Objective and Subjective Cognitive Deficits Associated with Cancer: Implications For Health

Professionals

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Some groups of people with cancer are at increased risk of impairment in cognition, the

higher mental functions of the brain. Although individual perceptions of cognitive function

are important to quality of life in their own right and can also correlate with objective

measures, their relationship to objective measures of cognitive performance is inconsistent.

This paper reviews relationships between objective and subjective cognitive performance and

cancer and proposes a model. Risk factors for cognitive impairment associated with cancer

that are incorporated in this model include infancy, older age, previous or coexisting

neurological impairment, comorbid illness associated with cognitive impairment, advanced

malignancy, chemotherapy, cranial radiotherapy, interleukins, surgery, hormonal

manipulations, analgesics, anticholinergics, and emotional distress. Increased awareness of

cognitive issues will help health practitioners to anticipate, identify and remedy cognitive

problems associated with cancer and its treatments, with important implications for patients'

quality of life and functional status.

Objective and Subjective Cognitive Deficits Associated with Cancer: Implications

For Health Professionals

There is growing recognition that cognitive function can be altered by many medical

conditions, including those not traditionally considered to be neurologically related (Zelinski,

Crimmins, Reynolds, & Seeman, 1998). Cognitive function refers to higher mental processes

of the brain such as perception, attention, memory, planning, problem-solving, reasoning, and

judgment. In oncology, treatment advances leading to improved survival have meant that

quality of life issues such as cognitive function have assumed greater significance in the past

few decades. Comparison of reviews over time shows the increasing interest in and evidence

base for neuropsychological impacts of cancer and cancer treatments (for example, Cull,

1990; Meyers, 2000; Silberfarb, 1983).

Despite increased recognition of this issue in the research literature, there continues to

be a paucity of theoretical development in this area and underutilisation of knowledge about

cognitive function in clinical practice. This paper seeks to address this deficiency by

stimulating further clinical applications, research, and theoretical development, first giving an

overview in the form of a proposed model of cognitive function. Next, the distinction

between objective and subjective dysfunction is examined more closely and factors associated

with deficits in these areas are discussed. The final section discusses clinical applications.

A Model of Cognitive Function in People With Cancer

Figure 1 proposes a model of factors contributing to cognitive impairment in people

with cancer. Objective and subjective impairment are presented as separate outcomes in the

model, since they sometimes show little relationship with each other. Two parts of the model

will be discussed in detail: the links between objective and subjective cognitive function and

emotion, and tumour and treatment effects on cognitive function.

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 receive the most focus in this paper. Previous reviews have discussed other physical health cognitive predictors, including age (for cognitive outcomes in children with cancer, see Challinor, Miaskowski, Moore, Slaughter, & Franck, 2000; Chen et al., 1998; for cognitive aging see Riedel & Jolles, 1996; Luszcz & Bryan, 1999) and general medical conditions (Siegler & Vitaliano, 1998; Zelinski et al., 1998).

An additional pathway shown in the model is psychosocial factors external to cancer, depicted as influencing emotional distress and correlating with physical health. Relationships between psychosocial variables such as stress, appraisal, coping, and personality with both physical and emotional health have been demonstrated in a number of contexts (for example, see reviews by Sabbioni, 1991; Temoshok, 1987; Temoshok, 1991). These mediators of emotional distress are important to consider because they provide potential treatment avenues for decreasing emotional dysfunction which may also assist in improving objective or subjective cognitive function. These two aspects of cognition and their relationships with emotion will now be discussed.

<center>Objective and Subjective Cognitive Function and Emotions</center>

Definitions

The distinction between objective and subjective cognitive performance has been raised by a number of previous authors (for example, Bender, Paraska, Sereika, Ryan, & Berga, 2001; Cull et al., 1996) and needs closer attention in determining appropriate clinical 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 community normative values. Global forms of cognitive impairment include delirium and dementia. Delirium is an

impairment of consciousness, orientation and memory that is usually temporary and reversible (Boyle, Abernathy, Baker, & Wall, 1998). Dementia involves significant loss of intellectual functions, with no alteration in consciousness, and is usually progressive and irreversible (Lezak, 1995). Deficits associated with cancer are sometimes global, but can often be more usefully described in terms of specific cognitive functions, such as attention, memory, or language production.

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. A key concept is emotional distress, which has been linked to subjective as well as objective cognitive function. People who are depressed may report poor memory in particular, far in excess of measured impairment (Lezak, 1995).

Empirical Findings

Several research groups have shown that people with health problems who reported subjective cognitive difficulties were more likely to have emotional difficulties than objective deficits in performance. Subjective cognitive impairment was more strongly related to depression and anxiety than to objective test 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 factors were more predictive of memory and concentration complaints in hemodialysis patients than were neuropsychological or medical factors (Brickman, Yount, Blaney, Rothberg, & Kaplan De-Nour, 1996). For people with memory problems who were not currently classified with dementia, 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).

Subjective performance, however, has not universally been associated with emotional distress and dissociated from objective performance. 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), 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).

It can be inferred that operational definitions and measurement issues are crucial for 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 its associations with 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; Oxman & Silberfarb, 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 patients who show cognitive impairment presumed to be secondary to depression, which is remediated if depression is successfully treated (Antikainen et al., 2001; Lezak, 1995). The 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 status can affect cognitive processes such as attention and memory.

Neurological dysfunction that disrupts cognition can also cause emotional distress, either through direct neurological processes 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 cases 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 cognitive 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).

<div align="center">Objective Cognitive Function</div>

<u>Tumour Effects</u>

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 (Silberfarb, 1983; Weitzner & Meyers, 1997). Patient groups that have

recently been considered as susceptible to cognitive dysfunction include those with primary or

secondary brain tumours (Silberfarb, 1983; Weitzner & Meyers, 1997), small-cell lung cancer

(Klein et al., 2001), and terminal malignancies from a variety of primary sites (Bruera, Miller,

McCallion 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; Silberfarb, 1983; 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 patients with small-cell lung cancer exhibit subclinical impairments in memory and planning tasks 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, Miller, McCallion et al., 1992; Pereira et al., 1997). Sepsis and brain metastases were the most frequently identified causes of impairment in these patients, after medications (such as palliating drugs and those used to modulate accompanying bowel and bladder smooth muscle dysfunction) which were the single most frequent cause (Bruera, Miller, McCallion 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.

<u>Treatment Effects</u>

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, palliative medications, and anticholinergic drugs.

<u>Chemotherapy.</u> Many different chemotherapy agents or combinations of agents have been associated with adverse cognitive changes (Boyle et al., 1998; Hughes, 1987). Silberfarb (1983) noted that most forms of chemotherapy have been implicated in adverse cognitive effects for at least some individuals. 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: assymetry 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 from

chemotherapy increased with higher 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.

Radiotherapy. Radiotherapy has been associated with cognitive impairment in some

individuals, including both children (Cousens, Waters, Said, & Stevens, 1988; Eiser, 1998)

and adults (Armstrong, Stern, & Corn, 2001; Olson, Riedel, & DeAngelis, 2000). Cranial

irradiation produces the greatest cognitive risk (Eiser, 1998), due to damage of subcortical

white matter (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). 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 et al., 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; Walker et al., 1997). Deficits were significantly worse

in people who received cytokines combined with chemotherapy, compared with

chemotherapy alone, but the 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. Hormonal ablation treatments, such as those used for breast or

prostate cancer, are also suspected to be associated with cognitive impairment (Green,

Pakenham, & Gardiner, 2000; Olin, 2001). In one randomised clinical study of men with

prostate cancer, men assigned to hormonal ablation with leuprorelin, goserelin, or cyproterone

acetate showed cognitive deficits in memory, attention, and executive function tasks

compared with their baseline performance and the performance of no-treatment controls

(Green et al., 2002). Similarly, a case report of a man aged 68, treated for prostate cancer

with goserelin, described adverse effects of delirium, ataxia, amnesia, fluctuating

consciousness, incontinence and impaired concentration that ceased when goserelin was

stopped (Australian Department of Human Services and Health, 1997). The same or similar

medications have been associated with memory impairment in women who were treated with

these drugs for gynecological problems (Newton, Slota, Yuzpe, & Tummon, 1996; Sherwin &

Tulandi, 1996). 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

these 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 over time. 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 cognitive 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). The adverse cognitive effects of these medications, which are frequently prescribed to alleviate smooth muscle dysfunction resulting from cancer and cancer treatments, are not well appreciated at a clinical level. This is particularly significant since many seemingly innocuous preparations have anticholinergic properties and the adverse effect of these drugs is cumulative.

<div align="center">Subjective Cognitive Function</div>

Within the oncology literature, few researchers have adequately 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 adults treated for lymphoma at least six months previously, 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). 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).

<div align="center">Clinical Implications</div>

<u>Assessment</u>

Identification of and treatment for cognitive deficits is crucial, since cognition is a key variable determining whether people can continue living independently or with minimal assistance (Wang, van Belle, Kukull, & Larson, 2002). For a person with cancer and his or her support network, cognitive assessment can provide information needed to plan certain practical issues, such as transport, work options, and support needs. Assessment may also assist staff to tailor interactions with individuals, such as reducing information processing demands for patients who have difficulty sustaining attention. Cognitive and emotional function should be assessed at presentation and then on an ongoing basis.

Screening measures of objective cognitive function, such as the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHough, 1975), Memorial Delirium Assessment Scale (Breitbart et al., 1997), NEECHAM Confusion Scale (Neelon, Champagne, Carlson, & Funk, 1996), and the Confusion Rating Scale (Williams, 1991), are relatively brief measures that can detect generalised dysfunction, have demonstrated sensitivity to changes in

cognition in people with cancer, and can be administered frequently. The MMSE and newer instruments each have acceptable reliability but Boyle and colleagues recommended the latter because they assist better with quantifying the severity of delirium (Boyle et al., 1998). For inpatients, mental status examination as often as three times per week has proven useful, and has identified cognitive dysfunction in some patients that had not previously been recognised by medical or nursing staff (Bruera, Miller, McCallion et al., 1992).

When more detailed assessment is required, referral to a neuropsychologist or clinical psychologist with neuropsychological expertise allows assessment with standard neuropsychological 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 (Spreen & 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 assocations 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 (Aaronson et al., 1993; Fayers, Aaronson, Bjordal, & Sullivan, 1997) and interview for cognitive problems in daily

life described by van Dam and colleagues (1998) have been associated more closely with emotional distress than objective cognitive function in reports to date.

Interventions

These include incorporating individual patient susceptibility when planning treatment regimens, 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 may choose to inform 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 prior to embarking upon 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, Miller, McCallion et al., 1992) and earlier stage (Butler & Copeland, 2002; Cimprich, 1995; Meyers, 2000; Weitzner & Meyers, 1997) cancer. One protocol for patients with terminal cancer initiated investigation whenever MMSE was less than 24 or decreased more than 30% from previous function (Bruera, Miller, McCallion et al., 1992). If these criteria were met, complete 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, Miller, McCallion 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 (Bruera, Miller, Macmillan, & Kuehn, 1992; 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 leukencephalopathy (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 associated with brain surgery or systemic treatments (Noble & Dietrich, 2002).

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, functional and affective 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. Although patients' subjective perceptions of health are very important, cognitive impairment is best measured by objective tests, because subjective impairment is often associated with emotional distress and sometimes has little correlation with objective function. The value of cognitive function in quality of life evaluations remains to be fully determined. 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.

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Caption to Figure

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.

CANCER TREATMENTS	PSYCHOSOCIAL FACTORS	PHYSICAL HEALTH
• Chemotherapy • Cranial radiotherapy • Interleukins • Hormonal suppression • Analgesics; surgery	• Other Stressors • Personality • Appraisal • Coping	• Cancer type, stage, grade • Comorbid Illnesses • Neurological History • Age

EMOTIONAL HEALTH
• Anxiety
• Depression
• Stress

OBJECTIVE COGNITIVE IMPAIRMENT

SUBJECTIVE COGNITIVE IMPAIRMENT