THE EFFECT OF CHEMOTHERAPY ON COGNITION IN PATIENTS WITH AND SURVIVORS OF COLORECTAL CANCER

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ABSTRACT

This thesis has explored the phenomenon that has been described as chemotherapy-related cognitive impairment (CRCI), both in the wider cancer patient population, as well as looking specifically at patients being treated for colorectal cancer. CRCI refers to the situation in which treatment with chemotherapy for cancer leads to a subsequent decline in the cognitive functioning of affected patients, evident in both self-report data and the results of psychological testing.

Four studies have been completed. The first study was a meta-analysis of the literature published up until 2010, which investigated the effect of treatment with chemotherapy on cognitive functioning across a number of different types of cancer. This study found that, although CRCI has been well documented as occurring in patients treated with chemotherapy for breast cancer, research is lacking in relation to other types of cancer, in particular colorectal cancer. This outcome justified the research that followed; the specific focus of which was to evaluate the effect of chemotherapy on cognition in patients with colorectal cancer.

Following the meta-analysis, a primary research study was conducted to assess the effect of chemotherapy on cognition in patients treated for colorectal cancer. This study comprised four sample groups, all of whom, with the exception of healthy, age-matched controls (n = 20), had been diagnosed with colorectal cancer: participants who have been treated with chemotherapy (n = 19), participants who received treatment with the anti-vascular drug Avastin (n = 12) and participants who have received only surgery (n = 10). Results supported previous reports that cognitive impairment may occur in patients treated for cancer, however suggestions that chemotherapy impacts cognition more than other forms of treatment was not

supported by the results, with the surgery patients being the only group to be significantly different in their cognitive performance from the healthy controls.

The next study (Study 3) investigated the relationship between subjective and objective measures of cognitive functioning in colorectal cancer patients. In general, the results revealed that patient perception of cognitive functioning was not significantly related to performance on objective cognitive tests, with the possible exception being tests of memory, indicating that a discrepancy may exist between objectively and subjectively measured CRCI. Depression and anxiety were negatively related and emotional wellbeing positively related to subjective reports of CRCI.

Study 4 (Chapter 5) aimed to assess whether locus of control, optimism / pessimism and depression influence recall of cognitive functioning after cancer treatment among colorectal cancer survivors. Two different groups were included in the sample: survivors of colorectal cancer (n = 88) and their spouses (n = 40). Recall of cognitive difficulties after cancer treatment was validated through significant correlation with recall of the participants' cognition after treatment, provided by their partners. Significant positive relationships were established between internal locus of control, optimism and perceived cognitive functioning and a negative relationship for depression. Regression analyses revealed that after controlling for depression, internal locus of control and optimism/pessimism contributed very little to the survivors' recall of cognitive functioning after cancer treatment. However, it was proposed that depression may moderate the relationship between internal locus of control and recall of cognitive functioning; hence if depression were to be treated, it is possible that internal locus of control would significantly contribute to recall of cognition after treatment. This was not the case for optimism/pessimism. These results were discussed in terms of their importance for researchers and clinicians alike. The

treatment experience of cancer patients and survivors must be considered in light of their level of depression and the extent to which they demonstrate an internal locus of control. Where depression is high, recall of cognitive impairment associated with treatment may be impacted.

DECLARATION

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CHAPTER ONE

Introduction

1.0 Preamble

Many patients who receive treatment with chemotherapy for cancer report experiencing difficulties across a range of cognitive functions. These include, but are not limited to, attention and concentration, various aspects of memory and speed of information processing. These patient reports have been supported by studies of breast cancer survivors' performance on objective cognitive tests (Vearncombe, Rolfe, Wright, Pachana, Andrew & Beadle, 2009; Wefel, Saleeba, Budzar & Meyers, 2010); however, little research has been conducted in relation to these deficits in patients with colorectal cancer, despite the high prevalence of this cancer and its high rates of survival. This thesis has investigated the effect of chemotherapy on cognition in patients with colorectal cancer, in addition to which individual characteristics contribute most to cognitive impairment, measured both objectively and subjectively, among these patients. The first chapter will provide a broad overview describing the state of the evidence for chemotherapy-related cognitive impairment (CRCI), followed by in-depth assessment of specific studies examining this issue.

1.1 Chemotherapy-Related Cognitive Impairment: An Overview

Chemotherapy-related cognitive impairment (CRCI), also known colloquially as 'chemobrain' or 'chemofog', refers to the situation whereby treatment of cancer patients with chemotherapy is followed by decline in their cognitive performance (Collins, Mackenzie, Stewart, Bielajew & Verma, 2009). CRCI is characterised by deficits across a number of different cognitive functions, with some authors reporting as few as one or two affected functions, while others report that many cognitive abilities are disrupted by chemotherapeutic treatment (Collins et al., 2009). The most commonly reported deficits associated with treatment with chemotherapy are in aspects of memory, executive functioning and speed of

information processing, operationalised in a variety of ways (Boykoff, Moieni & Subramanian, 2009; Collins, Mackenzie, Stewart, Bielajew & Verma, 2009; Falleti, Sanfilippo, Maruff, Weih & Phillips, 2005; Vardy & Dhillon, 2010; Wefel et al., 2004). Authors have also noted that following chemotherapy, many patients report inattention and difficulty thinking (Boykoff, Moieni & Subramanian, 2009; Collins et al., 2009; Falleti et al., 2005; Hampton, 2008; Hede, 2008) and impairments in objectively measured verbal learning, psychomotor processing speed, the ability to name objects, performance on complex visuoconstruction tasks and fine motor dexterity (Falleti et al., 2005; Myers, 2009; Wefel et al., 2004). Thus many different domains of cognitive functioning have been implicated as being affected by treatment with chemotherapy and further research into the domains affected by, as well as symptoms of CRCI is required.

The potential impact of these impairments on cancer survivors' quality of life is considerable. Together, these symptoms may result in patients experiencing problems with everyday functioning such as remembering to pay bills or take medication; some may be forced to cease employment as a consequence of CRCI symptoms, which in turn may lead to a further reduction in their quality of life. It is important to note that there is dispute about the prevalence of these difficulties; some authors report that the effects of CRCI generally go unnoticed by patients (Hermelink et al., 2010), whereas others have acknowledged that most patients with CRCI do notice changes in their cognitive functioning (Boykoff, Moieni & Subramanian, 2009; Hede, 2008). Additional investigation into patient reports of cognitive impairment following treatment with chemotherapy and the impact of individual characteristics on these reports is required to fully explain the CRCI phenomenon.

As highlighted above, estimates of the prevalence of CRCI differ widely within the literature, ranging from 14% to 85% of patients (Hede, 2008). The wide range in the estimate may, in part, reflect the fact that a number of cancer types and diverse treatment regimens

have been involved. However, many more CRCI studies have been conducted using breast cancer patients than any other cancer type and the prevalence of CRCI in alternative, less frequently researched cancer populations may differ. Also, the mechanisms through which cognition may be impacted by treatment have not yet been conclusively identified. Finally, it is possible that the impact of treatment varies between patients due to factors such as age, level of depression or anxiety, premorbid intelligence and menopausal status, and that strategies may need to be tailored to the individual patient for minimising the impact, or optimising return to pre-treatment cognitive performance (Hede, 2008; Hampton, 2008). Nonetheless, there is at least some consensus that CRCI affects approximately 30% of all patients treated with chemotherapy (Collins et al., 2009; Hermelink et al., 2007; Vardy & Dhillon, 2010).

Better understanding of biological mechanisms responsible for the experience of CRCI could provide a basis for developing support strategies for better coping with CRCI or minimising the impact of treatment. There has been speculation about possible causal mechanisms; Hede (2008) suggested that treatment with chemotherapy decreases the resting brain metabolism of the patient, which consequently leads to poorer cognitive performance and the reporting of cognitive complaints. In a similar vein, Hampton (2008) argued that chemotherapy is toxic to brain cells as well as cancer cells. Others have argued that treatment with chemotherapy leads to relatively rapid degeneration of brain and central nervous system tissue, including the myelin sheaths which serve to insulate and protect nerve cells and assist in the conduct of neural signals; when these myelin sheaths become damaged, the effectiveness of nerve conductivity is reduced, with possible cognitive deficits occurring as a result (Han, Yang, Dietrich, Luebke, Mayer-Proschel & Noble, 2008). It has also been suggested that DNA damage and elevated cytokine levels may result in cognitive impairment subsequent to a diagnosis of cancer (Collins et al., 2009; Hede, 2008; Vardy & Dhillon,

2010). Finally, oxidative stress that causes damage to the brain and central nervous system has also been identified as causing CRCI (Nelson, Nandy & Roth, 2007). Evidence as to the validity of these different mechanistic models of CRCI remains limited, although it is an important area for future research.

To summarise, the costs of CRCI at the level of the individual patient, as well as at the societal level, are potentially great. Patients who report being affected by CRCI describe difficulty performing common tasks that arise in their everyday lives, like remembering to pay bills or take their medication; as a result they also tend to experience a reduction in their overall quality of life (Collins et al., 2009). Their professional lives are often affected, with some CRCI sufferers experiencing an inability to perform particular tasks required of them as part of their work, which can lead to a great deal of stress and, in many cases, cessation of employment (Collins et al.). This may lead in turn to further decline in the quality of life of the patient. Thus CRCI can have economic implications for both the individual, in that they may no longer maintain a regular income, and for society because patients may no longer be working tax payers and, in some cases, may rely on financial support. Clearly, the social and economic flow-on effects of CRCI can be considerable, the more so if, even when the symptoms of CRCI have resolved, the patient finds it difficult to re-enter the workforce.

1.2 Confounding Factors in CRCI

Hede (2008) argued that the cognitive dysfunction commonly reported as experienced by cancer patients cannot be attributed to chemotherapy alone because a number of different factors may cause and/or exacerbate the symptoms of CRCI. A major possible confounding factor when investigating the occurrence of CRCI is that some patients report experiencing cognitive difficulties prior to receiving any treatment with chemotherapy. Estimates of the prevalence of cognitive dysfunction prior to treatment in cancer patients are around 30% (Hermelink et al., 2007; Vardy & Dhillon, 2010; Wefel et al., 2004); this figure is comparable

to the 30% prevalence figure for CRCI reported earlier. There are a number of possible reasons for the existence of cognitive impairment among some cancer patients prior to receiving treatment with chemotherapy. For example, CRCI could be artefacts of the differential prevalence of cancer in the community, i.e. diagnoses of cancer occur more frequently among populations with lower socioeconomic status, fewer years of education, lower intelligence and poorer cognitive functioning from the outset (Collins et al., 2009; Myers, 2009). Therefore, a comparison of cancer patients with healthy controls sometimes reveals poorer cognitive function as a result of these socioeconomic factors. It is important to conduct a baseline pre-chemotherapy assessment of cognitive functioning, or test for premorbid ability in order to adequately control for this confound. Alternatively, cognitive impairment, evident prior to treatment with chemotherapy, may be a consequence of the cancer itself or as a result of the pre-chemotherapy treatment, such as surgery or hormone therapy which are, in and of themselves, often associated with cognitive impairment (Collins et al., 2009; Hede, 2008; Vardy & Dhillon, 2010). Finally, it is possible that cognitive impairment may exist prior to exposure to chemotherapy because of the emotional impact that accompanies a diagnosis of cancer. This may lead to the development of depression and anxiety which are also often associated with cognitive deficits (Hede, 2008; Hermelink et al., 2010).

In broad terms, the most commonly identified confounding factors in CRCI research are anxiety, depression and fatigue (Hede, 2008; Hermelink et al., 2010). These experiences increase the difficulty of investigating CRCI; cancer patients experience anxiety, depression and fatigue from the outset, following a diagnosis of cancer. Because non-clinical levels of anxiety and depression may have an impact upon cognitive functioning, when conducting research in this area, it is important to control for these by potentially excluding patients with a current clinical diagnosis of anxiety or depression and/or by controlling for these constructs

when conducting statistical analyses. Trait negative affectivity, also known as a negative or pessimistic personality, has also been found to be related to cognitive impairment in cancer patients, but it is unknown whether this factor causes cognitive impairment in and of itself, or whether it simply exacerbates the patients' perceptions of CRCI (Hermelink et al., 2010).

Other factors that have been thought to influence the extent to which one is susceptible to CRCI, or the level of severity at which CRCI is experienced, include education and level of intelligence (Collins et al., 2009; Myers, 2009). Specifically, a review by Myers (2009), found higher levels of education and intelligence offer patients protection against CRCI and, in the case of impairment, patients who score more highly on IQ tests and/or are more highly educated, experience symptoms less severely and are better able to continue to engage in everyday activities. Additionally, even when reporting cognitive difficulties, highly educated people tend to perform well on neuropsychological tests and objective signs of CRCI are therefore less likely to be detected by these means.

Several authors have also questioned whether the cognitive impairment often reported by patients is a consequence of the cancer experience itself (Collins et al., 2009; Hede, 2008; Vardy & Dhillon, 2010). Not only are patients likely to be experiencing depression, anxiety and fatigue as a result of their diagnosis and treatment, but the cancer itself causes changes at the biological level, including elevated cytokine levels and DNA damage, which may at some point affect the patient's cognitive functioning. It is for these reasons that some authors claim that all cancer patients are at risk of experiencing cognitive deficits, regardless of whether or not they have received treatment with chemotherapeutic agents (Collins et al.; Hede; Vardy & Dhillon).

It has also been argued that, because cognitive deficits often exist post-diagnosis and prior to treatment with chemotherapy, it is likely that these occur as a result of the stress associated with the diagnosis of cancer, rather than the treatment itself (Hermelink et al.,

2007, 2010). Specifically, Hermelink et al., (2007) reported that, for five of six cognitive tests, the mean scores obtained following diagnosis and prior to the commencement of treatment were considerably lower than the test norms. Hermelink and colleagues suggested that this may be because the stress following a diagnosis of cancer results in post-traumatic stress disorder (PTSD), which is responsible for the cognitive decline. Moreover, this state may endure for an extended period of time following diagnosis and treatment, thereby explaining prolonged less effective cognitive performance and reported problems with cognition post-treatment or during remission.

It is also important to consider that treatments other than chemotherapy may additionally contribute to cognitive impairment among patients with cancer. One example of this is a similar phenomenon to CRCI, termed postoperative cognitive dysfunction (POCD). POCD has been observed to occur following many forms of surgical treatment, not only for cancer, and is thought to be a consequence of either the effects of general anaesthetics on the brain (Avidan & Evers, 2011; Chen et al., 2001), or as a result of the actions of the inflammatory system on the functioning of the brain (Avidan & Evers, 2011; Cibelli et al., 2010). As is the case for CRCI, the duration for which POCD symptoms have been thought to be present has been debated, with estimates varying from a few days, to three months post-surgery (Avidan & Evers, 2011; Moller et al., 1998). It is important to note that although these estimates overlap with part of the range of those for CRCI, the symptoms of CRCI have been reported to persist for much longer than three months.

POCD has been much more thoroughly examined than CRCI and it has been acknowledged that POCD tends to be both more prevalent and more severe among the elderly and that its symptoms tend to persist for a longer duration among this population, who may experience it for up to three months, compared to younger patients who may only experience its symptoms for a number of days, often resulting in a significantly reduced quality of life

for elderly individuals for a number of months after surgery (Avidan & Evers, 2011; Chen et al., 2001; Moller et al., 1998). For many patients diagnosed with cancer, surgery is the first intervention; many patients treated with chemotherapy would have received some surgical intervention prior, making it important to consider the possible role of POCD when conducting research in the area of CRCI. Assessing the cognitive functioning of patients before and after surgery and then again before, during and following chemotherapeutic treatment may address this issue. However, assessing patients on multiple occasions can lead to practice effects and recruiting patients prior to treatment may be difficult due to the need for timely intervention. While POCD and CRCI may result in similar symptomatology, POCD is caused by surgical intervention, believed to be as a consequence of sedation with general anaesthetic; in contrast, CRCI occurs as a result of exposure to chemotherapy. It is important to note that these are two distinct processes and are not directly related to one another.

A major confounding factor commonly acknowledged as responsible for the experience of cognitive decline, particularly within breast cancer CRCI research, is hormone therapy. This is because treatment with hormone therapy itself has been linked to possible cognitive compromise. Thus, when patients are treated with chemotherapy in conjunction with hormone therapy and cognitive deficits develop in the patient, it is difficult to ascertain whether these deficits are the result of CRCI, because of the hormone therapy treatment, or as a result of possible additive or interactive effects of the chemotherapy and hormone treatment (Hermelink et al., 2010).

Finally, it has also been reported that patients' prior knowledge of the 'chemobrain' experience can influence expectations, sufficient to increase the reporting of cognitive complaints by patients (Schagen, Das, & van Dam, 2009). In a

study of 261 breast cancer patients, Schagen, Das and van Dam (2009) found that participants who received information about CRCI prior to their participation in the study reported more cognitive complaints than participants who were not privy to this information.

This experience has been well-documented in the psychopharmacology and medical literature and is referred to as the "expectancy" effect. The power of expectancy effects among patients, associated with the delivery of drug treatment, is well documented. For example, Bjørkedal and Flaten (2011) reported, on the basis of a placebo controlled study, that participants' reports of pain associated with exposure to a laser were decreased when they were told they had received an analgesic with their caffeine as opposed to caffeine alone, despite their being no difference in the treatment. Moreover, the data indicated that the effect was mediated by expectancies about pain. In addition, in a study on the influence of psychological factors on chemotherapy toxicities, Whitford and Olver (2012) found that the contribution of expectations to the extent to which patients reported experiencing problems with concentration approached significance. Together, these studies indicate that patient expectations may have an impact on their perceived symptomatology, with Whitford and Olver demonstrating that this is also the case among cancer patient populations.

It is important to note that expectancy effects are, in turn, moderated by a patient's previous experiences. In the Schagen et al., (2009) study of CRCI, expectancies impacted only on those patients who had not received treatment with chemotherapy previously. Participants with a history of chemotherapeutic treatment reported more cognitive dysfunction at baseline. These results highlight the potential for both experimenter and participant expectancies to confound self-reported cognitive outcomes among cancer patients.

1.3 Interventions for CRCI

A number of different interventions have been proposed as being beneficial in ameliorating the symptoms of CRCI. An examination of these may assist in assessing the

extent to which CRCI is a result of biological or psychological assaults to the cancer patient. Some experts in the field of cognitive impairment draw an analogy between muscles in the body and the brain and argue rehabilitation of both should involve "practice" or use. For example, Hede (2008) suggested engagement with puzzles such as Sudoku may assist recovery from CRCI, implying that cognition needs some form of "rehabilitation" following assault from chemotherapy.

Clinically-focussed cognitive rehabilitation programs, similar to those utilised with traumatic brain injury patients, have also been suggested as useful in the treatment of CRCI (Ferguson et al., 2007). These programs are generally founded on cognitive behavioural strategies, including verbal self-guidance, in which the patient would be required to discreetly talk themselves through each step of a task high in attentional demand; verbal rehearsal of auditory information in order to aid memory; producing and adhering to written schedules; and using external cues to assist with memory. These strategies are taught to patients in order to improve memory, attention and concentration, self-awareness and self-regulation. The importance of relaxation, activity scheduling and time management skills, are also emphasised so as to provide effective mechanisms for cognitive compensation (Ferguson et al., 2007; Galantino, Greene, Daniels, Dooley, Muscatello & O'Donnell, 2012; Myers, 2009). In a study of 29 women who had received chemotherapy treatment for breast cancer an average of eight years prior, Ferguson et al., (2007) found that a memory and adaptation training intervention, which encompassed all of the cognitive-behavioural strategies outlined above, resulted in less cognitive complaints and reports of improved quality of life. Performance on a range of objective neuropsychological tests of cognition also generally improved, with large effect sizes being found. It is important to note that the results of this study are applicable only to survivors of breast cancer and it is possible that, because of the long duration between treatment cessation and receiving the cognitive intervention, the

women in this study responded differently to the memory and attention adaptation training than they would have either during treatment or immediately after treatment cessation. In addition, it is noteworthy that the study did not include a control group and was conducted over a six month period, thus it is possible that the cognitive impairment improved as a result of the passage of time rather than the effectiveness of the intervention. Further research utilising this intervention with current cancer patients is required in order to evaluate its direct impact on the symptoms of CRCI.

A nutritional intervention suggested as being useful for the treatment of the symptoms of chemotherapy-related cognitive impairment involves increasing intake of antioxidants that are found in foods such as tea and leafy green vegetables (Galantino et al., 2012; Nelson, Nandy & Roth, 2007). One hypothesis for the development of CRCI is that it occurs due to oxidative stress and subsequent damage to the cells of the brain and central nervous system, so that an increased intake of antioxidants may reduce and reverse the extent of this damage (Nelson, Nandy & Roth, 2007). However, it is important to note that this is simply a hypothesis based on the suspected mechanisms involved in the development of CRCI and is not founded on evidence for its effectiveness.

Physical activity has also been reported as effective for reducing CRCI symptomatology (Fardell, Vardy, Shah & Johnston, 2012; Fitzpatrick, Edgar & Holcroft, 2012; Hede, 2008). This is thought to be because physical exercise promotes improved blood flow, resulting in increased oxygenation of the brain tissue and better cognitive functioning (Nelson, Nandy & Roth, 2007). Fardell et al., (2012) found that where rats treated with 5-flourouracil and oxaliplatin chemotherapy, the same drugs used in the treatment of colorectal cancer, were provided with a running wheel overnight for four weeks, their cognitive performance was similar to that of rats that were not treated with chemotherapy on tasks of object recognition and spatial reference memory. These results raise the possibility that

targeted exercise programs delivered post-treatment may minimise the experience of, or result in a quicker recovery from, CRCI.

Non-aerobic forms of exercise may also assist cognitive recovery following cancer treatment. For example, in a case-study of four early-stage breast cancer patients, Galantino et al., (2012) reported that engaging in 70 minute yoga classes twice a week for 12 weeks improved cognitive functioning, in particular by improving speed of information processing and reducing the number of errors made on the CogState Computerised Assessment of Cognitive Functioning. However, these authors acknowledge that due to a very small sample size, more research is required to test the benefits of yoga for patients experiencing CRCI. Relaxation therapies such as meditation have also been shown to be useful in combating the symptoms of CRCI (Hede, 2008).

A number of pharmacological interventions have also been suggested as effective in the treatment of CRCI. The most common of these is treatment with erythropoietin medication, which has been shown to be related to a decline in the number of complaints about cognitive functioning reported by patients after a six month period (Galantino et al., 2012; Hermelink et al., 2010; Nelson, Nandy & Roth, 2007). The mechanism by which erythropoietin is thought to improve cognitive functioning in cancer patients after treatment with chemotherapy is by increasing the amount of haemoglobin in the blood which improves cognition and treats anaemia in cancer patients (Nelson, Nandy & Roth).

Some studies have indicated no beneficial effects of erythropoietin medication on CRCI (Mar Fan et al., 2009). Mar Fan et al., tested a sample of 87 participants, 45 of whom were treated with erythropoietin alpha; they found no evidence to suggest a protective effect of erythropoietin treatment on cognitive functioning as measured by the Highly Sensitive Cognitive Screen. Furthermore, higher levels of cognitive impairment were evident in those who received the erythropoietin treatment compared to those who did not. It is, however,

important to consider that this study utilised a somewhat small sample size of only 45 treatment participants and 42 controls, as well as a brief cognitive screening instrument, thus further research is required to support these findings before they can be considered with any confidence. Psychostimulant medications such as methylphenidate, which are most commonly used to treat conditions such as attention deficit hyperactivity disorder, have also been suggested as being effective in the treatment of cognitive impairment. Whether benefits are achieved by cancer patients remains to be established (Galantino et al., 2012; Nelson, Nandy & Roth, 2007).

In summary, a range of interventions have been proposed in the literature as being useful in alleviating the symptoms of CRCI. Many of these involve cognitive training strategies, either through clinically developed programs or using puzzles that can be done at home, to help individuals to strengthen their cognitive abilities through practice and use. Other interventions however, encourage the use of compensatory strategies to help the patient manage their CRCI more effectively, such as talking oneself through a task before completing it, or using meditation to help clear the mind before engaging in cognitively challenging activities. As mentioned earlier, some of the proposed interventions do not target cognition in such a direct manner and involve the consumption of foods high in antioxidants, or the prescription of drugs such as erythropoietin alpha or psycho-stimulant medication to improve cognitive functioning following cancer treatment. Finally, physical activity has also been recommended as being useful in reducing the symptoms of CRCI because it promotes better circulation of blood to the brain and central nervous system, which is known to encourage better cognitive functioning. It is evident that because no one clear mechanism for the development of CRCI has been established, a plethora of interventions accompany the many proposed mechanisms, with no gold standard intervention having yet emerged. The

diverse interventions for CRCI are reflected in the relatively inconsistent literature surrounding cognitive impairment in cancer patients.

1.4 Limitations of Existing CRCI Research

CRCI was first identified in the 1970s but it was not recognised as being a significant problem until the late 1990s and has only been extensively researched since that time (Myers, 2009). As a result of its relative infancy and the challenges associated with clinical research, much of the existing evidence is flawed. The nature of these problems is diverse. For example, most studies in this area have been small and have included few older patients, despite the fact that cancer is more commonly diagnosed at an older age (Hede, 2008). The average age of cancer diagnosis across all forms of cancer in Australia was 65.4 years in 2009 (Cancer Australia, 2013). Recruitment of participants in cancer-related research fields is often difficult, primarily because patients are either too ill to participate or too busy trying to maintain full time work and treatment-related commitments.

Another important shortcoming to research design in this area is that control groups commonly consist of healthy participants, rather than a comparison group consisting of cancer patients not undergoing chemotherapy (Collins et al., 2009; Wefel et al., 2004). This lack of an appropriate control group is problematic because the comparison of cancer patients being treated with chemotherapy with healthy control participants may lead researchers to conclude that impairment results from chemotherapy treatment when, in fact, cognitive deficits were already present because of other cancer-related variables, for example stress, among those undergoing treatment. The importance of pre-treatment assessments has also been stressed, because it is vital to determine whether the participants were performing at an impaired level prior to treatment (Wefel et al., 2004). This issue has been identified as being important because over time, it has become evident that cross-sectional studies in this area report finding evidence for CRCI much more frequently than prospective longitudinal studies

(Myers, 2009; Wefel et al., 2004). It is for this reason that Myers (2009) has recommended that studies investigating CRCI adopt the prospective longitudinal design. However, it is important to note that achieving this can be particularly difficult because, in addition to the problems associated with the recruitment of cancer patients for a cross-sectional study, adequate participant numbers need to be retained over time.

In order to combat many of the limitations of CRCI research, as well as to ensure that all research in this area conforms to the same standard, the International Cognition and Cancer Task Force (ICCTF) produced a set of recommendations for individual researchers to consult prior to conducting CRCI-related research (Wefel, Vardy & Schagen, 2011). These recommendations suggest that studies investigating CRCI should be longitudinal and observational in design and utilise a number of control groups including disease-specific and healthy control participants (Wefel, Vardy & Schagen, 2011). The ICCTF also strongly recommended that all studies investigating CRCI conduct cognitive assessments prior to the commencement of treatment, including before surgery, and has suggested that the Hopkins Verbal Learning Test-Revised, the Trail Making Test and the Controlled Oral Word Association Test of the Multilingual Aphasia Examination form the foundation of the assessment battery. These tests were selected because of their good psychometric properties, as well as the availability of non-English or sensitive versions of these tests for use with people of other languages, cultures or special populations. It is also recommended that researchers incorporate additional tests of working memory into the assessment battery (Wefel, Vardy & Schagen, 2011). It is important to note that these guidelines were developed in order to increase comparability across CRCI studies. However, because of the realities associated with conducting research with cancer patient populations, particularly the extreme difficulties with recruitment, it is often impossible for researchers to conform to all of the guidelines outlined by Wefel, Vardy and Schagen (2011).

1.5 Detailed Review of the CRCI Literature

1.5.1 Background

Although the experience of cognitive deterioration following treatment for cancer has been reported in a number of studies, the ability to generalise these findings is limited. The cancer type most predominantly focussed on in this research is breast; these studies will be reviewed with specific attention to the tests used to assess cognitive impairment. Biglia et al., (2012) found that following treatment with chemotherapy, patients with breast cancer experienced deficits in global cognitive functioning and visual selective attention as measured by the Mini Mental State Examination and Attentive Matrices, respectively. Trends towards less favourable outcomes were also noted in verbal skills, oral learning and short-term memory but impairments in these domains were not statistically significant. Similarly, a study of 138 breast cancer patients (Vearncombe, Rolfe, Wright, Pachana, Andrew & Beadle, 2009) found significant deficits in verbal memory as measured by the Auditory Verbal Learning Test (t = 4.40, p<.001), with decrements across multiple cognitive domains present among 16.9% of patients subsequent to treatment with chemotherapy. These domains included verbal learning and memory, as measured by the Auditory Verbal Learning Test, verbal fluency, as measured by the Controlled Oral Word Associated Test and the abstract reasoning component of executive functioning, evaluated by the Matrix Reasoning, Stroop and Card Sort tests.

Wefel, Saleeba, Budzar & Meyers (2010) found that 65% of their sample of 37 breast cancer patients experienced immediate short-term decline in learning and memory (measured by the Hopkins Verbal Learning Test); executive function (Multilingual Aphasia Examination Controlled Oral Word Association; and Trail Making part B tests) and processing speed (Digit Symbol of the Wechsler Adult Intelligence Scale-Revised and Trail Making Test Part A), following chemotherapeutic treatment. Moreover, 61% of patients

experienced delayed cognitive dysfunction, present at the follow-up assessment after 13 months. Interestingly, of those who did experience difficulties after a year, 30% had not previously experienced CRCI. The development of impairment during the follow-up period (late onset) is an unusual finding and certainly warrants further investigation in future research. Learning and memory measured by the Hopkins Verbal Learning Test was the broad cognitive domain most commonly impaired among the late onset CRCI cases in this study. However, it is important to note that 21% of 42 breast cancer patients were identified as being cognitively impaired relative to the age-matched norms for each of the cognitive tests, prior to the commencement of treatment. In general, this study shows that the experience of CRCI is diverse and thus likely to differ on a case-by-case basis, with impairment evident in some patients prior to treatment and emerging for the first time after the completion of treatment in others. Further research is necessary to more clearly understand individual differences which may lead to pre-treatment cognitive dysfunction, CRCI immediately after treatment or late-onset CRCI.

Other studies have reported the presence of a variety of forms of cognitive impairment in breast cancer patients, even prior to receiving treatment with chemotherapy. Reid-Arndt & Cox (2012) found that of 36 patients with breast cancer, 11% experienced deficits in verbal fluency and 27% in verbal memory, assessed using the Controlled Oral Word Association Test and the Auditory Verbal Learning Test, respectively, after receiving surgical intervention and before commencing additional treatment for their disease. Hence cognitive impairment was documented as occurring prior to receipt of any chemotherapy in these patients. Additionally, no effect of chemotherapy on cognition was noted in a study of 35 breast cancer patients by Biglia et al., (2010), in which memory, measured by the Numeric Matrix and Rey Auditory Verbal Learning tests, actually improved following treatment with chemotherapy. This result is, however, contradictory to the majority of the breast cancer

CRCI literature and should be interpreted with caution because it is possible that this finding was a consequence of learning effects. These can occur when administering the same tests to participants on multiple occasions over a short period of time and can only be controlled for through the use of a control group which was not included in this study (Biglia et al., 2010). In sum, the literature clearly shows impairment across a range of cognitive domains in breast cancer patients. However, it remains unclear whether this impairment occurs as a consequence of treatment, or whether it develops because of the cancer itself before treatment even commences.

Another commonly investigated cancer type in the CRCI literature is testicular cancer. Similar to the breast cancer literature, it has been found that chemotherapy may lead to impairment across a range of cognitive domains among patients with testicular cancer. A recent study with a sample of 69 newly diagnosed testicular cancer patients found that subsequent to treatment with chemotherapy, patients exhibited deficits in learning and memory, as evidenced by the Hopkins Verbal Learning Test, executive function as measured using part B of the Trail Making Test and upper extremity fine motor dexterity evaluated by the Grooved Pegboard test (Wefel et al., 2011). However, within the testicular cancer literature, results across studies have been mixed. For example, in a 12-month longitudinal study of 122 patients with testicular cancer, Skaali et al., (2011) reported that treatment with chemotherapy did not lead to declines in performance across a range of objective neuropsychological tests, while Pedersen, Rossen, Mehlsen, Pedersen, Zachariae & Von Der Masse (2009) established that men treated with chemotherapy and surgery for testicular cancer performed at a similar level on a battery of neuropsychological tests as men who received only surgical treatment. However, this study included a sample of men two to seven years post-treatment and it is therefore possible that treatment-related cognitive deficits may have dissipated by this time.

Ovarian cancer is another condition where research has demonstrated ambiguous evidence for CRCI. Some studies have found no effects of chemotherapy on objectively measured cognitive functioning in patients with ovarian cancer (Hensley et al., 2006; Mayerhofer et al., 2000); although Hensley et al., found that the more highly educated women in their sample reported experiencing cognitive difficulties following chemotherapeutic treatment. However, one study showed a clear effect of chemotherapy on cognition in patients with ovarian cancer; Hess et al., (2010) found that over 80% of the 27 participants in their study demonstrated a decline in their cognitive functioning, measured by tests of processing speed (subtests of the Cognitive Stability Index, Animal Decoding and Symbol Scanning), attention (Number Recall and Number Sequencing) and reaction time (Response Direction 1 & 2), from the baseline assessment to that conducted after six cycles of chemotherapy. More research is required to further confirm the presence of CRCI in ovarian cancer patients.

Studies by Kaasa and colleagues, (1988) investigating the occurrence of CRCI in non-small cell lung cancer patients, have found that individuals treated with chemotherapy tend to perform more poorly on tests of cognitive functioning, including the Revised Benton Visual Retention Test and the Verbal Learning and Trail Making Tests, than their counterparts who were treated with radiation therapy (Kaasa, Olsnes & Mastekaasa, 1988; Kaasa, Olsnes, Thorud & Host, 1988). However, in a study of 21 patients with small cell lung cancer, it was found that up to 80% of participants experienced cognitive deficits prior to receiving chemotherapeutic treatment and it was therefore concluded that this may be the result of disease-related factors, rather than being an example of CRCI (Meyers, Byrne & Komaki, 1995).

In summary, cognitive impairment has been found to exist before and after treatment with chemotherapy in patients with a range of different types of cancer including breast,

testicular, ovarian and non-small cell lung cancer. However, it is important to note that different cognitive domains are often found to be affected and to varying extents, depending upon the type of cancer being investigated. This is likely to be the case because different forms of cancer affect the biological processes within the body in different ways and are treated using different chemotherapy regimens comprising different chemical compounds, doses and toxicities. Further research is necessary in order to resolve inconsistencies in the literature regarding whether CRCI exists in cancer types other than breast and any areas of associated cognitive dysfunction.

1.5.2 Objectively-Measured Versus Self-Reported CRCI

Research indicates that patients' perceptions of their cognitive functioning and the results of objective neuropsychological tests of cognition are not always as closely related as might be expected. Many studies have found no relationship between self-reported and objectively-measured cognitive functioning; with no impairment being found by objective cognitive tests, despite patient complaints (Biglia et al., 2012; Hermelink et al., 2010; Skaali et al., 2011). Weis, Poppelreuter & Bartsch (2009) found evidence for CRCI using both objective and subjective measures of cognitive functioning. However, there was no significant relationship between these two types of measurement. More specifically, they found that 21% of their sample was cognitively impaired according to performance on the Test Battery for Assessment of Attention, the Rivermead Behavioural Memory Test, the Wechsler Memory Scale-Revised and the Learning and Memory Test, whereas 36% reported a decline in their cognitive functioning following treatment. Moreover, these two groups overlapped only marginally. Therefore, this study found that some patients reported cognitive impairment subsequent to treatment with chemotherapy, while some were found to have poorer cognitive functioning using objective cognitive tests; however, these were generally

two separate groups of patients. Several reasons for this discrepancy between objective and subjective measures of impairment have been proposed.

One possible explanation for a higher incidence of self-reported than objectively measured CRCI is that patients are aware of the CRCI phenomenon prior to participating in research studies and this 'priming', or expectancy, of the condition leads to higher levels of self-reported symptoms (Schagen, Das & Van Dam, 2009; Skaali et al., 2011). Alternatively, subjective and objective evaluations of cognition may be unrelated in CRCI studies because objective tests may not be sensitive enough to detect the subtle impairment present within this population of patients. If this is the case, the conclusion that CRCI does not exist based on objective measures alone would be inaccurate (Hermelink et al., 2010).

Other possible explanations for the mismatch between objective and subjective reports have been proffered. Hermelink et al., argued that "cancer patients' self-perceptions of cognitive dysfunction appear to be pessimistic interpretations of their cognitive functioning that are induced by treatment burden and negative affectivity regardless of whether or not neuropsychological compromise is actually present" (p. 1327). This suggests that the cognitive difficulties reported by patients subsequent to chemotherapeutic treatment may in fact be more of a psychological mindset rather than that actual cognitive impairment exists. Further support for this notion is found in the observation that patients who actually experience CRCI that has been detected using objective neuropsychological tests, do not usually notice the change in their cognitive functioning, so that the CRCI tends to go unreported (Hermelink et al., 2010). Therefore self-reported and objectively identified CRCI may be two separate phenomena; the former associated with a psychological mindset and the latter with cognitive dysfunction.

Overall, the literature suggests that more profound levels of cognitive decline may be self-reported by patients with cancer following treatment with chemotherapy than are

detected by objective cognitive tests. It is possible that this is the case because objective tests are not adequately sensitive to the subtle cognitive dysfunction experienced by these patients. Alternatively, it is possible that patients who are depressed or more pessimistic about their cancer may tend towards reporting CRCI symptoms as being more severe and persistent than is the case. Further research is required in this area to establish more conclusively which of these two explanations is more likely.

1.5.3 Factors that Contribute to CRCI and the Severity of its Symptoms

A number of variables have been identified by research as possibly exacerbating the symptoms of treatment-related cognitive dysfunction. The first and most commonly discussed of these includes emotion-related variables such as anxiety and depression. A study of breast cancer patients found that high levels of anxiety and depression were related to poorer appraisals of cognitive functioning by patients. However, objectively-measured cognitive performance was not influenced by emotional status (Biglia et al., 2012). Similarly, in a study of patients with testicular cancer, self-reported cognitive dysfunction was related to level of distress, as well as self-reported fatigue and lower levels of education (Skaali et al., 2011). Skaali et al., emphasised that it is important to consider that patient appraisals of cognitive impairment may be more reflective of emotional status than neurocognitive functioning. Nevertheless, it is important for physicians to attend to the cognitive complaints of patients because these may be indicative of psychological distress or fatigue, which may warrant intervention because these factors may impact upon the quality of life and ultimately, the survival, of the patient.

Reid-Arndt and Cox (2012) identified stress as exacerbating the symptoms of objectively-measured cognitive dysfunction in women treated with surgery for breast cancer, with self-reported stress being associated with a decline in verbal memory and verbal fluency. The authors proposed that stress alone may not be related to cognitive functioning following

surgical intervention for breast cancer but, rather, that coping style may underlie the relationship between stress and cognitive functioning. In their study of testicular cancer patients Wefel et al., (2011) reported that the only objectively-measured cognitive domain affected by emotion-related variables was psychomotor speed, with higher levels of depression and anxiety resulting in poorer cognitive functioning in this domain. They also found that cognitive functioning, as represented by scores on the Digit Span and Digit Symbol subtests of the Wechsler Adult Intelligence Scale-Revised, the Trail Making Test, Hopkins Verbal Learning Test and level of education were significantly positively correlated with coefficients ranging from .26 to .62 (Wefel et al., 2011). Therefore, it is possible that individual characteristics such as stress, depression, anxiety and lower levels of education are associated with poorer cognitive function in cancer patients.

Hermelink et al., (2010) confirmed that depression exacerbated CRCI symptoms, although the effect of anxiety was not replicated. Hermelink et al. emphasised that it is important to keep in mind that although depression appears to result in higher levels of perceived cognitive dysfunction in patients, perceived cognitive dysfunction may actually increase depression. They also found that a negative disposition is a predictor of self-reported cognitive impairment.

A range of other variables such as chemotherapy regimen, age, menopausal status and haemoglobin level, may mediate or moderate the relationship between chemotherapy and CRCI. Chemotherapy regimen was reported as a predictor of patient-appraised cognitive dysfunction because particular types and doses of chemotherapy, when compared to other chemotherapy types and doses, were found to be related to poorer reports of cognitive functioning (Hermelink et al., 2010).

Wefel, Saleeba, Budzar & Meyers (2010) found that age was a predictor of cognitive dysfunction among breast cancer patients, with older patients demonstrating higher levels of

cognitive impairment, as measured by the Trail Making and Hopkins Verbal Learning Tests, prior to the commencement of treatment than younger participants. It is possible, therefore, that these effects were solely due to the age of the patients rather than to cancer or chemotherapy-related factors.

In another study of breast cancer patients, anxiety and fatigue were again confirmed as predictors of cognitive impairment, while menopausal status was discussed as a factor that also exacerbates the symptoms of treatment-related cognitive impairment among breast cancer patients (Biglia et al., 2010). Conversely, Vearncombe et al., (2009) found that, among their sample of 136 breast cancer patients, depression, fatigue and reduced wellbeing were not significantly related to cognitive functioning. They did find that a decline in haemoglobin, often caused by anaemia, in conjunction with greater anxiety, predicted poorer performance on numerous measures of cognitive functioning, including two or more of the following: the Auditory Verbal Learning Test, Visual Reproduction, Digit Span Backwards, Symbol Digit Modalities Test, Test of Everyday Attention, Matrix Reasoning and the Controlled Oral Word Association Test. Together, these studies reveal that there are a wide range of possible factors that may impact on the extent to which a patient experiences CRCI and these include, but are not limited to, chemotherapy regimen, the age of the patient, depression, anxiety, fatigue, menopausal status and low levels of haemoglobin. The variety of factors implicated in moderating or mediating CRCI is evidence for the fact that more research is required in order to meaningfully establish which individual characteristics are most important in protecting against, minimising the effects of and aiding recovery from CRCI.

In sum, a number of factors have been found to contribute to the development of CRCI and the severity of its symptoms. The most frequently discussed of these include factors related to emotional wellbeing such as depression, anxiety and stress which are often

associated with greater patient reports of cognitive impairment following cancer treatment. However, emotional wellbeing is less commonly related to CRCI when measured using objective cognitive tests. Other factors including level of education, menopausal status, level of haemoglobin in the blood and, to some extent age, have also been found to impact on the extent to which CRCI is experienced using both subjective and objective measures of cognitive function.

1.5.4 Personality and CRCI

There are a range of factors associated with cognitive function in cancer patients. Another potentially important characteristic may be personality. This is an area of research that is emerging within the cancer domain and investigates the potential effects of personality on all areas of functioning during and after cancer treatment. The majority of work in this area has investigated the role of an optimistic personality in reducing the extent to which the patient experiences anxiety and depression and how s/he adopts strategies for improving quality of life. In a study of patients with urogenital cancer, Zenger, Brix, Borowski, Stolzenburg and Hinz (2010) found significant relationships between optimism, evaluated using the Life Orientation Test, and self-reported anxiety and depression (measured by the Hospital Anxiety and Depression Scale) and quality of life (assessed using the Health Survey – SF8). They did, however, question whether this outcome was because more optimistic individuals are less prone to developing anxiety and depression during cancer treatment, hence resulting in a better quality of life, or whether measures of both pessimism and depression have items with similar content, which may result in similar kinds of responses in questionnaires. In addition, these authors propose that if one is experiencing depression and anxiety, one is not also likely to be feeling optimistic and it may not therefore be that an optimistic personality style offers protection against depression and anxiety during cancer treatment but, rather, that those who are not suffering the effects of depression and anxiety

tend to be more optimistic than patients having to deal with these issues (Zenger et al., 2010). Zenger et al., also found that among urogenital cancer patients, those who were more optimistic tended to recover more quickly. They suggested that optimism is protective against stress and results in better coping strategies than those found in people with pessimistic personality types, thus allowing for the patient to focus on recovery rather than on their illness itself (Gustavsson-Lilius, Julkunen, Keskivaara, Lipsanen & Hietanen, 2012; Zenger et al., 2010). However, it is possible that this might reflect the tendency for more optimistic people to more readily report themselves as having recovered from their disease compared to more pessimistic individuals.

In contrast, other studies investigating the effects of personality on emotional coping during cancer have found that it is the presence of pessimism and not optimism that is related to greater symptoms of anxiety and depression (Colby & Shifren, 2013; Sucala & Szentagotai Tatar, 2010). Sucala and Szentagotai Tatar considered that this relationship exists because patients who exhibit a more pessimistic personality style also possess a belief system whereby they are unable to shift their negative mood and, as a result, experience greater levels of anxiety and depression. Additionally, Sucala and Szentagotai Tatar argued that optimism does not significantly relate to the extent to which patients experience symptoms of anxiety and depression, but rather that it is pessimism alone, or the lack thereof, that is related to these factors.

In a study of patients with breast, colorectal, lung or prostate cancer, Hulbert-Williams, Neal, Morrison, Hood & Wilkinson (2012) also found that optimism was not significantly related to anxiety, depression and quality of life. They did, however, establish that those with a more neurotic personality type tended to experience more severe anxiety and depression and a reduction in their overall quality of life during cancer treatment (Hulbert-Williams et al., 2012). Mazanec, Daly, Douglas and Lipson (2010) also found that optimism

did not significantly predict health-related quality of life among patients with a range of cancers, speculating that when optimists are faced with a stressful life event such as a diagnosis of cancer, they are not able to manage and take control of the situation in the way they usually would, thus their coping strategies are of little utility because of their poor control over these circumstances. In contrast, pessimism is useful because the diagnosis of cancer conforms to their pre-existing negative expectations of life, allowing them to cope more easily and successfully with the illness experience, because they can use their existing coping strategies. In this context, pessimism can be viewed as being important in facilitating the coping and recovery processes.

Locus of control is another individual difference measure that is of considerable interest when examining psychological and physical wellbeing in cancer patients. Locus of control is the overarching term used to describe the orientation to personal control that one generally adopts in life. The first is an internal locus whereby the person believes that they are responsible for and in control of everything that occurs in their life (Gerrig & Zimbardo, 2005). In contrast, an external locus of control refers to people who attribute everything that happens in their life as being out of their control and thus do not take responsibility or blame themselves for the things that happen in their lives (Gerrig & Zimbardo).

A considerable amount of research has explored the relationship between locus of control and wellbeing among cancer patients (Arraras, Wright, Jusue, Tejedor & Calvo, 2002; Marks, Richardson, Graham & Levine, 1986; Newsom, Knapp & Schulz, 2002; Taylor, Lichtman & Wood, 1984). In their 1986 study, Marks, et al. found a significant positive relationship between possessing an external locus of control and experiencing depression during cancer, with the severity of the disease acting to mediate this relationship. Similarly, in a study of both cancer-related and non-cancer-related chronic pain patients, possessing a more external locus of control was positively associated with the increased experience of

mood disorders such as anxiety and depression (Arraras et al., 2002). In their study, Arraras et al. hypothesised that the relationship between external locus of control and mood disorders is likely to be cyclical, i.e. the experience of depression and anxiety is likely to perpetuate an orientation towards an external locus of control, while an external locus of control may exacerbate mood disorder symptoms. However, this hypothesis was based only on the observed results and not directly tested.

In their study of breast cancer patients, Taylor, Lichtman and Wood (1984) found that within the context of a cancer diagnosis, possessing either a high internal locus of control, which reassures the patient that they themselves have control of their illness, or a high external locus of control, whereby the patient believes that their doctor has control of their disease, were significantly associated with the overall adjustment of the patient to their cancer diagnosis. By contrast, other researchers have argued that an internal locus of control is significantly related to depression in patients with cancer (Newsom, Knapp & Schulz, 2002). This is because the participants who possessed an internal locus of control commonly believed cancer could be controlled through the adoption of healthy behaviours and had consequently carefully controlled these factors in their lives. When these people were confronted with a diagnosis of cancer, they attributed their cancer to their own failure and found this difficult to deal with within the context of their belief framework; this resulted in the development of depression (Newsom, Knapp & Schulz, 1996).

In general, the literature remains inconclusive in regards to whether optimism and pessimism should be conceptualised as a single continuous variable, or two dichotomous variables; a conceptualisation which may have an impact on the interpretation of results. When considered as a single continuous variable, optimism appears to be negatively associated with depression and anxiety; while being positively related to health-related quality of life, in cancer patients. However, when optimism and pessimism are considered as

two separate variables, it is pessimism that is positively related to these emotional wellbeing variables, not optimism. The literature on the effect of locus of control on emotional wellbeing is equally contradictory, with some research finding that an external locus of control is significantly related to anxiety and depression, other research finding an internal locus of control is associated with anxiety and depression, with some authors concluding that having either an entirely internal or external locus of control promotes better emotional and psychological wellbeing in cancer patients. Further research is clearly necessary to establish the impact of these personality variables on emotional and cognitive functioning in colorectal cancer patients, the latter of which has attracted very little attention.

In summary, the literature regarding the causes, symptoms and even existence of CRCI is complex and unclear. Whether it occurs as a result of treatment or because of factors related to the cancer experience is a major source of debate. A discrepancy between self-reported and objectively assessed cognitive impairment has commonly been identified within the literature, whilst personality variables such as optimism/pessimism and locus of control have been identified as possible confounding factors when investigating cognitive and emotional impairment in patients with cancer.

1.6 Colorectal Cancer

Colorectal or bowel cancer is one of the most highly prevalent cancers in Australia, with a rate of morbidity second only to breast cancer in females and prostate cancer in males (Bowel Cancer Australia, 2010; Cancer Council Australia, 2009). Colorectal cancer is diagnosed in one in 10 Australian men and one in 15 Australian women by the age of 85 (Bowel Cancer Australia, 2010; Cancer Council Australia, 2009).

The rates of survival associated with colorectal cancer are relatively high and are always increasing as a consequence of improved and very well promoted screening procedures. However, the prognosis following diagnosis depends greatly on the stage of

advancement at which the cancer is diagnosed and, like most other types of cancer, with increasing disease severity the rate of survival declines dramatically (Bowel Cancer Australia, 2010). More specifically, for those diagnosed with colorectal cancer in its early stages (i.e. stages 1 or 2), only surgical intervention is required and there is an 87-90% chance of recovery. Patients who are diagnosed with stage 3 colorectal cancer, which most commonly must be treated using both chemotherapy and surgery, generally have approximately 57% chance of survival. However, for those diagnosed with widespread colorectal cancer, or stage 4 of the disease, there is only a 10% chance of recovery (Bowel Cancer Australia, 2010).

Although CRCI has been heavily researched in other highly prevalent types of cancer, in particular breast cancer, limited research has been conducted to date into the effects of chemotherapy on cognition in colorectal cancer patients. Research in this area may be conducted less frequently in some regions due to the stigma associated with the bowel and colon in some European countries (Bowel Cancer Australia, 2010; Cancer Council Australia, 2009). However, it is important that CRCI be investigated in patients with colorectal cancer, both due to its significant prevalence in Australian society, as well the high rate of survivorship for this disease when it is detected early.

1.7 Summary and Aims

This thesis has investigated the effects of treatment with chemotherapy on cognitive functioning in patients with colorectal cancer, as well as the impact of individual characteristics in the development and patient experience of CRCI. The overarching aim of the thesis was to establish whether chemotherapeutic treatment leads to a decrement in the cognitive performance of patients with colorectal cancer, in comparison with colorectal cancer patients who have been treated with surgery alone and age- and education-matched

healthy control participants. This study is important because little research has been conducted on this topic using samples of colorectal cancer patients.

This dissertation includes four studies. The first study is a meta-analysis of the effects of chemotherapy on various forms of cognition across a number of different cancer types. This study is important, firstly, because of the debate within the literature regarding the presence of CRCI, which questions both whether or not cancer patients do experience cognitive decline following treatment and, if this is the case, whether this is as a consequence of treatment or other disease-related factors.

Secondly, the meta-analytic review of the literature was intended to inform the foundation from which the other research studies within this thesis would be derived. The main aim of the meta-analysis was to provide a review of the literature in the area of CRCI research, as well as to compile the findings of existing studies and examine them quantitatively as one large sample, with the expectation that the conclusions drawn from multiple sources would be more reliable than any primary study on its own. Another aim of the meta-analysis was to assess whether treatment with chemotherapy leads to similar deficits in a wide range of cognitive functions, or whether some functions were more affected than others across a number of different types of cancer. It was expected that a quantitative review would provide a valuable contribution to the current controversy within the literature as to whether or not CRCI does exist.

Leading on from the meta-analysis, the second study directly investigated the effect of chemotherapy on a range of measures of cognition in patients with colorectal cancer by comparing the performance of four groups; colorectal cancer patients being treated with chemotherapy only, colorectal cancer patients being treated with chemotherapy and the anti-angiogenic drug Avastin, colorectal cancer patients being treated with surgery only, as well as an age- and education-matched healthy control group – across a range of

neuropsychological tests. This design was implemented in order to allow for evaluation of whether or not cognitive impairment, found to exist, is present because of treatment-related, disease-related or simply age-related factors. In addition, by including a healthy control group, it was possible to identify the occurrence of learning effects in the follow-up data, which were absent in some previous research. It is further important to note that colorectal cancer was chosen as the focus of this research project. This was identified as an important cancer site because very few studies have investigated CRCI in colorectal cancer patient populations, despite the high prevalence of this form of cancer throughout the world. The main aim of this study was to determine whether any reliable differences between the four groups existed, cross-sectionally, in performance on appropriate cognitive tests, selected so as to reliably evaluate the cognitive functioning of participants across a range of different cognitive domains. A section of the thesis reporting the 12 month follow-up results to this study has also been included but, because the response rate for the follow-up assessment was poor, it is acknowledged that these data were insufficient to meet the aim of testing for cognitive change over time.

The third study, which follows on from study 2, investigated the relationship between self-reports of cognitive functioning and objective cognitive assessment in patients being treated for colorectal cancer. It was important that this study be conducted with the colorectal cancer patient population because, as summarised earlier in this introduction, there has been a great deal of debate about the validity of neuropsychological and cognitive assessment tools in the detection of CRCI and the reliability of self-report measures of cognitive functioning; and no research studies had been conducted investigating CRCI in patients with colorectal cancer when this study was carried out. The aim of this third study was therefore to assess whether there was a discrepancy between deficits experienced and reported by patients and their cognitive test results. Further, it was anticipated that, if a discrepancy was found, then

an important question would be whether any other assessment tools, such as a test of everyday problem solving, would be better predictors of self-reported cognitive dysfunction than objective tests.

The fourth and final study investigated the effect of optimism and locus of control on reports of depression, fatigue and cognitive functioning measured retrospectively. This outcomes was measured through self-reports by colorectal cancer survivors of their treatment experiences of depression, fatigue and a decline in cognitive functioning. These data are important because many studies have found that these variables can and often do have an impact on physical and emotional functioning and, subsequently, quality of life, of a range of cancer patients. The aim of the final study was to explore, therefore, whether pessimism and locus of control influenced the extent to which cancer survivors reported themselves as having experienced higher levels of depression, fatigue and cognitive dysfunction during and immediately after their cancer treatment than experienced prior to diagnosis.

1.8 Chapter Summary and Future Directions

The literature reviewed in chapter one revealed no real consensus about the nature, prevalence, extent or causation of cognitive impairment following cancer treatment. A wide range of cognitive abilities are reported as being compromised following treatment with chemotherapy however, which of these and the extent to which they are affected, varies between studies. The majority of the existing CRCI research has been conducted with breast cancer patients, with few studies examining this phenomenon in other cancer types. As a result of the seemingly different outcomes of many of the studies in this field of research, it is difficult to draw a single informed conclusion about CRCI by solely considering the individual studies in isolation.

In order to evaluate and draw conclusions from this literature, a meta-analysis was conducted to assess the effects of chemotherapy on cognition in patients with cancer. This

was important for two reasons: firstly, to provide more clarity across studies by statistically combining results from controlled studies that allow for the control of potential confounds. This approach achieves a larger sample size than any single study on its own and provides a more informed conclusion about the potential nature of CRCI. The second reason for undertaking a formal meta-analysis was to provide some guidance into the most fruitful strategy for future research.

CHAPTER TWO

A Meta-Analysis of the Effects of Chemotherapy on Cognition in Patients with Cancer

2.0 Preface

The paper that follows has been published online by the journal 'Cancer Treatment Reviews', on December 10th, 2012. The authors include PhD candidate, Kristy Hodgson and her three supervisors in order of their contribution to the paper: Dr Amanda Hutchinson, Prof Carlene Wilson and Prof Ted Nettelbeck. The study in Chapter 2 is presented in the same manuscript form as it was when accepted for publication. The published manuscript and author contribution statements for this study are presented in Appendix A.

Abstract

Objective: The aim of this meta-analysis was to assess whether chemotherapy-related cognitive impairment is consistently observed in cancer patients and to identify the areas of cognition affected.

Methods: The meta-analysis included 13 studies and examined the effects of chemotherapy on seven different cognitive domains, across five cancer types. It was the intention of this meta-analysis to stringently exclude many studies, allowing for examination of cognition in carefully selected studies of chemotherapy recipients who do not have current mood or anxiety diagnoses (or psychiatric or substance abuse histories), without brain cancer and who have not had radiotherapy or hormone treatment. A moderator analysis examined whether patient age, treatment duration and time since treatment end significantly contributed to chemotherapy-related cognitive impairment.

Results: Evidence for the presence of cognitive impairment following cancer treatment was established for executive function and memory. No relationship was found between cognitive impairment and time since treatment cessation but a significant negative relationship was found for treatment duration. Age had no impact on treatment-related cognitive impairment.

Conclusions: Future research must be conducted on chemotherapy-related cognitive impairment in cancer types such as lymphoma and leukaemia, which have received a moderate amount of attention and colorectal cancer that has received little attention. This would enable us to determine the extent to which chemotherapy-related cognitive impairment is a universal phenomenon associated with the cancer experience and its treatment regardless of cancer type.

Key Words: Oncology, Chemobrain, Chemofog, Neuropsychological, Memory, Executive Function.

Introduction

Chemotherapy-related cognitive impairment, or CRCI, is commonly reported following the administration of chemotherapy treatment in patients with cancer (Collins, Mackenzie, Stewart, Bielajew & Verma, 2009). CRCI has been reported as being characterised by impairments in memory, attention, clarity of thought, executive functioning and speed of information processing (Boykoff, Moieni & Subramanian, 2009; Collins et al., 2009; Myers, 2009; Wefel, Lenzi, Theriault, Davis & Meyers, 2004; Weiss, 2008). The impact of these on everyday life is reported as considerable; patients with CRCI have reported experiencing difficulty undertaking and completing simple tasks including meal preparation, keeping track of and paying bills, or getting ready to go out and as needing additional time to perform these tasks. Furthermore, they may find it difficult to perform necessary work-related duties and subsequently may need to either change jobs or cease their employment entirely (Boykoff, Moieni & Subramanian, 2009). It has also been suggested that the cognitive deficits experienced by patients with CRCI result in difficulties in maintaining relationships because of the compensatory mechanisms that patients adopt, such as distancing themselves in order to conceal these impairments (Myers, 2009). Therefore, treatment-related cognitive impairment can have a significant impact upon cognitive, occupational and social functioning, all of which in turn contributes to significant personal distress and, in many instances, reduction to quality of life.

It has been estimated that by the year 2020, there will be approximately 70 million cancer survivors worldwide, a statistic that highlights the potential for CRCI to be a significant concern (Weiss, 2008). However, it is important to note that adverse effects on cognition associated with cancer treatment are not reported by every patient treated with chemotherapy, or in every research study analysing objective measures of performance. Estimates of the prevalence of CRCI differ widely, from 14 – 85%, a range too wide to

provide useful prediction about the experiences of people undergoing chemotherapy for treatment of cancer (Myers, 2009). The duration of the CRCI is also debated. It was assumed until recently that the symptoms of CRCI can last indefinitely (Wefel et al., 2004), but there is now a suggestion that cognition gradually improves upon cessation of treatment with chemotherapy (Fliessbach et al., 2005). It is also important to note that some authors have argued that approximately one third of cancer patients demonstrate cognitive impairment prior to the commencement of chemotherapeutic treatment due to factors associated with the cancer itself (Fliessbach et al., 2005; Wefel et al., 2004). All of these uncertainties have important implications for research design in this area.

Most research claiming evidence for the existence of CRCI has reported outcomes for women with breast cancer. In this population it has consistently been reported that treatment with chemotherapy leads to deficits in a number of cognitive domains, including attention and concentration, executive function, working memory, speed of information processing, mental flexibility, visual and verbal memory, verbal and mental fluency, and motor function (Downie, Mar Fan, Houede-Tchen, Yi & Tannock, 2006; Jansen, Dodd, Miaskowski, Dowling & Kramer, 2008; Schagen, van Dam, Muller, Boogerd, Lindeboom & Bruning, 1999: Yamada, Denburg, Beglinger & Schultz, 2010). Thus evidence of specific cognitive deficits accompanying or following chemotherapy for the treatment of breast cancer appears strong, although it has also been recognised that these deficits may occur prior to treatment due to factors associated with the disease, not as a result of treatment with chemotherapy (Collins et al., 2009).

In the few studies that have examined the effects of chemotherapy on cognition in patients with testicular cancer, conclusions have been mixed. Although some researchers have claimed, just as in the breast cancer literature, that there is strong evidence for the occurrence of CRCI following treatment with chemotherapy in this population (Schagen et

al., 1999); others have found no impairment at all in this group (Pedersen, Rossen, Mehlsen, Pedersen, Zachariae & von der Masse, 2009). The impairment of specific cognitive domains in patients with testicular cancer has not been examined.

Across all cancer types there is debate surrounding a number of factors that may moderate the effect of treatment with chemotherapy on cognitive impairment. For example, it has been argued that depression and anxiety in patients receiving chemotherapeutic treatment may exacerbate the symptoms of CRCI, leading to more subjective complaints regarding these symptoms (Bender et al., 2006). This is consistent with the negative association between anxiety and depression and cognitive functioning observed in the general population (Bender et al., 2006). However, others have found that depression and anxiety have no effect on the symptoms of CRCI and the way in which these symptoms are perceived by the patient. Therefore, further research is required in order to establish whether these factors actually impact CRCI.

When considering patients' perceptions about their possible cognitive impairment, it is important to note that self-reports of cognitive impairment do not correlate reliably with neuropsychological test results; patients' reports of deficits tend to exceed objective measurement of performance with neuropsychological testing (Downie et al., 2006; Myers, 2009). It is important to recognise that this could be because neuropsychological tests do not adequately capture the deficits that participants experience in their everyday lives (Downie et al., 2006).

There are several challenges to conducting research on CRCI. The most significant of these is the predominant use of cross-sectional data rather than a prospective study design. This arises because of the difficulties associated with conducting longitudinal research, particularly with a patient group. Specifically, it has been noted that when using cross-sectional data, the inferred deficits may be inflated compared to longitudinal data because

comparison to a pre-treatment baseline is not possible (Bender et al., 2006; Mehlsen, Pedersen, Jensen & Zachariae, 2009). Baseline comparison is important because it allows the determination of the extent to which impairment has resulted from the treatment, or was present prior to the commencement of treatment. If the latter is true, group differences might be explained by the cancer diagnosis rather than cancer treatment (Schagen et al., 1999).

Another limitation of many CRCI studies is that it is difficult to identify and recruit appropriate control groups in cancer research. For example, one may utilise healthy control participants who are not affected by the disease or by treatment variables. However, these participants would not be expected to experience the depression, anxiety or distress that often accompanies a cancer diagnosis, all of which have been found to impair cognition and everyday functioning (Boykoff, Moieni & Subramanian, 2009). Alternatively, cancer patients who are on a different medical treatment regimen, or who are not receiving treatment at all, have been utilised as a control group. This is problematic, however, because different treatments may only be used for people with less severe forms of cancer and it would not be ethical to withhold treatment in order to have a wait-list control. Therefore severity is a confounding variable. These problems could be overcome by using longitudinal studies that assess the same group of patients pre- and post-treatment. This approach is also not without difficulty because it requires recruiting participants who are already seriously ill for a longitudinal study with a long-term time commitment, retaining these participants in the study and considering ethical issues associated with any delays to the commencement of treatment to allow for the initial baseline cognitive testing. Moreover, this approach requires utilising people diagnosed with cancer, which confounds diagnosis and treatment.

Finally, many studies have not been able to achieve adequate sample sizes or approximately homogeneous samples and have included participants in their samples who were being treated with different chemotherapy regimens, or were receiving adjunctive

treatments such as hormone therapy, or radiation therapy (Jansen et al., 2008). Samples comprised of such divergent participants make it difficult to isolate the effects of chemotherapy on cognition. Studies examining CRCI are also prone to high rates of attrition because of death but also due to participants' unwillingness to discuss their cancer at follow-up because this can raise negative thoughts and feelings about possible relapse of the disease or death (Jansen et al., 2008).

The current meta-analysis was conducted in order to address the conflicts in primary research studies regarding the existence of CRCI, its duration and whether there are any differences occurring due to cancer type, by statistically combining the results of existing studies. Although meta-analyses in this area of research already exist, the present study differed from these in that they have only focussed on either breast cancer patients alone or, when considering a range of cancer sites, they have included all treatment types and failed to investigate the effects of chemotherapy alone. Both cross-sectional and longitudinal studies were included to test whether or not there is a real difference between the results yielded by these designs. The main aim was to assess whether treatment with chemotherapy leads to cognitive impairment in cancer patients in general, with the scope being all forms of cancer that have been studied. It was the intention of this meta-analysis to stringently exclude many studies, allowing for examination of cognition in carefully selected studies of chemotherapy recipients who do not have current mood or anxiety diagnoses (or psychiatric or substance abuse histories), without brain cancer and who have not had radiotherapy or hormone treatment. The hypotheses tested were (i) that treatment with chemotherapy leads to impairment across a range of cognitive domains and cancer types; (ii) that longer duration of treatment with chemotherapy is associated with increased impairment and (iii) that increased time since treatment cessation is associated with more improvement in cognitive performance.

Material and Methods

An exhaustive search of the PsycINFO and Pub-Med research databases was conducted in order to identify all studies examining chemotherapy and possible consequent cognitive impairment in patients with cancer, published up until 2010, when this meta-analysis was conducted. The terms that were utilised are listed in Table 1. The search was structured in such a way that the Boolean phrase ‘OR’ was placed between the terms listed vertically and the Boolean phrase ‘AND’ placed between those terms listed horizontally in the table.

Table 1

Terms Used to Search the Electronic Databases

Cancer Terms	Impairment Terms	Treatment Terms	Psychological Terms
Cancer	Cognition	Chemotherapy	Neuropsycholog*
Oncolog*	Chemobrain	Cyclophosphamide	Behaviour
	Chemofog	Methotrexate	Tests
	Cognitive	5-flourouracil	Measures
	Impairment	Doxorubicin	Assessment
		Bleomycin	
		Etoposide	
		Cisplatin	
		Epirubicin	

*Denotes that these terms may be searched for as they are written, or in their plural forms.

To be included in the present meta-analysis studies had to meet the following inclusion criteria; the study was published in English, reported primary data, had a sample size greater than one (i.e. not case studies), provided appropriate statistics for the calculation of effect sizes, had a control group and principally investigated the effects of chemotherapy on cognition. However, studies that investigated additional treatments separately from chemotherapy were included if they used a chemotherapy treatment group. In addition, the participants had to be aged over 21 years and, with the exception of control participants, must have undergone chemotherapy for cancer. Studies were excluded from this meta-analysis if participants had a current diagnosis of anxiety or depression, a history of psychiatric illness or substance abuse, a previous head injury resulting in loss of consciousness, a diagnosis of brain cancer, if they had received full cranial irradiation or radiotherapy, or if they were

receiving hormone therapy in addition to chemotherapy without a hormone-therapy only control group, because each of these variables can have a negative effect on cognitive functioning and may confound the effect of the treatment with chemotherapy. It is important to note that although many cancer patients experience anxiety and depression, these factors in themselves can contribute to impaired cognitive functioning. Therefore, studies including patients with a current diagnosis of these disorders were excluded in order to allow for a more pure examination of the effects of treatment with chemotherapy on cognitive dysfunction, without having to moderate for any possible effects of depression and anxiety.

Following careful examination of the title and abstract of each of the papers, with the inclusion and exclusion criteria in mind, 439 papers were selected for possible inclusion in the present study. The full text versions of these 439 papers were comprehensively scrutinised on the basis of the inclusion and exclusion criteria in order to determine their eligibility for inclusion in this meta-analysis. This resulted in the identification of 68 papers that were then evaluated for their eligibility against the inclusion and exclusion criteria. Of these, 57 were excluded, with 12 not containing adequate statistics for the calculation of a meta-analysis; 19 included patients who received hormone or radiotherapy; three did not use a control group or have a follow-up assessment; 9 included patients who had not received treatment with chemotherapy, but rather an alternative such as immunotherapy; one was a review article; nine included patients with cancer of the brain; three were off topic and one was a case study. This resulted in the final inclusion of 11 relevant papers. In addition, the reference lists of all eligible articles and relevant review articles were examined, identifying two more papers that met the inclusion criteria. In total 13 papers, yielding 997 participants (552 patients and 445 controls), were identified as eligible for inclusion in the present study. The most common reasons for studies being excluded from this meta-analysis were because

participants had a diagnosis of brain cancer, had received treatment with radiation therapy, or had been diagnosed with anxiety or depression.

Effect sizes were calculated using Cohen's *d,* weighted by the inverse of the variance, according to the method described by Lipsey & Wilson (2001). When calculating Cohen's *d* for each study, the control group data were subtracted from the data of the experimental groups. Thus, a positive effect size represents better performance in the experimental group, whereas a negative effect size corresponds to better performance in the control group. Cohen defined effect sizes of 0.2 as small, 0.5 as medium and 0.8 as large (Lipsey & Wilson, 2001).

The mean weighted effect size was calculated for each of the five different types of cancer addressed in the included papers; breast cancer, lymphoma, leukaemia, testicular cancer and a range of many different types of cancer combined. Effect sizes were grouped according to cognitive domains identified by Lezak, Howieson and Loring (2004). Domains were: verbal functions and language skills (which involves the ability to speak and use language both appropriately and effectively), memory (which refers to the ability to remember and recall information), construction (which encompasses drawing and building abilities), orientation and attention (assesses the extent to which one has an awareness of themself in relation to their surroundings and the ability to focus on the tasks one is doing within this context), concept formation and reasoning (encompasses the quality of thought and the thinking processes, as well as the ability to think with the intent of reaching a conclusion), executive functions (which include the ability to respond adaptively within the context of new situations) and perception (which encompasses the processes of becoming aware of stimuli in one's environment). Verbal functions and language skills were assessed by a variety of different tests including the WRAT-III Reading Subtest, the Boston Naming Test and the Controlled Oral Word Association Test (COWAT). Likewise, the memory domain was assessed by tests including the California Verbal Learning Test, as well as

Logical Memory and Family Pictures from the WMS-III. Examples from the cognitive domain of construction were the WAIS-III Block Design, as well as subtests from the Folstein Mini Mental State Examination and the Repeatable Battery of Adult Neuropsychological Status. Orientation and attention was a category composed of tests including WAIS-III Digit Symbol, Stroop Colour and Word Test and the Trail Making Test. The cognitive domain of concept formation and reasoning included the WAIS-III Arithmetic, Wisconsin Card Sorting Test and WAIS Similarities. Tests that assessed executive functions included, but were not limited to, the Intradimensional Extradimensional Shift Task, WAIS-III Coding and the Highly Sensitive Cognitive Screen. Finally, the cognitive domain of perception was comprised of tests such as Letter Cancellation and the Test of Facial Recognition.

A 95% confidence interval between the mean scores of the experimental and control groups was also calculated for each cancer type. It is from this calculation that statistical significance was derived; i.e. any 95% confidence interval that did not span zero denoted statistical significance. Fail safe N statistics were calculated for each comparison to indicate how many unpublished studies with non-significant results would be necessary to reverse the findings. Thus the higher the fail safe N, the more confidence one can place in the results.

To assess the effect of additional variables on the relationship between chemotherapy and cognitive function, it was important to conduct a moderator analysis. Age, a variable known to predict scores on cognition, was included as a moderator variable to determine whether it significantly contributed to the effect sizes. This analysis was conducted using Pearson's *r* correlations to assess the relationships between the mean weighted effect sizes for each study and age. The second and third hypotheses were also examined in this way, with the conduct of a moderator analysis for treatment duration and time since treatment cessation.

A second person evaluated the studies and categorised the tests in order to establish inter-rater reliability of the assignment of tests to cognitive domains. Most (124) of the 128 tests were independently categorised into the same domains by both raters with a resulting inter-rater reliability of 97%. Ratings by rater 1 were therefore applied to analyses that follow.

Results

Thirteen studies were included in the meta-analysis resulting in a sample of 997 participants (552 patients and 445 controls). Overall, 73% of the total sample was female. The mean age of participants was 55.98 years (SD = 8.71) [patients = 56.14 (SD = 8.23) and controls = 55.82 (SD = 9.16)]. Across the 13 studies, participants were described as receiving one of five different treatment regimens. Participants from one of the 13 studies received cyclophosphamide, methotrexate, 5-flourouracil (CMF), while participants from another two studies received chemotherapeutic treatment with bleomycin, etoposide, cisplatin (BEP). Participants from one of the 13 studies received treatment with cyclophosphamide, epirubicin and 5-flourouracil (CEF). Finally, eight studies reported that their participants received "various different chemotherapy regimens"; while another reported that its participants received only chemotherapy, without specifying the type.

Before conducting further statistical analyses, the relationship between study design, cross-sectional or longitudinal and the mean effect sizes was considered. An independent samples t-test revealed no statistically significant relationship between study design and mean effect size (t (55) = 1.34, p = 0.19). Consequently, results from studies employing both longitudinal and cross-sectional designs were combined for the purposes of the present meta-analysis.

The effect of chemotherapy on cognition in patients with cancer was measured for each of the seven cognitive domains. The cognitive domain most affected by treatment with

chemotherapy was executive function. For this domain, a small, statistically significant effect was revealed, depicting superior performance in the control group (Table 2). Other significant, but small, effects were found for memory and verbal function and language skills (Table 2). Extremely small effects were evident for construction, concept formation and reasoning, perception and orientation and attention, with higher scores in these domains being attained by the control group (Table 2). However, the small results of all studies are highlighted by the Fail-safe N analyses indicated that all results could be repudiated by any contrary result.

Table 2

Effect Size Statistics Associated with the 8 Cognitive Domains Defined by Lezak et al., (2004).

Domain	N Studies	Effect Size	95% CI lower	95% CI upper	Failsafe N
Executive function	6	-0.27*	-0.44	-0.09	0
Memory	12	-0.21*	-0.36	-0.07	0
Verbal function & language skills	9	-0.17*	-0.33	-0.00	0
Construction	9	-0.12	-0.28	0.04	0
Concept formation and reasoning	5	-0.10	-0.30	0.10	0
Perception	2	-0.06	-0.38	0.26	0
Orientation & attention	12	-0.02	-0.16	0.12	0

Note: N Studies = Number of studies contributing to the effect size, CI = Confidence Interval. Negative effect sizes indicate impairment in the treatment group. * = Statistically significant on the basis of the 95% CI not spanning zero.

These effect sizes were not as large and conclusive as was expected, based on the existing literature. Past research has certainly made it clear that CRCI is evident among breast cancer patients, often yielding results that are representative of large and statistically significant differences between the groups, but this was not found in the present study. Therefore, to explore why current results might differ so strongly from the results reported in individual studies, effect sizes were calculated for each individual study that was utilised in the calculation of the overall effect size for each cognitive domain.

As can be seen in Table 3, across the seven cognitive domains, the majority of the effect sizes produced revealed superior performance in the control group relative to the treatment group, although these effect sizes were commonly small, with statistically significant effect sizes established in five of the seven cognitive domains. However, each domain also yielded at least one study with results in the opposite direction. More specifically, the study by Collins et al. (2009) revealed better performance in the treatment group compared to the control group in the areas of executive function, construction, concept formation and reasoning, and orientation and attention (see Table 3). Similar results in the opposite, unexpected direction were reported by Ahles, et al. (2002) in the domains executive functioning and orientation and attention (see Table 3). Likewise, Yamada, et al.'s (2010) study revealed superior performance in the treatment group for memory and construction (see Table 3). Treatment outperformed the control group in Mehlsen, Pedersen, Jensen & Zachariae (2009) in verbal functions and language skills and concept formation and reasoning (see Table 3). In the cognitive domain of construction, an effect size in the opposite direction indicating better performance in the experimental group was established for Pedersen et al. (2009), Stewart, Collins, Mackenzie, Tomiak, Verma & Bielajew (2008) and in perception for Shilling, Jenkins, Morris, Deutsch & Bloomfield (2005) (see Table 3). Kvale, et al.

(2010), Scheibel, Valentine, O'Brien and Meyers (2004) and Schagen et al. (1999) all revealed better performance in the treatment group for orientation and attention (see Table 3).

Thus, comparison of the meta-analytic results with the results from individual studies indicates that the interpretation of meta-analytic outcomes can be compromised where the number of studies is small and the sample sizes and the control groups vary. In these circumstances, one study can have a critical influence.

Table 3

Individual Effect Sizes Associated with the Individual Studies that Contributed to the Overall Effect Size for Each Cognitive Domain

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
Executive function	-0.65*	Testicular	EORTC Cognitive – General cognition	AT	-1.01	-0.29	0	Schagen et al. (2008)
	-0.45	Lymphoma	Thumb Finger Sequencing; Finger Tapping	AT	-1.01	0.11	0	Ahles et al. (2002)
	-0.43	Breast	Fepsy Finger Tapping	AT	-0.9	0.04	0	Schagen et al. (1999)
	-0.12	Breast	Grooved Pegboard	AT	-0.49	0.25	0	Stewart et al. (2008)
	0.05	Breast	Grooved Pegboard	AT	-0.36	0.46	0	Collins et al. (2009)
	0.01	Breast	Thumb Finger Sequencing; Finger Tapping	AT	-0.46	0.48	0	Ahles et al. (2002)
Memory	-1.71*	Breast	RAVLT; 4WSMT; RCFT	NT	-2.97	-0.45	0	Bender et al. (2006)

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
	-0.55	Leukaemia	Consistent Long Term Retrieval; Delayed Recall	AT	-1.29	0.19	0	Scheibel, Valentine, O'Brien & Meyers (2004)
	-0.52	Lymphoma	CVLT; LM; Visual Reproduction	AT	-1.06	0.02	0	Ahles et al. (2002)
	-0.45	Breast	CVLT; LM; Visual Reproduction; RCFT Recall	NT	-1.01	0.11	0	Castellon et al. (2004)
	-0.32	Breast	RAVLT; RCFT Recall; WMS Recall	AT	-0.78	0.14	0	Schagen et al. (1999)
	-0.2	Breast	CVLT; LM; Visual Reproduction	AT	-0.67	0.27	0	Ahles et al. (2002)

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
	-0.19	Breast	CVLT; LM; RVLT; Family Pictures; CCCs	AT	-0.56	0.18	0	Stewart et al. (2008)
	-0.12	Breast	CVLT; LM; RVLT; Family Pictures; CCCs	AT	-0.53	0.29	0	Collins et al. (2009)
	-0.06	Testicular	TMT; RCFT; LM; RAVLT	AT	-0.52	0.4	0	Pedersen et al. (2009)
	-0.04	Breast	RCFT; LM; RAVLT	HC	-0.45	0.37	0	Shilling et al. (2005)
	-0.04	Breast	RCFT; LM; RAVLT	HC	-0.7	0.62	0	Mehlsen, Pedersen, Jensen & Zachariae (2009)
	0.03	Breast	RAVLT; RCFT; Benton Visual Retention Test	HC	-0.48	0.54	0	Yamada, Denburg, Beglinger & Schultz (2010)

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
Verbal functions & language skills	-1.2*	Leukaemia	COWAT	AT	-1.98	-0.42	0	Scheibel, Valentine, O'Brien & Meyers (2004)
	0.93*	Breast	WAIS-III C; Animals; F Words; N Words	HC	0.24	1.62	0	Mehlsen, Pedersen, Jensen & Zachariae (2009)
	-0.41	Breast	Word Fluency	AT	-0.87	0.05	0	Schagen et al. (1999)
	-0.32	Breast	COWAT; Animals;	NT	-0.88	0.24	0	Castellon et al. (2004)
	-0.19	Breast	Vocabulary; BNT; COWAT	AT	-0.66	0.28	0	Ahles et al. (2002)
	-0.15	Breast	BNT; COWAT	AT	-0.52	0.22	0	Stewart et al. (2008)
	-0.13	Breast	BNT; COWAT	AT	-0.54	0.28	0	Collins et al. (2009)

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
	-0.12	Testicular	WAIS-III C; Animals; F Words; N Words	AT	-0.58	0.34	0	Pedersen et al. (2009)
	-0.01	Lymphoma	Vocabulary; BNT; COWAT	AT	-0.54	0.52	0	Ahles et al. (2002)
Construction	-0.69*	Breast	Block Design; RCFT Copy	NT	-1.26	-0.12	0	Castellon et al. (2004)
	-0.46	Breast	Block Design	AT	-0.93	0.01	0	Ahles et al. (2002)
	-0.4	Breast	RCFT Copy	HC	-1.06	0.26	0	Mehlsen, Pedersen, Jensen & Zachariae (2009)
	0.29	Breast	RCFT Copy	HC	-0.22	0.8	0	Yamada, Denburg, Beglinger & Schultz (2010)
	-0.23	Breast	RCFT Copy	AT	-0.69	0.23	0	Schagen et al. (1999)

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
	-0.15	Lymphoma	Block Design	AT	-0.68	0.38	0	Ahles et al. (2002)
	0.1	Testicular	RCFT Copy	AT	-0.36	0.56	0	Pedersen et al. (2009)
	0.03	Breast	Block Design	AT	-0.38	0.44	0	Collins et al. (2009)
	0.01	Breast	Block Design	AT	-0.36	0.38	0	Stewart et al. (2008)
Concept formation & reasoning	-0.45	Breast	Arithmetic; WCST	HC	-0.96	0.06	0	Yamada, Denburg, Beglinger & Schultz (2010)
	-0.26	Testicular	Arithmetic	AT	-0.72	0.2	0	Pedersen et al. (2009)
	0.11	Breast	WCST; Arithmetic	AT	-0.3	0.52	0	Collins et al. (2009)
	-0.02	Breast	WCST; Arithmetic	AT	-0.39	0.35	0	Stewart et al. (2008)
	0.01	Breast	Arithmetic	HC	-0.65	0.67	0	Mehlsen, Pedersen, Jensen & Zachariae (2009)

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
Perception	-0.34	Breast	Benton Faces	HC	-0.85	0.17	0	Yamada, Denburg, Beglinger & Schultz (2010)
	0.12	Breast	Letter Cancellation	HC	-0.29	0.53	0	Shilling et al.(2005)
Orientation & attention	-0.53*	Breast	IED; Digit Span; Letter Number Sequencing; TMT	HC	-1.04	-0.02	0	Yamada, Denburg, Beglinger & Schultz (2010)
	0.44	Combination	UFOV; RST; TIADL	HC	-0.02	0.9	1	Kvale et al. (2010)
	-0.38	Breast	WAIS-III SS; TMT; Digit Span; Letter Number Sequencing; Stroop	HC	-1.04	0.28	0	Mehlsen, Pedersen, Jensen & Zachariae (2009)
	0.24	Lymphoma	Digit Symbol; TMT; CPT	AT	-0.32	0.8	0	Ahles et al. (2002)

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
	0.22	Leukaemia	Digit Symbol; TMT	AT	-0.5	0.94	0	Scheibel, Valentine, O'Brien & Meyers (2004)
	-0.2	Breast	Digit Span; Stroop; Letter Number Sequencing	HC	-0.61	0.21	0	Shilling et al. (2005)
	0.15	Breast	Digit Span; Digit Symbol; TMT; D2 Test; Stroop; Fepsy Binary Choice; Fepsy Visual Searching; Fepsy Visual Reaction	AT	-0.31	0.61	0	Schagen et al. (1999)
	-0.11	Breast	Digit Symbol; TMT; CalCAP; PASAT; Stroop	NT	-0.67	0.45	0	Castellon et al. (2004)

Domain	Effect Size	Cancer Type	Tests	Control group	95% CI lower	95% CI upper	Failsafe N	References
	-0.05	Testicular	Symbol Search; TMT; Digit Span; Letter Number Sequencing; Stroop	AT	-0.51	0.41	0	Pedersen et al. (2009)
	-0.05	Breast	PASAT; TMT; Digit Symbol; Symbol Search; Digit Span; Letter Number Sequencing; Spatial Span	AT	-0.42	0.32	0	Stewart et al. (2008)
	0.02	Breast	Digit Symbol; TMT; Attention CR; Attention RT	AT	-0.45	0.49	0	Ahles et al. (2002)

0	Breast	PASAT; TMT; Digit Symbol; Symbol Search; Digit Span; Letter Number Sequencing; Spatial Span	AT	-0.41	0.41	0	Collins et al. (2009)

Note: CI = Confidence Interval, Negative effect sizes indicate impairment in the treatment group. * = Statistically significant based on CI. AT = Alternative Treatment. HC = Healthy Controls. NT = No treatment, but still cancer patients.

Correlation analyses were conducted to examine the effect of treatment duration and time since treatment cessation on level of impairment. Eight studies provided data on duration of treatment and all 13 studies provided data on time since treatment cessation. A moderate, negative statistically significant relationship was found between level of cognitive impairment (as represented by the mean effect size) and duration of treatment (as operationalised by the number of cycles of chemotherapy received) (r = -0.63, p < 0.01, n= 726), therefore confirming the hypothesis that the greater the duration of treatment with chemotherapy, the more profound the impairment. However, a small statistically non-significant relationship was found between time since treatment cessation and level of cognitive impairment (r = -0.21, p = 0.12, n= 997), so that the third hypothesis was not supported.

A moderator analysis was conducted in order to assess whether the age of the participants contributed significantly to the size of the effect. Twelve studies provided age data. A small, statistically non-significant relationship was found between mean effect size and age (r = 0.13, p = .37). Therefore, age did not have a significant impact on the extent of cognitive impairment (as depicted through the mean effect size).

Discussion

The present study assessed the effect of chemotherapy on seven different cognitive domains, across a range of cancer types. It is important to note that a small effect at the sample level may have large and significant implications at the population level. Impairment subsequent to treatment with chemotherapy was apparent for the domains executive function and memory although the effect size was small. This is consistent with the literature reporting that impairments in memory and executive function occur subsequent to treatment with chemotherapy and often in

patients with breast cancer (Boykoff, Moieni & Subramanian, 2009; Collins et al., 2009; Wefel et al., 2004; Weiss, 2008).

Meta-analysis did not provide support for significant impairments to cognition following chemotherapy in the domains of construction, concept formation and reasoning or perception. A statistically significant result for verbal function and language represented only a marginal effect. This suggests that the cognitive sequelae of cancer treatment may be limited to a small number of specific domains. It is unclear whether different sites are associated with different domains largely because study numbers with cancer sites other than breast are very limited.

When the individual studies contributing to the meta-analytic results for each of the cognitive domains were analysed separately, some interesting insights were evident. Firstly, although significant effects were mostly small to moderate in size, they were largely consistent. For example, 11 out of 12 comparisons of memory performance indicated poorer performance after chemotherapy although for only one study did the 95% confidence interval not cross zero. Examination of outcomes for breast cancer patients in other domains indicated the same trend; small, largely non-significant differences but which, taken together, consistently indicate poorer performance among those receiving chemotherapy.

One study with leukaemia patients and one with lymphoma undertook reasonably comprehensive analyses of treatment effects across domains. These results indicated medium to large effect sizes. The results highlight the importance of addressing the potential adverse effects of treatment for cancer in sites other than the breast.

The meta-analysis of CRCI highlighted how research in this area is limited by both practical and methodological difficulties. These include the following; lack of

comparability of treatment and control groups, number of retests (including control of practice effects) and time between retesting, differences in characteristics of the people who constitute the 'control group' and inconsistency in the measures of cognition used in each domain. It is important to note that the small number of studies included in this meta-analysis has not been considered as a limitation. This is because it was the intention of this study to stringently exclude many papers in order to allow for examination of cognition in carefully selected studies of chemotherapy recipients who do not have current mood or anxiety diagnoses (or psychiatric or substance abuse histories), without brain cancer and who have not had radiotherapy or hormone treatment.

A number of limitations have been identified in some of the studies included in this meta-analysis that may have contributed to the production of results in the opposite direction to expected on the basis of the existing literature. The first of these limitations was the use of alternate-treatment control groups who received treatments other than chemotherapy, but which have also been documented as possibly affecting cognitive functioning. This limitation was apparent in a range of studies (Collins et al., 2009; Shilling et al., 2005; Stewart et al., 2008), in which the control participants received treatment with hormone therapy. This treatment had also been documented to result in cognitive impairment (Collins et al., 2009). Additionally, in one study the majority of the control group were also treated with radiation therapy prior to follow-up, which has also been linked to diminished cognitive functioning (Stewart et al., 2008).

A second major limitation found in a number of the studies included here was the long duration between treatment cessation and cognitive testing, with the period of time extending to 12 months. This a duration, post-treatment, at which some have

contended CRCI should be resolved (Ahles et al., 2002; Kvale et al., 2010; Pedersen et al., 2009; Schagen et al., 1999; Yamada et al., 2010). This was the case in five of the included studies and the number of years after treatment that assessment occurred varied from two to ten years (Ahles et al., 2002; Kvale et al., 2010; Pedersen et al., 2009; Schagen et al., 1999; Yamada et al., 2010). Another limitation affecting the success of the meta-analysis was the non-equivalence of the groups at baseline. In other words, in a few of the papers, the treatment group statistically significantly outperformed the control group prior to treatment. Alternatively, the treatment group demonstrated a higher premorbid IQ than the control group. This was the case in three of the studies (Collins et al., 2009; Schagen et al., 1999; Stewart et al., 2008). Lack of comparability at baseline means any comparisons made subsequently are likely to be erroneous.

In one study (Ahles et al., 2002); some members of the experimental and control groups received treatment with hormone therapy in the time between completion of treatment and assessment. Any such treatment confounds the results of the assessment because any changes may result from the treatment during this interval, as opposed to being due to the chemotherapy. Additionally, because some members of both groups were treated with hormone therapy and this is known to result in impaired cognitive functioning, it is possible that either group may perform more poorly than the other as a result of this and the intent to assess the effect of chemotherapy-related cognitive impairment is rendered moot.

Finally, in one of the studies (Schagen et al., 1999), a much higher percentage of the treatment group were tertiary educated compared to the control group. Again, this is an issue of comparability between the two groups because more education might both facilitate test performance and assist in the maintenance of cognitive

integrity under CRCI. In other words, it is possible that this could result in better performance in the experimental group relative to the control group because the former were more cognitively active to begin with.

Notwithstanding the difficulty in analysing trends in CRCI across cognitive domains and cancer sites, it is important to note that the meta-analysis did provide support for the contention that longer duration treatment would lead to poorer cognitive performance. However, time since treatment cessation was not associated with improvement in cognitive functioning; no statistically significant relationship was revealed between time since treatment cessation and cognitive impairment.

Both of these results may simply reflect the small CRCI effects revealed in the analysis and further research should continue to explore these issues. The potential moderating effect of age on CRCI should also be examined further, even though the current results showed no influence. It is important that studies continue to collect data on other potential moderators of the effect of treatment on cognition including depression, anxiety and fatigue, some of which have been examined in data reported in this meta-analysis (Boykoff, Moieni & Subramanian, 2009). The present study is limited by the inclusion and exclusion criteria employed because these resulted in a sample of only 13 studies. Like similar meta-analyses (Anderson-Hanley, Sherman, Riggs, Agocha & Compas, 2003), the present study could have achieved a much larger sample size had the protocol allowed the inclusion of studies where participants had been treated in the past by, for example, radiation. Thus, the small sample size and the stringent inclusion and exclusion criteria of the current study are both its strength and a limitation.

The current study has provided some support for the link between treatment with chemotherapy and impairment in the domains of memory and executive

function. Although small, the potential life significance should not be understated, with many studies of self-reported problems with everyday functioning, post-treatment highlighting real-world significance (Boykoff, Moieni & Subramanian, 2009; Myers, 2009). It is important to note that this meta-analysis consisted of many more breast cancer studies than studies of any other form of cancer. Therefore, it is possible that the results found by the current study are a product of the small number of studies included, which in themselves had conflicting findings and not of the true CRCI phenomenon occurring among cancer patients being treated for cancer in other sites. It is vital that research is conducted into the effect of chemotherapy on cognition in patients being treated for cancer types other than breast such as testicular cancer, lymphoma and leukaemia, as well as other types of cancer that were not included in this meta-analysis (e.g., colorectal). Primary studies in the future must carefully consider what constitutes an appropriate control group; The International Cognition and Cancer Task force recommend using several control groups consisting of both disease-specific controls and healthy participants who are subjected to the same cognitive assessment over the same period of time as the experimental group (Wefel, Vardy, Ahles & Schagen, 2011). Additionally, control should be included for differences in premorbid ability between the treatment and control groups, ideally designs should aim to conduct investigations less than 12 months post-treatment so that a clearer picture of CRCI can emerge. In addition, longer term follow-up assessments should also be carried out in a range of cancer sites to establish whether CRCI persists for different durations in different cancer types. With the conduct of this research future meta-analyses will have a larger pool of data to combine for each of these cancer types and knowledge regarding chemotherapy-related cognitive impairment can become more comprehensive than it is today. When evaluating

treatment outcomes and side-effects, cancer treatment researchers should routinely collect and report psychological data which are amenable to meta-analysis and moderator analysis: for example, mean and standard deviation scores on quantitative measures (psychometric inventories, patient self-rating scores) potentially including mood, anxiety, fatigue, subjective and objective cognitive impairment. That would allow use of data from more patients and more studies involving more treatment combinations - strengthening future meta-analyses within this important research and practice topic.

It is important to note that the process of meta-analysis provides results that have been averaged across a number of different studies, domains and outcome measures. Therefore an important result found in one study may be washed out by the null results of other studies. Hence the generalised conclusions drawn in this study may not be representative of the individual test results found by each of the 13 studies on their own. It is important to consider the results of individual tests in primary studies as well as the results of meta-analyses when conducting research.

In conclusion, this meta-analytic study has demonstrated that chemotherapy can lead to cognitive impairment in memory and executive function, particularly in breast cancer patients. CRCI may not be affected by the length of chemotherapeutic treatment, but the level of improvement of CRCI may not depend upon the time since treatment cessation, although currently the data are inadequate to support a confident conclusion in this regard.

2.1 Chapter Summary and Future Direction

A meta-analysis was conducted to assess the effect of chemotherapy on cognition in patients with cancer. Thirteen studies were included. Together these investigated five different types of cancer: breast, testicular, lymphoma, leukaemia and a range of different cancer types combined and analysed as one group. Although a range of cancer sites were included, breast was overwhelmingly the most prevalent focus.

The results of the meta-analysis suggested that treatment with chemotherapy can lead to declines in executive functioning and memory, an outcome that is consistent with the broader existing literature. A marginal effect of chemotherapy on verbal functioning and language skills was also identified. It is important to note, however, that each of these effect sizes was very small. Notwithstanding the small effect size, any perceivable diminution in cognitive performance is likely to cause distress. A positive relationship was also found between treatment duration and cognitive impairment, although no relationship was found between time since treatment cessation and cognitive performance.

The results from the meta-analytic study suggested that an empirical study that addressed a number of limitations identified by the meta-analysis could address the existence of CRCI among bowel cancer patients. The design issues to be considered in such a study are many and potentially difficult to address. The first of these was that past studies have often used alternative treatment control groups as a comparison to the chemotherapy treatment group. A weakness of this approach is that the alternative treatments that provide the basis for comparison with chemotherapy, such as hormone therapy and surgery, are themselves associated with cognitive impairment following treatment (Collins et al., 2009; Hede, 2008; Vardy & Dhillon, 2010).

Another major influence in study design is the need to control, either statistically or physically, the impact of potential study confounds. Studies of CRCI should include multiple control groups consisting of alternative disease-specific conditions, such as alternate- or, if possible, no-treatment groups, together with healthy comparison participants as recommended by the International Cognition and Cancer Task Force (Wefel, Vardy, Ahles & Schagen, 2011). Studies should also avoid including participants who have received treatments in addition to chemotherapy, although this may represent what patients are likely to be receiving, because this makes it difficult to identify which aspect of the treatment regime may lead to cognitive impairment. Alternatively, studies should use these groups of patients who have received treatment using multiple modalities for example chemotherapy and hormone therapy, as control groups and clearly distinguish between groups of patients who have received different combinations of treatments. Other confounds to consider include pre-morbid ability, age, education and affect, all of which would have a significant impact on measures of cognition.

These considerations suggest that a study designed to identify potential CRCI in bowel cancer patients should incorporate four comparison groups: a group of colorectal cancer patients treated with chemotherapy only; colorectal cancer patients treated with chemotherapy and the anti-angiogenic drug Avastin; colorectal cancer patients treated with surgery only and finally, a healthy age-matched control group. It is important to note that Avastin is an anti-angiogenic drug that is increasingly becoming the treatment of choice for patients with colorectal cancer. Additionally, Avastin works to decrease oxygen in the bloodstream and may therefore result in cognitive impairment and it is thus important to consider the effect of chemotherapy and Avastin versus chemotherapy alone in order to know whether either one of these

treatments results in cognitive impairment. This design allows for comparison of the influence of different chemical treatments (e.g. chemotherapy versus chemotherapy and Avastin) with surgery alone in order to establish whether any observed cognitive impairment may be the result of cytotoxic treatment, due to surgery, or even the experience of being diagnosed with cancer in and of itself.

A second major shortcoming identified in past research is that many studies reported a long time lapse between treatment cessation and cognitive testing. Testing should take place after a minimum of three months since the commencement of treatment and after treatment cessation. A maximum of 12 months between these two testing sessions is desirable because some studies suggest that CRCI resolves approximately 12 months post-treatment (Collins, Mackenzie, Stewart, Bielajew & Verma, 2009). The study that follows is comprised of two parts: the main study in which assessments took place during treatment and the follow-up study in which the assessment was conducted 12-months after the initial assessment. This was done in order to establish whether any cognitive deficits observed in the initial assessment persisted 12 months later. Because the majority of the baseline sample was lost to follow-up, the longitudinal study could not be powered and descriptive data only are provided in Appendix C.

A third problem that has plagued the CRCI literature is the non-equivalence of groups at baseline assessment. In many of the studies reviewed, the treatment group was found to outperform the control group prior to treatment, which influences the conclusions that can be drawn from the post-treatment assessment when comparing the groups and will work to produce a type II error. This is also the case where education attainment differs between groups; comparison becomes difficult because results may stem from these background differences. The most appropriate strategy

for dealing with this is to match groups, where possible, on education and premorbid ability. This strategy is feasible for the recruitment of healthy controls but much more difficult to achieve for treatment groups where statistical control of confounds may be needed.

The final issue highlighted in the review is the critical dependence on breast cancer patients for the establishment of the existence of CRCI. Clearly, additional empirical studies are required to establish the effects of chemotherapy on cognition in patients with other forms of cancer, in order to provide a more complete picture of the CRCI phenomenon across a wider range of different types of cancer. A focus on potential CRCI associated with treatment for bowel cancer is also important because of the high incidence of this cancer in the Australian population.

In summary, with the above limitations in mind, the importance of establishing the effect of chemotherapy on cognition in patients with colorectal cancer is critical. This is because colorectal cancer is highly prevalent within the Australian population; second only to breast cancer in women and prostate cancer in men (Bowel Cancer Australia, 2010; Cancer Council Australia, 2009). Each of the design limitations described above has been considered and attended to when designing the study that follows: Four groups were included, comprising patients who had received treatment with chemotherapy only, patients who had been treated with chemotherapy and the anti-angiogenic medication Avastin, a control group consisting of patients with colorectal cancer who had been treated using only surgical intervention and a healthy control group. All groups were matched on age, education and estimated premorbid ability; anxiety and depression were controlled for in all statistical analyses. Testing took place following a minimum of three months of chemotherapy, or as close to the completion of surgery as possible.

CHAPTER THREE

The Effect of Chemotherapy on Cognition in Patients treated for Colorectal Cancer

3.0 Preface

The study presented in Chapter 3 has been published online by the journal 'Advances in Cancer Research and Treatment', in 2012. The authors include PhD candidate, Kristy Hodgson, her three supervisors in order of their contribution to the paper: Prof Carlene Wilson, Dr Amanda Hutchinson and Prof Ted Nettelbeck, Dr Ganessan Kichenadasse and Dr Ian Zajac. The study in Chapter 3 is presented in the same manuscript form as it was when accepted for publication. The published manuscript and author contribution statements for this study are presented in Appendix B.

Abstract

Chemotherapy-related cognitive impairment (CRCI) is commonly reported following the administration of chemotherapy to cancer patients, with most confirmatory results obtained from samples of breast cancer patients. The aims were to assess whether CRCI is consistently observed in people treated for colorectal cancer, to assess the impact of different treatment regimens and to identify the domains of cognition affected.

This study comprised four sample groups, three of which had been diagnosed and treated for colorectal cancer; chemotherapy patients (n = 19), patients treated with chemotherapy and the anti-vascular drug Avastin^{TM} (n = 12) and surgery only patients (n = 10). A fourth, comparably aged and educated healthy control group was also included (n = 20). Each participant undertook approximately 90 minutes of testing, comprising nine neuropsychological tests, including a measure of everyday problem solving and self-report measures of anxiety, fatigue, depression and cognition.

Multivariate analysis of variance revealed no significant differences between the groups across the neuropsychological test total scores. However, a significant difference was found when those tests comprised of subscales were broken down into their components; comparison between the surgery and healthy control groups found a difference on the delayed recall component of the logical memory test, with the surgery group having performed more poorly. Significant relationships were found between years of education, premorbid ability and everyday problem solving ability and cognitive functioning. Results therefore have failed to support previous reports that cognitive impairment may occur in patients treated for cancer.

Key Words: chemotherapy, cancer, cognitive impairment

Introduction

Chemotherapy-related cognitive impairment (CRCI), known colloquially as chemobrain, involves a decrease in the cognitive processing capacity of an individual as a result of treatment with chemotherapy (Biglia et al., 2012). It has been estimated to affect between 12 and 95% of all cancer patients (Downie, Mar Fan, Houede-Tchen, Yi & Tannock, 2006; Hede, 2008; Iconomou, Mega, Koutras, Iconomou & Kalofonos, 2004; Jansen, Cooper, Dodd & Miaskowski, 2011; Mehnert et al., 2007; Prokasheva, Faran, Cwikel & Geffen, 2011; Skaali et al., 2011). However, these estimates differ widely between studies and a general consensus has been that it affects approximately 30% of patients undergoing treatment with chemotherapeutic agents (Collins, Mackenzie, Stewart, Bielajew & Verma, 2009; Hermelink et al., 2007; Vardy & Dhillon, 2010).

A diverse range of cognitive domains has been thought to be possibly affected by CRCI; various forms of memory, attention and concentration, information processing speed, motor function, language, executive function and visuospatial skills (Iconomou et al., 2004; Jansen, Dodd, Miaskowski, Dowling & Cramer, 2008; Mehnert et al., 2007; Prokasheva et al., 2011; Reid-Arndt, Hsieh & Perry, 2010; Skaali et al., 2011). Although not all patients treated with chemotherapy for cancer will experience CRCI, those who do have generally reported a diminished capacity to engage in everyday tasks, with consequential reduction in quality of life (Boykoff, Moieni & Subramanian, 2009; Hede, 2008; Myers, 2009). Although such experiences can be relatively short-term, CRCI has been reported as lasting up to 10 years after treatment (Iconomou et al., 2004).

Whether significant CRCI results from chemotherapy and, if so, what mechanisms are involved is a highly debated topic within the literature. A number of

mechanisms through which CRCI may arise have been proposed. For example, Jansen et al. (2008) and Myers (2009) hypothesised that CRCI occurs in response to the release of cytokines as a result of treatment. Dietrich, Han, Yang, Mayer-Proschel and Noble (2006) argued that CRCI occurs because chemotherapy is more harmful to brain cells than cancer cells and thus causes brain damage leading to cognitive impairment before the cancer cells have been eradicated. Others have also supported the notion that chemotherapy damages brain tissue, with Hampton (2008) and Meyers (2008) both claiming that CRCI occurs because of damage to the oligodendrocytes, which disrupts vital processes in the central nervous system. Other mechanisms proposed as causes of CRCI include hormonal and auto-immune responses (Meyers, 2008), damage to cerebral gray and white matter, microvasculature and DNA and oxidative stress (Myers, 2009).

There are a number of variables that have been reported to influence the occurrence of CRCI in patients with cancer. Specifically, it is thought that CRCI is less likely to occur and, if it does occur is less severe, in those patients who have higher premorbid IQ or who have received a higher level of education (Jansen et al., 2011). Alternatively, a propensity towards greater anxiety, depression and fatigue and chemotherapy-induced anaemia and menopause are thought to increase the likelihood and exacerbate the symptoms of CRCI (Jansen et al., 2011).

However, when conducting research into possible chemotherapy-related cognitive impairment, it is important to bear in mind that any impairment observed may not be due to the chemotherapy at all. CRCI research also overlaps with an area of research that investigates postoperative cognitive dysfunction (POCD). This is important because most cancer patients being treated with chemotherapy have also undergone surgical treatment for their cancer and POCD, much like CRCI, may

involve a reduction in the cognitive abilities of a patient as a consequence of surgical intervention.

The cause of POCD has been debated within the literature; it is thought to occur either due to the effects of general anaesthetics on the brain (Avidan & Evers, 2011; Chen et al., 2001), or as a consequence of the actions of the inflammatory system on brain functioning (Avidan & Evers, 2011, Cibelli et al., 2010). There is also debate surrounding the duration of POCD, with estimates ranging from a few days up to three months post-surgery (Avidan & Evers, 2011, Moller et al., 1998), durations consistent with some reports of CRCI although much shorter than the longer estimates sometimes claimed. It has, however, been established that POCD is both more prevalent and more severe among the older population and that these individuals are more likely to suffer its effects for longer and have a reduced quality of life as a result (Avidan & Evers, 2011, Chen et al., 2001, Moller et al., 1998). POCD is relevant to this study because it is possible that CRCI could be confused with POCD in patient groups treated using surgical methods in combination with chemotherapy. Therefore, a surgery-only treatment for cancer group was included in the present study, in order to evaluate this possibility.

It has been noted previously that objective neuropsychological tests may not be sufficiently sensitive to reflect the problems encountered in the everyday lives of patients and that, as a result, there is a discrepancy between the findings of objective testing and subjective impressions (self-report, others' opinions) in this area (Downie et al., 2006). Consequently, Hutchinson, Hosking, Kichenadasse, Mattiske and Wilson (2012) have called for the inclusion of a test that assesses everyday problem solving when evaluating the utility of neuropsychological assessment for measuring CRCI. In order to build upon the findings of existing studies, the present study will address this

concern by including the Everyday Problems Test (EPT) – a measure of problem solving abilities in situations regularly encountered in everyday life.

Colorectal cancer, also commonly known as bowel cancer, is a highly prevalent form of cancer in Australia; second only to breast cancer in women and prostate cancer in men (Bowel Cancer Australia, 2010; Cancer Council Australia, 2009). Specifically, by the age of 85 years, one in 10 Australian men and one in 15 Australian women will have been diagnosed with colorectal cancer. Due to improved and widely promoted screening techniques, the rates of survival associated with this form of cancer are ever increasing but survival rates decrease with increasing severity. To be precise, when diagnosed with early stage colorectal cancer, which requires only surgical treatment, one is currently expected to have an 87-90% chance of survival. Those with stage 3 of the disease, which usually involves both surgery and treatment with chemotherapy, are expected to have approximately a 57% chance of survival. Widespread stage 4 colorectal cancer, which can only be treated using chemotherapy, is associated with around a 10% chance of survival (Cancer Council Australia, 2009). Therefore, as a result of the high incidence of colorectal cancer in Australia in conjunction with the improving rates of survival if detected early, it is critically important to investigate the effects of treatment with chemotherapy on cognition in patients who have been diagnosed with this disease.

This study has aimed to test whether treatment with chemotherapy leads to cognitive impairment in patients with colorectal cancer. This is important because, despite its high prevalence in the Australian community, the effect of treatment on the cognitive functioning of patients with colorectal cancer is yet to be evaluated despite the extensive literature predominantly investigating this phenomenon in breast cancer. Specifically, we assessed the effect of treatment with chemotherapy on cognition in

patients with colorectal cancer and compared these effects with those of other treatments for this type of cancer including surgical treatment alone and treatment with anti-vascular drugs. The hypotheses tested were: (1a) that treatment with chemotherapy or chemotherapy and the anti-vascular drug leads to impairment across a number of cognitive tests for attention, memory and processing speed by comparison to matched controls and (1b) that cognitive impairment will also be evident in the surgery-only control group by comparison to matched controls as a result of POCD.

In addition, consistent with the literature, it was hypothesised that (2) those with greater levels of depression, anxiety and fatigue will exhibit worse cognitive function; (3) those with a higher level of education and/or higher premorbid ability will display higher cognitive functioning; and, (4) participants with higher scores on the Everyday Problems Test will have better cognitive functioning. It should be noted that impairment was measured as the average performance of each of the three treatment groups relative to that of a healthy, age- and education-matched control group.

Method

Patients with a diagnosis of colorectal cancer, treated with either surgery alone, chemotherapy with surgery and without surgery, or chemotherapy with the anti-vascular drug Avastin (bevacizumab) with and without surgery between October 2009 and April 2012 were recruited through the oncology departments at Flinders Medical Centre and the Royal Adelaide Hospital. To be included in the present study, patients were required to be aged over 50 years, have received a minimum of three months of chemotherapy, with or without Avastin and in the case where treatment had already been completed, be no more than one month post-treatment. Surgery patients

were also required to be no more than one month post-treatment. Patients were excluded if they had been treated with chemotherapy for any other instances of cancer, had a current diagnosis of anxiety or depression, or had a history of head injury, stroke, drug or alcohol abuse, or of a neurological or psychiatric condition. Healthy control participants were recruited through word-of-mouth at the two hospitals or were contacted from among people who had participated in previous unrelated research, run through the University of Adelaide. Healthy control participants, without the diagnosis/ treatment for colorectal cancer, were also required to conform to the same inclusion and exclusion criteria as the patient groups. Ethics approval was obtained through the University of Adelaide, Flinders University and Royal Adelaide Hospital Human Research Ethics Committees.

Eligible patients were first introduced to the study by their oncologist and provided with an information sheet. If interested in participating, their details were passed to the first author. They were contacted by phone to schedule a time to participate. The testing session took place either in the hospital at which the participant was receiving treatment, at their home, or at the University of Adelaide. At the testing session, participants were again provided with the information sheet, a consent form and instructed to read these and if willing to participate, provide consent. Participants were informed that they were free to withdraw from the study at any time without consequence. No-one withdrew.

Testing began with the Everyday Problems Test (EPT), which is a 21-item multiple-choice measure that assesses the extent to which a person can solve problems most likely encountered on a regular basis in their everyday lives, such as following recipes and filling out forms. Participants had a maximum of 20 minutes to complete this assessment. The EPT is both a reliable and valid measure with high test-retest

reliability (.83 - .91) and construct validity (.42 - .72) (Willis & Marsiske, 1993). Participants subsequently completed a number of scales assessing depression, anxiety and fatigue; the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Fatigue Assessment Scale. In addition, participants completed the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) and Functional Assessment of Cancer Therapy-Colorectal (FACT-C) subscales assessing self-reported cognitive functioning and quality of life subsequent to a diagnosis of cancer. The results of these self-report measures are not discussed here.

Following these questionnaires neuropsychological assessment involved the Trail Making Test (TMT), followed by the Controlled Oral Word Association Test (COWAT), Rey Auditory Verbal Learning Test (RAVLT), Digit Span test, Rey Complex Figure Test (RCFT), the Logical Memory test from the Wechsler Memory Scale III and the Inspection Time task (IT). Finally, the Wechsler Test of Adult Reading (WTAR) assessed premorbid intelligence, i.e. the predicted level of intelligence of the participants before they became ill based on their ability to pronounce words, some unknown to them, which is not affected by illness or treatment; followed by the Stroop test and Digit Symbol from the Wechsler Adult Intelligence Scale III. Table 1 describes the neuropsychological abilities evaluated by these tests as determined by their respective publishers; indicated in the manuals.

Table 1

Cognitive abilities Assessed by the Nine Neuropsychological Tests

Neuropsychological Test	**Cognitive Ability**
Trail Making Test	Executive Function
COWAT	Verbal Fluency
RAVLT	Verbal Learning and Memory
Digit Span	Working Memory
RCFT	Visuospatial Constructional Ability, Visuospatial Recall Memory and Processing Speed
Logical Memory	Verbal Learning and Memory
Inspection Time	Processing Speed
Stroop Colour and Word Test	Executive Function
Digit Symbol	Attention, Processing Speed and Visual Scanning and Memory

COWAT = Controlled Oral Word Association Test, RAVLT = Rey Auditory Verbal Learning Test, RCFT = Rey Complex Figure Test.

All neuropsychological tests were administered and scored according to the instructions outlined in their respective manuals. Each of these measures has been shown to be reliable and valid; the COWAT has a test-retest reliability of .70, while the RAVLT has an internal consistency of .70 for list A (Snow, Tierney, Zorzitto, Fisher & Reid, 1988). Digit span and logical memory have demonstrated test-retest reliabilities of .84-.93 and .74-.91 respectively, depending on age group (Tulsky, Zhu & Ledbetter, 1997). The Stroop test was shown to have a test-retest reliability of .73 for the colour-word component (Jensen, 1965), while that for Digit Symbol was .84-

.87, depending on the age group of participants (Tulsky, Zhu & Ledbetter, 1997). The RCFT had a test-retest reliability of .76 for the copy component and .89 for the recall component (Meyers & Meyers, 1995), while test-retest reliability for the Inspection Time task is usually .80 and higher (Grudnik & Kranzler, 2001). Each of these tests correlated well with other tests measuring the same construct. No reliability or validity data were available for the Trail Making Test. The results of this study were analysed using the Statistical Package for the Social Sciences (SPSS) version 18.

Results

Comparison between Treatment Groups

Sixty-one patients were recruited to participate in this study (30 male). Of these, 19 were treated with chemotherapy, an additional 12 with the anti-vascular drug Avastin (bevacizumab), 10 received only surgical intervention and 20 were age- and education-matched healthy controls. The decision was made to include 20 healthy controls based on the fact that the largest cancer treatment group consisted of only 19 patients and having relatively equal numbers in the chemotherapy and control groups was a goal of this research. The chemotherapy group comprised 17 patients who had been treated with surgery and chemotherapy and two participants who were treated using only chemotherapy. Of the Avastin group, seven were treated using surgery, chemotherapy and Avastin, while the other five were treated with chemotherapy and Avastin. As described above, participants in both the chemotherapy and Avastin treatment groups received chemotherapy. More specifically, nine participants were treated with oxaliplatin, calcium folinate and 5-flourouracil, eight using capecitabine (xeloda), six with calcium folinate and 5-flourouracil and one with capecitabine, calcium folinate, oxaliplatin and 5-flourouracil, capecitabine, 5-flourouracil and calcium folinate and capecitabine and oxaliplatin, respectively. Group-specific

descriptive statistics for age, level of education and premorbid ability are presented in Table 2. Univariate analyses of variance revealed no significant differences between the four groups in age, years of education and premorbid ability.

Table 2

Means and Standard Deviations (in parentheses) for Age, Level of Education and Premorbid Ability

Treatment Group	**n**	**Age (years)**	**Years of Education**	**Premorbid Ability**
Chemotherapy	19	66.95 (8.09)	11.44 (3.07)	40.16 (6.83)
Avastin	12	69.17 (7.35)	11.00 (3.02)	39.18 (5.95)
Surgery	10	69.20 (9.00)	10.80 (4.37)	37.30 (5.40)
Healthy Control	20	71.65 (6.39)	10.17 (2.87)	40.70 (6.05)

To investigate whether there was a difference between the four groups in terms of their cognitive performance a MANOVA was conducted using the subscale scores from each neuropsychological test. This analysis revealed a significant difference between the four groups in cognitive functioning ($F(45, 81) = 1.12$, $p < .01$). Post hoc testing showed that this difference was between the surgery and healthy control groups in the second recall component of the Logical Memory test. As can be seen in Table 3, the surgery group performed more poorly on this task than the healthy control group. The groups did not significantly differ in their performance on any of the other subtests. Descriptive statistics for these MANOVAs are displayed in Table 3. These results do not provide support for the first hypothesis that treatment for cancer would lead to cognitive impairment. Due to the large number of comparisons

across the four groups for the neuropsychological tests, it is likely that the one significant result occurred because of a Type II error rather than an actual effect.

In order to further evaluate whether treatment with chemotherapy leads to cognitive impairment, the chemotherapy and Avastin groups were combined to form one larger chemotherapy treatment group (n = 31). A MANOVA was conducted to establish whether or not there were any differences between this group, the surgery group (n = 10) and healthy controls (n = 20) in performance on the neuropsychological tests. This revealed no difference for the total neuropsychological test scores (F (20, 58) = 1.12, p = .36) or for the subtest scores (F (30, 56) = 1.26, p = .22). These results also fail to provide partial support for the first hypothesis. See Table 3 for descriptive statistics.

Table 3

Descriptive Statistics for Performance on Neuropsychological Tests of the Chemotherapy, Avastin, Surgery, Healthy Control and Chemotherapy and Avastin Combined Groups

	Means (SDs)				
Test	**Chemotherapy**	**Avastin**	**Surgery**	**Healthy Control**	**C&A Combined**
COWAT	38.27 (11.13)	37.71 (12.45)	32.71 (11.22)	42.38 (13.71)	38.06 (11.30)
Trails Part A*	49.23 (28.00)	48.26 (20.09)	53.57 (30.81)	40.58 (11.95)	48.87 (24.95)
Trails Part B*	116.44 (76.33)	103.26 (26.95)	129.75 (69.01)	117.17 (35.71)	111.56 (62.28)
Digit Span F	9.59	10.40	10.56	9.67 (2.55)	9.89

	Means (SDs)				
Test	**Chemotherapy**	**Avastin**	**Surgery**	**Healthy Control**	**C&A Combined**
	(2.58)	(1.58)	(2.19)		(2.26)
Digit Span B	7.65	7.50	7.33	8.22 (2.28)	7.59
	(2.60)	(1.27)	(2.24)		(2.17)
RCFT copy	32.23	32.29	30.50	32.84 (3.91)	32.25
	(3.18)	(3.86)	(3.62)		(3.35)
RCFT recall	14.64	12.57	7.21	14.44 (8.17)	13.83
	(7.65)	(5.89)	(6.54)		(6.91)
Inspection Time*	73.27	71.43	85.71	77.75	72.56 (27.95)
	(34.20)	(16.15)	(41.88)	(27.67)	
LM1 Recall	26.18	27.10	22.00	32.89	26.52
	(10.39)	(8.08)	(5.83)	(14.71)	(9.44)
LM1 Thematic	14.35	14.50	11.33	15.56 (3.36)	14.41
	(5.29)	(3.69)	(3.46)		(4.68)
LM2 Recall	15.59	15.30	10.00	19.22	15.48
	(6.80)	(7.54)	(5.15)	(10.04)	(6.94)
LM2 Thematic	8.88	9.30	7.33	10.44 (2.79)	9.04
	(3.81)	(2.98)	(2.74)		(3.47)
LM1 Learning	4.71	4.40	5.33	6.00 (3.04)	4.59
Slope	(2.17)	(2.01)	(2.55)		(2.08)
RAVLT	39.94	38.30	35.00	43.78	39.33 (11.33)
Immediate	(12.35)	(9.91)	(7.83)	(11.97)	
RAVLT	14.24	15.30	10.89	18.00 (6.58)	14.63

	Means (SDs)				
Test	**Chemotherapy**	**Avastin**	**Surgery**	**Healthy Control**	**C&A Combined**
Delayed	(8.96)	(5.72)	(6.49)		(7.81)
RAVLT	11.59	12.50	10.89	13.11 (1.62)	11.93
Recognition	(2.74)	(1.84)	(3.33)		(2.45)
RAVLT	2.88	3.60	2.78	4.44 (4.13)	3.15
Distractors*	(2.78)	(3.72)	(1.86)		(3.12)
Stroop	29.73	29.57	42.43	32.19	29.67
	(10.31)	(8.36)	(17.22)	(10.12)	(9.34)
Digit Symbol	54.18	52.29	51.86	55.13	53.44 (11.73)
	(14.34)	(7.39)	(18.72)	(14.47)	

*For the Trail Making Test, Inspection Time and RAVLT Distractors, a lower score indicates better performance.

Emotional Functioning

Correlation analyses evaluated relationships between depression, anxiety, fatigue and cognitive functioning. Depression and fatigue were not significantly related to performance on any of the neuropsychological tests and anxiety was related only to performance on the Trail Making Test (r = .25, p = .05); higher self-reported fatigue was associated with poorer Trail Making performance. Taken together, these results fail to support the hypothesis (2) that depression, anxiety and fatigue would be related to poorer cognitive functioning. Additionally, further correlations were conducted to examine the relationship between depression, anxiety and fatigue and performance on the neuropsychological tests for each of the five groups. Table 4 displays these correlations; most of which are in the opposite direction to what was predicted by the second hypothesis. Fatigue was related to cognitive performance in

the chemotherapy group however, this was only on a single subscale of two respective tests; anxiety was correlated with neuropsychological test performance for the Trail Making and Inspection Time tasks in the Avastin treatment group, while part A of the Trail Making Test was related to anxiety in the chemotherapy and Avastin combined group (Table 4).

Correlations were undertaken to assess whether years of education or premorbid intelligence were associated with cognitive function; significant positive correlations were found between both years of education and premorbid ability and a number of neuropsychological tests, as set out in Table 5. Hypothesis 3, that more education and premorbid ability will be related to better cognitive functioning, is therefore supported.

The Everyday Problems Test (EPT) was correlated with the different neuropsychological test scores to assess whether functioning in everyday life situations was related to neuropsychological test performance. Statistically significant correlations were revealed between the EPT and each of the neuropsychological tests, with the exception of the Stroop Colour and Word Test (see Table 6). This confirms hypothesis 4, that everyday problem solving ability and cognitive functioning are related.

Table 4

Relationships between Depression, Anxiety and Fatigue and Neuropsychological Test Performance across the Five Groups

Group	**Emotional Function Variable**	**Neuropsychological Test**	***r***	***p***
Chemotherapy	Fatigue Assessment Scale	Digit Span Forwards	-.57	.02
		Logical Memory 1	-.54	.03

Group	Emotional Function Variable	Neuropsychological Test	*r*	*p*
		Thematic		
Avastin	Beck Depression Inventory	RAVLT Immediate Recall	.76	.02
		RAVLT Recognition	.74	.04
	Beck Anxiety Inventory	Trail Making Test Part A*	.92	.00
		Trail Making Test Part B*	.92	.00
		Inspection Time*	.81	.03
		RAVLT Immediate Recall	.81	.01
Surgery	Beck Depression Inventory	Inspection Time*	-.76	.03
		Logical Memory 2 Recall	.67	.05
		Logical Memory 2 Thematic	.67	.05
		RAVLT Immediate Recall	.81	.01
	Beck Anxiety Inventory	Controlled Oral Word Association Test	.75	.03
	Fatigue Assessment Scale	Inspection Time*	-.80	.02
C&A	Beck Anxiety Inventory	Trail Making Test	.55	.01

Group	Emotional Function Variable	Neuropsychological Test	*r*	*p*
		Part A*		
	Fatigue Assessment Scale	Logical Memory 1	-.48	.03
		Thematic		
Healthy Control	Beck Anxiety Inventory	RAVLT Distractors	.54	.03
	Fatigue Assessment Scale	RAVLT Distractors	.68	.00

Table only contains significant results. *lower scores indicate superior performance. C&A = Chemotherapy + Avastin combined to form one drug treatment group.

Table 5

Significant Correlations between Years of Education and Premorbid Ability and the Neuropsychological Tests

Variable	**Test**	***r***	***p***
Years of Education	COWAT	.35	.01
	RCFT Recall	.32	.02
	Logical Memory 1 Recall	.34	.02
	Logical Memory 1 Thematic	.43	.00
	Logical Memory 2 Recall	.32	.02
	Logical Memory 2 Thematic	.38	.01
	Digit Symbol	.30	.04
Premorbid Ability	COWAT	.47	.00
	Digit Span Backwards	.40	.00
	RCFT copy	.27	.04
	RCFT recall	.36	.01
	Logical Memory 1 Recall	.32	.02
	Logical Memory 1 Thematic	.40	.00
	Logical Memory 2 Recall	.30	.03
	Logical Memory 2 Thematic	.42	.00
	RAVLT Immediate Recall	.37	.01
	RAVLT Delayed Recall	.36	.01
	Stroop	.21	.10
	Digit Symbol	.30	.04

Table 6

Significant Correlations between the EPT and Neuropsychological Tests

	Test	***r***	***p***
EPT	COWAT	.35	.02
	TMT Part A*	-.48	.00
	TMT Part B*	-.45	.00
	Digit Span Forwards	.53	.00
	Digit Span Backwards	.63	.00
	RCFT copy	.38	.01
	RCFT recall	.56	.00
	Inspection Time*	-.37	.02
	Logical Memory 1 Recall	.54	.00
	Logical Memory 1 Thematic	.45	.00
	Logical Memory 2 Recall	.48	.00
	Logical Memory 2 Thematic	.35	.02
	RAVLT Immediate Recall	.60	.00
	RAVLT Delayed Recall	.60	.00
	RAVLT Recognition	.38	.01
	RAVLT Distractors*	-.43	.00
	Digit Symbol	.71	.00

*In contrast to the other tests, lower scores on the Trail Making Test, Inspection Time task and RAVLT Distractors indicate better performance.

Discussion

This study examined the effect of chemotherapy on cognition in patients with colorectal cancer. Hypothesis 1 was not supported because patients being treated with chemotherapy or Avastin or with only surgical intervention did not perform statistically significantly worse than the healthy controls. This study therefore revealed no evidence of chemotherapy-related cognitive impairment (CRCI), post-operative cognitive dysfunction (POCD), or any other treatment- or cancer-related cognitive impairment. These findings are not consistent with the literature, which states that between 12 and 95% of patients treated with chemotherapy for cancer do experience symptoms of CRCI (Downie, Mar Fan, Houede-Tchen, Yi & Tannock, 2006; Hede, 2008; Iconomou, Mega, Koutras, Iconomou & Kalofonos, 2004; Jansen, Cooper, Dodd & Miaskowski, 2011; Mehnert et al., 2007; Prokasheva, Faran, Cwikel & Geffen, 2011; Skaali et al., 2011). However, none of the literature until now has investigated CRCI in patients with colorectal cancer and thus it is possible that CRCI simply does not exist in this patient group.

The second hypothesis, that participants with greater depression, anxiety and fatigue would exhibit lower levels of cognitive functioning was not supported. A significant correlation was revealed only between anxiety and performance on the Trail Making Test; however anxiety was unrelated to the other measures of cognitive functioning while depression and fatigue were not related to performance on any of the neuropsychological tests. This is also inconsistent with literature that has found that cognitive functioning declines in those with depression, anxiety and fatigue (Jansen et al., 2011).

Hypothesis 3, that participants with more years of education and greater premorbid ability will exhibit better cognitive functioning, was confirmed.

Statistically significant relationships were established between years of education and premorbid ability and a number of the cognitive tests. This is consistent with the existing literature. Jansen et al. (2011) also found that those with higher levels of education and intelligence tended to perform better on neuropsychological tests and retain a higher level of cognitive functioning compared to those with lower levels of these.

The fourth hypothesis, that those scoring higher on the Everyday Problems Test (EPT) will also demonstrate better cognitive functioning was also confirmed. Statistically significant correlations were established between the EPT and all of the neuropsychological tests, with the exception of the Stroop Colour and Word Test. This is an important finding in informing the literature. Past studies have called for research to be conducted into the relationship between everyday problem solving abilities and cognitive functioning in cancer patients (Hutchinson et al., 2012). This study has shown that neuropsychological tests are good predictors of the problems participants come across in their everyday lives and there are moderate to strong relationships between these two variables. Therefore, based on the findings of the present study, the recommendation can be made that it is acceptable for traditional objective neuropsychological tests to be used to assess the effects of CRCI in cancer patients because they are positively related to everyday problem solving ability (as evidenced by the EPT).

Limitations of Study

The present study had a number of limitations. A larger sample size and having a similar number of participants in each of the four groups, who were homogeneous in the treatment they received, would have provided the study with greater statistical power and, in turn, made the results more reliable and generalisable

to the colorectal-cancer patient population. Therefore, due to its small sample size, the results of the present study must be interpreted with caution. Future studies should aim to recruit a much larger number of participants in order to produce more reliable data and would therefore provide the researcher with the opportunity to delete participants with missing cases if that situation arose. However, this is difficult to do in practice, thus cross-institutional studies may be the only answer to less limited research with this patient group.

To conclude, this study investigated the effect of treatment with chemotherapy, Avastin and surgery on cognition in patients with colorectal cancer, with none of the three treatment groups exhibiting cognitive impairment relative to the healthy controls. The effects of level of education, premorbid ability and everyday problem solving on cognitive functioning in these patients were also investigated, with statistically significant correlations being found between each of these and many of the cognitive tests. Depression, anxiety and fatigue were established as being unrelated to cognitive functioning in this patient group. Future studies should also investigate the effects of chemotherapy on cognition in colorectal cancer patients, as well as examining further the relationship between everyday problem solving, using the EPT and/or alternative instruments, in cancer patients generally.

3.1 Chapter Summary and Future Directions

A cross-sectional study was conducted to assess the effect of chemotherapy on cognition in patients with colorectal cancer. Results indicated that chemotherapy did not have an impact on the cognitive functioning of the participants, with all groups performing at approximately the same level on the neuropsychological tests. Depression, anxiety and fatigue were generally unrelated to cognitive performance but premorbid ability, years of education and everyday problem solving ability were positively related to cognitive functioning; i.e. better premorbid and everyday problem solving abilities and more years of education were generally accompanied by better cognitive functioning. However, it is important to note that because higher levels of premorbid, everyday problem solving ability and years of education were associated with higher levels of cognitive functioning, this simply means that there was a predictable correlation between tests commonly used to validate IQ-type measures.

To try to address the possibility that CRCI may emerge at different points in time following treatment with chemotherapy, a longitudinal study was conducted. An attempt was made to contact all participants 12 months after their initial assessment for the cross-sectional CRCI study, discussed in Chapter 3; those reached were asked if they were willing to participate in this second follow-up assessment. Those who agreed completed exactly the same battery of cognitive tests as had been used in the first assessment. However, the majority of the participants in the baseline assessment were lost to attrition, with only 15 of the original 61 participants consenting to participate in the follow-up assessment. Of those who did not participate in the follow-up assessment seven participants were deceased, 11 were too ill, 10 were too busy, 12 simply refused participation without providing an explanation as to why and

the remaining six were unable to be contacted. Consequently the follow-up sample was too small to produce sufficient data to permit reliable statistical analysis. However, data collected during the follow-up assessment have been summarised in Appendix C.

It is worthwhile noting that anecdotal impressions relayed by the patients in this study who had reported experiencing a decline in cognitive function subsequent to their cancer treatment suggested that they had remained unconvinced by their neuropsychological test results. In short, these patients continued to believe that they had experienced loss of cognitive function although they did not actually receive feedback on their performance; and their responses to test outcomes that suggested otherwise were that the tests were insufficiently sensitive to register the changes experienced. These suggestions are, of course, entirely plausible; and it is therefore important that every effort be made to further test the validity of any self-report of poorer cognitive functioning in these patients.

To reiterate, the cross-sectional CRCI study revealed no effect of chemotherapy on cognition in patients with colorectal cancer. Although in line with the findings of the initial meta-analysis presented in Chapter 2, this was in contrast to much of the chemotherapy-related cognitive impairment (CRCI) literature, as well as being unrepresentative of the cognitive complaints commonly made by patients. Given the lack of correlation found between anecdotal evidence of self-reported change and measures of neuropsychological functions, a new study was designed to investigate further the relationship between objectively measured neuropsychological tests and subjective reports of cognitive functioning. This study compared patient self-reports of cognitive functioning with their cognitive functioning measured through

performance on objective neuropsychological tests, the aim being to evaluate the extent of disconnect between objective and subjective measures of cognition.

CHAPTER FOUR

Self-Reported Cognitive Function in Patients with Colorectal Cancer

4.0 Preface

Although the study reported in chapter 3 failed to find evidence of objectively measured symptoms of CRCI among patients receiving chemotherapeutic treatment for colorectal cancer, it is nonetheless the case that many patients undergoing treatment with chemotherapy report that they experience cognitive impairment, regardless of cancer type. Moreover, these experiences have been linked to various indices of psychological health like anxiety and depression that are known to correlate with emotional well-being. This inconsistency between objective and subjective measures is not currently well understood but may reflect shortcomings of objective tests of cognitive function that result in them being insufficiently sensitive to detect the nature or levels of dysfunction that patients insist that they experience. This possibility is explored further in the study that follows, using the same sample of colorectal cancer patients who participated in the study reported in Chapter 3 and for whom little evidence of CRCI had been found with the battery of objective tests of psychological functioning.

The account of the study that follows is presented in the form of a manuscript prepared for submission for publication to the journal 'Psycho-Oncology'. The author contribution statements for this manuscript are presented in Appendix F.

Abstract

Chemotherapy-related cognitive impairment (CRCI) refers to cognitive dysfunction experienced by cancer patients and attributed to treatment. The aim of this study was to determine the extent to which individual differences in self-reported cognitive function are explained by individual differences in non-cognitive variables in patients with colorectal cancer. Specifically, it investigated self-reported cognitive functioning and its relationship to education and premorbid ability, objectively evaluated cognitive functioning, problem solving ability in everyday situations, emotional functioning, fatigue and comments from others about cognitive functioning among a sample of colorectal cancer patients treated with chemotherapy (N = 26) or surgery (N = 10) and healthy aged-matched controls (N = 17). The age of participants ranged from 54 to 82 years across the three groups. Performance on a test of everyday problem solving was included to examine the extent to which self-reported cognition was associated with real world problem-solving abilities. A stepwise regression was conducted to assess the extent to which education, premorbid ability, objective cognitive test performance, everyday problem solving ability, emotional functioning, fatigue and cognition-related comments from others predict self-report of cognitive difficulties. This revealed that education and premorbid ability, objective cognitive test performance, everyday problem solving ability, emotional functioning, fatigue and cognition-related comments from others all accounted for some percentage of the variance in self-reported cognition, to varying extents, with all of these variables together accounting for 69% of the variance in subjective reports of cognitive dysfunction. Significant positive relationships were found between self-reported cognitive functioning and three cognitive tests of memory (Digit Span, Stroop and Logical Memory), but individual differences in performance were more strongly

associated with other included measures, including emotional functioning, patients' perceived comments from others about cognition, years of education and premorbid ability.

Cancer patients did not report more subjective cognitive complaints than healthy controls, although there was a near-significant trend towards higher levels of depression among cancer patients. Significant relationships were found for the whole sample between subjective assessments, objective measures of memory and all measures of affect, but not for everyday problem solving. It is therefore important that physicians evaluate patients in terms of all of these variables, but particularly emotional wellbeing, because this has a significant impact upon both psychological functioning and perceived cognitive functioning.

Introduction

Chemotherapy-related cognitive impairment (CRCI) refers to the phenomenon whereby the cognitive functioning of cancer patients appears to decline subsequent to treatment (Biglia et al., 2012). This has been demonstrated in patients undergoing chemotherapy although it has also been associated with radiotherapy and other forms of treatment including surgery (Biglia et al., 2012; Downie, Mar Fan, Houede-Tchen, Yi & Tannock, 2006; Iconomou, Mega, Koutras, Iconomou & Kalofonos, 2004; Jansen, Cooper, Dodd & Miaskowski, 2011; Mehnert et al., 2007; Prokasheva, Faran, Cwikel & Geffen, 2011; Skaali et al., 2011). Estimates of the prevalence of CRCI have been extremely diverse, ranging between 12-95% and therefore providing little certainty as to the true size of the relationship (Downie et al., 2006; Iconomou et al., 2004; Jansen et al., 2011; Mehnert et al., 2007; Prokasheva et al., 2011; Skaali et al., 2011). Moreover, there has been little consistency in the conclusions drawn about the areas of cognition implicated. Thus, CRCI has been reported to lead to deficits in

memory, attention and concentration, information processing speed, motor function, visual and verbal memory, language, executive function and visuospatial skill (Iconomou et al., 2004; Jansen, Dodd, Miaskowski, Dowling & Cramer, 2008; Mehnert et al., 2007; Prokasheva et al., 2011; Reid-Arndt, Hsieh & Perry, 2010; Skaali et al., 2011). Some studies have reported that the symptoms of CRCI may persist for up to 10 years post-diagnosis and treatment (e.g., Iconomou et al., 2004).

CRCI has been reported to be negatively moderated by intelligence and level of education, so that more intelligent and educated people are at less risk of developing CRCI than those scoring lower on IQ tests and/or with less education (Jansen et al., 2011). The experience of CRCI has also been reported to be affected by emotional factors such as anxiety and depression, biological/physical factors such as fatigue or chemotherapy-induced anemia or menopause and individual factors such as increasing age and menopausal status (Jansen et al.), with research indicating that as these factors increase or become more severe, CRCI is more likely to be reported.

The use of objective cognitive tests to establish the presence or absence of cognitive impairment in patients treated with chemotherapy for cancer has been the standard approach in studies investigating CRCI. However, where these batteries have incorporated subjective assessment, results obtained from the objective and subjective measures have often been inconsistent, with objective assessments failing to support subjective impressions of compromised cognition (Biglia et al., 2012; Hutchinson, Hosking, Kichenadasse, Mattiske & Wilson, 2012; Iconomou et al., 2004; Jansen et al., 2011; Jansen et al., 2008; Prokasheva et al., 2011; Schagen et al., 2007; van Dam et al, 1998; Schagen, Muller, Boogerd, Wall, Fortuyn & Rodenhuis, 1998). One explanation for this discrepancy is that the cognitive tests available do not always detect CRCI because test requirements are only minimally relevant to those tasks and

activities performed on a daily basis by those individuals who report deteriorating cognitive performance (Downie et al., 2006). Moreover, the short term and acute nature of the objective cognitive testing regimen may protect performance that is generally compromised in a more demanding real-world setting. In other words, even if an individual's memory has been compromised, it may be that during a test of short term memory confined to a brief testing session with minimal distraction, performance can be optimised.

Cognitive assessment tools generally have poor ecological validity. They have not been designed to describe functioning in everyday situations but instead, assess cognitive domains and abilities that may or may not reflect one's performance in many aspects of daily life depending on task demands. Downie et al., (2006) have speculated that this may be because cancer patients who perform activities that are highly cognitively demanding as part of their everyday lives will need to expend a great deal of energy in order to avoid CRCI symptoms, if they are to continue to function at levels previously accepted by those patients as normal. This situation is likely to sensitise such individuals to experiences of cognitive decline, so that they are more likely to detect and report cognitive impairment subsequent to cancer treatment. On the other hand, those individuals who have not previously engaged regularly in cognitively stimulating tasks would be less likely to report concern about any deficits. Downie et al.'s suggestion appears to run counter to the general finding that CRCI is negatively correlated with ability and education level (Jansen et al., 2011) if it is assumed that smarter individuals are more likely to face more cognitively challenging everyday activities. Nonetheless, it is plausible that objective cognitive tests will not detect a difference between individuals whose cognitive decline is similar but who have different expectations about their personal cognitive capabilities. An alternative

argument has been that the cognitive dysfunction associated with CRCI is much more subtle than dysfunction reflecting a discernible brain injury, for example and that these tests have not been designed to detect very low levels of cognitive impairment and therefore fail to do so in most cancer patients, despite the fact that many such patients report cognitive complaints (Prokasheva et al., 2011). These suggestions are plausible but to our knowledge no research has attempted to test them.

On the other hand, some researchers have simply rejected the validity of subjective reports of CRCI, presenting arguments that defend the integrity of objective cognitive assessments for use in evaluating treatment-related cognitive impairment. The authors of these studies (see below) have argued that objective cognitive tests are equally valid and sensitive across all individuals, as well as across different groups of participants, because all test takers are subject to the same standardised test conditions during the assessment (Hermelink et al., 2010). Others have argued that patients' reports of possible CRCI symptoms are not reflected in the cognitive test results because despite putative change, the current behaviours involved continue to fall within the normal range of functioning and patients need not therefore be worried by any such changes that they think that they have noticed in their cognitive functioning (Prokasheva et al., 2011). These differences in opinion notwithstanding, it remains the case that many cancer patients report experiencing cognitive decline following chemotherapy, even when objective tests of cognition have failed to identify such decline.

Wies, Poppelreuter and Bartsch (2009) failed to find a statistically significant correlation between subjective and objective assessments of cognitive functioning in patients treated with chemotherapy for cancer but argued that their weak correlations were consistently in the expected direction, with higher self-reports of cognitive

dysfunction being related to poorer performance on cognitive tests. They concluded that most studies have lacked sufficient power to detect small differences, suggesting that if these studies were based on larger samples, the relationship between subjective and objective measures of cognition would be significant. Consistent with this, a small number of studies have reported a statistically significant correlation between subjective self-report and objective measures of cognitive functioning. For example, Mehnert et al. (2007) found a significant correlation in the expected direction between objective measures of working memory, selective attention, visuospatial working memory and visual delayed recall and self-reported cognitive dysfunction in cancer patients treated with chemotherapy. Reid-Arndt, Hsieh and Perry (2010) also found a significant correlation between self-reported cognitive functioning, immediate memory and response inhibition.

Despite the poor reliability of correlations between subjective assessments of cognitive functioning and objective test results, subjective assessments have been found to reflect psychological wellbeing. For example, researchers have reported that self-reported cognitive difficulties were positively associated with concurrently reported higher levels of anxiety, depression and sadness (Biglia et al., 2012; Hermelink et al., 2010; Iconomou et al., 2004). Similarly, Reid-Arndt, Hsieh and Perry (2010) and Shilling and Jenkins (2007) established that those reporting better emotional well-being also reported significantly less cognitive difficulty. Schagen et al. (2008) found that higher emotional distress and fatigue accompanied concurrent reports of higher levels of cognitive dysfunction. In a study of testicular cancer patients, Skaali et al. (2011) also reported similar results, adding that these effects were more marked where participants had lower levels of education. In sum, the

literature suggests that self-reports of cognitive dysfunction are more consistently related to emotional wellbeing than to objectively-measured cognitive functioning.

Few studies have examined self-reported or objective cognitive function in patients with colorectal cancer. Colorectal cancer is any cancer of the bowel or colon. It is a commonly occurring form of cancer, ranked second in prevalence to breast cancer in women and prostate cancer in men in Australia. Furthermore, Australia has the highest rates of colorectal cancer of any country in the world, with approximately 14,234 Australians diagnosed every year, one in 12 Australians diagnosed before the age of 85 and approximately 4000 dying of the disease each year (Bowel Cancer Australia, 2010). When colorectal cancer is detected in its early stages (i.e. before it has spread beyond the bowel or colon) patients have a 90% chance of survival. Even when the disease is detected later in its progression, as has most often been the case, there is a 60% chance of survival (Bowel Cancer Australia, 2010). Thus, many people diagnosed with colorectal cancer survive the disease. Due to the prevalence and high survival rates of colorectal cancer, research into the effects of treatment on cognition is particularly important for quality of life post-treatment.

Most studies investigating the relationship between objective and subjective assessment of cognitive function and treatment with chemotherapy have used breast cancer populations (Biglia et al., 2012; Jansen et al., 2011; Jansen et al., 2008; Prokasheva et al., 2011). No research in this field has been conducted in relation to patients with colorectal cancer. The present study therefore examined whether there is a concurrent relationship between objective and subjective assessments of cognition in colorectal cancer patients. As noted above, objective cognitive tests may not tap into the problems encountered in the everyday lives of the patients, thereby explaining why there is a discrepancy between the findings of objective and subjective testing in

this area (Downie et al., 2006). The current study investigated whether this discrepancy exists among patients with colorectal cancer. Additionally, in response to the call for the inclusion of a test that assesses everyday problem solving when evaluating the utility of subjective assessment of cognitive dysfunction relative to objective measurement (Hutchinson, Hosking, Kichenadasse, Mattiske & Wilson, 2012), an objective measure of everyday problem solving was included. This measure, the Everyday Problems Test (EPT; Willis & Marsiske, 1993), is an objective measure of the problem solving abilities of participants in situations that would typically be encountered by most people on a regular basis. The ecological validity of this test is important because it is arguable that everyday problem solving ability may be a better predictor of perceived cognitive ability than widely used objective neuropsychological cognitive tests (Willis & Marsiske).

The aim of the present study was to determine the extent to which individual differences in self-reported cognitive function are explained by individual differences in non-cognitive variables in patients with colorectal cancer. The following hypotheses were generated from the foregoing review:

Better self-reported cognitive function is accompanied by:

1) More years of education and/or higher premorbid ability.
2) Better performance on objective tests of cognition.
3) Better everyday problem solving ability.
4) Lower anxiety.
5) Lower depression.
6) Better emotional wellbeing.
7) Lower fatigue.
8) Fewer comments from others about cognitive function.

Method

Participants

Patients treated for a diagnosis of colorectal cancer at Flinders Medical Centre and the Royal Adelaide Hospital between October 2009 and April 2012 were invited to participate in this study. Participants needed to meet the following inclusion criteria: they were fluent in English; if in the chemotherapy group, they had been diagnosed with colorectal cancer, had received a minimum of three months treatment and were a maximum of one month post-treatment; were aged 50 years and over; had no diagnosed clinically significant levels of anxiety, depression, neurological or psychiatric illness; had no history of head injury, stroke or drug and alcohol abuse; and had never received treatment for any other cancers. There were 53 participants (26 males) aged between 54 and 82 years. Participants were allocated to one of two groups depending upon the treatment they had received: one group included patients with colorectal cancer treated with chemotherapy, with or without surgery (n = 26); colorectal cancer patients treated only with surgery formed the second group (n = 10). A third group consisted of healthy age- and education-matched controls (n = 17), recruited through word of mouth at Flinders Medical Centre and from the community at large. Ethics approval for the conduct of this study was obtained through the Flinders University, University of Adelaide and Royal Adelaide Hospital Human Research Ethics Committees.

Test Materials

Objective Tests of Cognition

Eight objective measures of cognition were included: the Trail Making (TMT) and Stroop tests measured executive functioning; the Digit Span test evaluated working memory; the Inspection Time task assessed speed of information processing;

Digit Symbol measured attention, processing speed, visual scanning and memory; the Rey Complex Figure Test (RCFT) is comprised of two components, the copy component involved copying an image and evaluated visuospatial constructional ability, while the recall component involves drawing the same image from the copy component 30 minutes after having looked at it and assesses visuospatial recall memory and processing speed; and the Logical Memory and Rey Auditory Verbal Learning Tests (RAVLT) assessed verbal learning and memory.

All measures have been shown to have acceptable reliability and validity. Digit Span, Logical Memory and Digit Symbol have demonstrated test-retest reliabilities of .84 to .93, .74 to .91 and .84 to .87 respectively, depending on age group (Tulsky, Zhu & Ledbetter, 1997). Test-retest reliability for Stroop has been reported as .73 for the colour-word component (Jensen, 1965), .36 to .79 for part A and .44 to .89 for part B of the Trail Making Test (Bornstein, Baker & Douglas, 1987; Matarazzo, Wiens, Matarazzo & Goldstein, 1974; Dikmen, Heaton, Grant & Temkin, 1999). The RCFT has a test-retest reliability of .76 for the copy component and .89 for the recall component (Meyers & Meyers, 1995); and test-retest reliability for the Inspection Time task is .80 and higher (Grudnik & Kranzler, 2001).

The Wechsler Test of Adult Reading (WTAR) provided an estimate of the participants' level of functioning prior to treatment and permitted controlling for individual differences in ability prior to the onset of cancer. There is good evidence that reading ability does not decline with other cognitive faculties and therefore provides a good estimate of premorbid ability (Biglia et al., 2012). The WTAR requires participants to read a list of words with irregular pronunciations aloud; scores are based on the accuracy of pronunciation. This test has demonstrated very good internal consistency, with coefficients ranging between .87 and .97 (Wechsler, 2001).

Subjective Measures of Emotional and Cognitive Functioning

The Beck Depression Inventory (BDI) was included in the test battery in order to assess self-reported depression. The 21-item self-report questionnaire provides four statements for each item and the participant circles which of the four statements most closely applies to how they felt in the past week. The BDI has reported construct validity of .80 (Beck & Steer, 1984).

The Beck Anxiety Inventory (BAI), used to evaluate patient anxiety, also consists of 21 items and participants rate on a scale of 0-3 the extent to which they experienced symptoms of anxiety during the past month. The BAI has reported construct validity of .94 (Fydrich, Dowdall & Chambless, 1992).

The Fatigue Assessment Scale evaluates the extent to which fatigue was experienced by patients (Michielsen, De Vries, Van Heck, Van de Vijver, & Sijtsma, 2004). The FAS has been found to be both reliable (.87) and valid (.47) (Michielsen, et al.). Participants rated on a 5-point Likert scale ranging from 'never' to 'always' the extent to which they experienced symptoms of fatigue during cancer treatment and in the weeks immediately following.

The Functional Assessment of Cancer Therapy – Cognition (FACT-Cog) was included in the battery of tests to evaluate the self-reported cognitive functioning of participants. The FACT-Cog is a 37-item questionnaire used to rate how often one has been affected by cognitive functioning problems during the past seven days, using a 5-point Likert scale ranging from 'several times a day' to 'never'. Higher scores indicate better perceived cognitive functioning. There are four subscales: 'perceived cognitive impairments' (assesses the extent to which the patient believes cognition has been impaired during the past week and consists of items such as 'I have had trouble forming thoughts' and 'I have had trouble finding my way to a familiar

place'); 'comments from others' (whether other people have commented on perceived decline in the participant's cognitive functioning during this time, with items including 'Other people have told me I seemed to have trouble remembering information'); 'perceived cognitive abilities' (the extent to which particular cognitive functions are performed with ease, with items such as 'My mind is as sharp as it always has been'); and 'impact on quality of life' (the extent to which cognitive change during the past week has interfered with everyday life, with items including 'These problems (cognitive deficits) have interfered with my ability to work'. The FACT-Cog has been demonstrated as having high reliability (reliability = .96; Lai et al., 2009).

The 'emotional wellbeing' subscale (6 items) from the Functional Assessment of Cancer Therapy – Colorectal scale (FACT-C), is a 5-point Likert scale that measures self-report of coping with cancer, with response options ranging from 'not at all' to 'very much'. Higher scores equate to better emotional wellbeing. The FACT-C emotional wellbeing subscale has been found to have internal consistencies between .56 and .75 (Wood, Hahn, Mo, Hernandez, Tulsky & Cella, 1999).

Everyday Problem Solving Ability

The Everyday Problems Test (EPT) provided an objective assessment of performance on tasks that arise regularly in everyday life. The EPT consists of 21 questions that relate to everyday situations, like following recipes and paying bills. Participants complete as many of these questions as they can, as quickly as they can, within 20 minutes. The EPT has high test-retest reliability (.83 to .91) and construct validity (.42 to .72) (Willis & Marsiske, 1993). An example item from this test is included in Appendix D.

Procedure

Participants were informed about the study by their oncologist and provided with an information sheet. Contact details of those who agreed to participate were passed to the researcher by the oncologist. Consent was confirmed prior to testing, which was conducted either at the hospital, at the University of Adelaide, or at the participant's home. A pre-treatment baseline assessment could not be obtained because recruitment and assessment of patients before the commencement of treatment was not a viable option for the participating hospitals. Therefore a measure of premorbid ability, the WTAR, was included to control for pre-existing differences between the groups prior to treatment. Each assessment involving the full test battery took between 60-120 minutes to complete. Participants were reimbursed for their time and travel with an $80 (Australian) gift card.

Some of the data analysed in this study here have been presented in another paper (Chapter 3), but the analyses presented here are unique.

Results

Three univariate analyses of variance (ANOVA) revealed no statistically significant differences between the three groups on age, years of education and premorbid ability of participants. Although healthy controls tended to be slightly older than members of the other two groups (see Table 1), differences were small and no correction has been applied in the analyses that follow.

Table 1

Means, Standard Deviations and F Statistics for the Demographic Characteristics of the Sample

	Chemotherapy (n = 26) Mean (SD)	**Surgery (n = 10) Mean (SD)**	**Healthy Controls (n = 17) Mean (SD)**	**F**	***p***
Age (years)	67.3 (8.0)	69.2 (9.0)	72.9 (5.9)	2.84	.07
Years of Education	11.3 (3.2)	10.8 (4.4)	10.3 (3.1)	0.43	.65
Premorbid Ability (WTAR)	39.0 (6.6)	37.3 (5.4)	41.0 (5.7)	1.21	.31

Note: WTAR = Wechsler Test of Adult Reading.

Whether subjective assessments of cognitive functioning differed depending upon the type of treatment being received was tested by multivariate analysis of variance (MANOVA). Table 2 shows the means and standard deviations for the three groups: cancer patients treated with chemotherapy, cancer patients who received surgical intervention and the healthy controls, on the four subscales of the FACT-Cog. MANOVA found no statistically significant differences between the three groups for FACT-Cog scores on subscales measuring self-reported cognitive impairment, quality of life and comments from others about cognitive function.

Thus, neither the cancer experience, nor cancer treatment contributed to more reports of cognitive dysfunction. Because there were no differences between the groups, including between patients and controls, subsequent analyses were conducted with all groups combined to determine whether differences existed between objective cognitive test results and participants' perceptions of cognitive functioning.

Table 2

Means and Standard Deviations (in parentheses) for the FACT-Cog scores in the chemotherapy, surgery and healthy control groups

FACT-Cog Subscale*	Chemotherapy (n = 26)	Surgery (n = 10)	Healthy Control (n = 17)
Perceived Cognitive Impairments	50.6 (15.4)	54.2 (12.8)	57.7 (15.9)
Impact on Quality of Life	11.9 (4.1)	12.5 (4.3)	14.0 (4.0)
Comments from Others	14.6 (2.2)	14.8 (3.1)	15.1 (2.2)
Perceived Cognitive Abilities	18.2 (6.6)	18.4 (5.1)	19.2 (7.7)

*Note: For all subscales on the FACT-Cog, a higher score is indicative of better functioning.

Correlations

Correlation analyses were first conducted to assess the extent to which relationships existed between the subjective measures of emotional and cognitive functioning and objective cognitive measures (see Appendix E). Preliminary analyses subsequently informed regression analysis. As can be seen in Appendix E, years of education was positively correlated with premorbid ability, everyday problem solving ability and performance on the Rey Complex Figure, Logical Memory and Digit Symbol tests. Depression was positively associated with anxiety and fatigue and negatively correlated with self-reported cognitive impairment, emotional wellbeing, self-reported quality of life, comments from others and cognitive ability, premorbid ability and performance on the Rey Complex Figure Test. Negative relationships existed between anxiety and self-reported quality of life and emotional wellbeing,

while a positive relationship existed between anxiety and fatigue. Self-reported cognitive impairment and performance on the Trail Making Test were negatively associated with anxiety. Fatigue was negatively correlated with a number of variables including self-reported cognitive impairment, quality of life, comments from others and cognitive ability, emotional wellbeing, premorbid ability, everyday problem solving ability and performance on the Logical Memory test. Self-reported cognitive impairment was positively related to self-reported comments from others, cognitive ability, emotional wellbeing, quality of life and premorbid ability. Self-reported quality of life was positively related to emotional wellbeing, while self-reported cognitive ability was also positively correlated with premorbid ability, everyday problem solving ability, emotional wellbeing and performance on the Digit Span, Logical Memory and Stroop Tests. Premorbid ability, emotional wellbeing and performance on the Digit Span test were all positively related to self-reported comments from others, whilst self-reported cognitive ability was positively related to perceived comments from others. Positive correlations existed between premorbid ability and everyday problem solving ability and performance on the Digit Span, Logical Memory, Rey Auditory Verbal Learning and Digit Symbol Tests. Positive correlations were also present between premorbid ability and performance on the Trail Making and Rey Complex Figure tests. Everyday problem solving ability was positively moderately correlated with performance on the Trail Making, Digit Span, Rey Complex Figure, Inspection Time, Logical Memory and Rey Auditory Verbal Learning tests; while performance on the Digit Symbol test was strongly related to everyday problem solving ability. These results show that many of the variables in this study are intercorrelated. Therefore the relationships outlined above may be impacted upon by the other variables included in the study. A regression analysis is

hence important to establish the independent contribution of the self-reported affect and objective cognitive variables to self-reports of cognitive function.

Regression

Stepwise regression analysis was conducted in order to assess the extent to which self-reported cognitive functioning was predicted by (a) years of education and premorbid ability, (b) objective cognitive test performance, (c) everyday problem solving ability, (d) emotional functioning, (e) fatigue and (f) comments from others about cognition (Table 4). Each of these variables was entered into the regression model on the basis of the extent to which they correlated with self-reported cognitive functioning. This indicated that 14.1% of the variance in self-reported cognitive functioning was accounted for by years of education and premorbid ability. This fails to provide support for hypothesis 1, as more years of education and higher premorbid ability were not significantly associated with better self-reported cognitive function. It is important to note that years of education and premorbid ability were highly correlated, thus it was acceptable to confound them in a single hypothesis. An additional 7.9% of the variance in perceived cognitive function was accounted for by performance on objective tests of cognition when these were added to the model, but this was not significant, therefore not providing support for hypothesis 2 that better objective cognitive test performance is accompanied by better self-reported cognition.

Everyday problem solving ability predicted a further 6.2% of the variance in self-reported cognitive function, however this was not a statistically significant contribution and thus hypothesis 3 that better self-reported cognition is accompanied by better everyday problem solving abilities was not supported.

Emotional functioning accounted for an additional 22.5% of the variance in self-reported cognition when added to the model and this was statistically significant.

This is the single biggest contributor, although individual betas are small. This result provides support for hypotheses 4 to 6, as better self-reported cognitive functioning is accompanied by lower depression and anxiety, and better emotional wellbeing.

Fatigue only predicted an additional 0.1% of the variance in self-reported cognitive functioning, a contribution that failed to reach statistical significance. Therefore, hypothesis 7 which states that better self-reported cognition is accompanied by lower fatigue is not supported.

Patient reports of comments from others about their cognitive functioning were responsible for predicting an additional 18.7% of the variance in perceived cognitive functioning (Table 4). This result provides support for hypothesis 8 that better self-reported cognitive function is accompanied by fewer patient reports of receiving comments from others about their cognitive functioning. Combined, the variables presented in Table 4 accounted for 69% of the variance in self-reported cognitive functioning.

Table 4

Predictors of Self-Reported Cognitive Functioning – Regression Analyses

Predictor	**Variables**	**R**	**R^2**	**R^2 Change**	**Beta**	***t***	***p***
Education & Premorbid Ability		.375	.141	.141			.07
	Education				-.216	-1.24	.22
	Premorbid Ability				.416	2.39	.02*
Objective Tests		.469	.220	.079			.97
	Trail Making Test				.023	.09	.93
	Digit Span				-.011	-.04	.97
	RCFT Copy				-.116	-.46	.65
	RCFT Recall				-.040	-.16	.87
	Inspection Time				-.044	-.21	.84
	Logical Memory				.191	.68	.50
	RAVLT				.052	.21	.83
	Stroop Colour-Word				.162	.71	.49

Predictor	Variables	R	R^2	R^2 Change	Beta	*t*	*p*
	Digit Symbol				-.067	-.25	.81
Everyday Problem Solving	Everyday Problems Test	.531	.282	.062	.510	1.47	.15
Emotional Functioning		.711	.505	.223			.04*
	Depression				-.331	-1.30	.21
	Anxiety				-.137	-.55	.59
	Emotional Wellbeing				.150	.59	.56
Fatigue	Fatigue Assessment Scale	.712	.506	.001	-.058	-.23	.82
Comments From Others	Comments from Others	.832	.693	.187	.695	3.49	.00*

RCFT = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; * indicates statistical significance.

Emotional Wellbeing and Subjective Reports of Cognitive Functioning

MANOVA assessed whether the three groups (colorectal cancer patients treated with chemotherapy, colorectal cancer patients treated with only surgery and healthy controls) significantly differed on the three emotional functioning variables (depression, anxiety, self-reported emotional well-being), or fatigue. No significant difference was found between the three groups across these four variables (Table 5). However as can be seen in Table 5, a near-significant difference was found between the groups for depression. Therefore an independent samples t-test was conducted, combining the chemotherapy and surgery groups in order to assess whether there was a difference in depression between the cancer patients and healthy control group. This revealed a significant difference in the depression scores of cancer patients versus healthy controls (t (64) = 2.25, p = .028), with cancer patients reporting more depressive symptoms than controls.

Table 5

Means, Standard Deviations and F Statistics for the Emotion Variables and Fatigue across the Three Groups

	Chemotherapy (n = 26)	**Surgery (n = 10)**	**Healthy Controls (n = 17)**	**F**	***p***
Depression	9.0 (5.4)	9.1 (5.6)	5.5 (4.0)	2.9	.07
Anxiety	7.4 (7.3)	4.2 (3.2)	5.7 (4.8)	1.1	.34
Emotional Wellbeing	18.8 (3.5)	18.7 (4.0)	20.4 (3.6)	0.7	.49
Fatigue	20.8 (6.4)	20.4 (5.8)	18.0 (5.4)	1.2	.33

Discussion

This study investigated the extent to which individual differences in self-reported cognitive functioning are explained by individual differences in non-cognitive variables and cognitive variables, including years of education and premorbid ability, objective cognitive test performance, everyday problem solving ability, emotional functioning, fatigue and patient-reported comments from others regarding one's cognition. Hypothesis 1, which states that better self-reported cognitive function is accompanied by more years of education and/or higher premorbid IQ is not supported. Better self-reported cognition is not accompanied by better objective cognitive test performance, providing no support for hypothesis 2. Hypotheses 4 to 6 that better self-reported cognitive function is accompanied by lower depression and anxiety and better emotional wellbeing respectively, were supported with these affective variables predicting a significant 22% of the variance in self-reported cognitive functioning. However, hypothesis 3 that better everyday problem solving ability and hypothesis 7 that better self-reported cognitive function is accompanied by lower fatigue were not supported. The final hypothesis, 8, was confirmed as better self-reported cognition is associated with more patient reports of favourable comments from others about their cognitive function.

The regression analysis found that emotional functioning, which included anxiety, depression and emotional wellbeing accounted for the highest percentage of the variance (22%) in self-reported cognitive function. This highlights the importance of health professionals assessing depression and emotional wellbeing in cancer patients because these may have ramifications for the way patients perceive their cognitive and physical functioning. It is, however, important to note that, as was the case here, most studies have evaluated the relationship between affective variables

and self-reported cognitive functioning concurrently. Under these circumstances it is impossible to establish causality. For example, it is possible that affective measures predict patient-reported cognitive impairment because patients who have received a diagnosis of depression are subsequently more likely to report a decline in their cognitive functioning. However, it is also possible that patients' perceptions of cognitive impairment result in negative affect. For example, patients who believe that they are experiencing deficits in their cognitive functioning may consequently experience greater feelings of depression or anxiety. The only way in which the direction of these relationships can be established is through the conduct of studies utilising a longitudinal design. Therefore future longitudinal research should be conducted that investigates the relationship between self-reported cognitive dysfunction and negative affect among cancer patient populations.

Self-reported comments from others were also a significant contributor to the variance in self-reported cognitive function, behind only emotional functioning. However, comments from others were not directly obtained from others, but were reported by patients as having been made. It is possible that patients' reports about comments made by others will have been subject to the same confounds as self-reports of cognitive impairment, for example emotional functioning, premorbid ability and education. A more reliable way to measure the perceptions of others in regards to the patients' cognitive functioning would be to ask others directly, thus reducing the impact of extraneous patient-specific variables.

In terms of the relationship between objectively and subjectively measured cognition, significant relationships were found only between self-reported cognitive functioning and objectively measured working memory and between verbal learning and memory. However, these were not supported by the regression. This is consistent

with a small amount of literature in this field; some authors have found relationships between cognitive evaluation and subjective assessment of cognitive functioning in cancer patients (Mehnert et al., 2007; Reid-Arndt, Hsieh & Perry, 2010). Consistent with the present study, Mehnert et al., and Reid-Arndt, Hsieh and Perry found significant moderate relationships between objective measures of memory and self-reported cognitive functioning. It is clear that in both the existing literature and this study, memory has been identified as the ability by which objective and subjective measures of cognitive function are most closely related. It is likely that memory is the domain of cognition most closely related to self-reported cognitive functioning because it is the cognitive function most heavily relied on by patients in their everyday lives. Therefore patients are more likely to notice deficits in memory because of the impact these have on their daily functioning and they subsequently report problems with their memory.

The finding of support for hypotheses 4-6 because lower depression and anxiety and higher emotional wellbeing were associated with better self-reported cognitive function, is consistent with some literature. However, the absence here of a relationship between fatigue and self-reported cognitive function (hypothesis 7) is in contrast with the literature. In the breast cancer literature, it has been well-established that subjectively measured cognitive function is negatively associated with fatigue, anxiety and depression (Biglia et al., 2012; Hermelink et al., 2010; Iconomou et al., 2004; Schagen et al., 2007) and positively associated with emotional wellbeing (Biglia et al., 2012 Reid-Arndt, Hsieh & Perry, 2010; Shilling & Jenkins, 2007; Schagen et al., 2008). In other words, those who experience higher levels of fatigue, anxiety and depression also tend to report problems in cognitive functioning. This is an important finding, particularly in the clinical context. It highlights the need for

medical practitioners to assess patients' emotional wellbeing and fatigue because of the significant impact these factors have, not only on psychological wellbeing, but also on perceived cognitive impairment and in turn, quality of life. With regards to quality of life, current results suggest that these factors are much more important than premorbid ability.

Two limitations should be considered. Most importantly, larger numbers of participants in the study would have been desirable. This however, proved to be difficult to achieve when recruiting from cancer patient populations. This is because patients were often too ill, too busy managing treatment, working full-time and managing family commitments, or had already been recruited into other research studies.

To conclude, this study explored the extent to which individual differences in self-reported cognitive functioning is explained by individual differences in cognitive and non-cognitive variables; education and premorbid ability, objective cognitive test performance, everyday problem solving ability, emotional wellbeing, fatigue and cognition-related comments from others. All with the exception of fatigue, which strongly co-varied with all self-reported cognitive measures, to some and varying extents, contributed independently to the prediction of perceived cognitive function. These findings emphasise the need for medical practitioners to assess patients in terms of these variables, particularly their emotional status, in order to be aware of declines in psychological wellbeing and subsequent reductions in quality of life. Future research should evaluate whether other factors, for example attitude and level of positivity, influence self-reports of cognitive functioning.

4.1 Chapter Summary and Future Directions

A primary study was conducted in order to evaluate the extent to which individual differences in self-reported cognitive function are explained by individual differences in cognitive and non-cognitive variables, in a sample of patients with colorectal cancer who had received treatment with chemotherapy and/or surgery, as well as healthy age- and education-matched control participants. Variance in self-reports of cognitive function was explained, in order of independent contribution, by emotional functioning including depression and emotional wellbeing, self-reported comments from others, premorbid ability, objective cognitive tests specifically including the Digit Span, Logical Memory and Stroop tests and everyday problem solving ability. Only objective measures of memory and no other cognitive domains, were found to be related to patient reports of cognitive functioning. On the basis of these results, it is evident that the emotional functioning of patients, in particular depression and emotional wellbeing should be evaluated by physicians on a regular basis when managing the health of cancer patients, because this may have implications for how patients perceive their cognitive functioning. However, further longitudinal research must be conducted in order to establish whether poor emotional functioning leads to more reports of cognitive impairment, or whether it is the case that cognitive impairment results in poorer emotional functioning. Self-reported comments from others are also important to patients' perceptions of their cognitive functioning. However, because the reported comments from others were as reported by the patients and not directly obtained from significant others, it is important that future research should ascertain that validity of these opinions.

It is worthwhile noting that many of the patients in this study who reported experiencing a decline in cognitive function subsequent to their cancer treatment, also

indicated informally that they believed the results from neuropsychological tests that confirmed normal cognitive functioning were not reliable. Self-reports reflect the lived experience of patients and it is important that any variables related to poorer perception and thus self-report of cognitive functioning in these patients be identified. Additionally, factors such as emotional wellbeing and the perceptions of those around the patient in relation to their cognitive functioning, were considerably more important in predicting patient perceptions of cognitive impairment than objective measures of cognition. However, some of the variance in self-reports of cognitive functioning remains unaccounted for. Therefore, in light of all of these results, it is important to assess the extent to which other patient-specific variables may impact upon patient perceptions of cognitive functioning.

The study that follows will investigate the effect of personality variables such as locus of control, optimism /pessimism and depression on survivors' recollections of cognitive functioning during chemotherapy or in the months immediately following surgical treatment for colorectal cancer. The sample consists of survivors of colorectal cancer and their spouses and cognitive functioning and depression were measured retrospectively.

CHAPTER FIVE

The Effect of Optimism and Locus of Control on Recall of Psychological Wellbeing and Cognitive Functioning during Treatment in Colorectal Cancer Survivors

5.0 Preface

The utility of objective cognitive tests in assessing CRCI was questioned in Chapter 4. That chapter reported results from a study that found that, with the exception of memory, objective measures of cognition may not detect cognitive impairments even though these have been reported by patients following treatment for cancer. Factors related to emotional functioning, which included depression, anxiety and emotional wellbeing, as well as patient-reported comments from others about their cognitive functioning, were all found to correlate with self-reported cognitive impairment and regression analysis found that, together, they accounted for 22% of the variance in self-reported cognitive functioning, although none alone made a statistically significant contribution. This is because these three emotional functioning variables were all strongly intercorrelated. Additionally, these three were all strongly correlated with fatigue and this explains why fatigue did not contribute to the overall regression model. In short, the interrelationships among all four variables were so strong that entering the emotional functioning variables first into the regression model meant that fatigue could contribute nothing further.

In light of these strong intercorrelations only depression, which correlated most strongly with self-reported cognitive functioning, was retained in the study that follows, the aim of which was to investigate further the effects of non-cognitive influences on perceived cognitive functioning, subsequent to receiving cancer treatment.

Variables related to emotional and psychological functioning, such as depression, anxiety and emotional well-being have been reported in the literature as explaining variance in perceived cognitive functioning. The study in chapter 4 supported this suggestion; however it is possible that other measures of disposition, particularly some aspects of personality, may impact on reports of cognitive impairment following colorectal cancer treatment. The study presented in Chapter 5 has examined the effect of locus of control, optimism/pessimism and depression on reports of cognitive functioning measured retrospectively, in survivors of colorectal cancer.

Previous results that have highlighted a disconnect between objective and subjective report of cognitive difficulties in cancer patients have suggested the need to establish the validity of self-report (Chapter 4). The current study will assess the validity of patient's reports of cognitive impairment by comparing patients' self-reports about their recollections of cognitive functioning following cancer treatment with their spouses' recollections of any cognitive impairments apparent in the patient following cancer treatment.

The account of the study that follows is presented in the form of a manuscript, prepared for submission for publication to the journal 'Psycho-Oncology'. The author contribution statements for this manuscript are presented in Appendix I.

Abstract

Research conducted with a range of patients with different types of cancers has found that patients who are more optimistic or less pessimistic, as well as patients who adopt an internal locus of control, tend to report better psychological and physical adjustment than patients who do not possess these characteristics. The extent to which this result generalises to perceived cognitive impairment following cancer treatment is unknown. This study aimed to assess whether optimism and locus of control influence the psychological wellbeing and cognitive functioning of colorectal cancer patients as determined by recall and verified by third party assessment.

Two groups were included in the sample for this study: survivors of colorectal cancer (n = 88) and their spouses (n = 40). Patients' spouses were included in the sample in order to corroborate and test the validity of the recall data provided by patients. Each participant completed a paper-based questionnaire that assessed participants' recall of their own (or their spouses') cognitive and psychological functioning when they received treatment for cancer, as well as their optimism and locus of control.

A significant negative relationship was found between depression and patients' recollection of cognitive dysfunction following treatment. There was a significant positive relationship between internal locus of control and patients' recollection of cognitive functioning. External locus of control and optimism were not significantly related to cognitive functioning. Spousal perceptions were significantly positively related to the self-reports provided by patients, confirming the validity subjective recollection.

Introduction

The perception that individual traits are important in an individual's ability to cope during treatment for and recovery from cancer is widespread among the general population and is beginning to emerge in the scientific literature. Thus, a recent meta-analysis has confirmed that depression is a significant predictor of cancer mortality although not of disease progression (Satin, Linden & Phillips, 2009). Consistent with this, some facets of personality, for example optimism and locus of control, have been shown to be a significant predictor of important life outcomes, including mortality in the general population, with the size of the effect comparable to that found for the well-established relationship between SES and cognitive ability (Roberts, Kuncel, Shiner, Caspi & Goldberg, 2007). Recent research has suggested that specific traits may be more beneficial in aiding the recovery process than others; for example having a more optimistic personality or, as will be discussed further below, an entirely internal or external locus of control (Colby & Shifren, 2013; Sucala & Szentagotai Tatar, 2010; Zenger, Brix, Borowski, Stolzenburg & Hinz, 2010).

However, it is important to note that, despite the plethora of research investigating the association between traits like optimism, locus of control, coping and recovery after a diagnosis of cancer, no research to date has examined the impact of these characteristics on perceived cognitive function among cancer patients. There is a body of research that has investigated the impact of individual characteristics on self-reported cognitive functioning among healthy samples; for example, in their study of 96 healthy participants, Seidenberg, Taylor and Haitiner (1994) found that negative affectivity was more strongly correlated with self-reported cognitive functioning than positive affectivity (R^2 = .11 vs. .05). These results therefore provide a possible direction that cancer research might explore.

It is important that this gap in the cancer literature is addressed, particularly in the cancer patient population because this could potentially provide improved insight into additional variables (beyond depression, emotional wellbeing and objective cognitive test scores), that account for some of the variance in subjective measures of cognitive function. Evaluation of the literature on individual characteristics, wellbeing and coping during cancer may be useful in providing a foundation for investigation into the association between self-reported cognitive function, optimism and locus of control, because it may be assumed that poorer subjective reports of cognition will accompany poorer wellbeing and poorer coping during cancer.

The impact of optimism on morbidity and mortality

Optimism is a term that endeavours to capture individual differences in resilience (Williams, Davis, Hancock & Phipps, 2010). Scales measure the extent to which a person looks at life's events with a positive attitude. Pessimism is the opposite (Williams, et al.). For example, a person with an optimistic personality will expect the best from life, including outcomes from cancer treatment, whereas pessimists may expect things to go wrong for them. Most researchers have argued that optimism and pessimism are polar ends of a stable unitary personality dimension (Zenger et al, 2010), although some personality researchers have argued that optimism and pessimism are two independent variables, so that an individual person may express some degree of optimism but also some degree of pessimism within their personality (Sucala & Szentagotai Tatar, 2010; Williams et al., 2010). However, defining optimism and pessimism as extremes in a single continuous variable has been the model most commonly accepted when developing tools for measurement within the literature (Zenger et al., 2010). For the purposes of this study, this has therefore been the model adopted as the basis for measurement.

A review by Chida and Steptoe (2008) of the relationship between positive psychological wellbeing and mortality has provided convincing evidence from observational, cohort studies that positive psychological wellbeing, measured at either the state or trait level, is associated with reduced mortality in both healthy and diseased populations, the latter including patients with renal failure and HIV infection. The data for cancer patients were less convincing, although Allison, Guichard, Fung and Gilain (2003) had previously demonstrated that dispositional optimism improved one-year survival statistics for head and neck cancer patients by an odds ratio of 1.12.

Optimism has been anecdotally associated with whether or not a person 'fights' or 'gives in to' the cancer and is widely believed by the general population to be associated with the probability of recovery (Sucala & Szentagotai Tatar, 2010). Specifically, it is thought that optimistic people believe that they will recover from the disease and this positive thought is associated with a higher likelihood of remission. Conversely, pessimistic people are thought to focus on the negative aspects of the disease, including the likelihood of not surviving and these beliefs are held to result in resignation to the cancer and earlier death (Sucala & Szentagotai Tatar, 2010). This widespread belief in the power of 'positive' and 'negative' thinking, particularly among cancer patients themselves and their families, has prompted research into whether optimism predicts quality of life and cancer recovery.

The majority of the work conducted in this area has focussed primarily on the extent to which the personality trait optimism protects against depression and anxiety and is associated with a better quality of life (Williams et al., 2010; Zenger et al., 2010). For example, in a study of urogenital cancer patients, significant negative relationships were found between optimism and patient reports of depression and

anxiety and significant positive correlations were observed between optimism and quality of life (Zenger et al., 2010).

An optimistic personality style has also been established as being beneficial in patients' physiological and psychological recovery from cancer. For example, in the same study of urogenital cancer patients, Zenger et al. (2010) found that patients who possessed a more optimistic personality appeared to display better psychological wellbeing and were more likely to survive than those patients who demonstrated a more pessimistic personality. Some authors have proposed that, whereas pessimists tend to accept the negative implications of a cancer diagnosis, optimism may provide a buffer against stress by being associated with the use of more effective coping strategies. This allows these patients to develop a clear plan of how they intend to recover from their cancer (Williams et al., 2010; Zenger et al., 2010).

Other studies however, have not found evidence that an optimistic personality style is beneficial during the cancer experience. Instead, the suggestion has been that a more pessimistic personality style is associated with higher levels of depression and anxiety (Colby & Shifren, 2013; Hulbert-Williams, Neal, Morrison, Hood & Wilkinson, 2012; Sucala & Szentagotai Tatar, 2010), because those who possess a pessimistic personality believe that they are incapable of altering their unpleasant mood and they tend therefore to experience more depression and anxiety as a consequence of this pattern of thought (Sucala & Szentagotai Tatar). In contrast, some research using a single measure of optimism/pessimism has revealed no relationship between an optimistic/pessimistic personality style and better quality of life in cancer patients. In a study by Mazanec, Daly, Douglas and Lipson (2010), optimism was found to be unrelated to health-related quality of life among a group of cancer patients with various diagnoses. These authors theorised that when people with an optimistic

personality style are confronted with a highly stressful situation, such as being faced with a diagnosis of cancer, their usual coping mechanisms may not assist them because of the extent to which they lose control of the situation.

To summarise, studies have found a positive association between optimism, better coping and wellbeing during cancer (Sucala & Szentagotai Tatar, 2010; Zenger et al., 2010). These studies may encourage the assumption that more optimistic patients would also be less likely to report cognitive impairment subsequent to cancer treatment because of their more positive perceptions of their physical and mental wellbeing. When considering the results of other studies in conjunction with self-reports of cognitive function, Zenger et al. proposed that those with a more pessimistic personality style would also be more likely to report impairments in cognition subsequent to cancer treatment, because of their more negative outlook on life and their doubts about their ability to cope. If we accept that optimism and pessimism are usefully conceptualised as the extreme poles of a single variable, Zenger et al.'s suggestion is also consistent with the positive relationship between optimism and better coping and wellbeing. Thus, more optimistic patients should report less cognitive dysfunction, while pessimistic patients should report higher levels of cognitive impairment. On the other hand, it is possible that no association exists between optimism and pessimism and subjective reports of cognitive function, as was the case between optimism and pessimism and health-related quality of life in a study by Mazanec, Daly, Douglas and Lipson (2010). The question therefore remains open.

Locus of Control

Locus of control refers to the tendency for an individual to attribute causation for personal and environmental outcomes to either external factors, such as luck, other

people or other outside influences, or to internal factors, like ability, willingness to prepare in advance, or the kinds of decisions one makes. People who consistently make internal attributions are committed to taking responsibility for their own actions and are said to have an internal locus of control. On the other hand, those who tend to believe that they have little control over the events of their lives will tend to attribute life events to outside circumstances and are said to have an external locus of control.

A considerable amount of research has been conducted on the impact of locus of control on psychological wellbeing, particularly when confronted with a stressful life event, such as a diagnosis of cancer. Marks, Richardson, Graham and Levine (1986) reported that, for patients with an internal locus of control and optimistic attitude towards their cancer experience, the relationship between the severity of the cancer and the development of depression was less pronounced than in patients with an external locus and more pessimistic views. Thus, it is possible that these two factors (internal locus of control and optimism) are interrelated. A direct relationship between external locus of control and depression among patients with cancer was noted by Marks et al. Similarly, Arraras, Wright, Jusue, Tejedor and Calvo (2002) found that, across their sample of chronic pain patients, both with and without cancer; patients with a more external locus of control tended to experience poorer mood than those patients with a more internal locus of control. Importantly, these authors proposed that the relationship between anxiety, depression and locus of control is cyclical, with mood disorders such as anxiety and depression perpetuating a more external locus of control. They also noted that an orientation toward an external locus of control may also exacerbate the occurrence of anxiety and depression.

However, other research has found results that contradict the theory that an internal locus of control necessarily results in more favourable mental health

outcomes. Thus, Newsom, Knapp and Schulz (1996) reported that patients with recurrent cancer, who were more oriented towards an internal locus of control, experienced significantly more depression than those who adopted an external locus. They suggested that this might be because patients with an internal locus of control would tend to believe that their cancer was something that could have been prevented and they would therefore perceive the cancer as their own fault. Newsom et al. speculated that this self-blame could occur regardless of the healthy behaviours adopted by the patient in order to prevent cancer prior to their diagnosis. According to this theory, once the disease had developed, regardless of the patient's attempts to prevent it, the patient may feel unable to deal with a cancer diagnosis in the context of their belief framework, leading to the development of depression.

To summarise the foregoing studies, results have been contradictory in terms of whether an internal or external locus of control is associated with better coping. However, Taylor, Lichtman & Wood (1984) have offered a different perspective, proposing that, depending on circumstances, either an internal or external locus of control can result in positive outcomes. In their study of breast cancer patients, Taylor et al. found that an internal locus of control (with respect to controlling one's illness) or an external locus of control (with respect to the role of health professionals like doctors in controlling one's illness) could be positively related to the overall adjustment of the patient. The important factor influencing the overall adjustment of these patients to the diagnosis of their disease was that someone, either themselves or their doctor, exercised control over their cancer. In other words, possessing either the perception of control over their cancer, or believing that their doctor had control over their cancer resulted in better adjustment among breast cancer patients.

In sum, the literature on the effect of locus of control on coping during cancer has suggested a range of theories about how the former may influence the latter. Some studies have suggested that an internal locus of control is correlated with deeper depression, although, this outcome was specifically reported for patients with recurrent diagnoses of cancer (Newsom, Knapp & Schulz, 1996). Others have found that either a highly internal locus of control or external locus of control can be beneficial to the psychological wellbeing of cancer patients (Taylor, Lichtman & Wood, 1984). However, a majority consensus has been that internal locus of control and optimistic attitude will minimise the likelihood of developing depression, even among patients with a severe cancer diagnosis, whereas an external locus of control will be related to poor mood in cancer patients (Arraras et al., 2002; Marks et al., 1986). These different outcomes suggest that, whether solely an internal locus, only an external locus, or a high level of either is of benefit to the psychological wellbeing of cancer patients is currently uncertain.

The perspective that has informed the hypotheses for the current study is that an internal locus of control and optimism is associated with lower depression, because this argument has been supported by the larger number of studies with more consistent results. Nonetheless, a reasonable conclusion is that, as a consequence of the variation in results between different studies, it is difficult to determine to what extent locus of control is related to subjective cognitive function.

Although the current literature provides some insight into the importance of individual traits in coping with and recovery from a stressful life event, there are important gaps that must be addressed. Firstly, the role of individual differences in coping during the colorectal cancer experience has not been studied. This is an important gap because colorectal cancer is a highly prevalent form of cancer and is

associated with ever-increasing rates of survival due to improved and more readily-available screening programs. In addition, colorectal cancer patients often face physical changes that are not relevant to all cancer patients, such as incontinence, or short-term or permanent use of an ostomy appliance, which involves having a bag attached to their lower abdomen through which they must defecate following colorectal surgery. This is important because these changes may impact upon patients' cognitive functioning by increasing depression and reducing quality of life. Secondly, as discussed above, the research that has been conducted investigating the impact of locus of control on coping in cancer patients has revealed diverse findings, with little consistency between studies. It is important that more research is conducted on this topic to allow for reliable conclusions to be drawn regarding the role of locus of control in coping during the cancer experience. Finally, no research has been conducted to date that investigates the role of optimism and locus of control in patients' perceptions of cognitive functioning. Clearly, however, it is important that the relationship between these variables and perceived cognitive functioning should be evaluated, because perceived cognitive ability/dysfunction is associated with coping during cancer. In addition, it is worth noting that the impact of individual characteristics on perceived cognitive functioning outside of the scope of chemotherapy-related cognitive impairment (CRCI) has not yet been examined. This has made it necessary when formulating hypotheses regarding the role of personality in self-reports of CRCI, to rely on the literature on general coping.

The aim of this study was to evaluate retrospectively whether locus of control, optimism/pessimism and depression are associated with the extent to which survivors of colorectal cancer report having suffered cognitive difficulties following their cancer treatment. The research was therefore to some extent exploratory and the

importance of this is twofold. Firstly, the study has permitted evaluation of whether locus of control and optimism/pessimism account for additional variance in subjective reports; and secondly, the intention was to seek insight into the factors associated with depression, which has been shown to influence self-reports of cognitive functioning (Chapter 4).

The current study assessed the effects of locus of control, optimism/pessimism and depression on recollections of cognitive functioning during treatment in colorectal cancer survivors, measured retrospectively. These reports were compared with spouses' recollections of their partners' psychological wellbeing and cognitive function during their cancer experience. The inclusion of spouses' reports was important because it has allowed for the potential corroboration and validation of the subjective data obtained from the cancer patients. The hypotheses were: (1) that the recollections of spouses about a patient's cognitive functioning following cancer treatment corroborate those patients' recollections about themselves; (2) that higher levels of pessimism are correlated with higher levels of depression; (3) that higher levels of pessimism are correlated with recollections of cognitive dysfunction; (4) that a high internal locus of control is correlated with lower levels of depression; and (5) that higher internal locus of control is correlated with more favourable recollections of cognitive function following cancer treatment.

Method

Procedure

Survivors of colorectal cancer treated with surgery, chemotherapy or radiation therapy alone, or a combination of these and when possible their partners, were recruited via newspaper, noticeboard and newsletter advertisements between January and March, 2013.

To be included in this study, colorectal cancer survivors were required to have been diagnosed and received treatment for colorectal cancer within the past 20 years. The only inclusion criterion required for partners of the colorectal cancer survivors was that they had been the main support in the cancer survivor's life during their cancer experience. Participants were excluded if they were not capable of speaking and writing in fluent English. Cancer survivors were excluded if they had been diagnosed with a type of cancer other than colorectal, if they had ever received a diagnosis of anxiety or depression, had a history of head injury, stroke, drug or alcohol abuse, or neurological or psychiatric condition. Ethics approval was obtained through the University of Adelaide Human Research Ethics Committee.

Potential participants responded to the advertisement by phone or email. Interested participants were screened for eligibility over the phone and, if eligible, were invited to schedule a time to participate in the study. Assessment took place at either the University of Adelaide, Flinders Medical Centre, or at the participant's home. Participants provided informed consent and were told that they were free to withdraw from the study at any time without consequence; however, no one withdrew.

The battery of questionnaires, which included items both to explore recollections of the past but also more current circumstances, took approximately 30 minutes to complete. Those cancer survivors who had received chemotherapy and/or radiotherapy were instructed to think back to the time during their cancer treatment and those who had surgery alone were told to think back to the two or three months following their surgery and answer those questionnaires that explored recollections about the past accordingly. Similarly, partners were instructed in the same way and asked to answer these questionnaires based on their recollections of their partner's

experiences. They were specifically instructed not to answer these questionnaires in terms of how they themselves were feeling at the time their partner was undergoing cancer treatment. With the exception of the Beck Depression Inventory, none of the assessment tools had been designed or intended for retrospective use. However, careful consideration of all content suggested no reason why they should not be used in this way.

Measures

Perceived Cognitive Function

The Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog) assessed recollected cognitive function, measured across four subscales: perceived cognitive impairment (e.g. I have had trouble forming thoughts), perceived cognitive ability (e.g. I have been able to concentrate), perceived comments from others about cognitive function (e.g. Other people have told me I seemed to have trouble remembering information) and quality of life (e.g. I have been upset about these [cognitive] problems). The Functional Assessment of Cancer Therapy – Colorectal (FACT-C) assessed recollected general wellbeing, also measured using four subscales: physical wellbeing (e.g. I have a lack of energy), emotional wellbeing (e.g. I feel sad), functional wellbeing (e.g. I am able to work, including work at home) and social wellbeing (e.g. I feel close to my friends). Both the FACT-Cog and FACT-C include 37 questions, with five response options ranging from 0 (never/not at all) to 4 (several times a day/very much). Possible scores range from 0 to 148. A higher score is indicative of better functioning across all eight subscales of these two measures. Both the FACT-Cog and FACT-C have demonstrated reliability; FACT-Cog has reported reliability of .96 (Lai et al., 2009) and FACT-C has internal

consistencies between .56 and .86 across its four subscales (Wood, Hahn, Mo, Hernandez, Tulsky & Cella, 1999).

The Beck Depression Inventory (BDI) is a 21-item scale well suited to retrospective measurement. For each item, respondents select the one statement from a group of four statements that most applied to them either within the two to three months following surgery, or during treatment with chemotherapy, which ever applied to them. A response of 0 indicates very little depression, while a response of 3 is indicative of significant depression. Scores on the BDI range from 0, indicating that the person is not experiencing depression, to 63, which indicates severe depression. A score of 0-9 indicates that the person is not at all depressed; 10-18 is indicative of mild to moderate depression; 19-29 indicates that the person is experiencing moderate to severe depression; while all scores of 30 or greater are indicative of severe depression. The BDI is a valid measure, with construct validity of .80 (Beck & Steer, 1984).

Optimism and Locus of Control

Two measures required participating cancer survivors to answer in terms of their present mindset; or, for partners, in terms of how they perceived their spouse's present mindset to be. The Life Orientation Test is a measure of optimism/pessimism and requires the participant to rate the extent to which they agree/disagree (0 = strongly disagree to 4 = strongly agree) with each of 10 statements (e.g. "In uncertain times, I usually expect the best"; "It's easy for me to relax"). The Life Orientation Test has good reliability (test-retest reliability = .72; internal consistency = .69) (Hirsch, Britton & Conner, 2010). A higher score on this scale is indicative of a more optimistic personality.

The Multidimensional Locus of Control Scale, which evaluates whether individuals attribute life circumstances to forces internal or external to themselves, also requires the participant to rate the extent to which they agree/disagree with each of 24 statements (+3 agree strongly to -3 disagree strongly). Examples of the questions asked by this scale include the following: "Whether or not I get to be a leader depends mostly on my ability"; "to a great extent my life is controlled by accidental happenings"; "I feel like what happens in my life is mostly determined by powerful people". This scale is comprised of three separate subscales: (1) the internal subscale which evaluates the extent to which the person has an internal locus of control. A high score indicates high internal locus of control; (2) the powerful others and (3) the chance subscale. Both (2) and (3) assess the extent to which the person has an external locus of control, with higher scores indicative of an external locus of control. The internal subscale has reported test-retest reliability of .60; the chance subscale test-retest reliability =.58 and the powerful others subscale test-retest reliability =.74 (Moshki, Ghofranipour, Hajizadeh, & Azadfallah, 2007).

Results

Participants were 128 adults; 88 survivors of colorectal cancer and 40 partners to survivors. The colorectal cancer survivors had a mean age of 65.92 years (SD = 9.70) and 47 were male (53.41%). The mean time since treatment was 3.54 years (SD = 3.19). Twenty five participants had received surgical treatment only, 10 had received treatment with chemotherapy alone, 24 with surgery in addition to chemotherapy, 3 with surgery and radiotherapy, 19 with surgery, chemotherapy and radiotherapy and 4 with chemotherapy and radiotherapy. Treatment data were unavailable for three participants. The mean age of partners was 65.95 years (SD = 9.14), with 11 male participants (27.5%).

A multivariate analysis of variance was conducted to assess the extent to which the means of the three groups on all of the self-report, psychological and personality measures were equivalent. This revealed no significant differences between the scores of the survivors with and without partners, or survivors' partners ($F(26, 212) = 1.28$, $p = .173$). Descriptive statistics for the three groups on each of the measures are presented in Table 1.

Correlations

All correlations between survivors (n = 40) and their partners (n = 40) for all variables are included as Appendix H. There was substantial agreement between both retrospective recollections and current impressions registered by survivors and their partners. Most importantly, PCI (perceived cognitive impairment) scores from the FACT-Cog of the survivors and of their partners were moderately correlated ($r = .348$, $p = .03$). Similarly, scores for PCA (perceived cognitive ability) and OTH (comments from others) from the FACT-Cog were correlated ($r = .391$, $p = .01$; $r = .408$, $p = .01$). Taken together, these results support hypothesis 1, that the recollections of spouses about survivors' cognitive functioning following cancer treatment corroborate those survivors' recollections about themselves.

Table 1

Retrospective Recollections of Cognitive and Psychological Function during Treatment and Current Personality Traits

	Survivors with Partners (n = 40)		**Partners of Survivors (n = 40)**		**Survivors without Partners (n = 48)**	
Test	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
FACT-Cog PCI	53.69	14.86	55.46	14.27	56.43	17.13
FACT-Cog QOL	10.65	5.06	9.95	4.98	10.31	5.72
FACT-Cog OTH	14.68	2.10	14.51	2.00	14.90	5.38
FACT-Cog PCA	20.32	5.39	19.38	7.66	19.47	7.29
FACT-C PWB	17.35	7.27	17.02	6.98	17.16	7.50
FACT-C SWB	23.18	3.53	22.99	4.70	22.04	4.98
FACT-C EWB	19.86	4.58	17.09	4.33	17.69	5.42
FACT-C FWB	20.92	6.22	20.01	5.85	17.44	6.37
BDI	10.57	6.59	10.97	5.98	11.71	8.63
LOT	16.03	3.92	15.00	4.53	16.31	5.06
LOC-I	35.38	7.43	36.87	8.31	35.51	7.56
LOC-P	17.43	10.12	15.90	8.78	17.18	9.61
LOC-C	19.54	10.89	18.28	9.41	17.42	10.26

Retrospective: FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive. PCI = Perceived Cognitive Impairment. QOL = Quality of Life. OTH = Comments from Others. PCA = Perceived Cognitive Ability. PWB = Personal Wellbeing. SWB = Social Wellbeing. EWB = Emotional Wellbeing. FWB = Functional Wellbeing.

BDI = Beck Depression Inventory. Current: LOT = Life Orientation Test. LOC-I = Locus of Control – Internal. LOC-P = Locus of Control – Powerful Others. LOC-C = Locus of Control – Chance.

Correlation analyses were conducted in order to evaluate the relationship between locus of control, optimism/pessimism, depression and the perceived cognitive functioning variables assessed by the FACT-Cog and FACT-C for all cancer survivors (n = 88) (see Appendix G for full correlation matrix). A number of significant relationships were identified between these variables and these are presented in Table 2. A significant positive correlation was found between pessimism and depression (r = .32). This provides support for the second hypothesis, that higher levels of pessimism are correlated with higher levels of depression.

Hypothesis 3, that higher levels of pessimism are correlated with self-reported recollections about cognitive dysfunction following cancer treatment, was also confirmed. This is evident in the significant positive correlations between the Life Orientation Test measuring optimism and the perceived cognitive abilities subscale on the FACT-Cog (Table 2). To summarise higher pessimism was associated with poorer perceived cognitive ability as recollected by survivors.

A significant negative correlation between internal locus of control and depression (r = -.271) provided support for the fourth hypothesis, that higher internal locus of control is correlated with lower levels of depression. No significant correlations were found between the external locus of control scales (powerful others and chance scales) and depression.

Significant weak to moderate positive correlations were also found between internal locus of control and the two cognitive functioning subscales of the FACT-Cog measure, specifically perceived cognitive impairment and perceived cognitive

ability (Table 2). These results therefore provide support for hypothesis 5, that higher internal locus of control is correlated with more favourable recollections of cognitive functioning.

Regression Analyses

A series of stepwise regression analyses were conducted in order to ascertain the percentage of variance in survivors' recollections of cognitive impairment (PCI) that was accounted for by internal locus of control, external locus of control, optimism/pessimism and depression. The first analysis entered depression at step 1 because this variable correlated most highly with PCI (r = -.634, Appendix G). Depression accounted for 40% of the variance and entering internal locus of control (step 2), external locus of control (step 3) and optimism/pessimism (step 4) did not significantly improve prediction of the outcome, with the final model accounting for 43% of the variance in PCI.

Although relatively less important than depression, internal locus of control (LOC-I) was the only other personality variable correlated with PCI (r = .273, p = .01). Rerunning the regression analyses with LOC-I entered at step 1, external locus of control at step 2, optimism/pessimism at step 3 and depression at step 4 confirmed that internal locus of control accounted for 7% of the variance in PCI, with little contribution from the other personality variables, but depression added 33% variance to the final model.

Finally, given strong intercorrelations between all eight FACT-Cog and FACT-C variables (see Appendix G), a composite 'wellbeing' outcome variable was created that captured how survivors recollected thinking about their overall cognitive and emotional functioning. Two regression analyses essentially confirmed the foregoing: entering depression ahead of internal locus of control accounted for 59% of

the variance in the composite outcome variable within a full model accounting for 60%; but entering internal locus of control first accounted for 10% of the variance in the composite outcome, with depression adding a further 50%.

Table 2

Significant Correlations between Optimism/Pessimism and Internal Locus of Control with the Cognitive and Psychological Measures

Personality Variable	**Tests**	***r***	***p***
Optimism/Pessimism (LOT)	FACT-Cog QOL	.223	.037
	FACT-Cog PCA	.274	.010
	FACT-C SWB	.457	.000
	FACT-C EWB	.374	.000
	FACT-C FWB	.343	.001
	BDI	-.322	.002
Internal Locus of Control	FACT-Cog PCI	.273	.012
	FACT-Cog QOL	.325	.003
	FACT-Cog PCA	.276	.011
	FACT-C SWB	.242	.027
	FACT-C FWB	.293	.007
	BDI	-.271	.013

LOT = Life Orientation Test. FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive. PCI = Perceived Cognitive Impairment. QOL = Quality of Life. PCA = Perceived Cognitive Ability. PWB = Personal Wellbeing. SWB = Social Wellbeing. EWB = Emotional Wellbeing. FWB = Functional Wellbeing. BDI = Beck Depression Inventory.

Discussion

This study investigated the effects of locus of control, optimism/pessimism and depression on retrospective recollections about their cognitive functioning and psychological wellbeing in colorectal cancer survivors. Hypothesis 1, that the recollections of spouses about a patient's cognitive functioning following cancer treatment corroborate those patients' recollections about themselves, was confirmed. This finding strengthens the possibility that subjective measures of CRCI may be more reliable and valid than has commonly been held to be the case. Due to the lack of agreement between objective and subjective reports, patients have sometimes been made to feel that their experiences of cognitive decline following treatment were not real. That spouses have corroborated the recollections of their partners does not establish the validity of CRCI. The moderate effect sizes of these correlations do not establish perfect agreement and it cannot be assumed that partners' recollections are independent. Nonetheless, the extent of agreement among partners is sufficient to warrant entertaining the possibility that subjectively reported aspects of CRCI are present, even in the absence of objective data to the contrary.

The second hypothesis, which stated that higher levels of pessimism are correlated with higher levels of depression, was confirmed. This finding is consistent with the literature which states that optimism is associated with lower levels of depression (Zenger et al., 2010). This is important because depression has often been established to be associated with poorer cognitive function, measured using both subjective and objective methods. Thus, those with a highly optimistic outlook may be less likely to experience cognitive impairment following a cancer diagnosis and treatment than a patient with a more pessimistic outlook experiencing more depression. However, because the scores on the Life Orientation Test were analysed

on a continuous rather than dichotomous scale, with high scores indicative of more optimism and lower scores greater pessimism, it was not possible to assess whether this relationship was due to the lack of optimism or the presence of pessimism.

The third hypothesis, that higher levels of pessimism are correlated with self-reported recollections about cognitive dysfunction following cancer treatment, was also supported. Although the impact of pessimism and/or optimism on self-reported cognitive functioning has not been addressed previously, this finding is consistent with the literature which has reported that a more pessimistic personality style is associated with poorer recovery, overall wellbeing and quality of life (Zenger et al., 2010). In general, it is likely that pessimism plays a role in patient reports of cognitive functioning. However, spouses agree with patients' reports, providing patients' reports with greater validity. It is possible however, that this may be because pessimistic patients complain to their spouses about cognitive impairment subsequent to cancer treatment, influencing the perceptions of their spouses.

Hypothesis 4, that higher internal locus of control is correlated with lower levels of depression was supported. This result is supportive of some studies that have found that those with an external locus of control tend to experience more depressed mood. However, it has been noted that it is unknown whether an external locus of control perpetuates feelings of depression, or whether a depressed mood leads to a more external locus of control (Arraras et al., 2002; Marks et al., 1986). Alternatively, this finding also contrasts with research that found that an internal locus of control is related to higher levels of depression in cancer patients, the proposed explanation being that these patients have perceived the occurrence of their disease as being their fault, whereas those with an external locus of control could attribute their disease to factors outside of themselves (Newsom, Knapp & Schulz, 1996). The results of the

present study are clearly in line with the argument by Arraras et al. and Marks et al. that an internal locus of control is associated with lower levels of depression and an external locus of control is associated with more depression, not the opposite perspective offered by Newsom, Knapp and Schulz.

Hypothesis 5 that higher internal locus of control is correlated with more favourable recollections of cognitive function following cancer treatment, was confirmed. However, regression analyses have clearly established that the experience of depression is by far the most important influence on how survivors feel about the status of their cognitive functioning, at least in terms of how they recollect such circumstances across a distance of up to 20 years. However, the series of regression analyses that explored this outcome does raise a possibility that depression acts as a moderator variable that influences the relationship between internal locus of control and the self-reported experience of some level of cognitive dysfunction following cancer treatment. Clearly, this suggestion requires a more thorough explanation than has been possible within the limits of this study. It is, however, an important consideration insofar as, in principle, the impact of depression on behaviour and cognition may be controllable by other means. If so, then if this is achieved, whether someone has an internal or external locus of control may prove relevant to how that person deals with CRCI. The relationship between locus of control and perceived cognitive impairment has not previously been directly examined in the literature and current results are consistent with previous research that has reported that breast cancer patients possessing an internal locus of control, in the sense that they had control over their illness, have better recovery and overall functioning (Taylor, Lichtman & Wood, 1984).

Limitations of the study

The present study had two main limitations. The first characterises all research that utilises self-report data, in that the data may be biased and unreliable because it is derived from the opinions and beliefs of the participant themself. Secondly, data were gathered retrospectively, in some cases with a delay of 20 years. The decision was made to collect the data in this way in order to maximise the sample size, which is very difficult when recruiting patients during or soon following their cancer treatment because of the physical burden of their illness and side effects of treatment may make participation in research challenging. Others may have many conflicting commitments that arise through managing everyday life and the treatment of and recovery from their disease. Therefore, cancer survivors were recruited, even though there may have been some costs associated with retrospective reports including, but not limited to, accurate recall of the events surrounding their cancer journey.

A strength of this study was the inclusion of spouses' perceptions of the colorectal cancer survivors' cognitive functioning, psychological wellbeing and personality. Although we were only successful in recruiting fewer than half of the spouses of colorectal cancer patients, as shown by the fact that the means did not significantly differ between the three groups and self-reported cognition corresponded well between the patients and their partners, it is unlikely that the smaller number of partners recruited had a significant impact upon the conclusions drawn from this study.

To conclude, this study investigated the effects of optimism/pessimism, locus of control and depression on cognitive functioning in survivors of colorectal cancer. Significant relationships were established between depression, internal locus of control and cognitive functioning. Although depression accounted for by far the most

variance in measures of cognitive functioning, there are grounds for anticipating that this may operate as a moderator, so that the relative importance of internal locus of control may increase with lower levels of depression. Results have also confirmed the implication for existing research that the discrepancy between objective and subjective measures of cognitive functioning, with the exception of tests of memory, may be an artefact of not adequately controlling for the effects of these traits on patients' perceptions of CRCI. However, spousal reports of patient cognitive functioning following treatment were significantly related to the patients' reports themselves and there is therefore a possibility that CRCI effects, not detected by objective tests, can endure. Future research should be conducted into the effects of individual characteristics on cognitive and psychological functioning in cancer patients. CRCI studies that include subjective reports of cognitive impairment should, in future, measure the extent to which participants adopt an internal locus of control, because this has had the most impact upon subjective reports beyond the impact of the presence of depression, compared to an external locus of control and optimism/pessimism.

CHAPTER SIX

Conclusions

6.1 Overview of Thesis

Through the conduct of four related studies, this thesis has examined the phenomenon that has been described as chemotherapy-related cognitive impairment (CRCI), both in the wider cancer patient population, as well as looking specifically at patients being treated for colorectal cancer and the individual characteristics that impact upon cognitive impairment within this sample of survivors. To reiterate, CRCI refers to the situation in which treatment with chemotherapy for cancer leads to a subsequent decline in the cognitive functioning of affected patients, evident in self-report data and/or the results of psychological testing (Collins et al., 2009). The first study in this thesis revealed, through a meta-analysis, that although CRCI has been well documented as occurring in breast cancer patients treated with chemotherapy, research is lacking in relation to other types of cancer and in particular colorectal cancer, lymphoma and leukaemia. As a result, the specific focus of the following studies was to evaluate the effect of chemotherapy on cognition, while also exploring a range of factors that may contribute to CRCI such as anxiety, depression, fatigue, optimism and locus of control. Finally, the importance of considering the discrepancy between objective measures of cognitive decline and subjective, self-reported assessment was discussed.

6.1.1 Meta-Analysis

The first study was a meta-analysis of the effect of chemotherapy on cognition in patients with cancer. This aimed to assess whether CRCI is consistently observed in patients with a wide range of different types of cancer and, if so, to identify the areas of cognition affected. For the purposes of the meta-analysis, the cognitive tests from

each of the included studies were allocated into the domains conceptualised by Lezak (2004). The decision to adopt Lezak's categorisation of specific cognitive tests into these domains was made for a number of reasons which are outlined as follows: 1. There is disagreement among researchers about the categorisation of cognitive tasks, so that some tests have been held to measure a range of different constructs while, at the same time, there has been considerable overlap in terms of with which cognitive constructs particular cognitive tests have been associated. However, Lezak has provided a text that has provided a comprehensive review of currently available neuropsychological tests that has been widely accepted by experts in this field as setting a standard for assessment and which is therefore used here. 2. Patients experiencing cognitive difficulties may seek advice or an assessment from a neuropsychologist. Therefore adopting a neuropsychological approach makes the results clinically relevant in terms of applicability to this population. 3. The neuropsychological approach provides the basis for the development and testing of a biological mechanistic argument for CRCI causation. 4. The majority of the studies in the meta-analysis explicitly or implicitly adopted a neuropsychological testing approach.

The meta-analysis revealed that cognitive impairment following cancer treatment was apparent in memory and executive functioning. According to Lezak, the term 'memory' refers to the ability of humans to store information and retrieve it subsequently, while 'executive functioning' refers to the capacity for humans to establish what they need, set goals, formulate and execute plans to achieve these. These definitions for these two constructs have been adopted throughout this thesis.

In addition to identifying two main domains susceptible to chemotherapy, the meta-analysis indicated that time since treatment cessation was weakly and

negatively, but not statistically significantly related to cognitive impairment. It is likely that this was the case because impairment was evident in only two of seven cognitive domains identified, meaning that for five domains there was no evidence of CRCI during treatment and this did not change with time after treatment completion. By contrast, however, the meta-analysis indicated that treatment duration was significantly negatively related to deficits in cognitive functioning. This finding may reflect an association between cognitive impairment and the cumulative dose of chemotherapy and is consistent with the intuition that more chemotherapy may result in more severe cognitive difficulties. However, this could not be tested due to a lack of dose-related data. Further research into the question of whether there is a reliable association between the duration of treatment by chemotherapy, the cumulative effects of dosage, ongoing and subsequent cognitive functioning is warranted and likely to be important for clinicians as well as researchers in order to establish which patients are at greatest risk of developing cognitive impairment subsequent to treatment.

Notably, as most of the CRCI literature has involved breast cancer patients, the results of this quantitative review were primarily representative of this patient group. It was concluded on the basis of the meta-analysis that the cognitive sequelae of cancer treatment may be limited to executive functioning and memory and that it is unclear whether treatment at different cancer sites is associated with impairment in different cognitive domains because, as noted previously, few studies have been conducted on cancer types other than breast. Therefore, on the basis of this review, it was clear that further research into CRCI in cancer types other than breast was required, most notably colorectal cancer, due to its high prevalence and high rates of survival in Australia. It was as a consequence of the identification of this gap in the

literature that the remaining studies in this thesis recruited patients with colorectal cancer, together with healthy controls, with whom they could be compared.

6.1.2 Primary Study of the Effect of Chemotherapy on Cognition in Patients with Colorectal Cancer

Following the meta-analysis, the second study was conducted to assess the effects of chemotherapy on cognition in patients treated for colorectal cancer (chapter 3). The aims of this study were to assess whether CRCI is experienced by colorectal cancer patients; to assess the impact of different treatment regimens on cognition; and to identify the specific domains of cognition affected. Four participant groups were recruited into this study: colorectal cancer patients who were receiving treatment with chemotherapy, in order to assess the extent to which CRCI exists in this population; colorectal cancer patients who were receiving treatment with chemotherapy together with the anti-angiogenic drug Avastin, to establish whether this new form of treatment that is being more commonly used for patients with colorectal cancer causes any cognitive sequelae; colorectal cancer patients who were being treated using surgical intervention only, to distinguish whether the cognitive impairment experienced by some cancer patients is actually post-operative cognitive dysfunction (POCD); and an age- and education-matched healthy control group to allow for control of individual differences in cognitive performance assumed present at the time when patients first entered treatment. This design assumes that the cognitive abilities of healthy controls will have remained unchanged during the time elapsed between when patients began treatment and when cognitive testing was carried out. Clearly, this is a questionable assumption, but it is the only option available under circumstances where, as was the situation here, it is not possible to obtain pre-treatment cognitive assessments. It was important to have included these four different groups in this study in order to

evaluate whether any cognitive impairment detected was likely to be due to the chemotherapy, the Avastin treatment, surgical intervention, or solely as a result of the cancer experience itself.

The battery of cognitive tests used in this study consisted of the Trail Making and Stroop Colour and Word tests, which assess executive function; the Controlled Oral Word Association Test, a test of verbal fluency; the Rey Auditory Verbal Learning Test and the Logical Memory test (a subtest from the Wechsler Memory Scale), which assess verbal learning and memory, respectively; the Rey Complex Figure Test, which measures visuospatial constructional ability, visuospatial recall memory and processing speed; the Inspection Time task which is also a measure of processing speed; and the Digit Symbol Test, which assesses attention, processing speed and visual scanning and memory. These tests were selected for use in this study on the basis of their validity for the sensitive assessment of the specific cognitive domains previously shown as responsive to cancer treatment. Additionally, it was specifically important to investigate memory and executive function because these cognitive domains were identified by the meta-analysis (chapter 2) as being impaired subsequent to treatment with chemotherapy in cancer patients. However, additional areas of cognitive functioning, already identified in studies other than those included in the meta-analysis as showing impairment subsequent to chemotherapeutic treatment, were also investigated. This was done following detailed consideration of those studies included in the meta-analysis which revealed several methodological issues, such as the inclusion of predominantly breast cancer patient samples that were in some cases inadequate in size and the failure to attempt to control for levels of cognitive functioning in patients prior to treatment.

The suitability of a number of these tests was confirmed when in 2011, after data collection for the study had commenced, the International Cognition and Cancer Task Force (ICCTF) published a set of guidelines regarding the ways in which CRCI research should be conducted (Wefel, Vardy & Schagen, 2011). These guidelines recommended the use of specific cognitive tests when conducting CRCI research, specifically the Hopkins Verbal Learning Test, Trail Making Test and Controlled Oral Word Association Test of the Multilingual Aphasia Battery. Trail Making had been included in the test battery and inspection of the Controlled Oral Word Association Test and the Rey Auditory Verbal Learning Test used here confirmed that these were very similar to the tests recommended, measuring the same cognitive domains as the tests recommended in the guidelines. The inclusion of the additional tests listed above was consistent with the recommendation from the ICCTF to test as broadly as possible, in order to identify the overall scope of dysfunction.

Neither the cross-sectional nor longitudinal data revealed significant group differences on total test scores. However, when these tests were broken down into subtest scores, a significant difference was found between the surgery and healthy control groups on the delayed recall component of the Logical Memory test, a subtest from the Wechsler Memory Scale. Due to the large number of comparisons undertaken in these analyses, this statistically significant result should be considered with caution because of the possibility that it represents a type II error. Notwithstanding this possibility, the potential clinical and personal significance of any adverse cognitive consequence arising from treatment requires a careful consideration of this result.

It is possible that this result reflected postoperative cognitive dysfunction (POCD). This is important because most cancer patients being treated with

chemotherapy have also undergone surgical treatment for their cancer and POCD, much like CRCI is with chemotherapy, may be a consequence of surgical intervention. Therefore, it is important to consider that any impairment observed in cancer patients may not arise solely from chemotherapy. The cause of POCD has been debated within the literature; it is thought to occur either due to the effects of general anaesthetics on the brain (Avidan & Evers, 2011, Chen et al., 2001), or as a consequence of the actions of the inflammatory system on brain functioning (Avidan & Evers, 2011, Cibelli et al., 2010). There is also debate surrounding the duration of POCD, with estimates ranging from a few days up to three months post-surgery (Avidan & Evers, 2011, Moller et al., 1998). These estimates of duration are consistent with some reports of CRCI, although much shorter than the longer estimates of CRCI sometimes reported. It has, however, been established that POCD is both more prevalent and more severe among the older population, that these individuals are more likely to suffer its effects for longer and have a reduced quality of life as a result (Avidan & Evers, 2011, Chen et al., 2001, Moller et al., 1998). POCD is relevant to the studies reported here because it is possible that CRCI could be confused with POCD in patient groups treated using surgical methods in combination with chemotherapy. This is the case particularly because colorectal cancer is predominantly diagnosed in patients aged over 50 years (Bowel Cancer Australia, 2010). Therefore, a surgery-only treatment for cancer group was included in the primary study in order to evaluate this possibility.

The results of the cross-sectional baseline assessment indicated that cognitive functioning varied with the number of years of education, premorbid ability and everyday problem solving ability of the participant, regardless of group allocation. Additionally, no significant differences between the four groups were apparent at the

12-month follow-up assessment, although extreme caution is required when interpreting the results from the longitudinal follow-up because of the difficulties encountered in maintaining the clinical samples beyond the initial cross-sectional stage. As a consequence, this aspect of the study was severely underpowered. Problems associated with the recruitment and maintenance of clinical samples will be addressed further in section 6.2.

Although it was recognised that little confidence could be placed in the reliability of the results of the longitudinal follow-up, the cross-sectional results did permit the conclusion that CRCI, as identified by objective, neuropsychological tests, does not appear to persist in patients treated by chemotherapy for colorectal cancer.

6.1.3 Colorectal Cancer Literature

As has been reviewed in chapter 1, there was little research which had investigated the effect of chemotherapy on cognition in colorectal cancer patients at the time when studies reported in this thesis were carried out. However, the results of a very recent study by Andreis et al., published in 2013, are considered here because of similarities between their study and the work presented in this thesis. Andreis et al., investigated whether CRCI exists in colorectal cancer patients treated with chemotherapy. This study had a sample of 57 stage III colorectal cancer patients aged between 34 and 76 years who received chemotherapeutic treatment. They were assessed with a battery of cognitive and affective tests including the Mini Mental State Examination, Clock Drawing Test, Rey Complex Figure Test, Trail Making Test, Rey Auditory Verbal Learning Test, Psychological Distress Inventory, State and Trait Anxiety Inventory and the Beck Depression / Geriatric Depression Inventories (according to participant age).

The test battery used by Andreis et al., (2013) was similar to that used here in study 2. Both studies recruited samples consisting of colorectal cancer patients receiving treatment with FolFOX chemotherapy. However, Andreis et al., included all patients with colorectal cancer regardless of age, whereas those in our study were aged over 50 because this is the usual age after which the onset of colorectal cancer most commonly occurs. It is unlikely that this is an important distinction between the two studies because most diagnoses of colorectal cancer occur in people aged over 50 years, therefore this age most likely made up the majority of the sample in Andreis et al.'s (2013) study and consequently, there are unlikely to be significant differences between the two studies on the basis of this minor difference in inclusion criteria. Andreis et al. did not include a control group in their study but they did include a pre-treatment baseline assessment. In contrast, our study included both cancer and non-cancer control groups in order to account for performance changes over time and, as an alternative to the inclusion of a pre-treatment assessment, relied on the Wechsler Test of Adult Reading (WTAR) as an estimate of pre-morbid ability. Andreis et al. were more successful in recruiting an adequate number of participants, likely because most of the authors on the paper were employees within the oncology department from which patients were recruited. It is worth noting, however, that recruitment of the 57 patients included in their study still required a timeframe of 2-3 years. Andreis et al. found no evidence of CRCI in patients with colorectal cancer following treatment with chemotherapy. This result is consistent with the conclusions drawn in the CRCI studies presented as part of this thesis and therefore provides support for them. Nonetheless, this conclusion was clearly at odds with the beliefs of the participants of the studies presented in this thesis. Moreover, our outcome was consistent with reports in the literature that complaints of cognitive dysfunction

persist among cancer patients during and after treatment, regardless of whether such dysfunction can be detected by objective assessment. It was therefore important to investigate further the extent to which a discrepancy may exist between patient perception and objective assessment of cognitive functioning in those receiving treatment for colorectal cancer. This issue provided the basis for the third study in the thesis.

6.1.4 Primary Study on the Relationship between Objectively-Measured and Self-Reported Cognitive Functioning

There is significant research evidence to suggest that, notwithstanding ambiguity in results examining objective measures of cognitive functioning following cancer treatment, subjective reports of difficulties in solving everyday problems are common place and much more prevalent than objective measures of these problems (Biglia et al., 2012; Iconomou et al., 2004; Jansen et al., 2011; Jansen et al., 2008; Prokasheva et al., 2011; Schagen et al., 1998). The discrepancy in the reported prevalence of objective and subjective problems warrants attention because of the distress and reduced quality of life that patients report experiencing as a result of cognitive impairment subsequent to cancer treatment.

A number of explanations for this discrepancy have been suggested. First, some have argued that cognitive tests do not accurately tap into the types of problems faced by patients with CRCI on a daily basis (e.g., Downie et al., 2006), whereas others have contended that objective cognitive tests may not be sensitive to the subtle cognitive impairments associated with CRCI (Prokasheva et al., 2011). An alternative explanation is that self-report of these difficulties simply reflects the depression, fatigue and anxiety that may accompany the experience of cancer and the associated treatment.

The aim of the third study (chapter 4) was therefore to assess the relationship between subjective reports of cognitive dysfunction, measured by the Functional Assessment of Cancer Therapy (FACT) Cognitive and Colorectal Cancer Scales and the objective assessment of cognitive functioning in patients with colorectal cancer, measured by the test battery described in 6.1.2. The results indicated that patient perception of cognitive functioning was positively related to performance on three cognitive tests: the Logical Memory, Digit Span and Stroop Colour and Word tests; all of which evaluate the cognitive domain of memory. However, when considered using regression analyses with the rest of the test battery, objective cognitive test performance, other than memory, did not significantly predict self-reported cognitive functioning. This result was consistent with the findings of the meta-analysis in Chapter 2, which also showed a relationship between objective tests of memory and patients' perceptions of cognitive function, but not with objective tests that measure other domains of cognition. These findings therefore suggest that the aspects of cognition that appear to drive patient concern are likely to be influenced by perceived difficulties in remembering.

The results of the third study confirmed a discrepancy between assessments of cognitive functioning as measured by objective neuropsychological tests and self-reports by patients with colorectal cancer about their perceived cognitive functioning, with the possible exception of memory. Moreover, depression, anxiety and emotional wellbeing were all found to be significantly correlated with perceived cognitive functioning in the anticipated direction; i.e. poorer psychological well-being was associated with poorer self-reported functioning even though the sequence of this relationship was not discernible in the objective cross-sectional data, i.e. it is not possible to distinguish whether poorer psychological wellbeing resulted in poorer self-

reported cognitive function, or vice versa. Of course, correlation does not establish causality and it is possible that depression and anxiety engendered by the diagnosis and treatment of cancer would lead to perceptions of poorer performance. However, it is also plausible that perceived cognitive difficulties, whether real or imagined, would result in poorer psychological wellbeing and a consequent decline in the quality of life of the patient.

In the second study, patients' perceived cognitive functioning was, with the exception of memory, independent of objectively measured cognitive functioning. However, it was associated with emotional wellbeing. This observation therefore raised the question of whether other patient-specific factors impact upon self-reports of cognitive function. Because other psychological factors such as depression were found to be important throughout this thesis, the investigation was extended to an evaluation of how other individual variables might be relevant to an improved understanding of self-reported cognitive functioning and why this was frequently at odds with objective neuropsychological assessment. The final study, investigating the effect of optimism/pessimism, locus of control and depression on perceived cognitive functioning in survivors of colorectal cancer, was informed by the literature reporting the relationship between personality and coping during cancer (Colby & Shifren, 2013; Sucala & Szentagotai Tatar, 2010; Zenger, et. al., 2010).

6.1.5 Optimism and Locus of Control Study

A study on the effects of locus of control, optimism/pessimism and depression on survivors recollections of cognitive functioning after cancer treatment was important in order to ascertain the extent to which the variance in self-reports of cognitive function is accounted for by patient-specific psychological variables. In an attempt to understand better the phenomenon that is CRCI, the final study sought to

establish which variables contribute to the variance in self-reported recollections of cognitive impairment. The aim of this study was to assess retrospectively in survivors of colorectal cancer whether locus of control, optimism/pessimism and depression influence the extent to which colorectal cancer patients recall problems with their cognitive functioning after cancer treatment. Optimism/pessimism and locus of control were selected for analysis in the final study (Chapter 5) because of the common belief amongst the lay public that these traits impact upon one's ability to survive a cancer diagnosis. In order to ensure recruitment of an adequate sample size and overcome the limited statistical power achieved in the previous studies, these data were collected retrospectively from survivors of colorectal cancer. It is important to clarify that the study was retrospective, i.e. participants were not receiving treatment for cancer at the time of the assessment, but rather were instructed to reflect back upon the time during which they had been receiving cancer treatment and to answer the questionnaires accordingly.

This study revealed significant relationships between pessimism, depression, and cognitive dysfunction; internal locus of control, depression and cognitive functioning, using retrospective recall. However, regression analyses revealed that after controlling for depression, internal locus of control and optimism/pessimism contributed very little to survivors' recollection of cognitive functioning following cancer treatment. The possibility was raised that depression may act as a moderator variable that influences the relationship between internal locus of control and subjective experience of cognitive impairment following cancer treatment. This was not the case for optimism/pessimism. These results therefore confirmed the importance of individual differences to the psychological and cognitive wellbeing of patients following diagnosis and treatment of cancer and suggest a line of enquiry that

might be explored further by physicians managing the post-operative care of cancer patients. In particular, the results of this study revealed that self-reports of CRCI can to some extent, reflect higher depression, but it is also possible that after treating the depression, this may reflect an internal locus of control. External locus of control and optimism/pessimism did not significantly contribute to the variance in subjective cognitive impairment. It is important that depression and internal locus of control are considered both when conducting CRCI research, as well as when developing strategies to prevent and alleviate CRCI in cancer patient populations.

However, despite the main aim of this study being to investigate the relationships between optimism/pessimism, locus of control, depression and perceived cognitive functioning, a result of much greater significance both to this thesis as well as to the CRCI literature was revealed. Within this study, the spouse of the cancer survivor was included in the control group to corroborate the self-reports of colorectal cancer survivors in relation to the survivors' personality, cognitive functioning and psychological wellbeing. This was done because it has been suggested by some that the discrepancy between subjective and objective measures is due to unreliable patient reports. Significant moderate positive correlations existed between the scores of the cancer survivors and their partners on the two measures of cognitive functioning. This finding has important implications for the field of subjective measurement, as well as for the utility of objective assessment in CRCI research. It offers validity to self-report measures often dismissed among quantitative researchers. More importantly, this result suggests that the use of objective cognitive tests to confirm the existence of CRCI may inadvertently result in the failure to detect subtle, real world difficulties that are reported by both survivors and their spouses. These findings indicate that it is important that future CRCI research includes subjective measures of cognitive

functioning, confirmed by third party report, as this appears to be, at least among colorectal cancer patients, an insightful method of assessing the experience of chemotherapy

6.1.6 Conclusions

Overall, this thesis has sought to examine the effects of chemotherapy on cognition. Results have indicated that treatment with chemotherapy did not result in objectively-measured cognitive impairment in these patients. However, objective cognitive test results and patients' self-reported perceptions of cognitive functioning were frequently at odds, with only Digit Span and the Stroop test supporting self-report of difficulty. Spousal reports of cognitive dysfunction in their partner subsequent to treatment corresponded to those provided by the cancer survivors themselves, validating the use of subjective measures in CRCI research. While recollections of depression were found to significantly contribute to survivors' recollections of cognitive impairment after cancer treatment and it was proposed to act as a potential moderator between internal locus of control and recollection about cognitive functioning following cancer treatment. These results have at least raised the possibility that objective cognitive tests should not be accepted as the only valid indicator of the presence of cognitive impairments.

6.2 Limitations and Difficulties Associated with this Research

The most significant limitation of the research, which clearly limits the confidence with which results can be interpreted, was the small numbers of participants recruited. As a consequence, studies 2 and 3 (see chapters 3 and 4) were severely underpowered to detect small differences. Difficulties with sample size reflected problems with recruitment that, in the context of the limited time frame of a doctoral program, were impossible to overcome. The first and most significant

limitation to achieving the sample size planned initially to ensure adequate statistical power of the second and third studies was that, despite forward planning involving advice from oncology staff, the predicted large numbers of potential recruits did not eventuate. The research was conducted by a single researcher, with two hospitals participating, but one of these proved to be able to provide many fewer than anticipated participant referrals (Chapters 3 & 4). Once the first study was underway it was not possible to expand the recruitment strategy, even though the problem had been identified. It is the case that most studies in this area of research have involved multiple hospitals or research centres that have collaborated in order to ensure that an adequate sample size can be achieved. However, it was impossible for this study to be conducted in this way because it was run by a single PhD candidate and had to be completed within the 3 to 4 years of candidature. Moreover, with only two hospitals involved, the population from which the sample was drawn was eventually found to be too small to generate the kinds of numbers required to conduct a reliable study of this kind.

It is important to note that at the commencement of the study participant recruitment appeared relatively favourable. Although it was always recognised that achieving large numbers would be a challenge, discussions with medical staff led to the conclusion that sufficient numbers could be recruited to meet power requirements. Nevertheless, after spending a great deal of time speaking to and attempting to recruit patients into the study it became clear that recruitment of the required number of patients would be extremely problematic and, after two and a half years, recruitment of additional participants ceased due to time constraints. Recruitment of participants took an unexpectedly long time because patients undergoing treatment for cancer are subject to such a demanding set of circumstances, in particular juggling their medical

appointments and usual family, household and employment responsibilities. Therefore, committing the time and energy to participating in research was something that some patients felt unable to do. Moreover, as became apparent subsequently, it was already the case that these hospitals were involved in other ongoing research activities, with many of those people approached were already committed to a number of medical research projects and therefore did not feel able to take on further commitments.

A second major obstacle to recruiting patients arose as a consequence of flagging the involvement from medical staff. Ethics approval required that all recruitment was managed by hospital staff and the researcher therefore had to rely on potential recruits, identified by nursing staff, contacting the researcher rather than the other way around. However, although the staff involved were initially encouraging at the outset of the study, with the passage of time their interest tended to wane and they became less likely to discuss the study with their patients and refer interested patients to the researcher. This is of course understandable; the medical staff involved had higher priorities than the promotion of the study when consulting with patients and despite best efforts, recruitment of patients therefore waned over time. A possible way to overcome this problem would be to involve hospital staff directly by integrating data collection into their daily duties. However, this would require employing and training nursing staff to administer the test battery to patients, something that could only be achieved by additional funding.

It is also the case that many of the patients approached had pressing reasons for being unable to participate. Several patients who initially indicated that they were interested in participating in the study subsequently felt that they were too busy to participate because they were managing cancer treatment while still engaged in

fulltime or part-time employment. Others had already agreed to participate in other unrelated research projects and did not have the additional time to commit to the current study. Others became too sick to continue participation, or died during the course of the research. While most deaths occurred between the initial and 12-month follow-up assessments, there was one instance in which the patient was contacted to participate, but died before the scheduled assessment. Of the 61 people (41 cancer patients) who participated in the initial assessment, only 15 participated in the follow-up assessment 12 months later. Participants were contacted via mail followed by a telephone call to inform them of the 12-month follow-up assessment and every effort was made to ensure direct contact between the researcher and the participant, or their family if they had passed away, to ensure the maximum number of people possible was recruited for the second assessment. Despite these efforts, 70% of the already underpowered sample was lost to follow-up.

Another challenge when conducting research in this area arises because of the heterogeneity of the groups being compared. Patients with colorectal cancer and probably most cancer types, are often subject to a range of different types of treatment and what is beneficial for one patient is not always so for the next. Therefore, when conducting research on CRCI, treatments are often grouped together on the basis of their overarching type, for example chemotherapy or surgery, as was done for the studies included in this thesis. This approach is problematic, however, because different types and dosages of chemotherapy may be associated with varying levels of toxicity, with some contributing to CRCI and others not. Additionally, it is likely that some surgical procedures to remove cancer may be longer in duration and more complicated than others, which also may lead to some surgical procedures but not others resulting in post-operative cognitive decline. This may be due to the patient

being anaesthetised for longer or having a longer and more complex recovery period. Clearly, it is desirable that information on the type and duration of surgery should be provided but this is rarely so for published studies. Moreover, it was not possible within the scope of this thesis because access to patient records was very limited. This limitation is particularly difficult to overcome, especially when considered in conjunction with the recruitment-related difficulties often faced when conducting research with patients with cancer. However, details regarding the type and length of surgery ideally should be recorded and controlled for in statistical analyses, so that results are not limited by these confounds. If hospital staff were aware of the importance of this issue from the outset, it may prove possible to avoid the sorts of problems encountered when recruiting participants for the research described here.

6.3 Future Research

Despite the difficulties associated with CRCI research, the need for further investigation into a number of important issues identified here is evident. Firstly, there is a need for CRCI research in areas of cancer other than breast, in particular involving patients with cancers such as leukaemia and lymphoma, because these cancer types have been to some extent neglected within the CRCI literature. It is important to establish the extent of CRCI across all common types of cancer. It is also important for future CRCI research to be conducted with patients with colorectal cancer, to allow for meta-analytic studies to be conducted and more reliable conclusions drawn. However, it is important to note that since conducting the study detailed in Chapter 3, a number of similar studies have also been conducted with colorectal cancer patients, the findings of which are discussed in Section 6.4, to follow.

Future research should also further investigate the effects of both everyday problem solving abilities, personality and individual difference variables such as optimism/pessimism and locus of control on the extent to which CRCI is experienced. The studies included within this thesis were among the first to investigate these issues using a sample of colorectal cancer patients. All future CRCI research should consider including subjective measures of cognitive functioning in their assessment batteries because of the greater capacity of these measures to evaluate survivors' reported experiences of CRCI.

Finally, it would also be useful for future CRCI studies to investigate the impact of patient expectations on reports of cognitive impairment following cancer treatment. This is important because some research has found expectations to contribute to patient reports of problems with concentration, although this only approached significance (Whitford & Olver, 2012). Therefore assessing the extent to which expectancies influence patient reports of CRCI, across a number of different domains would be of great use in the field of CRCI research.

6.4 Final Comments

Overall, the results reported here suggest that although CRCI is evident among some cancer patient populations, in particular breast cancer, the evidence for their existence with colorectal cancer is less convincing. The current thesis did not find neuropsychological test evidence of CRCI in patients treated with chemotherapy for colorectal cancer. However, inadequate statistical power and heterogeneity in treatment type may have contributed to this result. Thus the cognitive effects of treatment remain unclear in this group; although a recent study involving a much larger sample size of colorectal cancer patients confirmed the null result (Andreis, et al, 2013).

Notwithstanding the limited objective confirmation of CRCI, patients with colorectal cancer report deficits in their cognitive functioning following cancer treatment even though these are not detected by cognitive tests. It is certainly possible that this is because the objective cognitive tests currently available are not sufficiently sensitive to detect more subtle cognitive impairments associated with CRCI, even though they are successful at detecting the more substantial cognitive impairment often associated with brain damage. It is also possible that available objective tests may not adequately tap into functional areas that impact upon daily activities and are therefore commonly noticed by patients. Spousal reports confirmed survivor retrospective recall of CRCI, establishing the validity of these subjective data, whilst also confirming that subjective and objective cognitive tests may measure different aspects of cognitive functioning.

The studies reported here also confirmed that other variables appear to correlate with a negative treatment experience. These include poor psychological or emotional functioning, fewer years of education, poorer premorbid ability, poorer everyday problem solving ability and a more external locus of control. Future CRCI research should consider or control for influence from these variables, as well as investigate other patient-specific factors that may impact upon subjective reports of cognitive impairment. For example, it may be useful to investigate the contribution of other personality traits such as neuroticism or conscientiousness, to self-reported cognitive impairment among cancer patients. Overall, it is very important that future CRCI research assess perceived cognitive impairment amongst the patients in their samples because the positive perceptions of patients, particularly in relation to cognitive functioning, are vital for maintaining the best possible quality of life throughout the cancer journey.

Appendix A

Published manuscript for study 1 and author contribution statements

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Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Kristy Hodgson		
Contribution to the Paper	Ms Hodgson contributed substantially to defining the parameters of the review; conducted the literature search; selected the papers for inclusion and extracted the necessary information from them; ran the necessary statistical analyses, and wrote the manuscript.		
Signature		Date	24/7/13

Name of Co-Author	Dr Amanda Hutchinson		
Contribution to the Paper	Dr Hutchinson provided direction with conduct of the meta-analysis, assistance with the conduct of the statistical analyses and feedback on drafts of the manuscript.		
Signature		Date	22.7.13

Name of Co-Author	Prof Carlene Wilson		
Contribution to the Paper	Prof Wilson generated the initial research question, provided guidance throughout the research process, and provided feedback on drafts of the manuscript.		
Signature		Date	22.7.13

Name of Co-Author	Prof Ted Nettelbeck		
Contribution to the Paper	Prof Nettelbeck provided feedback on drafts of the manuscript.		
Signature		Date	22.7.13

Appendix B

Published manuscript for study 2 and author contribution statements

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The Effect of Chemotherapy on Cognition in Patients Treated for Colorectal Cancer

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Abstract

Chemotherapy-related cognitive impairment (CRCI) is commonly reported following the administration of chemotherapy to cancer patients, with most confirmatory results obtained from the cohort of breast cancer patients. The aims of the present study were to assess whether CRCI is consistently observed in people treated for colorectal cancer, to assess the impact of different treatment regimens, and to identify the domains of cognition affected.

This study comprised four sample groups, three of which had been diagnosed and treated for colorectal cancer; chemotherapy patients (n = 19), patients treated with chemotherapy and the anti-angiogenic drug Avastin™ (n = 12), and surgery only patients (n = 10). A fourth, comparably aged and educated healthy control group was also included (n = 20). Each participant undertook approximately 90 minutes of testing, comprising nine neuropsychological tests, including a measure of everyday problem solving and self-report measures of anxiety, fatigue, depression and cognition.

Multivariate analysis of variance revealed no significant differences between the groups across the neuropsychological test total scores. However, a significant difference was found when those tests comprised of subscales were broken down into their components; comparison between the surgery and healthy control groups found a difference on the delayed recall component of the logical memory test, with the surgery group having performed more poorly. Significant relationships were found between years of education, premorbid ability and everyday problem solving ability and cognitive functioning. The current study identified no significant increase in cognitive impairment related to chemotherapy and anti-angiogenic drugs used to treat colorectal cancer.

Keywords: Chemotherapy, cancer, cognitive impairment.

Introduction

Chemotherapy-related cognitive impairment (CRCI), known colloquially as chemobrain, involves a decrease in the cognitive processing capacity of an individual as a result of treatment with chemotherapy (Biglia, Bounous, Malabaila, Palmisano, Torta, D'Alonzo, Sismondi & Torta, 2012). It has been estimated to affect between 12 and 95% of all cancer patients (Downie, Mar Fan, Houede-Tchen, Yi & Tannock, 2006; Hede, 2008; Iconomou, Mega, Koutras, Iconomou & Kalofonos, 2004; Jansen, Cooper, Dodd & Miaskowski, 2011; Mehnert, Schwerath, Schirmer, Schleimer, Petersen, Schulz-Kindermann, Zander & Koch, 2007; Prokasheva, Faran, Cwikel & Geffen, 2011; Skaali, Fossa, Andersson, Cvancarova, Langberg, Lehne &

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Dahl, 2011). However, these estimates differ widely between studies and a general consensus has been that it affects approximately 30% of patients undergoing treatment with chemotherapeutic agents (Collins, Mackenzie, Stewart, Bielajew & Verma, 2009; Hermelink, Untch, Lux, Kreienberg, Beck, Bauerfeind & Munzel, 2007; Vardy & Dhillon, 2010).

A diverse range of cognitive domains has been thought to be possibly affected by CRCI; various forms of memory, attention and concentration, information processing speed, motor function, language, executive function and visuospatial skill (Iconomou et al., 2004; Jansen, Dodd, Miaskowski, Dowling & Cramer, 2008; Mehnert et al., 2007; Prokasheva et al., 2011; Reid-Arndt, Hsieh & Perry, 2010; Skaali et al., 2011). Although not all patients treated with chemotherapy for cancer will experience CRCI, those who do have generally reported a diminished capacity to engage in everyday tasks, with consequential reduction in quality of life (Boykoff, Moieni & Subramanian, 2009; Hede, 2008; Myers, 2009). Although such experiences can be relatively short-term, CRCI has been reported as lasting up to 10 years after treatment (Iconomou et al., 2004).

Whether significant CRCI results from chemotherapy and, if so, what mechanisms are involved is a highly debated topic within the literature. A number of mechanisms through which CRCI may arise have been proposed. For example, Jansen et al. (2008) and Myers (2009) hypothesised that CRCI occurs in response to the release of cytokines as a result of treatment. Dietrich, Han, Yang, Mayer-Proschel and Noble (2006) argued that CRCI occurs because chemotherapy is more harmful to brain cells than cancer cells and thus causes brain damage leading to cognitive impairment before the cancer cells have been eradicated. Others have also supported the notion that chemotherapy damages brain tissue, with Hampton (2008) and Meyers (2008) both claiming that CRCI occurs because of damage to the oligodendrocytes, which disrupts vital processes in the central nervous system. Other mechanisms proposed as causes of CRCI include hormonal and auto-immune responses (Meyers, 2008), damage to cerebral gray and white matter, microvasculature and DNA, and oxidative stress (Myers, 2009).

There are a number of variables that have been reported to influence the occurrence of CRCI in patients with cancer. Specifically, it is thought that CRCI is less likely to occur and, if it does occur is less severe, in those patients who have higher premorbid IQ or who have received a higher level of education (Jansen et al., 2011). Alternatively, a propensity towards greater anxiety, depression and fatigue, and chemotherapy-induced anaemia and menopause are thought to increase the likelihood and exacerbate the symptoms of CRCI (Jansen et al., 2011).

However, when conducting research into possible chemotherapy-related cognitive impairment, it is important to bear in mind that any impairment observed may not be due to the chemotherapy at all. CRCI research also overlaps with an area of research that investigates postoperative cognitive dysfunction (POCD). This is important because most cancer patients being treated with chemotherapy have also undergone surgical treatment for their cancer and POCD, much like CRCI, may involve a reduction in the cognitive abilities of a patient as a consequence of surgical intervention.

The cause of POCD has been debated within the literature; it is thought to occur either due to the effects of general anaesthetics on the brain (Avidan & Evers, 2011, Chen, Zhao, White, Li, Tang, Wender, Sloninsky, Naruse, Kariger, Webb & Norel, 2001), or as a consequence of the actions of the inflammatory system on brain functioning (Avidan & Evers, 2011, Cibelli, Fidalgo, Terrando, Ma, Monaco, Feldmann, Takata, Lever, Nanchahal, Fanselow & Maze, 2010). There is also debate surrounding the duration of POCD, with estimates ranging from a few days up to three months post-surgery (Avidan & Evers, 2011, Moller, Cluitmans, Rasmussen, Houx, Rasmussen, Canet, Rabbitt, Jolles, Larsen, Hanning, Langeron, Johnson, Lauven, Kristensen,

Biedler, van Beem, Fraidakis, Silverstein, Beneken & Gravenstein, 1998), durations consistent with some reports of CRCI although much shorter than the longer estimates sometimes claimed. It has, however, been established that POCD is both more prevalent and more severe among the older population and that these individuals are more likely to suffer its effects for longer and have a reduced quality of life as a result (Avidan & Evers, 2011, Chen et al., 2001, Moller et al., 1998). POCD is relevant to this study because it is possible that CRCI could be confused with POCD in patient groups treated using surgical methods in combination with chemotherapy. Therefore, a surgery-only treatment for cancer group was included in the present study, in order to evaluate this possibility.

It has been noted previously that objective neuropsychological tests may not be sufficiently sensitive to reflect the problems encountered in the everyday lives of patients and that, as a result, there is a discrepancy between the findings of objective testing and subjective impressions (self-report, others' opinions) in this area (Downie et al., 2006). Consequently, Hutchinson, Hosking, Kichenadasse, Mattiske and Wilson (2012) have called for the inclusion of a test that assesses everyday problem solving when evaluating the utility of neuropsychological assessment for measuring CRCI. In order to build upon the findings of existing studies, the present study will address this concern by including the Everyday Problems Test (EPT) – a measure of problem solving abilities in situations regularly encountered in everyday lives.

Colorectal cancer, also commonly known as bowel cancer, is a highly prevalent form of cancer in Australia; second only to breast cancer in women and prostate cancer in men (Bowel Cancer Australia, 2010; Cancer Council Australia, 2009). Specifically, by the age of 85 years, one in 10 Australian men and one in 15 Australian women will have been diagnosed with colorectal cancer. Due to improved and widely romoted screening techniques, the rates of survival associated with this form of cancer are ever increasing but survival rates decrease with increasing severity. To be precise, when diagnosed with early stage colorectal cancer, which requires only surgical treatment, one is currently expected to have an 87-90% chance of survival. Those with stage 3 of the disease, which usually involves both surgery and treatment with chemotherapy, are expected to have approximately a 57% chance of survival. Widespread stage 4 colorectal cancer, which can only be treated using chemotherapy, is associated with around a 10% chance of survival (Cancer Council Australia, 2009). Therefore, as a result of the high incidence of colorectal cancer in Australia in conjunction with the improving rates of survival if detected early, it is critically important to investigate the effects of treatment with chemotherapy on cognition in patients who have been diagnosed with this disease.

This study has aimed to test whether treatment with chemotherapy leads to cognitive impairment in patients with colorectal cancer. This is important because, despite its high prevalence, the effect of treatment on the cognitive functioning of patients with colorectal cancer is yet to be evaluated despite the extensive literature predominantly investigating this phenomenon in breast cancer. Specifically, we assessed the effect of treatment with chemotherapy on cognition in patients with colorectal cancer and compared these effects with those of other treatments for this type of cancer including surgical treatment alone and treatment with anti-angiogenic drugs. The hypotheses tested were: (1a) that treatment with chemotherapy or chemotherapy and the anti-vascular drug leads to impairment across a number of cognitive tests for attention, memory and processing speed by comparison to matched controls, and (1b) that cognitive impairment will also be evident in the surgery-only control group by comparison to matched controls as a result of POCD.

In addition, consistent with the literature, it was hypothesised that (2) those with greater levels of depression, anxiety and fatigue will exhibit worse cognitive function; (3) those with a higher level of education and/or higher premorbid ability will display higher cognitive functioning; and, (4) participants with higher scores on the Everyday Problems Test will have better cognitive functioning. It should be noted that impairment was measured as the average performance of each of the three treatment groups relative to that of a healthy, age- and education-matched control group.

Method

Patients with a diagnosis of colorectal cancer, treated with either surgery alone, chemotherapy with surgery and without surgery, or chemotherapy with the anti-angiogenic drug Avastin (bevacizumab) with and without surgery between October 2009 and April 2012 were recruited through the oncology departments at Flinders Medical Centre and the Royal Adelaide Hospital. To be included in the present study, patients were required to be aged over 50 years, have received a minimum of three months of chemotherapy, with or without Avastin, and in the case where treatment had already been completed, be no more than one month post-treatment. Surgery patients were also required to be no more than one month post treatment. Patients were excluded if they had been treated with chemotherapy for any other instances of cancer, had a current diagnosis of anxiety or depression, or had a history of head injury, stroke, drug or alcohol abuse, or of a neurological or psychiatric condition. Healthy control participants were recruited through word-of-mouth at the two hospitals or were contacted from among people who had participated in previous unrelated research, run through the University of Adelaide. Healthy control participants, without the diagnosis/ treatment for colorectal cancer, were also required to conform to the same inclusion and exclusion criteria as the patient groups. Ethics approval was obtained through the University of Adelaide, Flinders Medical Centre and Royal Adelaide Hospital Human Research Ethics Committees.

Eligible patients were first introduced to the study by their oncologist and provided with an information sheet. If interested in participating, their details were passed to the first author. They were contacted by phone to schedule a time to participate. The testing session took place either in the hospital at which the participant was receiving treatment, at their home, or at the University of Adelaide. At the testing session, participants were again provided with the information sheet, a consent form and instructed to read these and if willing to participate, provide consent. Participants were informed that they were free to withdraw from the study at any time without consequence. No one withdrew.

Testing began with the Everyday Problems Test (EPT), which was a 21-item multiple choice measure that assessed the extent to which a person can solve problems most likely encountered on a regular basis in their everyday lives, such as following recipes and filling out forms. Participants had a maximum of 20 minutes to complete this assessment. The EPT is both a reliable and valid measure with high test-retest reliability (0.83 - 0.91) and construct validity (0.42 - 0.72) (Willis & Marsiske, 1993). Participants subsequently completed a number of scales assessing depression, anxiety and fatigue; the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Fatigue Assessment Scale. In addition, participants completed the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) and Functional Assessment of Cancer Therapy-Colorectal (FACT-C) subscales assessing self-reported cognitive functioning and quality of life subsequent to a diagnosis of cancer. The results of these self-report measures are not discussed here.

Following these questionnaires neuropsychological assessment involved the Trail Making Test (TMT), followed by the Controlled Oral Word Association Test (COWAT), Rey Auditory Verbal Learning Test (RAVLT), Digit Span test, Rey Complex

Figure Test (RCFT), the Logical Memory test from the Wechsler Memory Scale III and the Inspection Time task (IT). Finally, the Wechsler Test of Adult Reading (WTAR) assessed premorbid intelligence, i.e. the predicted level of intelligence of the participants before they became ill based on their ability to pronounce words, some unknown to them, which is not affected by illness or treatment; followed by the Stroop test and Digit Symbol from the Wechsler Adult Intelligence Scale III. Table 1 describes the neuropsychological abilities evaluated by these tests as determined by their respective publishers; indicated in the manuals.

Table 1. Cognitive Abilities Assessed by the Nine Neuropsychological Tests

Neuropsychological Test	Cognitive Ability
Trail Making Test	Executive Function
COWAT	Verbal Fluency
RAVLT	Verbal Learning and Memory
Digit Span	Working Memory
RCFT	Visuospatial Constructional Ability, Visuospatial Recall Memory and Processing Speed
Logical Memory	Verbal Learning and Memory
Inspection Time	Processing Speed
Stroop Colour and Word Test	Executive Function
Digit Symbol	Attention, Processing Speed and Visual Scanning and Memory

COWAT = Controlled Oral Word Association Test, RAVLT = Rey Auditory Verbal Learning Test, RCFT = Rey Complex Figure Test.

All neuropsychological tests were administered and scored according to the instructions outlined in their respective manuals. Each measure has been shown to be reliable and valid; the COWAT has a test-retest reliability of 0.70, while the RAVLT has an internal consistency of 0.70 for list A (Snow, Tierney, Zorzitto, Fisher & Reid, 1988). Digit span and logical memory have demonstrated test-retest reliabilities of 0.84-0.93 and 0.74-0.91, respectively, depending on age group (Tulsky, Zhu & Ledbetter, 1997). The Stroop test was shown to have a test-retest reliability of 0.73 for the colour-word component (Jensen, 1965), while that for Digit Symbol was 0.84-0.87, depending on the age group of participants (Tulsky, Zhu & Ledbetter, 1997). The RCFT had a test-retest reliability of 0.76 for the copy component and 0.89 for the recall component (Meyers & Meyers, 1995), while test-retest reliability for the Inspection Time task is usually 0.80 and higher (Grudnik & Kranzler, 2001). Each of these tests correlated well with other tests measuring the same construct. No reliability or validity data were available for the Trail Making Test. The results of this study were analysed using the Statistical Package for the Social Sciences (SPSS) version 18.

Results

Comparison between Treatment Groups

Sixty-one patients were recruited to participate in this study (30 male). Of these, 19 were treated with chemotherapy, an additional 12 with Avastin (bevacizumab), 10 received only surgical intervention and 20 were age- and education-matched healthy controls. The decision was made to include 20 healthy controls based on the fact that the largest cancer treatment group consisted of only 19 patients and having relatively equal numbers in the chemotherapy and control groups was a goal of this research. The chemotherapy group comprised 17 patients who had been treated with surgery and chemotherapy and two participants who were treated using only chemotherapy. Of the Avastin group, seven were treated using surgery, chemotherapy and Avastin, while the other five were treated with chemotherapy and Avastin. As described above, participants in both the chemotherapy and Avastin

treatment groups received chemotherapy. More specifically, nine participants were treated with oxaliplatin, calcium folinate and 5-flourouracil, eight using capecitabine (xeloda), six with calcium folinate and 5-flourouracil, and one with capecitabine, calcium folinate, oxaliplatin and 5-flourouracil, capecitabine, 5-flourouracil and calcium folinate, and capecitabine and oxaliplatin, respectively. Group-specific descriptive statistics for age, level of education and premorbid ability are presented in Table 2. Univariate analyses of variance revealed no significant differences between the four groups in age, years of education and premorbid ability.

Table 2. Means and Standard Deviations for Age, Level of Education and Premorbid Ability

Treatment Group	n	Age (years)	Years of Education	Premorbid Ability
Chemotherapy	19	66.95 (8.09)	11.44 (3.07)	40.16 (6.83)
Avastin	12	69.17 (7.35)	11.00 (3.02)	39.18 (5.95)
Surgery	10	69.20 (9.00)	10.80 (4.37)	37.30 (5.40)
Healthy Control	20	71.65 (6.39)	10.17 (2.87)	40.70 (6.05)

To investigate whether there was a difference between the four groups in terms of their cognitive performance a MANOVA was conducted using the subscale scores from each neuropsychological test. This analysis revealed a significant difference between the four groups in cognitive functioning ($F(45, 81) = 1.12$, $p < 0.01$). Post hoc testing showed that this difference was between the surgery and healthy control groups in the second recall component of the Logical Memory test. As can be seen in Table 3, the surgery group performed more poorly on this task than the healthy control group. The groups did not significantly differ in their performance on any of the other subtests. Descriptive statistics for these MANOVAs are displayed in Table 3. These results do not provide support for the first hypothesis that treatment (surgery or chemotherapy) for colorectal cancer would lead to cognitive impairment. Due to the large number of comparisons across the four groups for the neuropsychological tests, it is likely that the one significant result occurred because of a Type II error rather than an actual effect.

In order to further evaluate whether treatment with chemotherapy leads to cognitive impairment, the chemotherapy and Avastin groups were combined to form one larger chemotherapy treatment group (n = 31). A MANOVA was conducted to establish whether or not there were any differences between this group, the surgery group (n = 10) and healthy controls (n = 20) in performance on the neuropsychological tests. This revealed no difference for the total neuropsychological test scores ($F(20, 58) = 1.12$, $p = 0.36$) or for the subtest scores ($F(30, 56) = 1.26$, $p = 0.22$). These results also fail to provide partial support for the first hypothesis. See Table 3 for descriptives.

Table 3. Descriptive Statistics for Performance on Neuropsychological Tests of the Chemotherapy, Avastin, Surgery, Healthy Control and Chemotherapy and Avastin Combined Groups

	Means (SDs)				
Test	**Chemotherapy**	**Avastin**	**Surgery**	**Healthy Control**	**C&A Combined**
COWAT	38.27 (11.13)	37.71 (12.45)	32.71 (11.22)	42.38 (13.71)	38.06 (11.30)
Trails Part A*	49.23 (28.00)	48.26 (20.09)	53.57 (30.81)	40.58 (11.95)	48.87 (24.95)
Trails Part B*	116.44 (76.33)	103.26 (26.95)	129.75 (69.01)	117.17 (35.71)	111.56 (62.28)
Digit Span F	9.59 (2.58)	10.40 (1.58)	10.56 (2.19)	9.67 (2.55)	9.89 (2.26)
Digit Span B	7.65 (2.60)	7.50 (1.27)	7.33 (2.24)	8.22 (2.28)	7.59 (2.17)
RCFT copy	32.23 (3.18)	32.29 (3.86)	30.50 (3.62)	32.84 (3.91)	32.25 (3.35)
RCFT recall	14.64 (7.65)	12.57 (5.89)	7.21 (6.54)	14.44 (8.17)	13.83 (6.91)
Inspection Time*	73.27 (34.20)	71.43 (16.15)	85.71 (41.88)	77.75 (27.67)	72.56 (27.95)
LM1 Recall	26.18 (10.39)	27.10 (8.08)	22.00 (5.83)	32.89 (14.71)	26.52 (9.44)
LM1 Thematic	14.35 (5.29)	14.50 (3.69)	11.33 (3.46)	15.56 (3.36)	14.41 (4.68)
LM2 Recall	15.59 (6.80)	15.30 (7.54)	10.00 (5.15)	19.22 (10.04)	15.48 (6.94)
LM2 Thematic	8.88 (3.81)	9.30 (2.98)	7.33 (2.74)	10.44 (2.79)	9.04 (3.47)
LM1 Learning Slope	4.71 (2.17)	4.40 (2.01)	5.33 (2.55)	6.00 (3.04)	4.59 (2.08)
RAVLT Immediate	39.94 (12.35)	38.30 (9.91)	35.00 (7.83)	43.78 (11.97)	39.33 (11.33)
RAVLT Delayed	14.24 (8.96)	15.30 (5.72)	10.89 (6.49)	18.00 (6.58)	14.63 (7.81)
RAVLT Recognition	11.59 (2.74)	12.50 (1.84)	10.89 (3.33)	13.11 (1.62)	11.93 (2.45)
RAVLT Distractors*	2.88 (2.78)	3.60 (3.72)	2.78 (1.86)	4.44 (4.13)	3.15 (3.12)
Stroop	29.73 (10.31)	29.57 (8.36)	42.43 (17.22)	32.19 (10.12)	29.67 (9.34)
Digit Symbol	54.18 (14.34)	52.29 (7.39)	51.86 (18.72)	55.13 (14.47)	53.44 (11.73)

*For the Trail Making Test, Inspection Time and RAVLT Distractors, a lower score indicates better performance.

Emotional Functioning

Correlation analyses evaluated relationships between depression, anxiety, fatigue and cognitive functioning. Depression and fatigue were not significantly related to performance on any of the neuropsychological tests, and anxiety was related only to performance on the Trail Making Test (r = 0.25, p = 0.05); higher self reported fatigue was associated with poorer Trail Making performance. Taken together, these results fail to support the hypothesis (2) that depression, anxiety and fatigue would be related to poorer cognitive functioning. Additionally, further correlations were conducted to examine the relationship between depression, anxiety and fatigue and performance on the neuropsychological tests for each of the five groups. Table 4 displays these correlations; most of which are in the opposite direction to what was predicted by the second hypothesis. Fatigue was related to cognitive performance in the chemotherapy group however, this was only on a single subscale of two respective tests; anxiety was correlated with neuropsychological test performance for the Trail Making and Inspection Time tasks in the Avastin treatment group, while part A of the Trail Making Test was related to anxiety in the chemotherapy and Avastin combined group (Table 4).

Correlations were undertaken to assess whether years of education or premorbid intelligence were associated with cognitive function; significant positive correlations were found between both years of education and premorbid ability and a number of neuropsychological tests, as set out in Table 5. Hypothesis 3, that more education and premorbid ability will be related to better cognitive functioning, is therefore supported.

The Everyday Problems Test (EPT) was correlated with the different neuropsychological test scores to assess whether functioning in everyday life situations was related to neuropsychological test performance. Statistically significant correlations were revealed between the EPT and each of the neuropsychological tests, with the exception of the Stroop Colour and Word Test (see Table 6). This confirms hypothesis 4, that everyday problem solving ability and cognitive functioning are related.

Table 4. Relationships between Depression, Anxiety and Fatigue and Neuropsychological Test Performance across the Five Groups

Group	Emotional Function Variable	Neuropsychological Test	*r*	*p*
Chemotherapy	Fatigue Assessment Scale	Digit Span Forwards	-.57	.02
		Logical Memory 1 Thematic	-.54	.03
Avastin	Beck Depression Inventory	RAVLT Immediate Recall	.76	.02
		RAVLT Recognition	.74	.04
	Beck Anxiety Inventory	Trail Making Test Part A*	.92	.00
		Trail Making Test Part B*	.92	.00
		Inspection Time*	.81	.03
		RAVLT Immediate Recall	.81	.01
Surgery	Beck Depression Inventory	Inspection Time*	-.76	.03
		Logical Memory 2 Recall	.67	.05
		Logical Memory 2 Thematic	.67	.05
		RAVLT Immediate Recall	.81	.01
	Beck Anxiety Inventory	Controlled Oral Word Association Test	.75	.03
	Fatigue Assessment Scale	Inspection Time*	-.80	.02
C&A	Beck Anxiety Inventory	Trail Making Test Part A*	.55	.01
	Fatigue Assessment Scale	Logical Memory 1 Thematic	-.48	.03
Healthy Control	Beck Anxiety Inventory	RAVLT Distractors	.54	.03
	Fatigue Assessment Scale	RAVLT Distractors	.68	.00

Table only contains significant results. *lower scores indicate superior performance. C&A = Chemotherapy + Avastin combined to form one drug treatment group.

Table 5. Significant Correlations between Years of Education and Premorbid Ability and the Neuropsychological Tests

Variable	Test	*r*	*p*
Years of Education	COWAT	.35	.01
	RCFT Recall	.32	.02
	Logical Memory 1 Recall	.34	.02
	Logical Memory 1 Thematic	.43	.00
	Logical Memory 2 Recall	.32	.02
	Logical Memory 2 Thematic	.38	.01
	Digit Symbol	.30	.04
Premorbid Ability	COWAT	.47	.00
	Digit Span Backwards	.40	.00
	RCFT copy	.27	.04
	RCFT recall	.36	.01
	Logical Memory 1 Recall	.32	.02
	Logical Memory 1 Thematic	.40	.00
	Logical Memory 2 Recall	.30	.03
	Logical Memory 2 Thematic	.42	.00
	RAVLT Immediate Recall	.37	.01
	RAVLT Delayed Recall	.36	.01
	Stroop	.21	.10
	Digit Symbol	.30	.04

Table 6. Significant Correlations between the EPT and Neuropsychological Tests

	Test	*r*	*p*
EPT	COWAT	.35	.02
	TMT Part A*	-.48	.00
	TMT Part B*	-.45	.00
	Digit Span Forwards	.53	.00
	Digit Span Backwards	.63	.00
	RCFT copy	.38	.01
	RCFT recall	.56	.00
	Inspection Time*	-.37	.02
	Logical Memory 1 Recall	.54	.00
	Logical Memory 1 Thematic	.45	.00
	Logical Memory 2 Recall	.48	.00
	Logical Memory 2 Thematic	.35	.02
	RAVLT Immediate Recall	.60	.00
	RAVLT Delayed Recall	.60	.00
	RAVLT Recognition	.38	.01
	RAVLT Distractors*	-.43	.00
	Digit Symbol	.71	.00

*In contrast to the other tests, lower scores on the Trail Making Test, Inspection Time task and RAVLT Distractors indicate better performance.

Discussion

This study examined the effect of chemotherapy on cognition in patients with colorectal cancer. Hypothesis 1 was not supported because patients being treated with chemotherapy or Avastin or with only surgical intervention did not perform statistically significantly worse than the healthy controls. This study therefore revealed no evidence of chemotherapy-related cognitive impairment (CRCI), post-operative cognitive dysfunction (POCD), or any other treatment- or cancer-related

cognitive impairment in patients with colorectal cancer. These findings are not consistent with the literature, which states that between 12 and 95% of patients treated with chemotherapy for other types of cancers do experience symptoms of CRCI (Downie, Mar Fan, Houede-Tchen, Yi & Tannock, 2006; Hede, 2008; Iconomou, Mega, Koutras, Iconomou & Kalofonos, 2004; Jansen, Cooper, Dodd & Miaskowski, 2011; Mehnert, Schwerath, Schirmer, Schleimer, Petersen, Schulz-Kindermann, Zander & Koch, 2007; Prokasheva, Faran, Cwikel & Geffen, 2011; Skaali, Fossa, Andersson, Cvancarova, Langberg, Lehne & Dahl, 2011). Limited literature on the issue of CRCI in patients with colorectal cancer illustrates that lack of CRCI (Andreis, Ferri, Mazzocchi, Meriggi, Rizzi, Rota, et al., 2012). Thus it is possible that CRCI simply does not exist in this patient group. The possible mechanism behind the lack of CRCI needs further investigations despite animal studies with similar chemotherapy drugs demonstrating cognitive impairment.

The second hypothesis, that participants with greater depression, anxiety and fatigue would exhibit lower levels of cognitive functioning was not supported. A significant correlation was revealed only between anxiety and performance on the Trail Making Test; however anxiety was unrelated to the other measures of cognitive functioning while depression and fatigue were not related to performance on any of the neuropsychological tests. This is also inconsistent with literature that has found that cognitive functioning declines in those with depression, anxiety and fatigue (Jansen et al., 2011).

Hypothesis three, that participants with more years of education and greater premorbid ability will exhibit better cognitive functioning, was confirmed. Statistically significant relationships were established between years of education and premorbid ability and a number of the cognitive tests. This is consistent with the existing literature. Jansen et al. (2011) also found that those with higher levels of education and intelligence tended to perform better on neuropsychological tests and retain a higher level of cognitive functioning compared to those with lower levels of these.

The fourth hypothesis, that those scoring higher on the Everyday Problems Test (EPT) will also demonstrate better cognitive functioning was also confirmed. Statistically significant correlations were established between the EPT and all of the neuropsychological tests, with the exception of the Stroop Colour and Word Test. This is an important finding in informing the literature. Past studies have called for research to be conducted into the relationship between everyday problem solving abilities and cognitive functioning in cancer patients (Hutchinson et al., 2012). This study has shown that neuropsychological tests are good predictors of the problems participants come across in their everyday lives and there are moderate to strong relationships between these two variables. Therefore, based on the findings of the present study, the recommendation can be made that it is acceptable for traditional objective neuropsychological tests to be used to assess the effects of CRCI in cancer patients because they are positively related to everyday problem solving ability (as evidenced by the EPT).

Limitations of Study

The present study had a number of limitations. A larger sample size and having a similar number of participants in each of the four groups, who were homogeneous in the treatment they received, would have provided the study with greater statistical power and, in turn, made the results more reliable and generalisable to the colorectal-cancer patient population. Therefore, due to its small sample size, the results of the present study must be interpreted with caution. Future studies should aim to recruit a much larger number of participants in order to produce more reliable data and would therefore provide the researcher with the opportunity to delete participants with missing cases if that situation arose.

To conclude, this study investigated the effect of treatment with chemotherapy, Avastin and surgery on cognition in patients with colorectal cancer, with none of the three treatment groups exhibiting cognitive impairment relative to the healthy controls. The effects of level of education, premorbid ability and everyday problem solving on cognitive functioning in these patients were also investigated, with statistically significant correlations being found between each of these and many of the cognitive tests. Depression, anxiety and fatigue were established as being unrelated to cognitive functioning in this patient group. Future studies should investigate the effects of chemotherapy on cognition in a larger cohort of colorectal cancer patients, as well as examining further the relationship between everyday problem solving, using the EPT and/or alternative instruments, in cancer patients generally.

Reference

Andreis, F., Ferri, M., Mazzocchi, M., Meriggi, M., Rizzi, A., Rota, L., Di Biasi, B., Abeni, C., Codignola , C. & Rozzini, R., et al. (2012). Lack of a Chemobrain Effect for Adjuvant FOLFOX Chemotherapy in Colon Cancer Patients. A Pilot Study. *Support Care Cancer, Published Online.*

Avidan, M. S. & Evers, A. S. (2011). "Review of Clinical Evidence for Persistent Cognitive Decline or Incident Dementia Attributable to Surgery or General Anaesthesia," *Journal of Alzheimer's Disease,* 24(2), 201-216.

Biglia, N., Bounous, V. E., Malabaila, A., Palmisano, D., Torta, D. M., D'Alonzo, M., Sismondi, P. & Torta, R. (2012). "Objective and Self-Reported Cognitive Dysfunction in Breast Cancer Women Treated with Chemotherapy: A Prospective Study," *European Journal of Cancer Care,* 21, 485-492.

Bowel Cancer Australia (2010), Retrieved July 4, 2012 from http://www.bowelcanceraustralia.org/bca/index.php?option=com_content&view=article&id=163&Itemid=289#facts.

Boykoff, N., Moieni, M. & Subramanian, S. K. (2009). "Confronting Chemobrain: An in-Depth Look at Survivors' Reports of Impact on Work, Social Networks, and Health Care Response," *Journal of Cancer Survivorship,* 3, 223 – 232.

Cancer Council Australia (2009) Colorectal Cancer, Retrieved April 21, 2010 from http://www.cancer.org.au//aboutcancer/cancertypes/colorectalcancer.htm.

Chen, X., Zhao, M., White, P. F., Li, S., Tang, J., Wender, R. H., Sloninsky, A., Naruse, R., Kariger, R., Webb, T. & Norel, E. (2001). "The Recovery of Cognitive Function after General Anaesthesia in Elderly Patients: A Comparison of Desflurane and Sevoflurane," *Anaesthesia and Analgesia,* 93, 1489-1494.

Collins, B., Mackenzie, J., Stewart, A., Bielajew, C. & Verma, S. (2009). "Cognitive Effects of Chemotherapy in Post-Menopausal Breast Cancer Patients 1 Year after Treatment," *Psycho-Oncology,* 18, 134 – 143.

Dietrich, J., Han, R., Yang, Y., Mayer-Proschel, M. & Noble, M. (2006). "CNS Progenitor Cells and Oligodendrocytes Are Targets of Chemotherapeutic Agents in Vitro and in Vivo," *Journal of Biology,* 5, 22.1 – 22.23.

Downie, F. P., Mar Fan, H. G., Houede-Tchen, N., Yi, Q. & Tannock, I. F. (2006). "Cognitive Function, Fatigue and Menopausal Symptoms in Breast Cancer Patients Receiving Adjuvant Chemotherapy: Evaluation with Patient Interview after Formal Assessment," *Psycho-Oncology,* 15, 921-930.

Grudnik, J. L. & Kranzler, J. H. (2001). "Meta-Analysis of the Relationship between Intelligence and Inspection Time," *Intelligence,* 29, 523 – 536.

Hampton, T. (2008). "Studies Reveal Underlying Mechanism for Chemotherapy's Adverse Effects on Brain," *Journal of the American Medical Association,* 299, 2494.

Hede, K. (2008). "Chemobrain Is Real But May Need New Name," *Journal of the National Cancer Institute,* 100, 162 – 169.

Hermelink, K., Untch, M., Lux, M. P., Kreienberg, R., Beck, T., Bauerfeind, I. & Munzel, K. (2007). "Cognitive Function during Neoadjuvant Chemotherapy for Breast Cancer," *Cancer,* 109, 1905 – 1913.

Hutchinson, A. D., Hosking, J. R., Kichenadasse, G., Mattiske, J. K. & Wilson, C. (2012). "Objective and Subjective Cognitive Impairment Following Chemotherapy for Cancer: A Systematic Review," *Cancer Treatment Reviews,* Available Online.

Iconomou, G., Mega, V., Koutras, A., Iconomou, A. V. & Kalofonos, H. P. (2004). "Prospective Assessment of Emotional Distress, Cognitive Function, and Quality of Life in Patients with Cancer Treated with Chemotherapy," *Cancer,* 101(2), 404-411.

Jansen, C. E., Cooper, B. A., Dodd, M. J. & Miaskowski, C. A. (2011). "A Prospective Longitudinal Study of Chemotherapy-Induced Cognitive Changes in Breast Cancer Patients," *Support Care Cancer,* 19, 1647-1656.

Jansen, C. E., Dodd, M. J., Miaskowski, C. A., Dowling, G. A. & Kramer, J. (2008). "Preliminary Results of a Longitudinal Study of Changes in Cognitive Function of Breast Cancer Patients Undergoing Chemotherapy with Doxorubicin and Cyclophosphamide," *Psycho-Oncology,* 17, 1189-1195.

Jensen, A. R. (1965). "Scoring the Stroop Test" *Acta Psychologia,* 24, 398 – 408.

Lezak, M. D., Howieson, D. B. & Loring, D. W. (2004). Neuropsychological Assessment (4 Ed.), *New York: Oxford University Press.*

Mehnert, A., Scherwath, A., Schirmer, L., Schleimer, B., Petersen, C., Schulz-Kindermann, F., Zander, A. R. & Koch, U. (2007). "The Association between Neuropsychological Impairment, Self-Perceived Cognitive Deficits, Fatigue and Health-Related Quality of Life in Breast Cancer Survivors Following Standard Adjuvant Versus High Dose Chemotherapy," *Patient Education and Counselling,* 66, 108-118.

Meyers, C. A. (2008). "How Chemotherapy Damages the Central Nervous System," *Journal of Biology,* 7, 11.1 – 11.3.

Meyers, J. E. & Meyers, K. R. (1995). 'Rey Complex Figure Test and Recognition Trial: Professional Manual,' *Odessa, FL: Psychological Assessment Resources.*

Moller, J. T., Cluitmans, P., Rasmussen, L. S., Houx, P., Rasmussen, H., Canet, J., Rabbitt, P., Jolles, J., Larsen, K., Hanning, C. D., Langeron, O., Johnson, T., Lauven, P. M., Kristensen, P. A., Biedler, A., Van Beem, H., Fraidakis, O., Silverstein, J. H., Beneken, J. E. & Gravestein, J. S. (1998). "Long-Term Post-Operative Cognitive Dysfunction in the Elderly ISPOCD1 Study," *Lancet,* 351, 857-861.

Myers, J. S. (2009). "Chemotherapy-Related Cognitive Impairment: Neuroimaging, Neuropsychological Testing, and the Neuropsychologist," *Clinical Journal of Oncology Nursing,* 13, 413 – 421.

Prokasheva, S., Faran, Y., Cwikel, J. & Geffen, D. B. (2011). "Analysis of Memory Deficits Following Chemotherapy in Breast Cancer Survivors: Evidence from the Doors and People Test," *Journal of Psychosocial Oncology,* 29, 499-514.

Reid-Arndt, S. A., Hsieh, C. & Perry, M. C. (2010). "Neuropsychological Functioning and Quality of Life During the First Year after Completing Chemotherapy for Breast Cancer," *Psycho-Oncology,* 19, 535-544.

Skaali, T., Fossa, S. D., Andersson, S., Cvancarova, M., Langberg, C. W., Lehne, G. & Dahl, A. A. (2011). "Self-Reported Cognitive Problems in Testicular Cancer Patients: Relation to Neuropsychological Performance, Fatigue, and Psychological Distress," *Journal of Psychosomatic Research,* 70, 403-410.

Snow, W. G., Tierney, M. C., Zorzitto, M. L., Fisher, R. H. & Reid, D. W. (1988). 'One-Year Test-Retest Reliability of Selected Tests in Older Adults,' *Paper Presented at the Meeting of the International Neuropsychological Society, New Orleans.*

Tulsky, D., Zhu, J. & Ledbetter, M. F. (1997). 'WAIS-III WMS-III Technical Manual,' *San Antonio: The Psychological Corporation.*

Vardy, J. & Dhillon, H. (2010). "The Fog Hasn't Lifted on "Chemobrain" Yet: Ongoing Uncertainty Regarding the Effects of Chemotherapy and Breast Cancer on Cognition," *Breast Cancer Research and Treatment,* 121.

Willis, S. L. & Marsiske, M. (1993). 'Manual for the Everyday Problems Test, University Park: Department of Human Development and Family Studies,' *Pennsylvania State University.*

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Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Kristy Hodgson		
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Appendix C

The Effect of Chemotherapy on Cognition in Patients treated for Colorectal Cancer – 12 month follow-up

This study provides a 12 month follow-up to the initial evaluation of the effects of chemotherapy on cognition in patients with colorectal cancer conducted by Hodgson, Wilson, Hutchinson, Nettelbeck, Kichenadasse & Zajac (2012). This previous study revealed no evidence of CRCI however, a significant difference was identified between the surgery and healthy control groups on the second recall component of the Logical Memory test. Because a difference was found on only one subtest of a possible 10 neuropsychological tests and 17 subtests, this was dismissed as being due to a Type II error as opposed to evidence of POCD (Hodgson et al., 2012). Depression was not related to cognitive functioning, while anxiety was related to only two measures of cognition, the Trail Making Test and Inspection Time task and fatigue was related only to performance on the Trail Making Test (Hodgson et al., 2012). Years of education, premorbid ability and everyday problem solving ability were all related to a number of domains of cognitive functioning (Hodgson et al., 2012).

This study aimed to confirm the findings of the initial assessment that cognitive functioning remains intact following treatment with chemotherapy in patients with colorectal cancer. Specifically, we assessed whether the chemotherapy, surgery and healthy control groups differed from one another in terms of their performance on a number of objective neuropsychological tests, paying special attention to any differences between the surgery and healthy control group on the Logical Memory test. The following hypotheses were developed with the results of the initial study in mind: (1) that there would be a significant difference between the

surgery and healthy control groups on the second recall component of the Logical Memory test; (2) that anxiety and fatigue would be related to poorer performance on the Trail Making Test; (3) that education and premorbid ability would be related to cognitive functioning; and (4) that everyday problem solving ability would be related to cognitive functioning.

Method

Participants were included in the present study only if they participated in the initial assessment phase 12 months earlier (Hodgson, Wilson, Hutchinson, Nettelbeck, Kichenadasse & Zajac, 2012). As noted in the initial study, patients diagnosed with colorectal cancer and treated with either surgery alone, chemotherapy with or without surgical intervention, or chemotherapy and anti-angiogenic drug Avastin (bevacizumab) with or without surgery were recruited from Flinders Medical Centre and the Royal Adelaide Hospital between October 2009 and April 2012. To be included in the first study, patients were required to have had treatment with chemotherapy with, or without Avastin for a minimum of three months and have had no more than one month since the cessation of treatment. Patients who had been treated using surgical interventions were also required to be no more than one month post-surgery. Patients were excluded from the study if they had received chemotherapeutic treatment for any other cancer occurrences, had been currently diagnosed with anxiety or depression, or had a history of head injury, stroke, drug or alcohol abuse, or of a neurological or psychiatric disorder.

As also discussed in the initial study, healthy control participants were recruited via word-of-mouth at the two hospitals involved in the research, or were identified and contacted through suitable participant lists of previous studies conducted at the University of Adelaide. The healthy control participants were also

required to conform with the same inclusion and exclusion criteria as the cancer patients, except for those related to a diagnosis of cancer and its treatment. Ethics approval was granted by the University of Adelaide, Flinders University and the Royal Adelaide Hospital Human Research Ethics Committee.

All participants that completed the first assessment were contacted via mail reminding them of the study they participated in 12 months before and asking if they would like to participate in the follow-up assessment. In this letter, it was made clear that although they participated in the first study, they were not required to participate in the follow-up assessment. A short time later, participants were contacted over the phone and asked if they would like to participate and to schedule a time. Testing took place either at the hospital in which the patient received their cancer treatment, at their home, or at the University of Adelaide. At the assessment session, participants were provided with an information sheet and consent form and were instructed to read both and, if willing to participate, provide consent. Participants were again informed at the testing session that they were free to withdraw at any time without consequence. No one withdrew; however, only 25% of the initial sample agreed to participate in the follow-up session.

The same battery of tests was administered in the follow-up as were given during the initial assessment. As was described in the first study, testing commenced with the Everyday Problems Test (EPT) which consists of 21 multiple choice questions that assess problem solving ability in the context of everyday tasks, such as identifying from a log book which procedures must be undertaken at every car service or following instructions on how to correctly launder clothes under specific conditions (Hodgson et al., 2012). Participants are given 20 minutes to answer as many of the questions as they can. It has been demonstrated that the EPT is both reliable and valid,

with high test-retest reliability (.83 to .91) and construct validity (.42 to .72) (Willis & Marsiske, 1993). Participants were then required to complete a number of self-report questionnaires that assessed depression, anxiety and fatigue. These were the Beck Depression Inventory, the Beck Anxiety Inventory and the Fatigue Assessment Scale, whereby participants must circle which option on the scale best applies to how they have been feeling over the past week or fortnight, how they generally feel, respectively.

After the completion of the aforementioned questionnaires, the neuropsychological assessment commenced. Together, the Trail Making Test (TMT), Controlled Oral Word Association Test (COWAT) Rey Auditory Verbal Learning Test (RAVLT), Digit Span test, Rey Complex Figure Test (RCFT), the Logical Memory Test from the Wechsler Memory Scale III, the Inspection Time task (IT), the Digit Symbol test from the Wechsler Adult Intelligence Scale III and the Stroop Colour and Word test comprised the neuropsychological assessment battery for this study.

All of the cognitive assessments were conducted in accordance with the administration instructions detailed in their respective manuals. Each of the neuropsychological measures used in this study have been demonstrated to be both reliable and valid. The COWAT, which examines verbal fluency, has a test-retest reliability of .70, while the RAVLT, a test of verbal learning and memory, has an internal consistency of .70 for list A (Snow, Tierney, Zorzitto, Fisher & Reid, 1988). Digit Span, which measures working memory, and Logical Memory, a test of verbal learning and memory, have been shown to have test-retest reliabilities of .84 - .93 and .74 - .91, respectively, depending on the age group of the people being tested (Tulsky, Zhu & Ledbetter, 1997). Another measure of executive function, the Stroop Colour

and Word test has a test-retest reliability of .73 for the colour-word component (Jensen, 1965). The Digit Symbol test, a measure of attention, processing speed and visual scanning and memory, has demonstrated test-retest reliabilities of .84 - .87 depending upon the age group being assessed (Tulsky, Zhu & Ledbetter, 1997). The RCFT, which evaluates visuospatial constructional ability, visuospatial recall memory and processing speed, had a test-retest reliability of .76 for the copy component and .89 for the recall component (Meyers & Meyers, 1995). A test-retest reliability.80 and higher has been shown for the Inspection Time task, which measures processing speed (Grudnik & Kranzler, 2001). No reliability or validity data were available for the Trail Making Test, which is an assessment of executive function. The statistical analyses required for this study were conducted using the Statistical Package for the Social Sciences (SPSS) version 20.

Results

Comparison between Initial and Follow-up Assessments across the Three Groups

Of the 61 people who participated in the initial assessment for the chemobrain study, only 15 also participated in the 12-month follow-up assessment. Therefore, there were 46 participants who did not participate in the second cognitive evaluation. There were a number of reasons that were given as to why participants were unable to engage in the follow-up assessment and they are as follows: seven participants were deceased, 11 were too ill, 10 were too busy, twelve simply refused participation without providing an explanation as to why and the remaining six were unable to be contacted.

A multivariate repeated-measures ANOVA was conducted in order to explore whether performance across the cognitive tests differed for the three groups, both as one main sample and individually. For the whole sample, no significant difference in

cognitive functioning was found between the first and second assessments (F = .54 (5, 1), *p* = .768). In addition, no significant difference was apparent for performance across the cognitive tests between the two assessments when considering the three groups individually (F = 1.94 (10, 2), *p* = .388). Therefore, it can be concluded that the cognitive functioning of all participants in this study who were tested at both intervals remained relatively stable over this 12-month period. Therefore, the subsequent analyses will examine the three groups in terms of their cognitive functioning at the 12-month follow-up assessment only.

Discussion

This study provided a 12 month follow-up examination of the effect of chemotherapy on cognition in patients with colorectal cancer. Exploratory analyses revealed that there was no significant difference in the cognitive performance of participants between the two assessments, both across the sample as a whole, as well as within the three participant groups individually. This result is in contrast to the initial assessment in which a significant difference was found between the surgery and healthy control groups on the second recall component of the Logical Memory test (Hodgson et al., 2012). There are two possible reasons as to why the difference observed in the initial assessment had absolved by the 12 month follow-up. The first is that while the surgery patients were experiencing impairments in their verbal learning and memory abilities, as evident in the results of the second recall component of the Logical Memory test, by the 12 month follow-up these impairments had resolved and the affected surgery patients had returned to their normal, premorbid level of cognitive functioning. This theory is supported by some studies of post-operative cognitive dysfunction (POCD), which state that as a consequence of either the effects of general anaesthetics and/or the inflammatory system on the brain,

patients often experience a decline in their cognitive abilities up to three months after receiving surgical treatment (Avidan & Evers, 2011; Chen et al., 2001; Cibelli et al., 2010; Moller et al., 1998). However in contrast, other studies in this area of research argue that the symptoms of POCD commonly experienced by patients following surgical intervention are not persistent and last only a few days (Moller et al., 1998). The other possible explanation, which was outlined in the first paper, is that as a consequence of the large number of comparisons across the three groups for the cognitive tests, it is likely that the one significant result observed in the initial study occurred as a result of a Type II error rather than an actual effect.

Limitations of Study

This study was subject to a few main limitations. The most significant of these is the extremely small size of the sample which had resulted in the statistics produced being largely underpowered and ungeneralisable to the colorectal cancer population. In addition, within the very small sample that was used, the numbers of participants in each of the three groups varied widely and, in addition, a number of different chemotherapy types and regimens was also used to treat the patients in the sample. It is for these reasons also that the results of this study are not generalisable to the colorectal cancer population and, additionally, must be interpreted with caution. It is important that future studies attempt to address these issues from the very beginning by adopting a multi-institutional research format in order to recruit a much larger sample for the initial assessment, which will create a larger participant pool from which to draw the follow-up sample. The final limitation of this study is that the assessment battery that was used in the initial assessment session was also employed in the follow-up testing. As a result, learning and practice effects were observed for some of the tests, hence inflating the result that would have been produced otherwise,

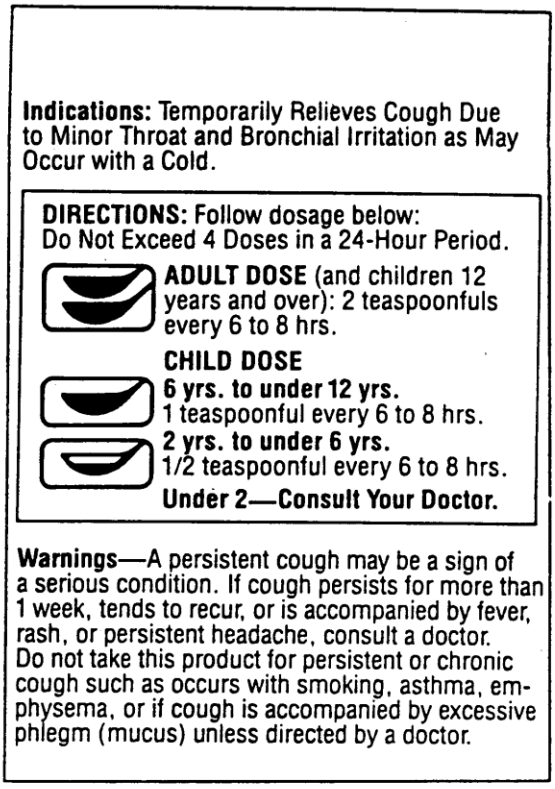
if different tests that measure the same baseline constructs had been used. Future research should aim to include either alternate versions of the same tests, or if unavailable, similar tests that measure the same underlying constructs, to avoid learning and practice effects.

In conclusion, this study provided a 12 month follow-up investigation into the effects of chemotherapy on cognition in patients with colorectal cancer, with no evidence of cognitive dysfunction in either of the two cancer patient groups relative to the healthy control group. Anxiety was established as being related to poorer cognitive functioning in a small number of tests however, depression and fatigue were not related to performance on any of the neuropsychological tests. The effects of years of education, premorbid ability and everyday problem solving abilities on cognitive function in these patients were also investigated, with each of these being significantly correlated with some areas of cognitive function. Future studies should aim to adopt a multi-institutional approach in order to maximise participant numbers from the very beginning, so that at follow-up an adequate sample size is still attainable after attrition.

Appendix D

Sample question from the Everyday Problems Test from study 3

Directions: Use of Cough Medicine



Indications: Temporarily Relieves Cough Due to Minor Throat and Bronchial Irritation as May Occur with a Cold.

DIRECTIONS: Follow dosage below:
Do Not Exceed 4 Doses in a 24-Hour Period.

ADULT DOSE (and children 12 years and over): 2 teaspoonfuls every 6 to 8 hrs.

CHILD DOSE
6 yrs. to under 12 yrs.
1 teaspoonful every 6 to 8 hrs.
2 yrs. to under 6 yrs.
1/2 teaspoonful every 6 to 8 hrs.
Under 2—Consult Your Doctor.

Warnings—A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor.

3. What is the maximum number of teaspoons you should take in 24 hours?

   a. 2
   b. 4
   c. 6
   d. 8

4. Mr. Jones smokes and has a smoker's cough. What is the maximum number of doses he should take per day?

   a. 0
   b. 2
   c. 4
   d. 8

Appendix E

Correlation matrix including all variables in study 3 (Chapter 4)

	Education	**BDI**	**BAI**	**FAS**	**PCI**	**QOL**	**OTH**	**PCA**	**WTAR**	**EPT**	**EWB**	**TMT**	**DSp**	**RCFT-C**	**RCFT-R**	**IT**	**LM**	**RAVLT**	**Stroop**	**DSy**
Education	1	-.138	-.065	-.069	.027	-.131	.155	.172	**.349**	**.390**	.052	.166	.227	**.303**	**.336**	.224	**.400**	.148	.218	**.421**
BDI		1	**.584**	**.634**	**-.550**	**-.356**	**-.366**	**-.399**	-.246	-.206	**-.601**	-.097	-.015	**-.325**	**-.329**	.004	-.119	-.117	-.167	-.205
BAI			1	**.513**	**-.385**	**-.498**	-.232	-.214	-.037	-.104	**-.527**	-.284	.000	-.167	-.073	.020	-.040	-.116	-.182	-.113
FAS				1	**-.547**	**-.448**	**-.475**	**-.512**	-.280	-.342	**-.536**	-.155	-.213	-.114	-.172	.141	-.306	-.213	-.263	-.165
PCI					1	**.336**	**.619**	**.626**	**.355**	.259	**.458**	.002	.201	.082	.019	-.160	.182	.147	.245	.076
QOL						1	.218	.121	-.005	.145	**.385**	-.021	.047	-.101	-.043	-.188	.077	.183	.199	.047
OTH							1	**.490**	.312	.226	**.375**	.019	.321	-.162	-.039	-.052	.238	.118	.260	.250
PCA								1	**.347**	.343	**.359**	-.016	.325	-.041	.186	-.051	**.389**	.201	.286	.101
WTAR									1	**.588**	.166	.256	**.447**	**.350**	**.449**	.151	**.484**	**.465**	.238	**.469**
EPT										1	.157	**.586**	**.664**	**.453**	**.527**	**.390**	**.559**	**.543**	.216	**.727**
EWB											1	-.041	.153	-.100	.170	-.251	.217	.125	.043	.114
TMT												1	**.392**	**.471**	.255	**.478**	.238	**.459**	.165	**.576**
DSp													1	.258	**.357**	.225	**.559**	**.419**	**.358**	**.473**
RCFT-C														1	**.532**	**.484**	.263	.293	.124	**.418**
RCFT-R															1	**.405**	**.454**	**.459**	.080	**.560**
IT																1	.221	.224	.203	**.555**

LM																	1	**.609**	.285	**.519**
RAVLT																		1	.255	**.474**
Stroop																			1	**.406**
DSy																				1

Figures in bold are significant at $p = .01$. Education = years of education. BDI = Beck Depression Inventory. BAI = Beck Anxiety Inventory. FAS = Fatigue Assessment Scale. PCI = Perceived Cognitive Impairment. QOL = Quality of Life. OTH = Comments from others. PCA = Perceived Cognitive Ability. WTAR = Wechsler Test of Adult Reading. EPT = Everyday Problems Test. EWB = Emotional Wellbeing. TMT = Trail Making Test. DSp = Digit Span Test. RCFT-C = Rey Complex Figure Test Copy. RCFT-R = Rey Complex Figure Test Recall. IT = Inspection Time. LM = Logical Memory. RAVLT = Rey Auditory Verbal Learning Test. Stroop = Stroop Colour and Word Test. DSy = Digit Symbol Test.

Appendix F

Study 3 author contribution statements

Statement of Authorship

Title of Paper	Self-Reported Cognitive Function in Patients with Colorectal Cancer
Publication Status	○ Published, ○ Accepted for Publication, ○ Submitted for Publication, ◉ Publication style
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Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Kristy Hodgson		
Contribution to the Paper	Ms Hodgson was responsible for the study design and procedures; recruited participants and collected data; ran the necessary statistical analyses, and wrote the manuscript.		
Signature		Date	24/7/13

Name of Co-Author	Prof Carlene Wilson		
Contribution to the Paper	Prof Wilson contributed to the broad direction of the study and provided feedback on drafts of the manuscript.		
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Contribution to the Paper	Dr Hutchinson contributed to the broad direction of the study and provided feedback on drafts of the manuscript.		
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Name of Co-Author	Prof Ted Nettelbeck		
Contribution to the Paper	Prof Nettelbeck provided feedback on drafts of the manuscript.		
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Author Contributions

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Name of Principal Author (Candidate)	Kristy Hodgson		
Contribution to the Paper	Ms Hodgson recruited participants and collected data; ran the necessary statistical analyses, and wrote the manuscript.		
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Name of Co-Author			
Contribution to the Paper			
Signature		Date	

Appendix G

Full Correlation Matrix of the Relationships between all Measures for Cancer Survivors (n = 83 – 88 because of missing data*)

	LOT	LOC-I	LOC-C	LOC-PO	QOL	PCA	OTH	PCI	SWB	EWB	FWB	PWB	BDI
LOT	1	.144	**-.336**	**-.421**	**.223**	**.274**	.117	.152	**.457**	**.374**	**.343**	.062	**-.322**
LOC-I		1	-.036	.109	**.325**	**.276**	.147	**.273**	**.242**	.109	**.243**	.114	**-.271**
LOC-C			1	**.681**	.116	.025	.098	.004	-.111	-.028	.053	.111	.158
LOC-PO				1	.070	-.002	.169	.023	.025	-.153	-.101	.046	.162
QOL					1	**.287**	**.304**	**.384**	**.264**	**.394**	**.486**	**.472**	**-.498**
PCA						1	**.305**	**.728**	**.326**	**.368**	**.480**	**.308**	**-.474**
OTH							1	**.344**	**.211**	**.226**	**.303**	**.339**	**-.461**
PCI								1	**.237**	**.386**	**.421**	**.440**	**-.589**
SWB									1	**.296**	**.446**	.199	**-.271**
EWB										1	**.638**	**.452**	**-.588**
FWB											1	**.581**	**-.614**
PWB												1	**-.607**
BDI													1

Values in bold are statistically significant at the .05 level. *FACT-Cog*: PCI = Perceived Cognitive Impairment. QOL = Quality of Life. PCA = Perceived Cognitive Ability. OTH = Self-reported Comments From Others. *FACT-C*: PWB = Personal Wellbeing. SWB = Social Wellbeing. EWB = Emotional Wellbeing. FWB = Functional Wellbeing. BDI = Beck Depression Inventory. LOT = Life Orientation Test (Optimism/Pessimism). LOC-I = Internal subscale of the Multidimensional Locus of Control Scale. LOC-C = Chance subscale of the Multidimensional Locus of Control Scale. LOC-PO = Powerful others subscale of the Multidimensional Locus of Control Scale.

*Note: Small differences between coefficients in the matrix and the outcome from regression analyses are the consequence of four incomplete data sets.

Appendix H

Full Correlation Matrix of the Relationships between Cancer Survivors (n = 40) and their Spouses (n = 40) on all Measures

Test	***r***	***p***
PCI	**.348**	.03
QOL	.149	.36
OTH	**.408**	.01
PCA	**.391**	.01
PWB	**.466**	.00
SWB	**.555**	.00
EWB	**.495**	.00
FWB	.073	.66
BDI	.291	.07
LOT	**.535**	.00
LOC-I	**.399**	.01
LOC-C	-.053	.75
LOC-PO	.197	.24

r values in bold are statistically significant. *FACT-COG:* PCI = Perceived cognitive impairment subscale of the Functional Assessment of Cancer Therapy (FACT-Cog), QOL = Quality of life subscale of the FACT-Cog, OTH = Comments from others subscale of the FACT-Cog, PCA = Perceived cognitive ability subscale of the FACT-Cog. *FACT-C:* PWB = Personal wellbeing subscale of the Functional Assessment of Cancer Therapy – Colorectal (FACT-C), SWB = Social wellbeing subscale of the FACT-C, EWB = Emotional wellbeing subscale of the FACT-C, FWB = Functional wellbeing subscale of the FACT-C. BDI = Beck Depression Inventory. LOT = Life

Orientation Test (Optimism/Pessimism). LOC-I = Internal subscale from the Multidimensional Locus of Control Scale, LOC-C = Chance subscale from the Multidimensional Locus of Control Scale, LOC-PO = Powerful Others subscale from the Multidimensional Locus of Control Scale.

Appendix I

Study 4 author contribution statements

Statement of Authorship

Title of Paper	The Effect of Personality on Reports of Psychological Wellbeing and Cognitive Functioning during Treatment in Colorectal Cancer Survivors
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Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Kristy Hodgson		
Contribution to the Paper	Ms Hodgson was responsible for the details of study design and procedures, recruited participants and collected data; ran the necessary statistical analyses, and wrote the manuscript.		
Signature		Date	26/8/13

Name of Co-Author	Prof Carlene Wilson		
Contribution to the Paper	Prof Wilson contributed to the broad direction of the study and provided feedback on drafts of the manuscript.		
Signature		Date	16/8/2013

Name of Co-Author	Dr Amanda Hutchinson		
Contribution to the Paper	Dr Hutchinson contributed to the broad direction of the study and provided feedback on drafts of the manuscript.		
Signature		Date	2/8/13

Name of Co-Author	Prof Ted Nettelbeck		
Contribution to the Paper	Prof Nettelbeck contributed to the broad direction of the study and provided feedback on drafts of the manuscript.		
Signature		Date	26.8.13

Reference List

Ahles, T.A., Saykin, A.J., Furstenberg, C.T., Cole, B., Mott, L.A., Skalla, K., Whedon, M.B., Bivens, S., Mitchell, T., Greenberg, R., & Silberfarb, P.M. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *Journal of Clinical Oncology, 20,* 485-493.

Allison, P., Guichard, C., Fung, K., & Gilain, L. (2003). Dispositional optimism predicts survival status one year after diagnosis in head and neck cancer patients. *Journal of Clinical Oncology, 21,* 543 – 548.

Anderson-Hanley, C., Sherman, M.L., Riggs, R., Agocha, V.B., & Compas, B.E. (2003). Neuropsychological effects of treatments for adults with cancer: A meta-analysis and review of the literature. *Journal of the International Neuropsychological Society, 9,* 967-982.

Andreis, F., Ferri, M., Mazzocchi, M., Meriggi, M., Rizzi, A., Rota, L., Di Biasi, B., Abeni, C., Codignola, C., Rozzini, R., & Zaniboni, A. (2012). Lack of a chemobrain effect for adjuvant FOLFOX chemotherapy in colon cancer patients. A pilot study. *Support Care Cancer,* published online.

Arraras, J.I., Wright, S.J., Jusue, G., Tejedor, M., & Calvo, J.I. (2002). Coping style, locus of control, psychological distress and pain-related behaviours in cancer and other diseases. *Psychology, Health and Medicine, 7,* 181 – 187.

Avidan, M.S. & Evers, A.S. (2011). Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anaesthesia. *Journal of Alzheimer's Disease, 24,* 201-216.

Beck, A. T., & Steer, R.A. (1984). Internal Consistencies of the Original and Revised Beck Depression Inventory. *Journal of Clinical Psychology, 40*, 1365-7.

Bender, C.M., Sereika, S.M., Berga, S.L., Vogel, V.G., Brufsky, A.M., Paraska, K.K., & Ryan, C.M. (2006). Cognitive impairment associated with adjuvant therapy in breast cancer. *Psycho-Oncology, 15,* 422-430.

Biglia, N., Bounous, V.E., Malabaila, A., Palmisano, D., Torta, D.M.E., D'Alonzo, M., Sismondi, P. and Torta, R. (2012). Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study. *European Journal of Cancer Care, 21,* 485-492.

Bornstein, R. A., Baker, G. B., & Douglass, A. B. (1987). Short-term retest reliability of the Halstead-Reitan Battery in a normal sample. *J.Nerv.Ment.Dis., 175,* 229-232.

Bowel Cancer Australia (2010), retrieved July 4, 2012 from http://www.bowelcanceraustralia.org/bca/index.php?option=com_content&view=article&id=163&Itemid=289#facts.

Boykoff, N., Moieni, M., & Subramanian, S.K. (2009). Confronting chemobrain: An in-depth look at survivors' reports of impact on work, social networks, and health care response. *Journal of Cancer Survivorship, 3,* 223-232.

Cancer Australia (2013). Cancer in Australia Statistics, retrieved March 2, 2013 from canceraustralia.gov.au/affected-cancer/what-cancer/cancer-australia-statistics.

Cancer Council Australia (2009). Colorectal Cancer, retrieved April 21, 2010 from *http://www.cancer.org.au//aboutcancer/cancertypes/colorectalcancer.htm*.

Castellon, S.A., Ganz, P.A., Bower, J.E., Petersen, L., Abraham, L., & Greendale, G.A. (2004). Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *Journal of Clinical and Experimental Neuropsychology, 26,* 955-969.

Cella, D. (2010). Retrieved February 20, 2010 from http://www.facit.org/FACITOrg/Questionnaires.

Chen, X., Zhao, M., White, P.F., Li, S., Tang, J., Wender, R.H., Sloninsky, A., Naruse, R., Kariger, R., Webb, T., & Norel, E. (2001). The recovery of cognitive function after general anaesthesia in elderly patients: a comparison of desflurane and sevoflurane. *Anaesthesia and Analgesia, 93,* 1489-1494.

Chida, Y., & Steptoe, A. (2008). Positive psychological wellbeing and mortality: a quantitative review of prospective observational studies. *Psychosomatic Medicine, 70,* 741 – 756.

Cibelli, M., Fidalgo, A.R., Terrando, N., Ma, D., Monaco, C., Feldmann, M., Takata, M., Lever, I.J., Nanchahal, J., Fanselow, M.J., & Maze, M. (2010). Role of interleukin 1-β in postoperative cognitive dysfunction. *Annals of Neurology, 68,* 360-368.

Colby, D.A., & Shifren, K. (2013). Optimism, mental health and quality of life: a study amongst breast cancer patients. *Psychology, Health and Medicine, 18,* 10 – 20.

Collins, B., Mackenzie, J., Stewart, A., Bielajew, C., & Verma, S. (2009). Cognitive effects of chemotherapy in post-menopausal breast cancer patients 1 year after treatment. *Psycho-Oncology, 18,* 134–143.

Dietrich, J., Han, R., Yang, Y., Mayer-Proschel, M., & Noble, M. (2006). CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents *in vitro* and *in vivo. Journal of Biology, 5, 22.1 – 22.23.*

Dikmen, S. S., Heaton, R. K., Grant, I., & Temkin, N. R. (1999). Test-retest reliability and practice effects of expanded Halstead-Reitan Neuropsychological Test Battery. *J.Int.Neuropsychol.Soc., 5,* 346-356.

Downie, F.P., Mar Fan, H.G., Houédé-Tchen, N., Yi, Q., & Tannock, I.F. (2006). Cognitive function, fatigue, and menopausal symptoms in breast cancer patients receiving adjuvant chemotherapy: Evaluation with patient interview after formal assessment. *Psycho-Oncology, 15,* 921-930.

Elklit, A., & Blum, A. (2011). Psychological adjustment one year after the diagnosis of breast cancer: A prototype study of delayed post-traumatic stress disorder. *British Journal of Clinical Psychology, 50,* 350 – 363.

Espen, B., & Flaten, M.A. (2011). Interaction between expectancies and drug effects: an experimental investigation of placebo analgesia with caffeine as an active placebo. *Psychopharmacology, 215,* 537 – 548.

Falleti, M.G., Sanfilippo, A., Maruff, P., Weih, L., & Phillips, K. (2005). The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. *Brain and Cognition, 59,* 60 – 70.

Ferguson, R.J., Ahles, T.A., Saykin, A.J., McDonald, B.C., Furstenberg, C.T., Cole, B.F., & Mott, L.A. (2007). Cognitive-behavioural management of chemotherapy-related cognitive change. *Psycho-Oncology, 16,* 772 – 777.

Fitzpatrick, T.R., Edgar, L., & Holcroft, C. (2012). Assessing the relationship between physical fitness activities, cognitive health, and quality of life among older cancer survivors. *Journal of Psychosocial Oncology, 30,* 556 – 572.

Fliessbach, K., Helmstaedter, C., Urbach, H., Althaus, A., Pels, H., Linnebank, M., Juergans, A., Glasmacher, A., Schmidt-Wolf, I.G., Klockgether, T., & Schlegel, U. (2005). Neuropsychological outcome after chemotherapy for primary CNS lymphoma: A prospective study. *Neurology, 64,* 1184-1188.

Fydrich, T., Dowdall, D., & Chambless, D.L. (1992). Reliability and Validity of the Beck Anxiety Inventory. *Journal of Anxiety Disorders, 6(1),* 55-61.

Galantino, M.L., Greene, L., Daniels, L., Dooley, B., Muscatello, L., & O'Donnell, L. (2012). Longitudinal impact of yoga on chemotherapy-related cognitive impairment and

quality of life in women with early stage breast cancer: a case series. *Explore, 8,* 127 – 134.

Gerrig, R.J. & Zimbardo, P.G. (2005). *Psychology and Life* (17th Edition). Allyn and Bacon: Boston.

Gold, J.I., Douglas, M.K., Thomas, M.L., Elliott, J.E., Rao, S.M., & Miaskowski, C. (2012). The relationship between posttraumatic stress disorder, mood states, functional status, and quality of life in oncology outpatients. *Journal of Pain and Symptom Management, 44,* 520 – 531.

Grudnik, J. L., & Kranzler, J.H. (2001). Meta-analysis of the relationship between intelligence and inspection time. *Intelligence, 29,* 523 – 536.

Gustavsson-Lilius, M., Julkunen, J., Keskivaara, P., Lipsanen, J., & Hietanen, P. (2012). Predictors of distress in cancer patients and their partners: The role of optimism in the sense of coherence construct. *Psychology and Health, 27,* 178 – 195.

Hampton, T. (2008). Studies reveal underlying mechanism for chemotherapy's adverse effects on brain. *Journal of the American Medical Association, 299,* 2494.

Han, R., Yang, Y.M., Dietrich, J., Luebke, A., Mayer-Proschel, M., & Noble, M. (2008). Systemic 5-flourouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. *Journal of Biology, 7,* 12.1 – 12.22.

Hede, K. (2008). Chemobrain is real but may need new name. *Journal of the National Cancer Institute, 100,* 162 – 169.

Hensley, M.L., Correa, D.D., Thaler, H., Wilton, A., Venkatraman, E., Sabbatini, P., Chi, D.S., Dupont, J., Spriggs, D., & Aghajanian, C. (2006). Phase I/II study of weekly paclitaxel plus carboplatin and gemcitabine as first-line treatment of advanced-stage ovarian cancer: pathologic complete response and longitudinal assessment of impact on cognitive functioning. *Gynecologic Oncology, 102,* 270 – 277.

Hermelink, K., Kuchenhoff, H., Untch, M., Bauerfeind, I., Lux, M.P., Buhner, M., Manitz, J., Fensterer, V., & Munzel, K. (2010). Two Different Sides of 'Chemobrain': Determinants and Nondeterminants of Self-Perceived Cognitive Dysfunction in a Prospective Randomised Multicentre Study. *Psycho-Oncology, 19*, 1321-1328.

Hermelink, K., Untch, M., Lux, M.P., Kreienberg, R., Beck, T., Bauerfeind, I., & Munzel, K. (2007). Cognitive function during neoadjuvant chemotherapy for breast cancer. *Cancer, 109,* 1905 – 1913.

Hess, L.M., Chambers, S.K., Hatch, K., Hallum, A., Janicek, M.F., Buscema, J., Borst, M., Johnson, C., Slayton, L., Chongpison, Y., & Alberts, D.S. (2010). Pilot study of the prospective identification of changes in cognitive function during chemotherapy treatment for advanced ovarian cancer. *Journal of Supportive Oncology, 8,* 252 – 258.

Hulbert-Williams, N., Neal, R., Morrison, V., Hood, K., & Wilkinson, C. (2012). Anxiety, depression and quality of life after cancer diagnosis: what psychosocial variables best predict how patients adjust? *Psycho-Oncology, 21,* 857 – 867.

Hurria, A., Rosen, C., Hudis, C., Zuckerman, E., Panageas, K.S., Lachs, M.S., Witmer, M., van Gorp, W.G., Fornier, M., D'Andrea, G., Moasser, M., Dang, C., Van Poznak, C., Hurria, A., Holland, J. (2006). Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. *Journal of the American Geriatric Society, 54,* 925-931.

Hutchinson, A.D., Hosking, J.R., Kichenadasse, G., Mattiske, J.K., & Wilson, C. (2012). Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review. *Cancer Treatment Reviews,* Available online.

Iconomou, G., Mega, V., Koutras, A., Iconomou, A.V., & Kalofonos, H.P. (2004). Prospective assessment of emotional distress, cognitive function, and quality of life in patients with cancer treated with chemotherapy. *Cancer, 101,* 404-411.

Jansen, C.E., Cooper, B.A., Dodd, M.J., & Miaskowski, C.A. (2011). A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients. *Support Care Cancer, 19,* 1647-1656.

Jansen, C.E., Dodd, M.J., Miaskowski, C.A., Dowling, G.A., Kramer, J. (2008). Preliminary results of a longitudinal study of changes in cognitive function in breast cancer patients undergoing chemotherapy with doxorubicin and cyclophosphamide. *Psycho-Oncology, 17,* 1189-1195.

Jensen, A.R. (1965). Scoring the stroop test. *Acta Psychologia, 24,* 398 – 408.

Kaasa, S., Olsnes, B.T., & Mastekaasa, A. (1988). Neuropsychological evaluation of patients with inoperable non-small cell lung cancer treated with combination chemotherapy or radiotherapy. *Acta Oncologica, 27,* 241 – 246.

Kaasa, S., Olsnes, B.T., Thorud, E., & Host, H. (1988). Reduced short-term neuropsychological performance in patients with nonsmall-cell lung cancer treated with cisplatin and etoposide. *Treatment Modalities in Lung Cancer. Antibiotic Chemotherapy, 41,* 226 – 231.

Kvale, E.A., Clay, O.J., Ross-Meadows, L.A., McGee, J.S., Edwards, J.D., Unverzagt, F.W., Ritchie, C.S., & Ball, K.K. (2010). Cognitive speed of processing and functional declines in older cancer survivors: an analysis of data from the ACTIVE trial. *European Journal of Cancer Care, 19,* 110-117.

Lai, J., Butt, Z., Wagner, C., Sweet, J.J., Beaumont, J.L., Vardy, J., Jacobsen, P.B., Shapiro, P.J., Jacobs, S.R., & Cella, D. (2009). Evaluating the dimensionality of perceived cognitive function. *Journal of Pain and Symptom Management, 37,* 982 – 995.

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological Assessment* (4th edn). Oxford University Press: New York.

Lipsey, M.W., & Wilson, D.B. (2001). *Practical Meta-analysis* (Vol. 49). Sage Publications: Thousand Oaks, CA.

Marks, G., Richardson, J.L., Graham, J.W., & Levine, A. (1986). Role of health locus of control beliefs and expectations of treatment efficacy in adjustment to cancer. *Journal of Personality and Social Psychology, 51,* 443 – 450.

Matarazzo, J. D., Wiens, A. N., Matarazzo, R. G., & Goldstein, S. G. (1974). Psychometric and clinical test-retest reliability of the Halstead impairment index in a sample of healthy, young, normal men. *J.Nerv.Ment.Dis., 158,* 37-49.

Mayerhofer, K., Bodner-Adler, B., Bodner, K., Saletu, B., Schindl, M., Kaider, A., Hefler, L., Leodolter, S. & Kainz, C. (2000). A paclitaxel-containing chemotherapy does not cause central nervous adverse effects: a prospective study in patients with ovarian cancer. *Anticancer Research, 20,* 4051 – 4056.

Mazanec, S.R., Daly, B.J., Douglas, S.L., & Lipson, A.R. (2010). The relationship between optimism and quality of life in newly diagnosed cancer patients. *Cancer Nursing, 33,* 235 – 243.

Mehlsen, M., Pedersen, A.D., Jensen, A.B., & Zachariae, R. (2009). No indications of cognitive side-effects in a prospective study of breast cancer patients receiving adjuvant chemotherapy. *Psycho-Oncology, 18,* 248-257.

Mehnert, A., Scherwath, A., Schirmer, L., Schleimer, B., Petersen, C., Schulz-Kindermann, F., Zander, A.R., & Koch, U. (2007). The association between neuropsychological impairment, self-perceived cognitive deficits, fatigue and health-related quality of life in breast cancer survivors following standard adjuvant versus high dose chemotherapy. *Patient Education and Counselling, 66,* 108-118.

Meyers, C.A. (2008). How chemotherapy damages the central nervous system. *Journal of Biology, 7,* 11.1 – 11.3.

Meyers,C.A., Byrne, K.S., & Komaki, R. (1995). Cognitive deficits in patients with small cell lung cancer before and after chemotherapy. *Lung Cancer, 12*, 231 – 235.

Meyers, J.E. & Meyers, K.R. (1995). *Rey complex figure test and recognition trial: professional manual*, Odessa, FL: Psychological Assessment Resources.

Michielsen, H.J., De Vries, J., Van Heck, G.L., Van de Vijver, F.J.R., & Sijtsma, K. (2004). Examination of the dimensionality of fatigue. The construction of the Fatigue Assessment Scale (FAS). *European Journal of Psychological Assessment, 20*, 39 – 48.

Moller, J.T., Cluitmans, P., Rasmussen, L.S., Houx, P., Rasmussen, H., Canet, J., Rabbitt, P., Jolles, J., Larsen, K., Hanning, C.D., Langeron, O., Johnson, T., Lauven, P.M., Kristensen, P.A., Biedler, A., van Beem, H., Fraidakis, O., Silverstein, J.H., Beneken, J.E., & Gravestein, J.S. (1998). Long-term post-operative cognitive dysfunction in the elderly ISPOCD1 study. *Lancet, 351*, 857-861.

Moshki, M., Ghofranipour, F., Hajizadeh, E., & Azadfallah, P. (2007). Validity and reliability of the multidimensional health locus of control scale for college students. *BMC Public Health, 7*, 1471 – 2458.

Myers, J.S. (2009). Chemotherapy-related cognitive impairment: Neuroimaging, neuropsychological testing, and the neuropsychologist. *Clinical Journal of Oncology Nursing, 13*, 413-421.

Nelson, C.J., Nandy, N., & Roth, A.J. (2007). Chemotherapy and cognitive deficits: mechanisms, findings and potential interventions. *Palliative and Supportive Care, 5,* 273 – 280.

Newsom, J.T., Knapp, J.E., & Schulz, R. (1996). Longitudinal analysis of specific domains of internal control and depressive symptoms in patients with recurrent cancer. *Health Psychology, 15,* 323 – 331.

Pedersen, A.D., Rossen, P., Mehlsen, M.Y., Pedersen, C.G., Zachariae, R., & von der Maase, H. (2009). Long-term cognitive function following chemotherapy in patients with testicular cancer. *Journal of the International Neuropsychological Society, 15,* 296-301.

Prokasheva, S., Faran, Y., Cwikel, J., & Geffen, D.B. (2011). Analysis of memory deficits following chemotherapy in breast cancer survivors: evidence from the doors and people test. *Journal of Psychosocial Oncology, 29,* 499-514.

Reid-Arndt, S.A., Hsieh, C., & Perry, M.C. (2010). Neuropsychological functioning and quality of life during the first year after completing chemotherapy for breast cancer. *Psycho-Oncology, 19,* 535-544.

Roberts, R.W., Kuncel, N.R., Shiner, R., Caspi, A., & Goldberg, L.R. (2007). The power of personality: the comparative validity of personality traits, socioeconomic status and cognitive ability for predicting important life outcomes. *Perspectives on Psychological Science, 2,* 313 – 345.

Satin, J.R., Linden, W., & Phillips, M.J. (2009). Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer, 115,* 5349 – 5361.

Schagen, S.B., Boogerd, W., Muller, M.J., Huinink, W.T., Moonen, L., Meinhardt, W., & Van Dam, F.S. (2008). Cognitive complaints and cognitive impairment following BEP chemotherapy in patients with testicular cancer. *Acta Oncologica, 47,* 63-70.

Schagen, S.B., Das, E., & van Dam, F.S.A.M. (2009). The influence of priming and pre-existing knowledge of chemotherapy-associated cognitive complaints on the reporting of such complaints in breast cancer patients. *Psycho-Oncology, 18,* 674 – 678.

Schagen, S.B., van Dam, F.S., Muller, M.J., Boogerd, W., Lindeboom, J., & Bruning, P.F. (1999). Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer, 85,* 640-650.

Scheibel, R.S., Valentine, A.D., O'Brien, S., & Meyers, C.A. (2004). Cognitive dysfunction and depression during treatment with interpheron-alpha and chemotherapy. *Journal of Neuropsychiatry and Clinical Neurosciences, 16,* 185 - 191.

Seidenberg, M., Taylor, M.A., & Haitiner, A. (1994). Personality and self-report of cognitive functioning. *Archives of Clinical Neuropsychology, 9,* 353 – 361.

Shilling, V., & Jenkins, V. (2007). Self-Reported Cognitive Problems in Women Receiving Adjuvant Therapy for Breast Cancer. *European Journal of Oncology Nursing, 11*, 6-15.

Shilling, V., Jenkins, V., Morris, R., Deutsch, G., & Bloomfield, D. (2005). The effects of adjuvant chemotherapy on cognition in women with breast cancer - preliminary results of an observational longitudinal study. *The Breast, 14,* 142-150.

Skaali, T., Fossa, S.D., Andersson, S., Cvancarova, M., Langberg, C.W., Lehne, G., & Dahl, A.A. (2011). Self-reported cognitive problems in testicular cancer patients: relation to neuropsychological performance, fatigue, and psychological distress. *Journal of Psychosomatic Research, 70*, 403-410.

Snow, W.G., Tierney, M.C., Zorzitto, M.L., Fisher, R.H., & Reid, D.W. (1988). One-year test-retest reliability of selected tests in older adults. Paper presented at the meeting of the International Neuropsychological Society, New Orleans.

Stewart, A., Collins, B., Mackenzie, J., Tomiak, E., Verma, S., & Bielajew, C. (2008). The cognitive effects of adjuvant chemotherapy in early stage breast cancer: a prospective study. *Psycho-Oncology, 17,* 122-130.

Sucala, M.L., & Szentagotai Tatar, A. (2010). Optimism, pessimism and negative mood regulation expectancies in cancer patients. *Journal of Cognitive and Behavioural Psychotherapies, 10,* 13 – 24.

Taylor, S.E., Lichtman, R.R., & Wood, J.V. (1984). Attributions, beliefs about control, and adjustment to breast cancer. *Journal of Personality and Social Psychology, 46,* 489 – 502.

Tulsky, D., Zhu, J., & Ledbetter, M. (1997). WAIS-III WMS-III Technical Manual, San Antonio: The Psychological Corporation.

van Dam, F.S.A.M., Schagen, S.B., Muller, M.J., Boogerd, M., Wall, E.V.D., Fortuyn, M.E.D., & Rodenhuis, S. (1998). Impairment of Cognitive Function in Women Receiving Adjuvant Treatment for High-Risk Breast Cancer: High-Dose Versus Standard-Dose Chemotherapy. *Journal of the National Cancer Institute, 90,* 210-218.

Vardy, J. & Dhillon, H. (2010). The fog hasn't lifted on "chemobrain" yet: ongoing uncertainty regarding the effects of chemotherapy and breast cancer on cognition. *Breast Cancer Research and Treatment, 121.*doi: 10.1007/s10549-009-0719-0.

Ward, W.L., Hahn, E.A., Mo, F., Hernandez, L., Tulsky, D.S., & Cella, D. (1999). Reliability and validity of the Functional Assessment of Cancer Therapy – Colorectal (FACT-C) quality of life instrument. *Quality of Life Research, 8,* 181 – 195.

Wechsler D. (2001). *Wechsler Test of Adult Reading (WTAR).* San Antonio, TX: Harcourt Assessment.

Wefel, J.S., Lenzi, R., Theriault, R.L., Davis, R.N., & Meyers, C.A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer, 100,* 2292-2299.

Wefel, J.S., Vardy, J., Ahles, T., & Schagen S.B. (2011). International cognition and cancer task force recommendations to harmonise studies of cognitive function in patients with cancer. *The Lancet Oncology*; doi:10.1016/S0140-6736(08)61345-8.

Weiss, B. (2008). Chemobrain: a translational challenge for neurotoxicology. *Neurotoxicology, 29,* 891-898.

Weis, J., Poppelreuter, M., & Bartsch, H.H. (2009). Cognitive Deficits as Long-Term Side-Effects of Adjuvant Therapy in Breast Cancer Patients: 'Subjective' Complaints and 'Objective' Neuropsychological Test Results. *Psycho-Oncology, 18,* 775-782.

Whitford, H.S., & Olver, I.N (2012). When expectations predict experience: the influence of psychological factors on chemotherapy toxicities. *Journal of Pain and Symptom Management, 43,* 1036 – 1050.

Williams, N.A., Davis, G., Hancock, M., & Phipps, S. (2010). Optimism and Pessimism in Children with Cancer and Healthy Children: Confirmatory Factor Analysis of the Youth Life Orientation Test and Relations with Health-Related Quality of Life. *Journal of Paediatric Psychology, 35,* 672 – 682.

Willis, S.L., & Marsiske, M. (1993). *Manual for the everyday problems test.* University Park: Department of Human Development and Family Studies, Pennsylvania State University.

Yamada, T.H., Denburg, N.L., Beglinger, L.J., & Schultz, S.K. Neuropsychological outcomes of older breast cancer survivors: Cognitive features ten or more years after chemotherapy. *The Journal of Neuropsychiatry and Clinical Neurosciences, 22,* 48-54.

Zenger, M., Brix, C., Borowski, J., Stolzenburg, J., & Hinz, A. (2010). The impact of optimism on anxiety, depression and quality of life in urogenital cancer patients. *Psycho-Oncology, 18,* 879 – 886.