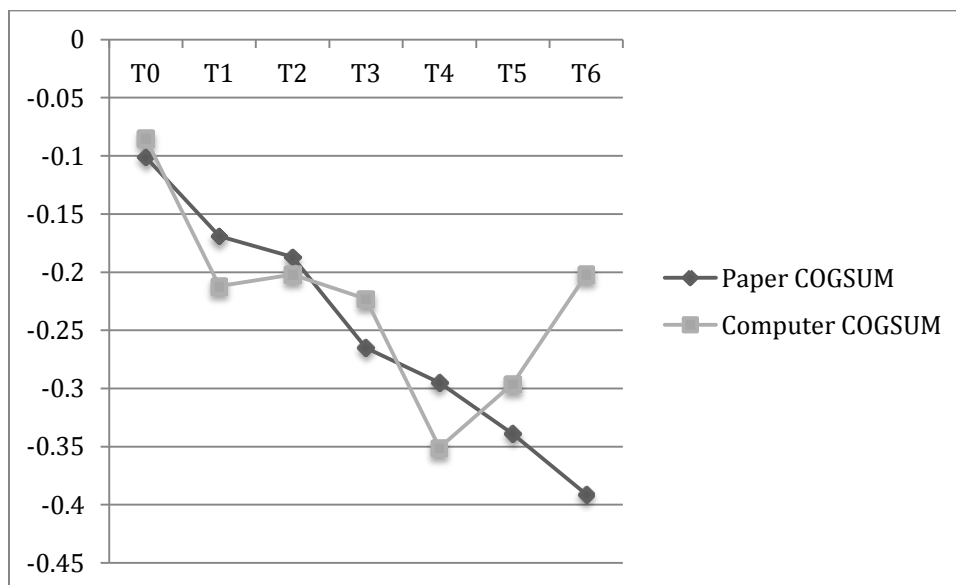

Figure 2. Mean paper and computer COGSUM values for breast cancer patients at each time point

Appendix

Model 1: Full two-level hierarchical model to assess change over time in Paper COGSUM, Computer COGSUM, and paper- and computer-based domain scores

Level 1: $Y_{ti} = \pi_{0i} + \pi_{1i}(\text{time}_{ti}) + e_{ti}$

Level 2: $\pi_{0i} = \beta_{00} + r_{0i}$

$\pi_{1i} = \beta_{10} + r_{1i}$

> Note: Time was uncentered. In all models, Level 1 refers to modeling repeated measurements across time within the individual; Level 2 refers to modeling between-individual intercepts and slopes (population estimates); Y_{ti} refers to the dependent variable Y at time "t" for individual "i"; individual and mean (population estimated) intercepts are represented by π_{0i} and β_{00} respectively; e_{ti} and r_i indicate within and between individual residuals respectively; all other parameters represent individual (π) and population estimated (β) slopes.

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General Discussion

The purpose of this dissertation was to critically explore the methodological and interpretive limitations of the extant CRCI research and to attempt to address some of these limitations using more powerful statistical techniques, in particular, multilevel modeling. By taking advantage of multiple measurement points in the data, multiple sources of neuropsychological measurements, and strong statistical techniques, this thesis provides methodological guidelines for CRCI research. In addition to a review paper emphasizing study methodology issues, this dissertation included analyses of an existing data set to address two specific issues of importance to CRCI researchers: 1) the disparity between objective and subjective measures of cognitive function and 2) the potential role of computerized cognitive testing of CRCI. Ultimately, the goal of this work is to improve patient care and quality of life.

Methodological Issues in CRCI Research

To address the limitations of past CRCI research, an examination of the extant literature was conducted. Despite years of important research into CRCI that has contributed to the evidence for its existence and its long-term effects on women with breast cancer, several limitations and confounds were noted. The first of these limitations was the cross-sectional design of many studies. This approach fails to control for baseline cognitive functioning (Cimprich et al., 2010; Schilder et al., 2010; Wefel et al., 2004), which can result in failure to detect subtle but meaningful decline if scores still fall within normal limits despite the loss. In recognition of this, many studies now take a prospective, longitudinal approach as is recommended by the ICCTF (Wefel, Vardy, Ahles, & Schagen, 2011). To further illustrate the importance of longitudinal study designs, previous studies published using data from this lab, including the current dissertation data, have demonstrated that while static scores of cognitive

functioning remain in the normal range compared to published norms both before and after exposure to chemotherapy, the examination of change scores within individuals revealed significant declines in cognitive functioning (Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009; Collins et al., 2013; Collins, MacKenzie, Tasca, Scherling, & Smith, 2014; Stewart et al., 2008).

Another limitation noted in CRCI research was the lack of control groups or the use of improper control groups. While the type of control group is less critical in prospective, longitudinal study designs where disease and host effects are accounted for by multiple measurements in the same individual, it is still important to have a control group to account for practice effects and other possible confounds. This has been previously demonstrated using the current dissertation data such that when overall cognitive scores of breast cancer patients were examined across time without any correction for practice effects, no significant changes in scores were observed; however, once positive practice effects were removed, through the use of control group data, the decline in cognitive summary scores became evident (unpublished observations; Collins et al., 2013).

One of the major limitations identified in the examination of previous CRCI research was the statistical approach taken to the analysis of data. Many studies to date have failed to find group differences in mean cognitive function as a result of aggregate, group level approaches to data analysis. Given that CRCI is a subtle phenomenon and only affects a subgroup of individuals, the use of mean comparison analyses are likely insufficient to detect these changes. More individual-level analyses are recommended, in addition to group analyses, in an effort to identify possible CRCI within a given sample of individuals. Furthermore, with the aforementioned recommendation of longitudinal study designs, the proper statistical techniques

such as reliable change indices or, preferably, regression-based change models are recommended to determine changes in cognitive functioning over the course of chemotherapy while accounting for practice effects (Ouimet, Stewart, Collins, Schindler, & Bielajew, 2009; Wefel et al., 2011).

Given the limitations described above, recommendations regarding future study design and methodology were discussed. These included using a prospective, longitudinal design with proper control groups, either healthy or diseased, and using strong statistical techniques for data analysis. In particular, throughout this dissertation, the use of change scores across multiple key measurement points are recommended over scores at single time points as change scores may reveal more subtle variations in cognition over the course of chemotherapy.

Subjective-Objective Disparity in CRCI Research

This dissertation also addressed another important question in CRCI research: the disparity between objective measures of cognitive performance and subjective reports of cognitive abilities in breast cancer patients after exposure to chemotherapeutic agents (Debess, Riis, Engebjerg, & Ewertz, 2010; Green, Pakenham, & Gardiner, 2005; Hermelink, Küchenhoff, & Untch, 2010; Hermelink et al., 2007; Jenkins et al., 2006; Mehnert et al., 2007; Pullens, De Vries, & Roukema, 2010). We hypothesized that the correlation might be stronger if we were to examine change over time in these measures, rather than correlation between scores at a single time point, as has typically been done. Our hypothesis, that the trajectory of change in the objective and the subjective cognitive measures would be highly and positively correlated was not supported. Despite this negative finding, we contend that this work contributes significantly to the current CRCI literature by suggesting a more appropriate level of analysis. Furthermore, the finding that there is no significant relationship between objective and subjective reports of cognitive decline even at the level of change corroborates the existing evidence that these

measures are tapping different constructs (Debess, Riis, Engebjerg, & Ewertz, 2010; Green, Pakenham, & Gardiner, 2005; Hermelink, Küchenhoff, & Untch, 2010; Hermelink et al., 2007; Jenkins et al., 2006; Mehnert et al., 2007; Pullens, De Vries, & Roukema, 2010).

The Usefulness of a Computerized Cognitive Test for Detecting CRCI

The second set of analyses explored the question as to whether a computerized cognitive measure, CNS-VS in this case, might be a practical substitute for lengthy and intensive traditional measures of neuropsychological testing in the assessment of CRCI. Our hypothesis that both measures would significantly covary over time was not supported, suggesting that the CNS-VS and traditional neuropsychological tests are measuring different constructs. This was further supported by the lack of correlations of domain scores yielded from each battery and the lack of correspondence between these tests in their identification of "decliners" and "non-decliners". We did, however, find that the CNS-VS measure was able to detect mild cognitive decline over the course of chemotherapy in breast cancer patients.

Taken together, our findings indicate that the CNS-VS was not sufficiently sensitive to CRCI in individual breast cancer patients to be used as a clinical tool within this population. Similarly, the CNS-VS was not able to detect changes at the domain level making it insufficient for determining individual strengths and weaknesses within a given cognitive profile. Despite these limitations, the CNS-VS was able to detect changes in cognitive functioning at the aggregate group level suggesting that it may be a practical screening tool within research settings (e.g., screening of adverse cognitive side effects of drugs, etc.).

Recommendations and Future Directions

These studies have illustrated how we can improve study design and data analysis techniques to explore outstanding issues of concern in the CRCI arena. There are many

remaining questions to be addressed. For example, other methodological shortcomings may contribute to the disparity in subjective and objective measures of cognition in cancer patients. One possibility that has yet to be explored regards the equivalence of the measures used for objective and subjective assessment of cognitive functioning. Whereas objective measures of cognitive functioning are well established and have empirically derived domains, subjective measures of cognition have not been as rigorously assessed and may not be measuring the same domains as the objective measures. Additionally, objective measures of cognition are carried out in time-limited and highly controlled environments with the goal of eliciting optimal performance, whereas subjective measures are more likely to capture a longer timeframe and, hence, variations in cognitive ability as a result of fluctuation in environments (and degree of distraction) and in psychological states such as stress and fatigue. To address this limitation, future studies might include more ecologically valid objective measures of cognitive abilities that incorporate conditions such as multi-tasking and distraction, as well as varying levels of stress fatigue and thus more closely approximate "real life" situations. To this end, more recent research has begun to examine virtual reality-based neuropsychological assessments and may hold promise for future CRCI research (Parsons, 2015). Future research would also greatly benefit from examining qualitative studies of patient experiences in order to help guide the development of more ecologically valid measures that directly address patient reports of cognitive changes in a greater effort to measure their experiences objectively.

With respect to the second research question, the results indicating discrepancies between overall scores on paper-based and computerized batteries as well as between their respective domain scores, suggest that these tests are not measuring the same constructs. Despite the fact that the CNS-VS measures are based on traditional neuropsychological tests, the findings of this

dissertation and of other work (Gualtieri & Hervey, 2015) indicate that these measures do not have concurrent validity. In fact, a study by the developers of the CNS-VS (Gualtieri & Hervey, 2015) found results similar to ours with respect to domain scores and suggest that computerized tests are more heavily influenced by general factors such as cognitive and motor speed that account for a large portion of the variability on all component tests, resulting in a uni-dimensional factor structure. Future researchers using computerized testing should exercise caution in interpreting results. Furthermore, future research should focus on the development of computerized testing with an emphasis on increasing concurrent validity to traditional measures.

Given the limitations that arise from small sample sizes, cross-sectional studies, lack of proper controls, and improper statistical analysis, future studies would benefit from addressing these methodological limitations in an effort to improve and clarify CRCI research. The confounds inherent to working with cancer patients, in whom randomized controlled trials are rarely ethical and treatment is inextricably linked to host and disease factors, further emphasize the need for sound methodology to control for confounds that are under our control. In particular, we recommend (1) prospective, longitudinal study designs with baseline measurements prior to commencement of chemotherapy, (2) the use of control groups (either healthy or diseased), and (3) analysis of change scores (i.e., regression-based methods) both at the group and individual level. Our recommendations fall in line with suggestions laid out by the ICCTF (Wefel et al., 2011) for improving consistency across studies to allow cross-study comparison and data pooling. This, in turn, will promote a better understanding of the multifaceted nature of CRCI, which will contribute to the development of appropriate detection techniques and interventions.

Given that the driving force behind early CRCI research was the patient experience, clinical translation of knowledge should be a major focus for future directions within this field.

Despite general consensus within the research community regarding the existence of CRCI, there remains doubt within the clinical community suggesting a failure on our part as researchers in terms of clinical translation. With this failure, comes a lack of knowledge dissemination to the patients who directly experience CRCI. Qualitative study results suggest that women are often not provided with information about CRCI, including information about the risks of CRCI prior to beginning treatment and information about what can be done if a patient is currently experiencing CRCI (Boykoff, Moieni, & Subramanian, 2009; Fitch, Armstrong, & Tsang, 2008; review by Myers, 2013; Von Ah, Habermann, Carpenter, & Schneider, 2013). This information is critical for patient care. Just as physicians provide information regarding the physical side effects of chemotherapy, the potential cognitive side effects should also be explored with patients and their families. Similarly, during and post-chemotherapy, just as physical side effects are treated, treatment options for CRCI should be explored. Treatment should include both cognitive rehabilitation training such as mindfulness-based attention training, and treatment of all other psychosocial factors contributing to CRCI, such as psychological distress, lack of social support, etc.

Conclusions

Significant advances in CRCI research have been made over the past 20-25 years. Despite these advances, which have contributed to the objective evidence of the cognitive side effects of adjuvant chemotherapy (Hodgson, Hutchinson, Wilson, & Nettelbeck, 2013; Jim et al., 2012; review by Phillips & Bernhard, 2003), questions still remain regarding the quality of studies conducted and the lack of clinical translation of these findings. Patients continue to be underserved with respect to their cognitive complaints following chemotherapy. There are several reasons for these problems, which have been addressed in this dissertation. The

overarching purpose of this dissertation was to explore and address the methodological confounds and limitations of current CRCI research to determine more appropriate approaches for future research. In doing so, the dissertation addressed two research questions highly relevant in the field of CRCI research and provided guidelines for future research in order to improve patient care and quality of life.

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Appendix A

The Ottawa Hospital | L'Hôpital d'Ottawa

Monday, July 14, 2008

Dr. Barbara Collins
Ottawa Hospital - Civic Campus
Department of Psychiatry

Dear Dr. Collins:

Re: Protocol #   2008284-01H   **A Prospective Dose-Response and fMRI Study of the Effects of Chemotherapy on Neural Function in Early-Stage Breast Cancer Patients**

Protocol approval valid until -   **Monday, July 13, 2009**

Appendix B

Université d'Ottawa   University of Ottawa
Bureau d'éthique et d'intégrité de la recherche   Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Barbara	Collins	Social Sciences / Psychology	Supervisor
Erin	O'Farrell	Social Sciences / Psychology	Student Researcher

File Number: H08-14-04

Type of Project: PhD Thesis

Title: A prospective dose-response and fMRI study of the effects of chemotherapy on neural function in early-stage breast cancer patients

Renewal Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
09/11/2016	09/10/2017	Approved

Special Conditions / Comments:
N/A