

Cognitive deficits associated with cancer: A model of subjective and objective outcomes

Author

Green, HJ, Pakenham, KI, Gardiner, RA

Published

2005

Journal Title

Psychology, Health and Medicine

DOI

[10.1080/13548500500093308](https://doi.org/10.1080/13548500500093308)

Rights statement

© 2005 Taylor & Francis. This is the author-manuscript version of the paper. Reproduced in accordance with the copyright policy of the publisher. Please refer to the journal link for access to the definitive, published version.

Downloaded from

<http://hdl.handle.net/10072/16907>

Griffith Research Online

<https://research-repository.griffith.edu.au>

Cognitive Deficits Associated With Cancer: A Model of Subjective and Objective Outcomes

Heather J. Green^{1,2}, Kenneth I. Pakenham³, & Robert A. Gardiner⁴

¹Inner North Brisbane Mental Health Service, Brisbane, Australia

²LPC-CNRS & Université de Provence, Marseille, France

³School of Psychology and ⁴Department of Surgery at Mayne School of Medicine, The University of Queensland, Brisbane, Australia

** PREPRINT: In press in *Psychology, Health and Medicine*, to be published in 2005**

Short Title: SUBJECTIVE AND OBJECTIVE

Correspondence should be addressed to: Dr Heather J. Green, Inner North Brisbane Mental Health Service, 162 Alfred Street, Fortitude Valley Qld 4006, Australia

Fax: +61 (0) 7 3834 1696; Phone: +61 (0) 7 3834 1605; Email:

Heather_Green@health.qld.gov.au

Abstract

Cancer and its treatment can affect many different aspects of quality of life. As a construct measured subjectively, quality of life shows an inconsistent relationship with objective outcome measures. That is, sometimes subjective and objective outcomes correspond with each other and sometimes they show little or no relationship. In this article, we propose a model for the relationship between subjective and objective outcomes using the example of cognitive function in people with cancer. The model and the research findings on which it is based help demonstrate that, in some circumstances, subjective measures of cognitive function correlate more strongly with psychosocial variables such as appraisal, coping, and emotions than with objective cognitive function. The model may provide a useful framework for research and clinical practice in quality of life for people with cancer.

Cognitive Deficits Associated With Cancer: A Model of Subjective and Objective Outcomes

In oncology, treatment advances leading to improved survival have meant that quality of life issues have assumed greater significance in the past few decades. One such issue is cognition. Comparison of reviews over time shows the increasing interest in and evidence base for neuropsychological impacts of cancer and cancer treatments (for example, Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Cull, 1990; Meyers, 2000; Silberfarb, 1983). Although neuropsychological issues may seem most relevant when cancer directly involves the brain, through either primary or secondary brain tumours, there are a number of additional ways in which cognition can be altered in people with cancer.

In examining the literature on cognitive function in people with cancer, we were struck by the lack of integration between neuropsychological and quality of life accounts. More recent work has used a more integrated approach (Cull et al., 1996; Poppelreuter et al., 2004; Tannock, Ahles, Ganz, & Van Dam, 2004). Neuropsychology has developed valuable methods for quantifying cognitive function, focusing mostly on objective measurement, whereas the construct of “quality of life” focuses on subjective experience (Bowling, 1991). To facilitate clinical and theoretical applications, this article examines the literature on subjective and objective cognitive function in people with cancer and proposes a model. The review is not exhaustive, but is intended to provide guidance for further theoretical development. The proposed model also has the potential to stimulate further exploration of the relationship between subjective and objective outcomes in domains other than cognitive function.

First, theoretical and empirical bases of objective and subjective cognitive function are discussed. Next, research findings in people with cancer are examined. The model is then presented. The final section discusses clinical implications.

Objective and Subjective Cognitive Function and Emotions

Theoretical Background

The distinction between objective and subjective cognitive performance has been raised by a number of authors (for example, Cull et al., 1996; Tannock et al., 2004) and needs closer attention in determining appropriate practice regarding assessment and management of cognitive problems. Objective cognitive function is most accurately assessed by neuropsychological tests that meet psychometric criteria such as reliability and validity and are referenced to appropriate normative values. Deficits associated with cancer are sometimes global, such as delirium (Boyle, Abernathy, Baker, & Wall, 1998), but can often be more usefully described in terms of specific cognitive functions, such as attention, memory, or executive processes (Troy et al., 2000).

People's perceptions of their cognitive function have a different theoretical basis to objective indicators. Subjective perceptions are important in terms of the construct of "quality of life" which is considered to be multidimensional and subjective (Bowling, 1991). However, these perceptions sometimes show little or no relationship with objective measures of cognitive performance but instead correlate with emotional distress (Cull et al., 1996; van Dam et al., 1998). A dominant paradigm in the chronic illness field used to account for individual differences in subjective outcomes is the Lazarus and Folkman (1984) stress and coping model. According to stress and coping theory, outcomes that occur in response to a stressor are mediated by the individual's appraisal of the stressor and his or her coping resources and strategies. Reviews by Sabbioni (1991) and Temoshok (1987; 1991) have found significant associations of variables such as stress, appraisal, coping, and personality with physical and emotional outcomes in people with cancer. More research is required on the relationship between stress and coping predictors and subjective cognitive function, but a

number of studies have explored the connection with emotional distress, as summarised in the following section.

Empirical Findings

Several research groups have shown that people with health problems who reported subjective cognitive decrements were more likely to have emotional difficulties than objective deficits. Subjective cognitive impairment was more strongly related to depression and anxiety than to objective performance in people aged under and above 50 years who attended a memory clinic (Derouesne, Lacomblez, Thibault, & LePoncin, 1999), people who underwent surgery (Johnson et al., 2002; Moller et al., 1998), people with multiple sclerosis (Maor, Olmer, & Mozes, 2001), and people with chronic fatigue (Short, McCabe, & Tooley, 2002). Similarly, affect and personality were more predictive of memory and concentration complaints in haemodialysis patients than were neuropsychological or medical factors (Brickman, Yount, Blaney, Rothberg, & Kaplan De-Nour, 1996). For people with memory problems, patients' cognitive complaints correlated with depression but not with neuropsychological test performance and did not predict which patients developed dementia in the next two years (Tierney, Szalai, Snow, & Fisher, 1996). A study of 302 community-dwelling adults aged 75 years who did not have dementia found that subjective memory problems were not correlated with objective memory performance but showed small, significant correlations with depression and anxiety (Jungwirth et al., 2004).

Other studies have found subjective cognitive performance to be unrelated to emotional distress and associated with objective cognitive functioning. For people with acquired brain injury, a memory questionnaire and daily memory checklist correlated with neuropsychological tests of memory (Ownsworth & McFarland, 1999). Similarly, subjective cognitive deficits have been associated with the risk of developing a first psychotic episode in people at elevated risk of schizophrenia (Hambrecht, Lammertink, Klosterkotter, Matuschek,

& Pukrop, 2002), the risk of developing dementia in elderly adults with normal Modified Mini-Mental State Examination score at baseline after controlling for age, gender, and depressive symptoms (St John & Montgomery, 2002), memory, attention, and executive function scores in people with multiple sclerosis (Matotek, Saling, Gates, & Sedal, 2001; Randolph, Arnett, & Higginson, 2001), neuropsychological performance in people with subjective memory impairment (Clarnette, Almeida, Forstl, Paton, & Martins, 2001), and the extent of white matter lesions measured with magnetic resonance imaging in 1,049 older adults who did not have dementia (de Groot et al., 2001).

Inconsistent findings regarding the associations between subjective cognitive functioning and both emotional distress and objective performance may be due to variations in operational definitions and measurement of subjective impairment. Studies that have found closer correspondence between subjective and objective cognitive measures appear to have more often used specific behavioural checklists (for example, Ownsworth & McFarland, 1999) and included control groups (for example, Clarnette et al., 2001; Matotek et al., 2001). Reports of changes in cognitive function may be more closely linked to objective function than participants' estimates of absolute function (de Groot et al., 2001; Hambrecht et al., 2002). Stronger associations between subjective and objective performance have been reported in people with higher levels of either education (Randolph et al., 2001) or objective performance (de Groot et al., 2001).

Emotions and Objective Performance

A further consideration in understanding the role of emotional distress is the link between it and objective performance (Cull, 1990). Reviews have found that approximately 25-45% of people with cancer show significant psychiatric difficulties, such as depression and anxiety, associated with diagnosis and treatment (Harrison & Maguire, 1994; Hughes, 1987). In both younger and older adults without cancer, major depression has been associated with

deficits in attention, memory, language and perception (Christensen, Griffiths, MacKinnon, & Jacomb, 1997; Lamberty & Bieliauskas, 1993). Sub-clinical depression does not appear to significantly affect cognitive function (Lamberty & Bieliauskas, 1993). A diagnostic category of “pseudodementia” is sometimes used for people who show cognitive impairment presumed to be secondary to depression, which is remediated if depression is successfully treated (Antikainen et al., 2001; Lezak, 1995). These impairments may affect only some individuals with depression, and are seen as “an attentional-motivational deficit” (Lezak, 1995).

Neurological and psychosocial studies have supported an influence of emotions on cognitive processes (Ciompi, 1991). For example, positron emission tomography scans of 10 young men undertaking verbal information-processing tasks showed differential cognitive processing with mood. Depressed mood, but not neutral or elated moods, attenuated task-related activation in anterior cingulate cortex (a brain area involved in executive and emotional functions; Baker, Frith, & Dolan, 1997). Clinically depressed people (Winter & Kuiper, 1997) or healthy individuals experiencing experimentally-induced depressive states (Varner & Ellis, 1998) show increased recall of negative emotion words. In contrast, nondepressed people show greater recall for positive adjectives, and mildly depressed recall an equal balance of both (Winter & Kuiper, 1997). Similarly, anxious people display greater attention to and recall for fear-relevant stimuli (Winter & Kuiper, 1997). Thus, emotional states can affect cognitive processes such as attention and memory.

Neurological dysfunction that disrupts cognition can also cause emotional distress, either directly or as a secondary reaction to loss of abilities (Hughes, 1987; Meyers, 2000; Reitan & Wolfson, 1997). For example, when chemotherapy was supplemented with interleukin treatment, both negative mood and cognitive impairment increased in patients, compared with chemotherapy alone (Walker et al., 1997). Affective symptoms in people with cancer may indicate underlying neurological deficits (Oxman & Silberfarb, 1987). In one

series of 100 consecutive psychiatric referrals from an oncology service, 40 people showed evidence of an organic brain syndrome and, importantly, 26 of these had not been recognised by the referring physician (Levine, Silberfarb, & Lipowski, 1978).

In summary, people who experience significant emotional disruption associated with cancer may be at risk of cognitive dysfunction secondary to emotional disturbance. If this occurred, the expected pattern of performance would be intact temporal orientation and relatively intact performance on recognition tasks, even if immediate recall were impaired (Lezak, 1995). Emotional disruption and cognitive impairment can also have a common cause, being due to underlying neurological dysfunction.

Based on the reports described above, subjective cognitive assessment cannot be assumed to be a good indicator of objective cognitive function, unless the instrument's validity for this purpose has been established. Subjective reports appear to cover a spectrum from those sharing substantial variance with emotional distress but none with objective performance, to those with strong correspondence with objective performance and no correspondence with affect. We therefore consider objective and subjective cognitive changes separately in reviewing a sample of studies on contributing factors during the following sections. More detailed reviews on this topic include those by Meyers (2000) and Reeb and Regan (1998). A meta-analysis by Anderson-Hanley and colleagues provides a quantitative overview (Anderson-Hanley et al., 2003).

Objective Cognitive Function

Tumour Effects

The risk of impairment differs according to the site of malignancy. Presently available data limit comparisons of the nature and prevalence of cognitive impairment between specific types of cancer because cognitive effects have been defined and measured differently by separate researchers (Armstrong, Gyato, Awadalla, Lustig, & Tochner, 2004; Weitzner &

Meyers, 1997). Patient groups that have recently been considered as susceptible to cognitive dysfunction include those with primary or secondary brain tumours (Weitzner & Meyers, 1997), small-cell lung cancer (Klein et al., 2001), and terminal malignancies from a variety of primary sites (Bruera et al., 1992; Pereira, Hanson, & Bruera, 1997).

Localised or metastatic tumours in brain are thought to frequently disrupt mental functions, especially problem-solving skills and coping with novel situations (Meyers, 2000; Weitzner & Meyers, 1997). In summarising literature with wide variation in definitions and methods of assessing impairment, previous reviewers have concluded that cognitive impairments affect a high number of people with primary or secondary brain tumours, especially if subtle impairments are included (Benesch et al., 2001; Weitzner & Meyers, 1997). Rates of neuropsychological impairment as high as 100% have been reported, in 68 people who had neurosurgery for recently diagnosed glioma compared with healthy controls (Klein et al., 2001). However, this figure is likely to overestimate changes that are clinically significant. Metastatic tumours to brain are relatively common, occurring in 20-40% of patients with non-neurological solid primary malignancies (Meyers, 2000).

Tumours can also have indirect, nonlocalised effects on brain function. Of eight people with multiple myeloma admitted to a general hospital, four exhibited delirium (Silberfarb & Bates, 1983). Many people with small-cell lung cancer exhibit subclinical impairments in memory and planning before treatment, in the absence of brain metastases (Meyers, 2000). In comparisons with people without cancer, a 52% rate of neuropsychological impairment was found among 50 people with small-cell lung cancer (Klein et al., 2001). A slowly progressive neurological syndrome has been described in treated patients with small cell lung cancer but without central nervous system metastases, 26-50 months after cranial irradiation and systemic chemotherapy (So, O'Neill, Frytak, Eagan, & al, 1987). The 6 patients described by So et al. showed apathy, abulia, memory loss, gait

ataxia, and corticospinal tract signs. Certain leukaemia patients are potentially at risk of cognitive impairment because of elevated circulating levels of cytokines, which have been associated with cognitive and mood dysfunction (Licinio, Kling, & Hauser, 1998; Walker et al., 1997).

Advanced disease appears to significantly increase cognitive vulnerability. Systemic effects of tumours that can disrupt cognitive function in advanced cancers include hypercalcaemia caused by bone metastases (Boyle et al., 1998), metabolic disturbances and infections (Meyers, 2000) as well as multiple system failure terminally (Pereira et al., 1997). Both prospective and retrospective studies have shown that as many as 68-83% of people receiving palliative care for terminal cancer scored in the impaired range on the Mini-Mental Status Examination at some time before death (Bruera et al., 1992; Pereira et al., 1997). Sepsis and brain metastases were the most frequently identified causes of impairment in these patients, after medications which were the most frequent cause (Bruera et al., 1992; Pereira et al., 1997). Further research with specific groups of people with cancer would be beneficial, especially if more studies included non-cancer comparison groups.

Treatment Effects

The potential for cognitive deterioration can also increase due to treatment. Cancer treatments that have been associated with cognitive impairment include chemotherapy, cranial irradiation, cytokines, hormonal ablation, palliative medications, and anticholinergic drugs.

Chemotherapy. Many different chemotherapy agents or combinations of agents have been associated with adverse cognitive changes (Boyle et al., 1998; Hughes, 1987). Neurotoxic agents most frequently affect visuoperceptual, psychomotor constructional skills, reaction time, verbal conceptualisation, short-term memory, attention, and executive processes, possibly through selective actions on the frontal lobes, hippocampus and amygdala (Troy et al., 2000). In other words, diffuse effects are seen on tests requiring sustained

attention and rapid information processing (Meyers, 2000). For example, of 28 women aged 28-54 who had undergone chemotherapy for breast cancer within the last 12 months but not within 2 weeks of testing, 75% scored in the range of moderate cognitive impairment compared with age, gender and education norms on a comprehensive neuropsychological battery (Wieneke & Dienst, 1995). The group performed significantly lower than norms in five of seven cognitive areas, with only verbal fluency and abstract reasoning remaining intact.

Neurotoxic effects of chemotherapy are usually reversible but sometimes persist after treatment ends (Cull, 1990). Of women with breast cancer who were randomly assigned to high- or standard-dose chemotherapy, cognitive impairment two years after treatment was found in 32% of women in the high-dose group, compared with 17% of women assigned to standard-dose, and 9% of women with Stage I breast cancer who were not treated with chemotherapy (van Dam et al., 1998). Significant neurophysiological differences were also detected in a subset of the women tested with quantitative electroencephalograms at two years post-treatment: asymmetry of the alpha rhythm of at least 5 Hz was found in 7/17 high dose patients, 2/16 standard dose patients, but 0/14 comparison group patients (Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001).

A strength of the study of van Dam and colleagues was its use of random assignment to treatment. The study demonstrated that the risk of cognitive impairment increased with higher chemotherapy doses. Fortunately, the cognitive deficits appeared to have remediated by 4-year follow up, although there were some indications of differential attrition of participants with lower baseline cognitive scores because of increased rates of disease progression (Schagen et al., 2002). Another research group found that, of 128 patients who were disease-free at least 5 years after diagnosis with breast cancer or lymphoma, those treated with systemic chemotherapy scored significantly lower on a battery of

neuropsychological tests than those treated with local therapy (Ahles et al., 2002). Deficits were found after controlling for age and education and were most pronounced for verbal memory and psychomotor functioning (Ahles et al., 2002). These chemotherapy treatment studies have provided stronger evidence of impairment than studies using mental status examinations, because they used well-developed measures of specific functions and compared patients' performance with either normative data or other patient groups. A recent review of psychometrically controlled chemotherapy studies in women with breast cancer found that studies reported cognitive deficits in 16-50% of participants (Tannock et al., 2004).

Radiotherapy. Radiotherapy has been associated with cognitive impairment in some individuals, including both children (Cousens, Waters, Said, & Stevens, 1988; Eiser, 1998) and adults (Armstrong et al., 2004; Olson, Riedel, & DeAngelis, 2000). Cranial irradiation produces the greatest cognitive risk (Eiser, 1998), due to damage of subcortical white matter (Armstrong et al., 2004; Meyers, 2000). A number of studies have reported increased cognitive effects from cranial irradiation in children younger than 5 at the time of treatment (Cousens et al., 1988; Kaleita, 2002; Winqvist, Vainionpaa, Kokkonen, & Lanning, 2001), although others have found no age effect (Iuvone et al., 2002). Because of such findings, cranial irradiation is now avoided for infants younger than 2 years (Eiser, 1998). A recent review has outlined a number of aspects of cognitive impairment associated with cranial radiotherapy, including evidence for a dose-response relationship and differences between early, largely reversible deficits found within several months of radiotherapy and persisting deficits, which are more often associated with late effects that develop 12 months or more after treatment (Armstrong et al., 2004).

In 20 adults treated with cranial radiotherapy for low-grade brain tumours, verbal-semantic recall was impaired, but other attentional and memory processes were not affected (Armstrong, Stern, & Corn, 2001). Of 62 people with low grade oligodendrogliomas or

mixed gliomas who received radiotherapy, radiotherapy-associated cognitive changes were found in 13 people (Olson et al., 2000). In contrast, a study of 13 adults with brain tumours found cognitive deficits before radiotherapy in attention, memory and visuospatial construction compared with healthy controls, but these deficits did not worsen when participants were retested 2 weeks and 3 months after completing radiotherapy (Lilja, Portin, Hamalainen, & Salminen, 2001).

Cytokines. Cytokine treatment with interferon has been associated with impaired performance on attentional tasks, such as Digit Symbol and Trailmaking B (Capuron, Ravaud, & Dantzer, 2001; Licinio et al., 1998). Deficits were significantly worse in people who received cytokines combined with chemotherapy, compared with chemotherapy alone, and impairments were reversed with cessation of cytokine treatment (Walker et al., 1997). The early onset of cytokine cognitive effects was shown in a study which found that people treated with interleukin-2 showed a decline in performance in spatial working memory and planning that was apparent at both 5 days and 1 month of treatment compared with pre-treatment (Capuron et al., 2001). In the same study, people treated with interferon alpha showed no deficits in those tasks but instead showed increased reaction times (Capuron et al., 2001). These findings emphasise the potential for exogenously produced and delivered cytokines to impair cognition, and draw attention to the need to measure cognitive effects of endogenous (internally produced) cytokines as mentioned earlier.

Hormonal Ablation. Several reviews have noted associations between hormonal ablation treatments, such as those used for breast or prostate cancer, and cognitive impairment (Olin, 2001; Tannock et al., 2004; Thompson, Shanafelt, & Loprinzi, 2003). In a randomised 12-month clinical study completed by 62 men with prostate cancer, men assigned to hormonal ablation with leuprorelin, goserelin, or cyproterone acetate showed cognitive deficits in memory, attention, and executive function compared with their baseline performance and the

performance of no-treatment controls (Green et al., 2002; Green et al., 2004). A study of 19 men treated with 9 months of intermittent androgen suppression with leuprolide and flutamide, compared with community controls, found that spatial rotation performance declined during androgen blockade but most cognitive functions were unimpaired (Cherrier, Rose, & Higano, 2003). Salminen and colleagues also found that 25 men treated for 12 months with androgen deprivation for prostate cancer showed practice effects and did not decline in cognitive performance (Salminen et al., 2003). A recent review of cognitive studies in women with cancer suggested that one of the routes of impairment associated with chemotherapy may be endocrine effects resulting in accelerated loss of sex steroids (Olin, 2001).

Surgery. Surgical procedures, especially in older adults, have been associated with adverse cognitive effects in both acute (Milisen, Abraham, & Broos, 1998) and longer-term phases (Goldstein, Fogel, & Young, 1996). While cognitive effects of cardiac surgery have been known for some time (Emskoetter & Lachenmayer, 1990), adverse cognitive effects of non-cardiac surgery have been also been demonstrated in both small-sample studies using mental status examination (Milisen et al., 1998) and large international studies using comprehensive neuropsychological testing and control groups (Johnson et al., 2002; Moller et al., 1998). Of 1218 adults aged 60 or more who underwent non-cardiac surgery, 26% were impaired on a neuropsychological battery 1 week after surgery and 10% remained impaired 3 months later (Moller et al., 1998). A related study in adults aged 40-60 who had non-cardiac surgery found postoperative cognitive impairment in 19% at 1 week and 6% at 3 months (Johnson et al., 2002). Surgical treatments for cancer would be predicted to lead to acute cognitive deficits for some individuals and chronic impairments for a smaller proportion of patients. In support of this prediction, impaired attentional performance post-surgery, compared with pre-surgery, has been found in women treated for breast cancer (Cimprich,

1998). However, the study did not establish whether deficits persisted. Many other surgical treatments for cancer have yet to be assessed for cognitive effects.

Additional Treatments. Several other treatments have shown some evidence of cognitive effects. In a group of 40 adult patients assessed at least 2 years after bone marrow transplantation, 60% showed mild to moderate cognitive impairment on neuropsychological tests compared with community norms (Harder et al., 2002). Palliative medications that have been associated with impairment include analgesics, such as opioids (Pereira et al., 1997), corticosteroids, such as prednisone (Wolkowitz, Reus, Canick, Levin, & Lupien, 1997), psychotropic medications (Meyers, 2000), and antiemetics (Meyers, 2000). The potential for cognitive impairment associated with anticholinergic medications, especially in elderly people, is also increasingly recognised (Mintzer & Burns, 2000; Tune, Carr, Hoag, & Cooper, 1992).

Subjective Cognitive Function

Concerns about adverse subjective cognitive effects associated with cancer or its treatment have become increasingly common among cancer support groups, leading to use of terms such as “chemo-brain” (Tannock et al., 2004). Within oncology, comparatively few researchers have measured both objective and subjective cognitive function. Similar to the literature in people with other health conditions discussed above, some studies have found emotion-linked subjective performance and others have found correlated subjective and objective deficits.

Cull and colleagues found that, of 91 adults treated for lymphoma at least six months previously (62 with chemotherapy, 27 with no chemotherapy, and 2 with treatment not reported), 52% reported memory problems and 30% difficulty concentrating (Cull et al., 1996). However, self-reported deficits did not correlate with objective performance and were instead associated with higher anxiety, depression, and fatigue. This suggested to the

researchers that perceived decrements in cognition were more closely related to emotional and physical status than objective cognitive functioning (Cull et al., 1996). Similarly, in women treated with standard- or high-dose chemotherapy for breast cancer, two measures of subjective cognition correlated with each other and with anxiety and depression, but showed no relationship with objective cognitive function (van Dam et al., 1998). A study of 102 people with cancer of areas other than brain, before and after chemotherapy, found that a subjective cognitive measure had no correlation with Mini-Mental Status Examination score but correlated significantly with anxiety and depression (Iconomou, Mega, Koutras, Iconomou, & Kalofonos, 2004). In 61 people with cancer aged 25-87, the subjective item 11 on the Zung Self-Rating Depression Scale “My mind is as clear as it used to be” correlated with depression and showed poor sensitivity and specificity in identifying cognitive dysfunction as measured by a Trail-Making task, a Stroop task, and the Dementia Rating Scale (Kibiger, Kirsh, Wall, & Passik, 2003).

One study specifically designed to examine the relationship between subjective and objective cognition in people with cancer found that 24% of the 119 participants showed clinically impaired neuropsychological performance. However, there were no significant correlations between neuropsychological test performance and subjective reports of everyday cognitive performance (Poppelreuter et al., 2004). These subjective reports instead correlated with affective measures, more strongly with depression than anxiety (Poppelreuter et al., 2004). In contrast, for people who remained progression-free for at least 2 years after bone marrow transplantation, subjective cognitive complaints did correlate significantly with moderate to severe cognitive deficits measured by neuropsychological testing (Harder et al., 2002).

A Model of Cognitive Function in People With Cancer

Based on the above literature, Figure 1 proposes a model of factors contributing to cognitive impairment in people with cancer. Objective and subjective impairment are presented as separate outcomes. The article has discussed two parts of the model in detail: the links between objective and subjective cognitive function and emotion, and tumour and treatment effects on cognitive function. Findings that psychosocial factors can influence emotional distress and correlate with physical health have been incorporated as a pathway in the model.

Insert Figure 1 about here

Three factors contributing to objective impairment are proposed: physical health, medical treatments, and emotions. Within predictors listed under physical health, tumour effects have received the most focus in this article. Previous reviews have discussed other physical health cognitive predictors, including age (for children, see Challinor, Miaskowski, Moore, Slaughter, & Franck, 2000; Chen et al., 1998; for cognitive aging see Luszcz & Bryan, 1999; Riedel & Jolles, 1996) and general medical conditions (Siegler & Vitaliano, 1998; Zelinski, Crimmins, Reynolds, & Seeman, 1998). Researchers specifically addressing chemotherapy have proposed a model which shares some similarities with the current model (Tannock et al., 2004); however, the model presented in this paper was developed independently.

Clinical Implications

Assessment

Identification of and treatment for cognitive deficits is important, since cognition is a key variable determining whether people can live independently or with minimal assistance (Wang, van Belle, Kukull, & Larson, 2002). Cognitive assessment can provide information needed to plan practical issues such as transport, work, and support needs. Assessment may

also assist staff to tailor communication, such as reducing information processing demands for patients who have difficulty sustaining attention. Cognitive and emotional function should be assessed at presentation and on an ongoing basis.

Screening measures for global dysfunction were reviewed by Boyle and colleagues (Boyle et al., 1998). The review identified several relatively brief measures that can detect generalised dysfunction, have demonstrated sensitivity to cognitive changes in people with cancer, and can be administered frequently (Breitbart et al., 1997; Folstein, Folstein, & McHough, 1975; Neelon, Champagne, Carlson, & Funk, 1996; Williams, 1991). For inpatients with advanced malignancy, mental status examination as often as three times per week has identified cognitive dysfunction in some patients that had not previously been recognised by medical or nursing staff (Bruera et al., 1992).

When more detailed assessment is required, referral to a neuropsychologist or clinical psychologist with neuropsychological expertise allows assessment with standard tests that provide more specific information about the nature and severity of cognitive dysfunction and are able to detect more subtle forms of impairment. Major cognitive domains to assess include attention, memory, language, visuomotor, and executive functions. For surgical patients, a useful research battery for detecting postoperative cognitive function included visual verbal learning (based on Rey's Auditory Verbal Learning Test; Lezak, 1995), concept shifting (based on Trailmaking; Lezak, 1995), the Stroop colour word interference test (Sprenen & Strauss, 1991), letter-digit coding (based on Digit Symbol; The Psychological Corporation, 1997), and a paper and pencil memory scanning test (Moller et al., 1998). The same or similar tasks have shown sensitivity to cognitive effects of cancer treatments (van Dam et al., 1998; Walker et al., 1997; Wieneke & Dienst, 1995).

If subjective cognitive function is of concern, behavioural checklists that have shown associations with objective deficits in people without cancer include the Daily Memory

Checklist (Ownsworth & McFarland, 1999), Cognitive Failures Questionnaire (Broadbent, Cooper, Fitzgerald, & Parkes, 1982), Subjective Memory Questionnaire (Bennett-Levy & Powell, 1980), and an inventory of everyday memory experiences (Herrmann & Neisser, 1978). Measures such as the two-item Cognitive Function subscale (Fayers, Aaronson, Bjordal, & Sullivan, 1997) and interview for cognitive problems in daily life (van Dam et al., 1998) have been associated more closely with emotional distress than objective cognitive function in reports to date.

Interventions

Interventions suggested by this model include incorporating individual patient susceptibility when planning treatment, educating patients and families about current and anticipated cognitive function, identifying factors contributing to an individual's difficulties, and remediating these factors when possible. Staff should be informed so that they can tell patients that procedures such as chemotherapy and cranial radiotherapy are associated with cognitive dysfunction for some individuals and that, in many situations, there is likely to be improvement over time if treatments disrupt cognition (Moller et al., 1998; Walker et al., 1997). In people with elevated risk of cognitive dysfunction, all potentially problematic medications and procedures should be reviewed before embarking on definitive cancer treatment which may adversely affect cognition.

Treating cognitive dysfunction associated with cancer has previously been described for both terminal (Boyle et al., 1998; Bruera et al., 1992) and earlier stage (Butler & Copeland, 2002; Meyers, 2000) cancer. One protocol for people with terminal cancer initiated investigation whenever MMSE was less than 24 or decreased more than 30% from previous function (Bruera et al., 1992). If these criteria were met, medical and laboratory evaluations were undertaken, medications were reviewed and, if possible, all drugs that could contribute to cognitive dysfunction were discontinued or reduced in dose. Additionally, if

indicated by the medical examination, computerised tomography or pulse oximetry was performed (Bruera et al., 1992). We recommend that emotional distress should also be evaluated and treated. Also, alternative criteria for cognitive dysfunction should be considered, given the limitations of the MMSE.

Pharmacological agents may assist in preventing (Troy et al., 2000) or remediating (Weitzner & Meyers, 1997) cognitive impairment associated with cancer treatment. However, before adding medications, it is prudent to review those currently being prescribed so that preparations with adverse cognitive properties might be removed or replaced with alternatives. Alberts and Noel (1995) reviewed the potential for agents such as nerve growth factor and amifostine to prevent neurotoxicity associated with cisplatin. Methylphenidate has been reported to have benefits for alleviating cognitive dysfunction in people with cancer (Rozans, Dreisbach, Lertora, & Kahn, 2002; Weitzner & Meyers, 1997), including in a randomised placebo-controlled trial which found a specific benefit for sustained attention (Thompson et al., 2001). Corticosteroid use was also reported to have possible cognitive benefits for people with gliomas (Klein et al., 2001) or treatment-associated leukoencephalopathy (Noble & Dietrich, 2002) although this class of drugs has also been implicated in adverse cognitive effects (Wolkowitz et al., 1997). Neural stem cells have been suggested as a possible future avenue for treating both brain tumours and treatment-associated cognitive dysfunction (Noble & Dietrich, 2002). However, any effort to modify adverse impacts needs to be considered in the context of the overall patient and cancer program.

Cognitive rehabilitation treatment may also assist, especially for persisting impairment (Meyers, 2000; Wilson, 1997). Ideally, cognitive rehabilitation addresses cognitive problems in the context of social, emotional, and functional difficulties (Wilson, 1997). Assessment of impairments in these domains and the impact of impairments on daily life is followed by individual or group therapy designed to overcome the effects of impairments (Ownsworth &

McFarland, 1999; Weitzner & Meyers, 1997). Multidisciplinary rehabilitation teams, including health professionals such as psychologists, speech pathologists and occupational therapists, are recommended (Weitzner & Meyers, 1997; Wilson, 1997). Cognitive rehabilitation programs have begun to be reported for people with cancer, including children (Butler & Copeland, 2002) and older adults (McDougall Jr, 2001).

Conclusion

The research studies discussed in this paper support the proposition that cancer and its treatment is linked in a significant minority of patients with cognitive dysfunction serious enough to warrant investigation and treatment. Subjective perceptions of cognitive impairment are important to quality of life and sometimes show significant relationships with objective measures. However, this is not true of all subjective measurement; other measures are associated with emotional distress more strongly than with objective function. Further research needs to inform clinicians so that they might consider multiple causal pathways associated with cognitive dysfunction, including precancer function, comorbid conditions, tumour effects, depression, anxiety, and current medical treatments, in order to minimise adverse effects from both tumour and treatment in at-risk patients. The subjective and objective distinction also needs further attention for other, non-cognitive outcomes associated with quality of life.

References

AHLES, T. A., SAYKIN, A. J., FURSTENBERG, C. T., COLE, B., MOTT, L. A., SKALLA, K., WHEDON, M. B., BIVENS, S., MITCHELL, T., GREENBERG, E. 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.

ALBERTS, D. S., & NOEL, J. K. (1995). Cisplatin-associated neurotoxicity: Can it be prevented? Anti-Cancer Drugs, *6*, 369-383.

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 JINS, *9*, 967-982.

ANTIKAINEN, R., HANNINEN, T., HONKALAMPI, K., HINTIKKA, J., KOIVUMAA-HONKANEN, H., TANSKANEN, A., & VIINAMAKI, H. (2001). Mood improvement reduces memory complaints in depressed patients. European Archives of Psychiatry and Clinical Neuroscience, *251*, 6-11.

ARMSTRONG, C. L., GYATO, K., AWADALLA, A. W., LUSTIG, R., & TOCHNER, Z. A. (2004). A critical review of the clinical effects of therapeutic irradiation damage to the brain: the roots of controversy. Neuropsychology review, *14*, 65-86.

ARMSTRONG, C. L., STERN, C. H., & CORN, B. W. (2001). Memory performance used to detect radiation effects on cognitive functioning. Applied Neuropsychology, *8*, 129-139.

BAKER, S. C., FRITH, C. D., & DOLAN, R. J. (1997). The interaction between mood and cognitive function studied with PET. Psychological Medicine, *27*, 565-578.

BENESCH, M., LACKNER, H., SCHAGERL, S., GALLISTL, S., FREY, E. M., & URBAN, C. (2001). Tumor- and treatment-related side effects after multimodal therapy of childhood intracranial germ cell tumors. Acta Paediatrica, *90*, 264-270.

BENNETT-LEVY, J., & POWELL, G. E. (1980). The Subjective Memory Questionnaire (SMQ). An investigation into the self-reporting of "real-life" memory skills. British Journal of Social and Clinical Psychology, *19*, 177-188.

BOWLING, A. (1991). Measuring health: A review of quality of life measurement scales. Buckingham: Open University Press.

BOYLE, D. M., ABERNATHY, G., BAKER, L., & WALL, A. C. (1998). End-of-life confusion in patients with cancer. Oncology Nursing Forum, *25*, 1335-1343.

BREITBART, W., ROSENFELD, B., ROTH, A., SMITH, M. J., COHEN, K., & PASSIK, S. (1997). The Memorial Delirium Assessment Scale. Journal of Pain and Symptom Management, *13*, 128-137.

BRICKMAN, A. L., YOUNT, S. E., BLANEY, N. T., ROTHBERG, S., & KAPLAN DE-NOUR, A. (1996). Pathogenesis of cognitive complaints in patients on hemodialysis. General Hospital Psychiatry, *18*, 36-43.

BROADBENT, D. E., COOPER, P. F., FITZGERALD, P., & PARKES, K. R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. British Journal of Clinical Psychology, *21*, 1-16.

BRUERA, E., MILLER, L., MCCALLION, J., MACMILLAN, K., KREFTING, L., & HANSON, J. (1992). Cognitive failure in patients with terminal cancer: A prospective study. Journal of Pain and Symptom Management, *7*, 192-195.

BUTLER, R. W., & COPELAND, D. R. (2002). Attentional processes and their remediation in children treated for cancer: a literature review and the development of a therapeutic approach. Journal of the International Neuropsychological Society, *8*, 115-124.

CAPURON, L., RAVAUD, A., & DANTZER, R. (2001). Timing and specificity of the cognitive changes induced by interleukin-2 and interferon-alpha treatments in cancer patients. Psychosomatic Medicine, *63*, 376-386.

CHALLINOR, J., MIASKOWSKI, C., MOORE, I., SLAUGHTER, R., & FRANCK, L. (2000). Review of research studies that evaluated the impact of treatment for childhood cancers on neurocognition and behavioral and social competence: Nursing implications. Journal of the Society of Pediatric Nurses, *5*, 57-74.

CHEN, E., ZELTZER, L. K., BENTLER, P. M., BYRNE, J., NICHOLSON, H. S., MEADOWS, A. T., MILLS, J. L., HAUPT, R., FEARS, T. R., & ROBISON, L. L. (1998). Pathways linking treatment intensity and psychosocial outcomes among adult survivors of childhood leukemia. Journal of Health Psychology, *3*, 23-38.

CHERRIER, M. M., ROSE, A. L., & HIGANO, C. (2003). The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. Journal of Urology, *170*, 1808-1811.

CHRISTENSEN, H., GRIFFITHS, K., MACKINNON, A., & JACOMB, P. (1997). A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. Journal of the International Neuropsychological Society, *3*, 631-651.

CIMPRICH, B. (1998). Age and extent of surgery affect attention in women treated for breast cancer. Research in Nursing and Health, *21*, 229-238.

CIOMPI, L. (1991). Affects as central organising and integrating factors: A new psychosocial/biological model of the psyche. British Journal of Psychiatry, *159*, 97-105.

CLARNETTE, R. M., ALMEIDA, O. P., FORSTL, H., PATON, A., & MARTINS, R. N. (2001). Clinical characteristics of individuals with subjective memory loss in Western Australia: results from a cross-sectional survey. International Journal of Geriatric Psychiatry, *16*, 168-174.

COUSENS, P., WATERS, B., SAID, J., & STEVENS, M. (1988). Cognitive effects of cranial irradiation in leukaemia: A survey and meta-analysis. Journal of Child Psychology and Psychiatry and Allied Disciplines, *29*, 839-852.

CULL, A. (1990). Invited review: Psychological aspects of cancer and chemotherapy. Journal of Psychosomatic Research, *34*, 129-140.

CULL, A., HAY, C., LOVE, S. B., MACKIE, M., SMETS, E., & STEWART, M. (1996). What do cancer patients mean when they complain of concentration and memory problems? British Journal of Cancer, *74*, 1674-1679.

DE GROOT, J. C., DE LEEUW, F. E., OUDKERK, M., HOFMAN, A., JOLLES, J., & BRETELER, M. M. (2001). Cerebral white matter lesions and subjective cognitive dysfunction: the Rotterdam Scan Study. Neurology, *56*, 1539-1545.

DEROUESNE, C., LACOMBLEZ, L., THIBAUT, S., & LEONCIN, M. (1999). Memory complaints in young and elderly subjects. International Journal of Geriatric Psychiatry, *14*, 291-301.

EISER, C. (1998). Practitioner review: Long-term consequences of childhood cancer. Journal of Child Psychology and Psychiatry, *39*, 621-633.

EMSKOETTER, T., & LACHENMAYER, L. (1990). The susceptibility of the central nervous system to open heart surgery. In A. E. WILLNER & G. RODEWALD (Eds.), Impact of cardiac surgery on the quality of life: neurological and psychological aspects. (pp. 97-104). New York: Plenum Press.

FAYERS, P., AARONSON, N., BJORDAL, K., & SULLIVAN, M. (1997). EORTC QLQ-C30 scoring manual (revised). Brussels: EORTC Study Group on Quality of Life.

FOLSTEIN, M. F., FOLSTEIN, S. E., & MCHOUGH, P. R. (1975). Mini-Mental State: A practical method for grading the cognitive status of patients for the clinician. Journal of Psychiatric Research, *12*, 189-198.

GOLDSTEIN, M. Z., FOGEL, B. S., & YOUNG, B. L. (1996). Effect of elective surgery under general anesthesia on mental status variables in elderly women and men: 10-month followup. International Psychogeriatrics, *8*, 135-149.

GREEN, H. J., PAKENHAM, K. I., HEADLEY, B. C., YAXLEY, J., NICOL, D. L., MACTAGGART, P. N., SWANSON, C., WATSON, R. B., & GARDINER, R. A. (2002). Altered cognitive function in men treated for prostate cancer with LHRH analogues and cyproterone acetate: A randomised controlled trial. BJU International, *90*, 427-432.

GREEN, H. J., PAKENHAM, K. I., HEADLEY, B. C., YAXLEY, J., NICOL, D. L., MACTAGGART, P. N., SWANSON, C. E., WATSON, R. B., & GARDINER, R. A. (2004). Quality of life compared during pharmacological treatments and clinical monitoring for non-localized prostate cancer: a randomized controlled trial. BJU international, *93*, 975-979.

HAMBRECHT, M., LAMMERTINK, M., KLOSTERKOTTER, J., MATUSCHEK, E., & PUKROP, R. (2002). Subjective and objective neuropsychological abnormalities in a psychosis prodrome clinic. British Journal of Psychiatry, *43* (suppl.), s30-s37.

HARDER, H., CORNELISSEN, J. J., VAN GOOL, A. R., DUIVENVOORDEN, H. J., EIJKENBOOM, W. M. H., & VAN DEN BENT, M. J. (2002). Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. Cancer, *95*, 183-192.

HARRISON, J., & MAGUIRE, P. (1994). Predictors of psychiatric morbidity in cancer patients. British Journal of Psychiatry, *165*, 593-598.

HERRMANN, D. J., & NEISSER, U. (1978). An inventory of everyday memory experiences. In M. M. GRUENBERG & P. E. MORRIS & R. N. SYKES (Eds.), Practical Aspects of Memory (pp. 35-51). London: Academic.

HUGHES, J. E. (1987). Psychological and social consequences of cancer. Cancer Surveys, *6*, 455-475.

- 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.
- IUVONE, L., MARIOTTI, P., COLOSIMO, C., GUZZETTA, F., RUGGIERO, A., & RICCARDI, R. (2002). Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. Cancer, *95*, 2562-2570.
- JOHNSON, T., MONK, T., RASMUSSEN, L. S., ABILDSTROM, H., HOUX, P., KORTTILA, K., KUIPERS, H. M., HANNING, C. D., SIERSMA, V. D., KRISTENSEN, D., CANET, J., IBANAZ, M. T., MOLLER, J. T., & ISPOCD2 INVESTIGATORS. (2002). Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology, *96*, 1351-1357.
- JUNGWIRTH, S., FISCHER, P., WEISSGRAM, S., KIRCHMEYR, W., BAUER, P., & TRAGL, K. H. (2004). Subjective memory complaints and objective memory impairment in the Vienna-Transdanube aging community. Journal of the American Geriatrics Society, *52*, 263-268.
- KALEITA, T. A. (2002). Central nervous system-directed therapy in the treatment of childhood acute lymphoblastic leukemia and studies of neurobehavioral outcome: Children's Cancer Group trials. Current Oncology Reports, *4*, 131-141.
- KIBIGER, G., KIRSH, K. L., WALL, J. R., & PASSIK, S. D. (2003). My mind is as clear as it used to be: A pilot study illustrating the difficulties of employing a single-item subjective screen to detect cognitive impairment in outpatients with cancer. Journal of pain and symptom management, *26*, 705-715.
- KLEIN, M., TAPHOORN, M. J., HEIMANS, J. J., VAN DER PLOEG, H. M., VANDERTOP, W. P., SMIT, E. F., LEENSTRA, S., TULLEKEN, C. A., BOOGERD, W.,

BELDERBOS, J. S., CLEIJNE, W., & AARONSON, N. K. (2001). Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. Journal of Clinical Oncology, *19*, 4037-4047.

LAMBERTY, G. J., & BIELIAUSKAS, L. A. (1993). Distinguishing between depression and dementia in the elderly: A review of neuropsychological findings. Archives of Clinical Neuropsychology, *8*, 149-170.

LAZARUS, R. S., & FOLKMAN, S. (1984). Stress, appraisal and coping. New York: Springer Publishing.

LEVINE, P. M., SILBERFARB, P. M., & LIPOWSKI, Z. J. (1978). Mental disorders in cancer patients: A study of 100 psychiatric referrals. Cancer, *43*, 1385-1391.

LEZAK, M. D. (1995). Neuropsychological assessment (3rd ed.). New York: Oxford University Press.

LICINIO, J., KLING, M. A., & HAUSER, P. (1998). Cytokines and brain function: relevance to interferon-alpha-induced mood and cognitive changes. Seminars in Oncology, *25* (Suppl. 1), 30-38.

LILJA, A. M., PORTIN, R. I., HAMALAINEN, P. I., & SALMINEN, E. K. (2001). Short-term effects of radiotherapy on attention and memory performances in patients with brain tumors. Cancer, *91*, 2361-2368.

LOEHLIN, J. C. (1992). Latent variable models: An introduction to factor, path, and structural analysis (2nd ed.). Hillsdale, NJ; London: Lawrence Erlbaum.

LUSZCZ, M. A., & BRYAN, J. (1999). Toward understanding age-related memory loss in late adulthood. Gerontology, *45*, 2-9.

MAOR, Y., OLMER, L., & MOZES, B. (2001). The relation between objective and subjective impairment in cognitive function among multiple sclerosis patients - the role of depression. Multiple Sclerosis, *7*, 131-135.

- MATOTEK, K., SALING, M. M., GATES, P., & SEDAL, L. (2001). Subjective complaints, verbal fluency, and working memory in mild multiple sclerosis. Applied Neuropsychology, *8*, 204-210.
- MCDUGALL JR, G. J. (2001). Memory improvement program for elderly cancer survivors. Geriatric Nursing, *22*, 185-190.
- MEYERS, C. A. (2000). Neurocognitive dysfunction in cancer patients. Oncology, *14*, 75-79.
- MILISEN, K., ABRAHAM, I. L., & BROOS, P. L. O. (1998). Postoperative variation in neurocognitive and functional status in elderly hip fracture patients. Journal of Advanced Nursing, *26*, 59-67.
- MINTZER, J., & BURNS, A. (2000). Anticholinergic side-effects of drugs in elderly people. Journal of the Royal Society of Medicine, *93*, 457-462.
- 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., FRADIAKIS, O., SILVERSTEIN, J. H., BENEKEN, J. E. W., GRAVENSTEIN, J. S., & THE ISPOCD INVESTIGATORS. (1998). Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet, *351*, 857-861.
- NEELON, V. J., CHAMPAGNE, M. T., CARLSON, J. R., & FUNK, S. G. (1996). The NEECHAM Confusion Scale: Construction, validation, and clinical testing. Nursing Research, *45*, 324-330.
- NOBLE, M., & DIETRICH, J. (2002). Intersections between neurobiology and oncology: tumor origin, treatment and repair of treatment-associated damage. Trends in Neurosciences, *25*, 103-107.

- OLIN, J. J. (2001). Cognitive function after systemic therapy for breast cancer. Oncology, *15*, 613-618.
- OLSON, J. D., RIEDEL, E., & DEANGELIS, L. M. (2000). Long-term outcome of low-grade oligodendroglioma and mixed glioma. Neurology, *54*, 1442-1448.
- OWNSWORTH, T. L., & MCFARLAND, K. (1999). Memory remediation in long-term acquired brain injury: Two approaches in diary training. Brain Injury, *13*, 605-626.
- OXMAN, T. E., & SILBERFARB, P. M. (1987). Psychiatric aspects of cancer in the aged. Cancer Surveys, *6*, 511-520.
- PEREIRA, M., HANSON, J., & BRUERA, E. (1997). The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer, *79*, 835-842.
- POPPELREUTER, M., WEIS, J., KULZ, A. K., TUCHA, O., LANGE, K. W., & BARTSCH, H. H. (2004). Cognitive dysfunction and subjective complaints of cancer patients. a cross-sectional study in a cancer rehabilitation centre. European journal of cancer Oxford, England 1990, *40*, 43-49.
- RANDOLPH, J. J., ARNETT, P. A., & HIGGINSON, C. I. (2001). Metamemory and tested cognitive functioning in multiple sclerosis. The Clinical Neuropsychologist, *15*, 357-368.
- REEB, R. N., & REGAN, J. M. (1998). Survivors of pediatric cancer: Cognitive sequelae. Journal of Psychological Practice, *4*, 61-76.
- REITAN, R. M., & WOLFSON, D. (1997). Emotional disturbances and their interaction with neuropsychological deficits. Neuropsychology Review, *7*, 3-19.
- RIEDEL, W. J., & JOLLES, J. (1996). Cognition enhancers in age-related cognitive decline. Drugs and Aging, *8*, 245-274.

ROZANS, M., DREISBACH, A., LERTORA, J. J., & KAHN, M. J. (2002). Palliative uses of methylphenidate in patients with cancer: a review. Journal of Clinical Oncology, *20*, 335-339.

SABBIONI, M. E. E. (1991). Cancer and stress: A possible role for psychoneuroimmunology in cancer research? In C. L. COOPER & M. WATSON (Eds.), Cancer and stress: psychological, biological and coping studies (pp. 3-26). Chichester, England: John Wiley and Sons.

SALMINEN, E., PORTIN, R., KORPELA, J., BACKMAN, H., PARVINEN, L. M., HELENIUS, H., & NURMI, M. (2003). Androgen deprivation and cognition in prostate cancer. British journal of cancer, *89*, 971-976.

SCHAGEN, S. B., HAMBURGER, H. L., MULLER, M. J., BOOGERD, W., & VAN DAM, F. S. (2001). Neurophysiological evaluation of late effects of adjuvant high-dose chemotherapy on cognitive function. Journal of Neuro-Oncology, *51*, 159-165.

SCHAGEN, S. B., MULLER, M. J., BOOGERD, W., ROSENBRAND, R. M., VAN RHIJN, D., RODENHUIS, S., & VAN DAM, F. S. (2002). Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. Annals of Oncology, *13*, 1387-1397.

SHORT, K., MCCABE, M., & TOOLEY, G. (2002). Cognitive functioning in chronic fatigue syndrome and the role of depression, anxiety, and fatigue. Journal of Psychosomatic Research, *52*, 475-483.

SIEGLER, I. C., & VITALIANO, P. P. (1998). Introduction to the special section: In search of a double paradigm. Health Psychology, *17*, 483-485.

SILBERFARB, P. M. (1983). Chemotherapy and cognitive defects in cancer patients. Annual Review of Medicine, *34*, 35-46.

SILBERFARB, P. M., & BATES, G. M. (1983). Psychiatric complications of multiple myeloma. American Journal of Psychiatry, *140*, 788-789.

SO, N. K., O'NEILL, B. P., FRYTAK, S., EAGAN, R. T., & AL, E. (1987). Delayed leukoencephalopathy in survivors with small cell lung cancer. Neurology, *37*, 1198-1201.

SPREEN, O., & STRAUSS, E. (1991). A compendium of neuropsychological tests: Administration, norms, and commentary. New York: Oxford University Press.

ST JOHN, P., & MONTGOMERY, P. (2002). Are cognitively intact seniors with subjective memory loss more likely to develop dementia? International Journal of Geriatric Psychiatry, *17*, 814-820.

TANNOCK, I. F., AHLES, T. A., GANZ, P. A., & VAN DAM, F. S. (2004). Cognitive impairment associated with chemotherapy for cancer: report of a workshop. Journal of clinical oncology official journal of the American Society of Clinical Oncology, *22*, 2233-2239.

TEMOSHOK, L. (1987). Personality, coping style, emotion and cancer: Towards an integrative model. Cancer Surveys, *6*.

TEMOSHOK, L. (1991). An integrative model for studies in biopsychosocial oncology. In J. TEN HAVE-DE LABIJE & H. BALNER (Eds.), Coping with cancer and beyond: cancer treatment and mental health (pp. 65-80). Amsterdam: Swets and Zeitlinger.

THE PSYCHOLOGICAL CORPORATION. (1997). Wechsler Adult Intelligence Scale - Third edition; Wechsler Memory Scale - Third edition: Technical manual. San Antonio: The Psychological Corporation; Harcourt Brace and Company.

THOMPSON, C. A., SHANAFELT, T. D., & LOPRINZI, C. L. (2003). Andropause: symptom management for prostate cancer patients treated with hormonal ablation. Oncologist, *8*, 474-487.

THOMPSON, S. J., LEIGH, L., CHRISTENSEN, R., XIONG, X., KUN, L. E., HEIDEMAN, R. L., REDDICK, W. E., GAJJAR, A., MERCHANT, T., PUI, C. H., HUDSON, M. M., & MULHERN, R. K. (2001). Immediate neurocognitive effects of methylphenidate on learning-impaired survivors of childhood cancer. Journal of Clinical Oncology, *19*, 1802-1808.

TIERNEY, M. C., SZALAI, J. P., SNOW, G., & FISHER, R. H. (1996). The prediction of Alzheimer disease: The role of patient and informant perceptions of cognitive deficits. Archives of Neurology, *53*, 423-427.

TROY, L., MCFARLAND, K., LITTMAN-POWER, S., KELLY, B. J., WALPOLE, E. T., WYLD, D., & THOMSON, D. (2000). Cisplatin-based therapy: A neurological and neuropsychological review. Psycho-Oncology, *9*, 29-39.

TUNE, L., CARR, S., HOAG, E., & COOPER, T. (1992). Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. American journal of psychiatry, *149*, 1393-1394.

VAN DAM, F. S. A. M., SCHAGEN, S. B., MULLER, M. J., BOOGERD, W., WALL, E., 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.

VARNER, L. J., & ELLIS, H. C. (1998). Cognitive activity and physiological arousal: Processes that mediate mood-congruent memory. Memory and Cognition, *26*, 939-950.

WALKER, L. G., WALKER, M. B., HEYS, S. D., LOLLEY, J., WESNES, K., & EREMIN, O. (1997). The psychological and psychiatric effects of rIL-2 therapy: A controlled clinical trial. Psycho-Oncology, *6*, 290-301.

- WANG, L., VAN BELLE, G., KUKULL, W. B., & LARSON, E. B. (2002). Predictors of functional change: a longitudinal study of nondemented people aged 65 and older. Journal of the American Geriatrics Society, *50*, 1525-1534.
- WEITZNER, M. A., & MEYERS, C. A. (1997). Cognitive functioning and quality of life in malignant glioma patients: A review of the literature. Psycho-Oncology, *6*, 169-177.
- WIENEKE, M. H., & DIENST, E. R. (1995). Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. Psycho-Oncology, *4*, 61-66.
- WILLIAMS, M. A. (1991). Delirium/acute confusional states, evaluation devices in nursing. International Psychogeriatrics, *3*, 301-308.
- WILSON, B. A. (1997). Cognitive rehabilitation: How it is and how it might be. Journal of the International Neuropsychological Society, *3*, 487-496.
- WINQVIST, S., VAINIONPAA, L., KOKKONEN, J., & LANNING, M. (2001). Cognitive functions of young adults who survived childhood cancer. Applied Neuropsychology, *8*, 224-233.
- WINTER, K. A., & KUIPER, N. A. (1997). Individual differences in the experience of emotions. Clinical Psychology Review, *17*, 791-821.
- WOLKOWITZ, O. M., REUS, V. I., CANICK, J., LEVIN, B., & LUPIEN, S. (1997). Glucocorticoid medication, memory and steroid psychosis in medical illness. In P. M. MOORE & R. G. LAHITA (Eds.), Neuropsychiatric manifestations of systemic lupus erythematosus (Vol. 823, pp. 81-96). New York: The New York Academy of Sciences.
- ZELINSKI, E. M., CRIMMINS, E., REYNOLDS, S., & SEEMAN, T. (1998). Do medical conditions affect cognition in older adults? Health Psychology, *17*, 504-512.

Figure Captions

Figure 1.

A proposed model of factors contributing to objective and subjective cognitive impairment in people with cancer. The model follows conventions of path diagrams (Loehlin, 1992): straight arrows indicate putative causal relationships, curved arrows indicate putative correlations between source variables, and residual arrows on the dependent variables (emotional health, objective impairment, and subjective impairment) are used to indicate possible additional sources of variance in dependent variables apart from the source variables directly represented in the diagram.

