CHEMOTHERAPY-INDUCED COGNITIVE CHANGES

A thesis submitted to The University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences

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Thesis abstract

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The present thesis, entitled **Chemotherapy-induced cognitive changes**, is being submitted in the alternative format, by **Oana Calina Lindner** to **The University of Manchester** for the degree of **Doctor of Philosophy** in the **Faculty of Medical and Human Sciences, School of Psychological Sciences**. The thesis consists of five empirical studies, written in article formats and three connecting chapters. The General introduction in Chapter 1, places the thesis in the context of late effects research in cancer survivors. I describe the prevalence of physical and emotional late effects, before going into more details on cognitive late effects. Chapter 2 provides a meta-analytical summary of cognitive impairments following chemotherapy in adult patients. It has already been published in Neuropsychology in 2014. Chapter 3 describes the general objectives and hypotheses of the empirical studies, and Chapter 4 provides more details on the General methods utilized in all the studies. The studies focus on pre- and post-treatment young adult cancer patients who were compared to age-, sex-, and education-matched controls. The instruments include a comprehensive neuropsychological battery, a newly designed memory task, and a complex battery of self-assessment questionnaires. Chapter 5 is the first empirical study, which will be submitted to Journal of Clinical Oncology. It describes the pattern of neuropsychological status of young adult cancer patients following treatment for lymphoma, sarcoma, breast cancer, and germ cell tumour. The impairments were specific to executive functioning, verbal memory, and visuospatial abilities. Uniquely, the chapter depicts differences between cancer groups. Because chemotherapy may not be the primary factor triggering such effects, Chapter 6 details the neuropsychological profile of a group of young adult pre-treatment patients diagnosed with the same malignancies. This chapter will be submitted to Journal of Neuropsychology. Impairments were observed on tests of attention, executive functioning and visuospatial abilities. Both Chapters 5 and 6 emphasize the importance of matching on full scale IQ in cross-sectional studies and they provide evidence that patients' performance on tests of verbal memory and executive functioning may vary as a function of age. Chapter 7 will be submitted to Psycho-Oncology and it suggests the presence of acute memory deficits after the first treatment. Finally, Chapter 8, which will be submitted to Psychosomatic Medicine, provides an in-depth description of the psycho-emotional status of cancer survivors. It describes higher levels of anxiety, depression, fatigue, and cognitive complaints, which mediated the relationship between illness perceptions and quality of life. The complex interaction between these psycho-emotional factors is interpreted within the framework of cognitive-behavioural therapies, which may provide a method to decrease the emotional burden of survivorship in clinical practice. Finally, Chapter 9 summarizes all the empirical findings whilst connecting them to previous literature and specifying future research direction.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Acknowledgements

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List of Abbreviations

ABVD - adryamicin, bleomycin, vinblastine, dacarbazine

Bcan - breast cancer

BEP - bleomycin, etoposide, cisplatin

C - controls

cAMP - Cyclic adenosine monophosphate

CisDox-MTX - cisplatin, doxorubicin, high dose methotrexate

CFS – cerebrospinal fluid

CNS - central nervous system

COWA - Controlled Oral Word Associations

CP - Concentration performance (measure in D2 Concentration-Endurance)

CR - Cued recall

CRUK - Cancer Research UK

CVLT - California Verbal Learning Test

DKEFS - Delis-Kaplan Executive Function System

E% - Percentage of errors (measure in D2 Concentration-Endurance)

EORTC - European Organisation for Research and Treatment of Cancer

FEC-T - fluorouracil, epirubicin, cyclophosphamide, taxotere

FFD - Freedom from distractibility

FR - Free recall

FSIQ - full scale intelligence quotient

GCT - germ cell tumour

HL - Hodgkin's lymphoma

ICCTF - International Cognition and Cancer Task Force

IL - interleukin

IP - illness perceptions

IVA= ifosfamide, vincristine, actinomycin

L1, L2, L3 - Lists 1,2 and 3 (Memory task)

M - mean

MMSE - Mini Mental State Examination

NART - National Adult Reading Test

NCRI - National Cancer Research Institute

nHL - nonHodgkin's lymphoma (includes B-cell and Burkitt's lymphoma)

NTS - neurotransmitter

ONS - Office of National Statistics

PIQ - Performance intelligence quotient

PKA - protein kinase A

QoL - quality of life

RAVLT - Rey Auditory Verbal Learning Test

RBANS - Repeatable Battery for the Examination of Neuropsychological Status

RCHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone

RCODOX - rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, methotrexate, cytarabine

ROCFT - Rey-Osterrieth Complex Figure Test

S - sarcoma

SD - standard deviation

SIOP - Speed of Information Processing

TEA - Test of Everyday Attention

TMT - Trail Making Task

TN - total number of items (measure in D2 Concentration-Endurance)

TNE - total number of items minus errors (measure in D2 Concentration-Endurance)

TNF-α - tumour necrosis factor alpha

TOMM - Test of Memory Malingering

VIDE/VAI= vincristine, ifosfamide, doxorubicin, etoposide, actinomycin

VIQ - Verbal intelligence quotient

VMI - visuomotor integrtion

WCST - Wisconsin Card Sorting Task

WISC - Wechsler Intelligence Scale for Children

WMS - Wechsler Memory Scales

WTAR - Wechsler Test of Adult Reading

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Studies

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Publications

Lindner, C.O., Phillips, B., McCabe, G. M., Mayes, A., Wearden, A., Varese, F., Talmi D. (2014). A meta-analysis of cognitive impairment following adult cancer chemotherapy. *Neuropsychology*. 28 (5):726-740.

Mereuţă C.O., Crăciun C. (2009). "Parents' illness perceptions, maladaptive behaviors, and their influence on the emotional distress of the child – a pilot study on a Romanian pediatric cancer group". *Cognition, Brain, Behavior*, 2: 207-219.

Fourteen national and international conferences, of which I mention:

Lindner, C.O., McCabe, G.M., Mayes, A., Wearden, A. Talmi, D (2014). Research findings in chemo-brain. Invited speaker in *Teenage Cancer Trust International Conference*, London, UK.

Lindner, C.O., McCabe, G.M., Mayes, A., Wearden, A., Talmi, D. (2014). The psycho-social impact of chemotherapy-induced cognitive deficits. *British Psychosocial Oncology Society*, Preston, UK.

Lindner, C.O., McCabe, G.M., Mayes, A., Wearden, A., Talmi, D. (2014). Chemotherapy, distress, and cognitive impairments in young adult cancer survivors. *International Neuropsychological Society*, Seattle, US.

Lindner, C.O., McCabe, G.M., Mayes, A., Wearden., A., Talmi, D. (2014). Acute and chronic effects of chemotherapy on memory. *International Cognition and Cancer Task Force*, Seattle, US.

Lindner, C.O., McCabe, M., Mayes, A., Talmi, D. (2013). Chemotherapy-induced memory changes. *British Psychosocial Oncology Society Conference*, Southampton, UK.

Alternative format

The present thesis is presented in the alternative format as approved by the Graduate Office of the School of Psychological Sciences, Faculty of Medical and Human Sciences, University of Manchester. Chapter 2 is a meta-analysis, which has already been published in *Neuropsychology*, while Chapters 5 to 8 are independent papers, which are due to be submitted for publication. All work included in this thesis, including ethical approvals, participant recruitment, testing, data analysis and write-up were conducted by the PhD candidate, Oana Calina Lindner, under the supervision of: Prof. Andrew Mayes, Prof. Alison Wearden, Dr. Martin McCabe, and Dr. Deborah Talmi,.

Chapter 1. General introduction

The present PhD thesis focuses on examining the cognitive changes associated with chemotherapy in young adult cancer patients who have been treated for a range of malignancies without central nervous system (CNS) involvement. Throughout the present introductory chapter, I will first describe the general healthcare context of the empirical studies conducted within this thesis, namely that of late effects research.

Late effects represent the lasting consequences of cancer and its treatment on patients' general well being, which can be experienced weeks to years following treatment. They span over physical, emotional, and cognitive consequences. I will detail the crucial impact of late effects on the well-being of patients, as well as the crucial need for continuous research efforts targeted at non-CNS cancer patients, given the increases in the rates of cancer survival. Despite the complex interconnected nature of the three classes of late effects (physical, emotional, and cognitive), they have not received an equal amount of priority, both in terms of research, management (through interventions) and service provision.

The most commonly known and researched side effects of cancer treatments are their physical late effects. The emphasis placed on them throughout the years has resulted in procedures being in place for the continuous monitoring of patients' cardiac or pulmonary functioning. Since the 1970s, the emphasis on patients' psycho-emotional well being has also increased through the evidence provided by studies within psycho-oncology. However, as will be shown in the corresponding sub-chapter, cases of depression or

anxiety may still go unrecognized and unmanaged despite their influence on a person's quality of life.

In the last decade, the cognitive deficits associated with cancer and its treatment have begun to receive attention from research communities. However, these consequences do not have a long research history, hence the level of awareness regarding them differs between countries and they are still sometimes regarded as anecdotal (Mitchell & Turton, 2011). Nevertheless, research groups from multiple countries, which are presently organised within the International Cognition and Cancer Task Force (ICCTF), produced a significant amount of evidence and hypotheses regarding the types and potential causes of neuropsychological deficits in non-CNS cancer patients. Results to date have mostly focused on pre- and post-treatment leukaemia patients with a mean age of 10, or breast cancer patients with a mean age of 50.

From these studies we learned that the long-term delivery of drugs such as asparaginase, vincristine, cytarabine, high dose systemic methotrexate, cyclophosphamide, etoposide, thioguanine, and mercaptopurine, during key brain development stages (ages 1-14) was associated with significant neuropsychological insult. It was observable decades after treatment (Krull, Brinkman, et al., 2013), was associated with a lower IQ, and performance decreases across all cognitive functions, especially executive functions, attention, and memory (Krull et al., 2012). These cognitive deficits have been associated with a general reduced brain volume and specific white and grey matter decreases in the caudate nucleus, amygdala, and hippocampus (Zeller et al., 2013).

From previous studies we have also learned that women treated in mid-adulthood with treatments that included fluorouracil, cyclophosphamide, methotrexate, epirubicin, docetaxel, and doxorubicin suffer from late cognitive difficulties (Deprez et al., 2010;

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Koppelmans et al., 2013). These patients also receive hormonal inhibitors such as tamoxifen and anastrazole, which have also been associated with cognitive side-effects, thus the comparative contribution of chemotherapy versus hormonal treatments to neuropsychological insult is difficult to define (Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009; Fardell et al., 2014; Jenkins et al., 2004). These behavioural results have been associated with reductions in white and grey matter generalized across the whole brain and specific reductions in the volumes of the hippocampus, frontal, temporal, and cerebellar areas, left parietal cortex and left cingulate gyrus (McDonald & Saykin, 2013).

More recently, patients treated for colon cancer, with oxaliplatin and fluorouracil, who were on average 67 years old, showed decrements in verbal memory and impaired executive functioning before chemotherapy. However, 54% of the sample improved their functioning within 6-months after the end of treatment, and only a subgroup of 33% had decrements, which were associated with older age and a lower educational level (Cruzado et al., 2014). Pre- and post-treatment deficits have also been reported in young adult testicular cancer patients, 46% of whom had lower than expected performance on verbal memory, motor and executive functioning before commencing treatment (Wefel et al., 2011). In a subsequent study, the longitudinal pattern of deficits in germ cell tumour patients was explored (Wefel et al., 2014). Those exposed to chemotherapy had stronger declines on tests of psychomotor speed and memory one year following treatment. The deficits were dependent on the dose of treatment and age, patients under 30 years old having more deficits than older counterparts.

There are also studies that have reported cognitive effects in Hodgkin's lymphoma patients. In one study (Ahles et al., 2002) older (mean age 59) lymphoma patients performed worse on verbal memory tests compared to norms, whereas breast cancer

patients performed worse on psychomotor speed compared to the same normative data. Younger lymphoma patients (Krull et al., 2012) who had been treated with anthracyclines and mediastinal radiotherapy, on average 27.1 years earlier, had a lower performance in attention, working, short- and long-term memory, as well as executive functioning (verbal fluency) compared to norms. Half of these post-treatment patients showed leukoencephalopathy on MRI scans, and 37% had evidence of cardiovascular injury. Finally, a very recent study focused on 60-year old B-cell non-Hodgkin's lymphoma patients. They reported higher emotional distress, fatigue and cognitive complaints, and also had worse attention and executive functioning, than norms and controls. The impairment was more severe in patients treated with rituximab and bendamustine than in those receiving RCHOP. These results were associated with an increase in electroencephalography-measured alpha peak frequency in frontal regions, as well as with higher blood levels of interleukin-6 (IL-6) and lower levels of brain derived neurotrophic factor (Zimmer et al., 2014).

The consequences of cancer treatment on cognitive functioning is described further in the last part of the introductory section, after I describe the physical and psycho-emotional late effects of treatment. Chapter 2 will provide a more in-depth description of the cognitive deficits experienced by adult patients through the means of my recently published meta-analysis (Lindner et al., 2014). In the latter, I emphasized that deficits in attention and various aspects of memory were detectable in patients with breast cancer and germ cell tumours in cross-sectional designs, but not in longitudinal designs, which were highly heterogeneous. This paper provides insights in the potential causes of the different sets of results, as well as their high heterogeneity.

While trying to decrease the inherent heterogeneity specific to psycho-oncology research by following the recommendations suggested through the meta-analysis, I ran five main empirical studies, which are described in Chapters 5 to 8. I start by describing the neuropsychological status of post-treatment cancer patients aged 16 to 50, by comparing them both to published normative data and controls, individually matched on age, sex, and education. Given the poor performance of patients in neuropsychological tests normally associated with fronto-temporal-parietal functioning, in Chapter 6 I describe the baseline performance of a group of patients of the same ages and diagnoses. In this chapter, I further accentuate the necessity of evaluations before commencing chemotherapy, given that patients had deficits in tests normally associated with fronto-parietal functioning, but not in memory tests. In Chapter 7 I describe the first study which investigated whether the memory impairments associated with chemotherapy are detectable acutely, only 24 hours following the first treatment. The study was run on a subgroup of the patients described in Chapter 6. I designed a novel verbal learning task, which was aimed at discriminating between memory processes such as encoding, consolidation, and retrieval. In this subgroup, information retrieval was intact, but patients had a faster forgetting rate compared to their matched controls immediately after the first treatment, a difference that was not present beforehand. Encoding, or the rate of learning was different between the two groups irrespective of the treatment, but this difference was suppressed when controlling for differences in pre-morbid intelligence. Importantly, the results of these empirical studies validated the suggestions made in the meta-analysis regarding the need to control for other potential difference between patients and controls. Both pre- and post-treatment patients were different from controls on full scale IQ (FSIQ), whilst post-treatment patients were also different from their matched controls on anxiety, depression, fatigue, and subjective cognitive complaints. Consequently, the results obtained in the

neuropsychological assessments control for the differences in FSIQ, and I present the amount of variance explained by the psycho-emotional factors.

To facilitate a holistic interpretation of results, in the last empirical study presented in Chapter 8, I provide a theoretical interpretative framework for understanding the complex interplay between illness perceptions, mood, fatigue, cognitive complaints, and quality of life. Given that a method for tackling the objective cognitive deficits experienced by cancer patients is yet to be validated for clinical practice, the psycho-emotional consequences of the diagnosis and treatment described in Chapter 8, could still be approached by integrating these variables within the cognitive-behavioural paradigm.

Hence, given their complex interconnection with cognitive functioning across the lifespan, the next sub-chapters will briefly focus on the physical and psycho-emotional aspects characterising cancer patients as a group, before focusing exclusively on chemotherapy-induced cognitive changes.

1.1. Cancer prevalence and survival

Throughout the world, cancer incidence is increasing. In 2011 in the United Kingdom, there were 331,487 newly diagnosed cases and the number was prospected to increase by approximately 3% every year (Maddams, Utley, & Møller, 2012). Thus, research into the treatment of the different malignancies has become a priority for most national and international funding bodies. While the data is not yet available for adult cancers, the National Cancer Research Institute (NCRI, 2014) reports that in 2008 up to 35% of national health funding had been allocated to research into the treatment of paediatric cancers.

The consistent funding efforts towards research in this area have resulted in fast-paced technological advances in radiotherapy, chemotherapy, highly targeted biological

agents, and novel combinations of drugs, which have led to more patients surviving cancer. In 2010, there were 51% cancer survivors in the UK across all types of diagnoses and ages. Of these, as many as 63% of survivors were of working age (ONS, 2011).

Through a dynamic prediction algorithm applied to the increase in cancer and survival statistics up to 2010 it has been suggested that the number of cancer survivors would increase by 100,000 every year, which translates to almost a quarter of people up to the age of 65 being cancer survivors by 2040 (Maddams et al., 2012). At present there are 2 million people living with or beyond cancer in the UK (CRUK, 2014a).

It is estimated that up to 78% of these survivors have cognitive difficulties (Schagen & Wefel, 2013). Based on the 2011 survival data for working-age adults, this would mean that just under 165,000 people of working age in the UK, who have survived a non-CNS cancer, may experience neuropsychological difficulties, in addition to potential psycho-emotional and physical co-morbidities. The estimated cost of job seekers' allowance and tax exemption for the working-age cancer survivors who may suffer from cognitive deficits and who could fail to re-enter the job market would translate into just over 2.5 billion pounds per year. It follows that finding the appropriate interventions to help patients adapt to their post-treatment status becomes paramount.

This is the reason why the potential late effects of treatment on patients' quality of life become a high concern. In this context, late effects research is understood as the management of symptoms arising after the treatment of cancer (Stein, Syrjala, & Andrykowski, 2008). Contrasting the positive trend in the successful treatment of cancer, owing to the targeted distribution of funds towards research in this area, the NCRI reports that only 11.8% of the research funds were allocated towards survivorship and late effects research in paediatric cancer alone. This percentage is higher than the funds allocated to

survivorship research across all cancer groups, suggesting that survivorship issues in paediatric and adult cancers are unequally addressed (McCabe et al., 2013).

Resources allocated towards late effects research is of relevance to all cancer diagnoses, and especially for young working age adults, in whom cancer incidence is increasing (Bleyer, O'Leary, Barr, 2006) and have a high likelihood of returning into work and education following treatment. Generally, compared to adults over 60, young adults have better general health and respond more effectively to treatment, which results in higher survival rates. One of the exceptions is breast cancer patients, for whom five-year survival is 3% higher if diagnosed between ages 40-74 compared to a diagnosis under the age of 40 (Chia et al., 2004). This trend was associated with the fact that breast cancer tumours in younger women are usually more aggressive (Mathew, Pandey, & Rajan, 2004). Specifically for the UK, in 2010, 66% of cancer survivors of all malignancies were young adults aged 15 to 49. The highest survival rates for this age group were for testicular cancer (98%), followed by Hodgkin's lymphoma and melanoma (92%), breast cancer (87%) and non-Hodgkin's lymphoma and uterine cancer (81%) (CRUK, 2014b).

Given the increases in cancer prevalence and survival over five and ten years, research efforts targeted at decreasing long-term treatment side effects and increasing cancer patients' quality of life becomes vital. The following sections will detail some of the most frequent late effects experienced by cancer patients who have been treated for non-CNS malignancies.

1.2. Late effects in post-treatment cancer patients

Late effects research had initially focused on the consequences experienced by paediatric cancer patients, given the highly aggressive treatments and the critical development period during which they are administered. Consequently, in the United

States comprehensive guidelines have been designed (Landier, Leonard, & Ruccione, 2013) to provide a framework for research, follow-up evaluations, and to address any additional educational needs of paediatric cancer patients. Similar guidelines are available for the follow-up appointments in the United Kingdom (CCLG, 2005), but they are not yet as comprehensive, by mostly focusing on the physical late effects patients could experience as a results of their treatment, as opposed to psycho-social and educational needs.

Despite the additional support strategies developed for younger age groups, we do not yet have a similar body of knowledge and resources to manage late effects in adult cancers (Ganz, 2001; McCabe et al., 2013). However, adult post-treatment patients equally face ongoing physical symptoms, risk of secondary chronic illnesses, medical and psychological co-morbidities, as well as neuropsychological consequences. Ongoing physical symptoms following treatment may lead to increased levels of distress and fatigue, as well as contribute to mild cognitive deficits. For example, cardiovascular risk factors have been associated with mild neuropsychological difficulties (Yaffe et al., 2014). Consequently, the next sub-chapters will offer a brief overview of each of these side effects, which interact in defining the experience of survivorship in cancer patients.

1.2.1. Physical late effects of cancer treatment

The concept of "cancer survivor" is defined as "any person diagnosed with cancer, from the time of initial diagnosis until his or her death" (Feuerstein, 2007). The term is frequently used in parallel to that of "post-treatment patient", suggesting that malignancy should be viewed as a chronic condition and people affected by it are regarded as patients under ongoing care (Ganz, 2001). Ongoing physical symptoms experienced by cancer

survivors, as well as the threat of secondary malignancies and relapse are monitored

through follow-up evaluations.

The types, frequency, and severity of physical toxicities vary depending on the type

and dosage of treatment administered. They can be acute (e.g. sepsis, acute renal failure) or

and chronic toxicities, which may extend to several organ systems and are more frequent

(Oeffinger & Hudson, 2004). Chronic toxicities may include cardiac, pulmonary, renal and

neurological toxicities, as well as haematological, endocrine, gastrointestinal, and

genitourinary complications. We will focus on detailing some of the most common late

physical effects, of which cardiac and pulmonary late toxicities are most frequent (ASCO,

2007).

Cardiac toxicity is the most common consequence of chemotherapy, but it also has

a high variance depending on its type. For example, asymptomatic bradycardia has been

identified in 30% of patients treated with paclitaxel (Yeh et al., 2004), whereas

electrocardiographic ischaemic-type changes have been reported after just 5 days in 68%

of patients treated with 5-fluorouracil (Bovelli, Plataniotis, & Roila, 2010). In 4%-36% of

patients cardiac toxicity was due to the administration of anthracyclines (e.g. doxorubicin,

daunorubicin), and in 7%-28% of patients it was associated with alkylating agents (e.g.

cyclophosphamide). Other drugs, such as 5-fluorouracil, have been correlated with angina-

like chest pain in 1%-68% of patients, while cisplatin has been demonstrated to increase

the risk of thromboembolism.

Radiotherapy may cause damage to any normal tissue circumscribed by the

radiation field; the estimated incidence of cardiotoxicity due to radiation is 10%-30%

within 5 to 10 years following treatment (Carver et al., 2007). For instance, mediastinal

radiation produces injury to heart tissues and structures. It has been associated with

complications such as pericarditis, myocardial fibrosis, and coronary artery disease in Hodgkin's lymphoma patients. Radiotherapy to the breasts is associated with increased mortality due to cardiovascular disease (Bovelli et al., 2010). Its effects may be augmented by concomitant treatment with other cardiotoxic agents, such as the anthracycline doxorubicin. Therefore, standard post-treatment care for patients who have had cardiac tissue irradiated, or have been administered anthracyclines or certain monoclonal antibodies includes cardiac monitoring prior, during, and up to 10 years following treatment, even if patients are asymptomatic but had been treated with a high dose regimen (Bovelli, et al., 2010).

Whilst diagnosed in less than 10% of patients, secondary *pulmonary toxicity* can arise within weeks or years following treatment. It has been associated with local irradiation, antitumour antibiotics (bleomycin), alkylating agents (cyclophosphamide), antimetabolites (methotrexate), taxanes (docetaxel), and immune modulatory agents such as interferons, and tumour necrosis alpha (TNF-α , Limper, 2004). Pulmonary toxicity is a less frequent complication of cancer treatment than cardiac toxicities, and have a highly variable presentation, but can lead to premature respiratory insufficiency. Consequently, decreased pulmonary function is particularly evaluated in patients who received radiotherapy and high doses of bleomycin (Ganz, 2001). The incidence of pneomonitis, most frequent in patients treated for lung cancer, has been reported in 5-15% of patients (Carver et al., 2007).

Neurological complications (Keime-Guibert, Napolitano, & Delattre, 1998) can be both peripheral and central, resulting from both chemotherapy and radiotherapy. While leukoencephalopathy is rarely observed, peripheral neuropathy is present in up to 60% of patients receiving docetaxel, while chronic encephalopathy and seizures are associated

with high dose methotrexate. The type, frequency and severity of neurological toxicities are dependent on the chemotherapy drugs and doses used. They may result from the administration of alkaloids (vincristine, vinblastine), taxanes (docetaxel, paclitaxel), antibiotics (bleomycin), anthracyclines (doxorubicin), antimetabolites (methotrexate, fluorouracil), and alkylating agents (cycloposphamide, cisplatin). For example, cisplatin has been associated with permanent vestibular syndrome, and retinal cone dysfunction through its toxic effects on cranial nerves (Grisold, Cavaletti, & Windebank, 2012).

Another more general and common effect that may be present before, during and as a late effect of cancer treatment is *anaemia* (Ross, Putnam, & Adams, 2006). Up to thirty percent of patients are affected and it may be related both to the malignancy and the treatment. It is associated with disrupted iron metabolism, reduction in the number of bone marrow progenitor cells, increase in inflammatory cytokines, and erythropoietin deficiency (Fardell, Vardy, Johnston, & Winocur, 2011). It is an important symptom given that it can be chronic, and lower haemoglobin levels have been previously associated with a lower quality of life (Ludwig & Fritz, 1998). Crucially, it has also been linked to a 65% increase in the risk of mortality in patients who had been treated for lung, uterine, head and neck, prostate cancer, as well as lymphoma and multiple myeloma (Caro et al., 2001).

Endocrine toxicities resulting from dysfunctions of the pituitary, thyroid, and gonadal glands are common in patients receiving radiotherapy to the affected organs, hormonal treatments, and alkylating agents. Specifically, breast cancer patients may experience temporary or permanent premature menopause (more common in women who are 40 or older), both because of chemotherapy and hormonal treatments. Other secondary toxicities that can have both acute and chronic presentations, but are less frequent, are *nephrotoxicity*, *hematological*, and *immunological* impairments. In some cases, such as

myelodysplastic syndrome following treatment with alkylating agents, the toxicities may be fatal.

Many of these late effects can become co-morbid chronic medical conditions in post-treatment patients. Consequently, addressing and focusing on them is a priority within late effects research. Apart from the chronic illnesses to which post-treatment patients are predisposed, the diagnosis itself and its treatment may also have detrimental effects on patients' long-term psycho-emotional wellbeing.

1.2.2. Psycho-emotional late effects in cancer treatment

The psychological late effects of cancer treatment include anxiety, depression, fatigue, subjective cognitive complaints, negative illness perceptions, which may all have an impact on quality of life. However, they also include cognitive side effects, expressed through declines in neuropsychological tests. Although all these effects are part of the broader category of psychological late effects, they require separate descriptions. Thus, the present sub-chapter will deal with self-reported psycho-emotional late effects such as mood, quality of life, illness perceptions, and cognitive failures, whereas the next sub-chapter will only describe the neuropsychological effects reported in the literature.

The mid-1970s mark the beginning of research in psycho-oncology, as a field tackling psychological and social aspects of cancer diagnosis, treatment, and survival. This is the time when the first cancer support initiatives were formed and the first research priorities were defined (Holland, 2003). Owing to the research efforts that have taken place in this area throughout the last 40 years, we can now speak of a multifaceted understanding of the care needs of oncology patients and survivors, their caregivers, novel methods of enhancing medical practice and a more efficient doctor-patient communication (Surbone et al., 2010). We now have the benefit of a more detailed description of the types of negative

psycho-emotional consequences of cancer treatment, which complement ongoing physical symptoms in cancer patients.

Emotional distress in cancer patients may result from both the diagnosis and the experience of the treatment. It is characterised through depression, anxiety, and posttraumatic stress, although some of these cases may also be unrecognised and under-diagnosed (Aldridge & Roesch, 2007; Tatrow & Montgomery, 2006). The reported proportion of patients affected by clinical level depression and anxiety varies between 23% and 66% (Nezu, Nezu, Felgoise, Zwick, 2003). Thoughts on their prevalence are polarized; some studies suggest that only a subgroup of patients experience emotional problems, while others raise concern that cancer patients experience a high level of emotional co-morbidities. For example, a recent meta-analysis (Mitchell et al., 2011) suggests that depression occurred in 20.7% of the patients, anxiety in 17.9%, but the incidence was not statistically different from their incidence in healthy controls. However, the control participants included both volunteers from the general population and spouses of the patients, which may have reduced the differences between groups. Importantly, in a study conducted on 215 patients with mixed cancer diagnoses, 53% had no symptoms of emotional distress. However, the remainder of 47% exhibited clinical level psychological problems. Of this group, 68% had generalized anxiety disorder or major depression, while the rest showed mental disorders of an organic nature, personality or other anxiety disorders (e.g. phobias, posttraumatic stress, etc.). Ninety percent of such issues have been suggested to be linked to the particular characteristics of the illness or treatment (Bukberg, Penman, & Holland, 1984). The most recent study in the UK focused on five types of diagnoses (Walker et al., 2014), demonstrating that major depression was most prevalent in lung cancer (13.1%), followed by gynaecological cancers (10.9%), breast cancer (9.3%), colorectal cancer (7%), and genitourinary cancer (5.6%). Furthermore, it has been

suggested that as many as 25% of cancer patients suffer from unrecognized and untreated long-term depression (Bottomley, 1998), and such symptoms can increase the risk of mortality by 17%, especially in leukaemia and lymphoma patients (Kissane, 2014).

Cancer-related fatigue is another consequence, defined as a subjective feeling of chronic and persistent physical and mental tiredness, which does not decrease following rest (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003). It has been demonstrated to interfere with patients' daily functioning and to last from months to years following treatment (Curt, 2000; Portenoy & Itri, 1999). It is believed to be caused by a multitude of factors, including anaemia, poor nutrition and gastrointestinal problems, depression, anxiety, and sleep disturbance (Iop, 2004). Inflammatory cytokines such as interleukin-1 and 6, as well as TNF-α have been associated with its severity (Ahlberg et al., 2003; Glaspy, 2001). Several studies demonstrated that it is present in 65%-100% of patients undergoing radiotherapy (Blesch et al., 1991; Ream & Richardson, 1996) and 82%-96% of those receiving and who have finished chemotherapy (Tavio, Milan, & Tirelli, 2002; Tierney et al., 1991). It has been shown to be associated with physical limitations in up to 69% of patients, 71% lost one or more days of work, and up to 59% felt limited in pursuing social activities (Mendoza et al., 1999). The prevalence of fatigue varies across diagnoses and treatments. For example, it is present in 36%-68% of lung cancer patients treated with vinorelbine, cisplatin, and topotecan (Ardizzoni et al., 1997), in 62% of breast cancer patients treated with docetaxel and trastuzumab (Esteva et al., 2002) and in 41% of ovarian cancer patients treated with doxorubicin (Gordon et al., 2000). It is important to note, however, that just like pain, fatigue is a subjectively-defined concept. We presently have hypotheses regarding the physiological mechanisms underlying the conscious feeling of fatigue, but the factors outlined thus far may only be a short list of the multitude of physical changes that may induce fatigue.

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Commonly related to increased levels of emotional distress and fatigue are *subjective cognitive complaints* (Broadbent, Cooper, FitzGerald, & Parkes, 1982). They represent self-reported cognitive failures in areas of perception, memory, concentration or motor function. These symptoms have been reported in several clinical populations, such as patients with chronic fatigue syndrome (Wearden & Appleby, 1996), chronic pain (Roth, Geisser, Theisen-Goodvich, & Dixon, 2005), HIV infection (Carter, Rourke, Murji, Shore, & Rourke, 2003), and in post-treatment cancer patients (Kohli et al., 2007; Pullens, De Vries, & Roukema, 2010). Ninety five percent of breast cancer patients report cognitive difficulties 2-6 weeks following their treatment (Fan et al., 2005). However, this rate decreases over time, 71% of patients reporting them at 6 months and 60% at 18 months (Shilling & Jenkins, 2007). Subjective cognitive complaints are reported even if the objective cognitive performance appears to be intact; these feelings of poorer concentration or "mental fog" and the reports of cognitive failures are generally associated with low mood, increased levels of fatigue and subsequent inefficient distribution of processing strategies (Roth et al., 2005; Wearden & Appleby, 1996). They are also a complaint in normal aging, being reported by 50% of people over the age of 55 (Gauthier et al., 2006), and have been associated with higher levels of neuroticism and gender rather than actual cognitive performance (Kliegel, Zimprich, & Eschen, 2005; Slavin et al., 2010). Despite being associated with subjective reports of low mood and, in other clinical groups they have frequently been a symptomatic expression of several cognitive conditions with an organic nature. Subjective cognitive complaints have previously been associated with mild cognitive impairments in diagnoses such as vascular aging (Dufouil, Fuhrer, & Alpérovitch, 2005), multiple sclerosis (Marrie, Chelune, Miller, & Cohen, 2005), epilepsy-induced transient amnesia (Butler et al., 2007), and are predictive of later dementia in approximately half of the patients with mild cognitive impairments (Mitchell, 2008). They

have also been associated with mild brain atrophy or white matter lesions in older adults, even in the absence of objective cognitive impairments (de Groot et al., 2001; Wang et al., 2012). Consequently, in cancer patients it becomes paramount to differentiate between emotional or fatigue-induced cognitive failures due to a low level of concentration on tasks, versus a clinically significant state of organic cognitive impairment due to chemotherapy or the associated physical late effects summarised above (Gauthier et al., 2006). However, such a differentiation may be difficult to pursue because subjective cognitive complaints are more often associated with low mood and fatigue than with objective cognitive tests, potentially due to the different paradigmatic approaches of the two sets of measurements. Furthermore, in many instances both low mood and organic changes (i.e. cortisol) may be associated with objective cognitive deficits, creating additional difficulties in defining the exact causal factors of either subjective or objective neuropsychological difficulties.

Similarly, patients have been known to show negative or dysfunctional *illness perceptions*, which are frequently associated with higher levels of depression, anxiety, and a low quality of life (Millar, Purushotham, McLatchie, George, & Murray, 2005; Petrie, Jago, & Devcich, 2007). Illness perceptions are defined as the personal representation of symptoms, causes, length, consequences and the level of control patients have over their illness (Weinman, Petrie, Moss-morris, & Horne, 1996). The concept is based the Common Sense Model of Illness proposed by Leventhal (Hagger & Orbell, 2003; Leventhal, Brissette, & Leventhal, 2003) which describes the role played by the cognitive and emotional representations of an illness in the development and maintenance of adaptive coping strategies when faced with a health-related threat, such as the diagnosis of cancer. It summarizes the main factors influencing how the illness-related information is processed, organized in a coherent form, and in which way that coherent form guides the

patient coping behaviours. It emphasizes the interplay between negative cognitive interpretations, negative emotional responses and maladaptive coping strategies. The model was used in the development of the Illness Perception Questionnaire (Weinman et al., 1996) which evaluates the main cognitions related to an illness, such as perceived consequences, causes, or timeline. Consequently, the concept of illness perceptions summarizes the main factors influencing how illness-related information is processed, how the information is organized in a coherent form, and how that coherent form guides the coping behaviours of the patient. For example, in post-treatment head and neck cancer patients an increased attention to symptoms, and the belief in a greater probability of recurrence was associated with self-blame, a stronger emotional reaction to the illness, and lower quality of life (Scharloo et al., 2005). In another study with lymphoma and myeloma patients, higher physical symptom awareness and a longer perceived timeline of the illness predicted the maintenance of depression symptoms (Millar et al., 2005). In a group of patients with a range of malignancies, negative views regarding the consequences of their diagnoses mediated the relationship between the number of patients' symptoms and their distress, explaining 15% of anxiety and 5% of the variance in depressed mood. The perceived symptoms predicted 7% of the anxiety symptoms (Thuné-Boyle, Myers, & Newman, 2006).

Post-treatment patients also experience a low *quality of life*. It has been associated with the number of symptoms reported and the level of patients' physical functioning (Aaronson et al., 1993). Whilst it is unclear what percentage of variability in quality of life is separately accounted for by physical and emotional co-morbidities, all the physical and psychological late effects discussed thus far have an impact on patients' quality of life (Harrington, Hansen, Moskowitz, Todd, & Feuerstein, 2010; Linden, Vodermaier, Mackenzie, & Greig, 2012; Mao et al., 2007; Walker et al., 2014). Furthermore, a higher

number of physical and emotional symptoms and a poorer quality of life have been suggested to result in negative consequences on the ability to work, lower employment rates, and an early age of retirement (Lindbohm et al., 2014; Short, Vasey, & Tunceli, 2005). It is not yet clear to what extent patients' symptoms and the social and financial consequences of cancer treatment are also associated with neuropsychological impairments after treatment (Ahles & Saykin, 2001; Ahles & Saykin, 2007). However, in the context of rapid developments in cancer treatments, associations between cognitive, psycho-emotional, and physical side effects of treatment will need to be more clearly defined. Consequently, we will next discuss what is currently known about the late cognitive effects reported in post-treatment cancer patients.

1.2.3. Cognitive late effects of cancer treatment

Cognitive impairments have received less attention than some other late effects of treatment, but they have started to become more preeminent in the professional and public literature in the last decade. They include most cognitive functions, including memory, attention, executive functions, and processing speed (Ahles & Saykin, 2007). The literature is divided into three main parts focusing on preclinical animal models, studies with paediatric patients (patients treated between 1 and 16 years old), and studies with adult patients (patients treated between from 40 years old into late adulthood). Each set of studies provides us with different, but complementary information on the potential aetiology and distribution of cognitive impairments following non-CNS cancer treatments.

Studies with animal models have been extremely informative regarding the brain regions affected and types of neural insults that result from the administration of specific chemotherapy agents (Table 1). They focused on cognitive tests such as spatial memory, object and place learning, fear and reward conditioning. These studies reported severe

impairments in spatial and object memory, which were associated with insults to the hippocampus, subventricular region and corpus callosum (Dietrich, Han, Yang, Mayer-pröschel, & Noble, 2006). Cognitive improvements following chemotherapy have only been reported in one study (Lee, Ingram, & Longo, 2006) in which spatial memory improvements were observed following treatment with cyclophosphamide and 5-fluorouracil. The finding was explained by the use of female rats, in which the oestrogen cycle may have been disrupted by chemotherapy. While in humans, oestrogen may have a negative effect on memory when present at a low level, in rats it has a positive effect on learning behaviours (Maki, Rich, & Rosenbaum, 2002). Apart from Lee et al.'s (2006) study, animal models have consistently demonstrated longer exploration times and difficulties in the retrieval of learned object/locations when treated intraperitoneally with methotrexate (Gandal, Ehrlichman, Rudnick, & Siegel, 2008; Li, Vijayanathan, Gulinello, & Cole, 2010; Lyons et al., 2011) and 5-fluorouracil (Mustafa, Walker, Bennett, & Wigmore, 2008). Cyclophosphamide alone or combined with doxorubicin and methotrexate resulted in impaired behaviour on inhibitory avoidance tasks (Reiriz et al., 2006), and led to a decrease in freezing responses to aversive stimuli (Macleod et al., 2007). The same drugs impaired exploratory behaviour and performance in passive avoidance memory tests especially when administered before training (Konat, Kraszpulski, James, Zhang, & Abraham, 2008; Liedke et al., 2009). Decreased freezing responses in contextual fear conditioning task were observed up to one month post-treatment (Seigers et al., 2008). However, a key finding of these studies is that chemotherapy agents do not always trigger these effects when administered on their own, but when administered in combination. For example, methotrexate and 5-fluorouracil impaired acquisition and retrieval latencies in reward learning tasks when administered together, but not individually (Foley, Raffa, & Walker, 2008).

	Author	Spatial memory	Object memory	Habituation	Conditioning	Exploratory behaviour	Hippocampus	Thalamus	Corpus callosum	Cortex
1	Borzan (2004)									
2	Boyette-Davis (2009)									
3	Calsteren (2009)	Light			Dark	Light				
4	Dietrich (2006)				Dark				Dark	
5	Eijkenboom (1999)	Dark					Dark			
6	ElBeltagy (2010)	Dark	Dark		Dark		Dark			
7	Fardell (2010	Dark	Dark							
8	Foley (2008)				Dark					
9	Gandal (2008)		Dark	Dark	Dark					
10	Konat (2008)				Dark	Light				
11	Lee (2006)	Crossed					Light			
12	Li (2010)	Dark				Light	Dark			
13	Liedke (2009)				Dark	Dark				
14	Lyons (2010)	Dark					Dark			
15	MacLeod (2007)				Dark					
16	Mondie (2010)	Dark	Dark							
17	Mullenix (1990)					Dark				
18	Mullenix (1994)					Dark				
19	Mustafa (2008)	Dark					Dark			
20	Pyter (2010)	Dark	Dark		Light					
21	Reiriz (2006)				Dark					
22	Rzeski (2004)						Dark	Dark		Dark
23	Seigers (2008)	Dark					Dark			
24	Seigers (2009)	Dark			Dark		Dark		Dark	
25	Seigers (2010a)						Dark			
26	Seigers (2010b)				Dark					Dark
27	Stock (1994)		Light		Light					
28	Winocur (2006)	Dark	Dark							
29	Yang (2010)		Dark		Dark		Dark			
30	Yanovski (1989)		Light		Light		Light	Light	Light	Light

Table 1. Summary of chemotherapy-induced cognitive changes in animal models.

*Light grey-Functions that were assessed, but no significant impairments were found; Dark grey – Functions that were assessed and significant impairments were found;

Crossed – Functions that were assessed and significant improvements were found.

Another key finding in animal models was the potential neural insults produced by chemotherapy, when drugs were administered in weight-adapted dosages and through the same pathways as in human patients. Neural reactions to these drugs were dendritc swelling (Rzeski et al., 2004), reduced proliferation of neural and glial cells, and cell death (Seigers et al., 2008, 2010). The mechanisms through which they occur due to different chemotherapy agents were apoptosis, inflammation, inhibition of neuro- and gliogenesis and oxidative stress. Table 2 offers a summary of the mechanisms through which neural insult may occur due to different agents (Seigers, Schagen, Tellingen, & Dietrich, 2013).

Because of the limited possibilities in identifying and explaining the exact pattern of cognitive deficits in human cancer patients in a homogenous manner, free from additional clinical bias, animal models are of particular importance (Seigers & Fardell, 2011). They provide an insight into the mechanisms underlying the neural insult associated with several chemotherapy agents. However, we note that despite the wealth of information they provide, preclinical studies are not a perfect model for the effect of chemotherapy in humans. That is because with a sole exceptions (Pyter et al., 2010) these studies used healthy animals, not accounting for the possible effect of the cancer itself. In patients, cognitive deficits such as poor attention and processing speed, may be detectable even before the chemotherapy onset which may imply that the neuropsychological difficulties may result from an interaction of cancer-related symptoms and chemotherapy-related late effects (for example, see Ahles et al., 2008; Cimprich et al., 2010). Hence, the malignancy may contribute to a lower than expected performance in some patients, implying that there may be additional factors that could predispose some patients to chemotherapy-induced cognitive deficits.

Drug/ Mechanism	Cell death	Blood supply	CFS composition	Histone acetylation	Inflammation	Morphology	Neuro-and Gliogenesis Inhibition	NTS release	Oxidative stress
Carmustine	▓						▓		▓
Cisplatin	▓					▓	▓		
Cyclophosph amide	▓			▓	▓	▓	▓		▓
Cytarabine	▓					▓	▓		
Doxorubicin	▓				▓		▓		▓
5-fluorouracil	▓				▓		▓		
Ifosfamide	▓					▓			
Methotrexate	▓	▓	▓	▓	▓	▓	▓	▓	▓
Paclitaxel							▓		
ThioTEPA	▓					▓			
Vincristine						▓			

Table 2. Mechanisms of chemotherapy-induced neural changes in animal models.

*Adapted from Seigers et al., 2013. CFS = cerebrospinal fluid; NTS=neurotransmitter

To date, research with human participants has been highly focused on the cognitive status of breast cancer patients (Lindner et al., 2014) and survivors of childhood acute lymphoblastic leukaemia (Genschaft et al., 2013; Krull, Brinkman, et al., 2013). This means that there is a high degree of variance between the populations from which currently available findings have been derived - children who were exposed to aggressive treatment, including treatments directed to the CNS at a very young age, and breast cancer survivors who were usually older.

Studies in paediatric cancer have focused either on evaluating neuropsychological performance in recently treated paediatric patients or adult survivors who had been treated during childhood. This set of studies provides an insight into the detrimental effects of highly aggressive, CNS-directed treatment in children aged 1 to 16 years old. Despite the large number of studies conducted on this group since the 1980s, there are presently only two meta-analyses summarizing the results of previous literature (Campbell et al., 2007; Peterson et al., 2008). They provide interesting, yet inconclusive information about cognitive impairments following chemotherapy. Campbell et al., (2007) reported generalized impairments of all neuropsychological functions following treatment, while Peterson et al. (2008) reported cognitive improvements for the same functions, as well as for additional functions not examined in the first meta-analysis (Figure 1). The discrepancy in results may stem from the article selection criteria applied by the 2 meta-analyses, the first including 28 studies, and the second 13 studies.

Cognitive function	Study	Effect size	CI lower	CI upper
FSIQ	Campbell*	-0.71	-0.88	-0.54
	Peterson*	0.55	0.27	0.83
VIQ	Campbell*	-0.58	-0.76	-0.41
	Peterson*	0.46	0.11	0.81
PIQ	Campbell*	-0.66	-0.82	-0.49
	Peterson*	0.42	0.03	0.81
Verbal memory	Campbell*	-0.39	-0.63	-0.14
	Peterson	1.16	0.54	1.79
Visual memory	Campbell*	-0.62	-0.95	-0.28
	Peterson	1.03	0.64	2.7
Spatial abilities	Campbell*	-0.57	-0.81	-0.32
	Peterson	0.27	0.34	0.88
Attention	Campbell*	-0.57	-0.71	-0.42
	Peterson*	0.28	0.04	0.52
Executive function	Campbell*	-0.46	-0.61	-0.3
	Peterson*	0.41	0.06	0.88
Speed of processing	Campbell*	-0.52	-0.75	-0.29
	Peterson	0.48	0.02	0.98
Psychomotor	Campbell*	-0.34	-0.5	-0.17
	Peterson	0.39	0.08	0.69
FFD	Peterson	0.54	0.25	0.83
Perceptual organization	Peterson	0.7	0.4	0.99
VMI	Peterson	0.37	0.19	0.93
Arithmetic	Campbell*	-0.6	-0.82	-0.39
	Peterson	0.4	0.19	0.99
Spelling	Campbell*	-0.42	-0.63	-0.2
Verbal abilities	Campbell*	-0.57	-0.74	-0.39
	Peterson*	0.65	0.03	1.27
Verbal comprehension	Peterson	0.48	0.38	1.33

Figure 1. Forest plot of summary effect sizes obtained by two previous meta-analyses of studies with children.

Note. *$p < 0.05$. FSIQ=full scale IQ, VIQ=verbal IQ, PIQ=performance IQ, FFD=freedom from distractibility, VMI = visuomotor integration.

Given these discrepant results, I ran a review of 30 studies published between 1980 and 2012. Most studies (87%) focused on leukaemia while the reminder focused on patients treated for other haematological malignancies and Wilms tumour. Patients had been treated between the ages of 2 to 15 ($m=9.7$, $sd=3.6$). A meta-analytical summary of the neuropsychological results from both cross-sectional and longitudinal studies suggested deficits across most cognitive functions, especially full scale IQ, verbal and performance IQ, memory, attention, arithmetic, and motor functions (Figure 2).

Cognitive function		Effect size	CI lower	CI upper	I^2	p	N	K
FSIQ		-0.38	-0.61	-0.16	0.77	0.00	23	28
VIQ		-0.27	-0.54	0.00	0.80	0.00	17	20
PIQ		-0.39	-0.65	-0.13	0.79	0.00	18	21
MEMORY		-0.48	-0.78	-0.17	0.93	0.00	16	58
Immediate		-0.17	-0.36	0.02	0.19	0.26	9	12
Delayed		-0.16	-0.46	0.14	0.53	0.05	6	7
Recognition		-1.28	-2.63	0.07	0.97	0.00	2	6
Verbal		-0.47	-0.84	-0.10	0.86	0.00	12	20
Visual		-0.26	-0.75	0.24	0.93	0.00	10	24
SPATIAL ABILITIES		-0.21	-0.87	0.45	0.97	0.00	9	21
ATTENTION		-0.35	-0.51	-0.20	0.85	0.00	18	64
Focused		-0.51	-0.94	-0.08	0.93	0.00	10	19
Capacity		-0.37	-0.54	-0.20	0.72	0.00	12	26
EXECUTIVE FUNCTION		-0.31	-0.63	0.02	0.47	0.04	7	12
PROCESSING SPEED		-0.12	-0.55	0.31	0.67	0.03	5	5
FFD		-0.51	-0.88	-0.14	0.57	0.07	4	4
PERCEPTUAL ORGANIZATION		-0.26	-0.68	0.16	0.74	0.00	6	6
VMI		-0.40	-0.61	-0.20	0.48	0.02	12	16
ARITHMETICS		-0.26	-0.43	-0.10	0.42	0.02	14	21
CODING		-0.24	-0.50	0.03	0.52	0.04	8	8
VERBAL ABILITIES		-0.21	-0.35	-0.07	0.67	0.00	17	47
MOTOR FUNCTION		-0.21	-0.36	-0.06	0.25	0.15	7	20
Dominant		-0.16	-0.46	0.13	0.46	0.09	4	7
Non-Dominant		-0.28	-0.58	0.02	0.34	0.20	3	5

Figure 2. Forest plot of estimated effect sizes in paediatric patients compared to any control group.

Note. N=number of studies; K=number of effect sizes from all studies, I^2=heterogeneity

The list of 30 studies included in this short meta-analytical summary can be viewed in Appendix 1. The methods used to derive the depicted results were the same as the ones reported in the statistical analyses of Chapter 2. These results were consistent with a more recent cohort study demonstrating that survivors of childhood leukaemia suffered from high impairment rates (28.6% to 58.9%) of most cognitive functions decades after treatment. The strongest impairments were found in attention and executive functions and were related to a reduced level of educational attainment and high rate of unemployment (Krull, Brinkman, et al., 2013). Another study (Zeller et al., 2013) demonstrated that survivors experienced issues in processing speed, executive functions and verbal memory, which were associated to reduced grey and white matter volumes, and smaller volumes of the caudate nucleus, amygdala, and hippocampus. However, just as in my brief meta-analytical summary, the results in both these large recent studies suggested a high level of

heterogeneity in behavioural performance, some patients performing 5 standard deviations below the norm, whilst other as high as 1.5 SDs above it.

Studies with adult patients provide highly heterogeneous results, as neuropsychological deficits are suggested to vary between 17% and 78% (Schagen & Wefel, 2013; Shilling, Jenkins, & Trapala, 2006). As in paediatric studies, and opposed to animal models, the research topic itself raises a few challenges (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008). These relate to the recruitment and evaluation of patients and appropriately age-, sex-, and education-matched controls, the heterogeneous nature of the treatments and clinical co-morbidities, and the discrepancy in the instruments used (Freeman & Broshek, 2002; Jansen, Miaskowski, Dodd, & Dowling, 2007). Nevertheless, at present we know that post-treatment patients have difficulties in tests related to memory, attention, executive functions, and processing speed compared both to healthy controls and patients who had not undergone chemotherapy (Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Lindner et al., 2014; Minisini et al., 2004). Chapter 2 will describe the specific findings of this set of studies in more detail.

1.3. Scope and outline of the thesis

In this introduction, I demonstrated the increasing demand to focus on the quality of life of a growing segment of population – cancer survivors. I have outlined several late effects that have an impact on survivors' quality of life, spanning over physical, emotional, and cognitive symptoms.

Alongside the ongoing priority of finding better treatments, assuring a higher quality of life for the growing numbers of survivors should become an equally important target for research efforts. This becomes even more important given the high number of patients under the age of 60, who are expected to live beyond cancer and whose return into

work and education may be hampered by cognitive impairments associated with their treatment. Although there are presently no studies addressing the connection between the cognitive deficits and employment rates following chemotherapy, there are reasons to believe that some patients may find it more difficult to return to the workforce. That is because cognitive impairment can negatively impact patients' functional independence (Schagen et al., 2014) and induce limitations on daily activities (Cimprich, Ronis, & Martinez-Ramos, 2002; Hewitt, Rowland, & Yancik, 2003).

From the brief summary provided thus far, it follows that cognitive changes induced by chemotherapy are a multi-faceted phenomenon, requiring a collaborative and multi-disciplinary explanation, spanning over oncology, genetics, pharmacology, neuroscience, and psychotherapy, and even health economics. Furthermore, just as both survival rates and quality of life have been demonstrated to vary as a function of malignancy, age, stage at diagnosis, and sex (CRUK, 2014b; Harrington et al., 2010), the impact on cognitive functioning may not be present in the same manner in all post-treatment patients (Ahles, Root, & Ryan, 2012). Developing and recommending intervention and prevention strategies for chemotherapy-induced cognitive impairments, requires us to define the concept and to specify which patients would be more predisposed that others. Although up to 78% of post-treatment breast cancer patients have been postulated to be affected by cognitive impairment (Schagen & Wefel, 2013), it is not yet clear whether there are any predisposing factors, whether they are present in all cancer groups, and whether they are long-lasting as opposed to transient. Consequently, a definition of chemotherapy-induced cognitive changes needs to specify:

- The affected *populations' demographic* and *clinical characteristics*; this would help identify the target population who may be in most need of the

interventions, and potential predictors of the cognitive impact of treatment in specific subgroups.

- The *types of functions* that are more likely to be impaired in specific subgroups, given that cognitive functioning, as well as structural and functional brain changes may differ between treatment types; this part of the definition would guide the search for targeted pharmacological prevention techniques, and appropriate interventions after the insult has occurred.

- The *duration* of the cognitive impairments. It may be that the issues are constrained to the duration of the treatment and shortly after (Hermelink et al., 2008; Wefel, Saleeba, Buzdar, & Meyers, 2010), or they may persist for decades following treatment (de Ruiter et al., 2011; Koppelmans, Breteler, et al., 2012). Similarly, they may have a traumatic or a progressive nature. Either of these situations would require a different intervention avenue.

- *Other factors* that may contribute to their development, such as genetic predispositions (Ahles et al., 2003; Krull, Bhojwani, et al., 2013; Small et al., 2011), low mood (Walker et al., 2014) and chronic fatigue (Servaes, van der Werf, Prins, Verhagen, & Bleijenberg, 2001). It is not yet clear whether the impairments are primarily driven by chemotherapy itself and how much anxiety, depression, and cancer-related fatigue may contribute to the observed neuropsychological difficulties.

The present thesis aims to contribute to the existing literature on chemotherapy-induced cognitive changes, by concentrating on a group that has not yet been the focus of previous research: working-age cancer patients, aged 16 to 50. A further extension of previous knowledge is the description of these effects in patients diagnosed and treated for four types of non-CNS malignancies: lymphoma, breast cancer, germ cell tumour, and

sarcoma. The studies included in the thesis are of an exploratory nature, as this group has not been extensively investigated, despite patients aged 16 to 50 usually having a better prognosis in most malignancies (ONS, 2011). The aim is to describe this groups' cognitive and emotional status in a holistic manner, while drawing on previous literature on chemotherapy-induced cognitive impairments, psycho-oncology and neuropsychology, which provided an interpretative schema for the individual studies. This approach will be useful to determine how much of the cognitive insult may be attributed to chemotherapy alone, versus other factors such as the malignancy itself or psycho-emotional consequences such as low mood and fatigue. It will also provide information on the needs that could be addressed in this population through future clinical interventions.

To fully describe the complexity and factors that may contribute to the cognitive deficits in this group, I have written the thesis in the alternative format, by organizing it into five individual articles, which can be viewed within the framework of previous literature focusing on adult patients. The papers provide a description of the neuropsychological status of the patients after and prior to their treatment, define the characteristics of their memory impairments as early as 24 hours post-treatment, and describe their psycho-emotional status, focusing on mood, fatigue, subjective cognitive complaints, illness perceptions, and quality of life.

Consequently, through the means of a meta-analysis, in **Chapter 2**, I provide a description of neuropsychological impairments following chemotherapy in adult patients. This chapter has already been published in *Neuropsychology* (Lindner et al., 2014). I observed that methodological differences between studies resulted in the high variability of cognitive impairments reports in previous literature. Based on the recommendations and ongoing questions resulting from this quantitative review, **Chapter 3** outlines the

objectives and hypotheses of the individual studies. **Chapter 4** provides a detailed account of the *Methods*, by describing the rationale behind choosing our participant groups, the three classes of instruments utilised (a newly designed memory test, a comprehensive neuropsychological battery, and a range of self-assessment questionnaires), as well as the recruitment, and testing procedures common to all studies.

Chapter 5 describes the neuropsychological impairments of young adult post-treatment cancer patients, both compared to standardized norms and healthy volunteers matched on age, sex, and education. The first major finding was that pre-morbid full scale IQ (FSIQ), age, mood, fatigue, and cognitive complaints played specific roles in the identification of cognitive impairments. The second finding was that after controlling for FSIQ, mood, fatigue, and cognitive complaints, patients performed poorly on tests of executive functions, visuospatial abilities, and verbal memory. Expanding on previous findings, our results suggest that the pattern of impairments differed between the four cancer groups.

Chapter 6 describes the pattern of neuropsychological difficulties in a subgroup of newly diagnosed cancer patients prior to their treatment. Similarly to the results presented in Chapter 5, FSIQ had an impact on the range of observed cognitive differences between patients and controls. After controlling for it, pre-treatment patients had difficulties in attention, executive functions, and visuospatial abilities, which varied with age. Interestingly, this group was not different from controls in mood, fatigue, and cognitive complaints. Chapters 5 and 6 are planned to be submitted to *Journal of Clinical Oncology* and *Journal of Neuropsychology*, respectively.

Chapter 7 focuses on whether the highly cited memory disruptions identified in long-term cancer survivors, are detectable as early as after the first treatment. Through the

aid of a newly designed memory task, patients demonstrated a faster forgetting rate as early as 24 hours post-treatment. Encoding was different between groups following treatment and retrieval was numerically, but not significantly different between groups following treatment. However, both these differences were suppressed after controlling for FSIQ. Despite the small sample size, the effect of treatment on forgetting was robust; additional studies will be needed to confirm whether this is a consolidation or retrieval deficit. This chapter will be submitted to *Psycho-Oncology.*

As the cognitive difficulties identified in the previous chapters cannot yet be addressed through pharmacological interventions, cognitive-behavioural therapies may provide a useful strategy. They would provide a method of differentiating between cognitive deficits that may be due to the organic effects of cancer and treatment versus increased distress and fatigue, by first aiming to decrease the latter. To this end, **Chapter 8** describes the psycho-emotional status of post-treatment patients. They have a high number of subjective cognitive complaints, negative illness perceptions, higher levels of fatigue and distress, and a low quality of life. Uniquely, I utilise the *Antecedent-Belief-Consequences* model of cognitive-behavioural therapies to describe how the relationship between factors may influence quality of life. Illness perceptions and subjective cognitive complaints mediated the effects of mood and fatigue on quality of life. This chapter is due to be submitted to *Psychosomatic Medicine.*

Finally, **Chapter 9** offers a general discussion of the findings in all of these studies, how they relate to previous results and the emerging recommendations for future work.

Chapter 2. A meta-analysis of cognitive impairment following adult cancer chemotherapy

Abstract

Objective Chemotherapy-induced cognitive impairments are reported by many cancer survivors. Research to date has not provided a clear description of their nature, extent, mechanisms, and duration. To investigate the impairments and factors that could influence their identification and severity, the present meta-analysis brings together research on this topic in adult cancer patients. ***Method*** Our random-model meta-analysis includes 44 studies investigating the cognitive performance of adults treated with chemotherapy for non-central nervous system malignancies, primarily breast and testicular cancer. We conducted several subgroup analyses to identify the level of cognitive impairments in longitudinal and cross-sectional studies. We also pursued several multilevel model regressions to investigate the impact of methodological (study quality) and clinical moderators (diagnosis, age, time since treatment) on the observed effect sizes. ***Results*** Cognitive impairments were found in cross-sectional studies in immediate free recall, delayed memory, verbal memory, delayed recognition memory, selective attention, and attention capacity. Surprisingly, prior to chemotherapy, patients performed better than matched controls. In longitudinal studies, patients' performance increased from baseline to follow-up, an effect that was stronger in patients than controls. None of the chosen moderators influenced the magnitude of estimated summary effect sizes. ***Conclusions*** The likelihood to identify impairments rests on the type of design employed, as memory and attention impairments are only detected in cross-sectional studies. We discuss the lack of significant impact of moderators on the effect sizes despite the heterogeneity of results, while providing recommendations towards decreasing the heterogeneity in future studies.

cancer, chemotherapy, cognitive impairment, neuropsychology, chemo-brain, cognition

2.1. Introduction

Cognitive impairments may contribute to a lower quality of life following cancer diagnosis and treatment (Short et al., 2005). Despite this, healthcare systems in many countries do not have the appropriate resources to help people cope with chemotherapy-induced cognitive impairments (Ferguson et al., 2007). Furthermore, the continuous care needs of survivors, in terms of their cognitive deficits, and how these might relate to potentially higher distress levels and lower quality of life are yet to be identified. This is a problem given the increasing number of people living with and beyond cancer (Maddams et al., 2009). The limited knowledge regarding this phenomenon may be due to several factors.

First, chemotherapy-induced cognitive changes in adult patients do not have a long research history. Consequently, guidelines for conducting neuropsychological research with former adult patients were proposed only recently by the International Cognition and Cancer Task Force (ICCTF) (Wefel, Vardy, Ahles, & Schagen, 2011). Second, research in this area may have possibly been hampered by inconsistencies in previous findings regarding cognitive impairments. On the one hand, there are differences between the degrees of objective impairment reported by different studies, being identified in 12% to 68% of cancer survivors (Ahles & Saykin, 2007; Shilling et al., 2006). On the other hand, subjective impairments are reported by up to 80% of these patients (Kohli et al., 2007). Inconsistencies in the percentage and types of impairments reported by the literature yielded some uncertainty about which functions are impaired, and may have reduced the emphasis on evidence-based intervention strategies to help patients overcome these problems (Ferguson et al., 2007).

Previous reviews claimed that the lack of cohesion within the literature might stem from variability in several factors: participant demographics (Ahles et al., 2003), treatment protocols (Freeman & Broshek, 2002; Hurria, Somlo, Ahles, & Ph, 2007; Jansen, Miaskowski, Dodd, Dowling, 2005), and variability in the neuropsychological tests used in assessments (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Jansen et al., 2008). Additional confounding may be due to: limited consideration of practice effects, (Vardy et al., 2008), whether patients are compared to norms or matched controls, whether matching includes age, gender, and intelligence/education (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Jansen, Miaskowski, Dodd, Dowling, 2005), and differences in the statistical cut-offs for defining the impairments (Hurria et al., 2007; Wefel et al., 2011). However, other than the impact of comparing patient results to norms or controls, most of these potential moderators have not been systematically investigated in relation to the degree of observed impairments. We will further give a brief account of the results obtained by previous literature that sought to identify the nature and extent of impairments.

Conclusions from previous meta-analyses

Four previous meta-analyses have summarized the cognitive outcomes of earlier studies (Anderson-Hanley et al., 2003; Falleti, Sanfilippo, Maruff, & Weih, 2005; Jansen, Miaskowski, Dodd, Dowling, 2005; Stewart et al., 2008). Relative to controls, survivors exhibited a broad range of mild to moderate cognitive deficits in attention, information processing, verbal and visual, long-term and working memory, spatial skills, language, executive and motor functioning, summarized in Figure 3.

While the four analyses agreed on the direction of the effects, there was less agreement on their magnitude, despite analysing approximately the same literature; for example, the effect size of speed of processing impairment ranges from low (Stewart et al., 2008), through medium (Jansen, Miaskowski, Dodd, Dowling, 2005), to large (Anderson-Hanley et al., 2003).

Cognitive function	Study	Effect size	CI lower	CI upper
Memory	Falleti	-0.26	NA	NA
Short term	Stewart	-0.31	-0.53	-0.09
Long term	Stewart	-0.26	-0.46	-0.05
Verbal	Anderson	-0.61	-1.22	0
	Jansen	-0.37	-0.83	0.09
Visual	Anderson	-0.41	-0.82	0.01
	Jansen	-0.51	-1.01	-0.01
Working memory	Stewart	-0.24	-0.47	-0.01
Spatial abilities	Anderson	-0.28	-0.55	-0.01
	Falleti	-0.48	NA	NA
	Jansen	-0.11	-0.57	0.34
	Stewart	-0.3	-0.49	-0.1
Attention	Anderson	-0.24	-0.49	0.02
	Falleti	-0.03	NA	NA
	Jansen	-0.17	-0.62	0.27
	Stewart	-0.13	-0.32	0.07
Executive function	Anderson	-0.61	-1.01	-0.2
	Falleti	-0.18	NA	NA
	Jansen	-0.26	-0.74	0.2
Speed of processing	Anderson	-0.7	-1.12	-0.29
	Jansen	-0.44	-0.96	0.07
	Stewart	-0.22	-0.43	0
Language	Falleti	-0.41	NA	NA
	Jansen	-0.33	-0.78	0.13
	Stewart	-0.37	-0.56	-0.18
Motor function	Anderson	-0.27	-0.52	-0.02
	Falleti	-0.51	NA	NA
	Jansen	-0.36	-0.8	0.1
	Stewart	-0.24	-0.52	-0.04

Figure 3. Forest plot of summary effect sizes obtained by four previous meta-analyses of studies with adults.

Note. We present the type of cognitive function reported by each study, as well as the effect size, and its *95% confidence interval (CI)*. Falleti et al. (2005) did not report CIs

In addition to variability in designs and reported outcomes in primary studies, there was also variation between the meta-analyses in the reporting of key methodological factors. As an example, these meta-analyses reported 11, 12, 18, and 20 items from the 27-item checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) (Moher, 2009). The items missed most frequently were those pertaining to the process of study screening, the reporting of confidence intervals, consistency, and risk of bias analyses (Anderson-Hanley et al., 2003; Falleti et al., 2005; Jansen, Miaskowski, Dodd, Dowling, 2005; Stewart et al., 2008). Detailed literature search techniques were not always reported and the meta-analyses were based on small numbers of studies (n=6, 7, 16, 29 respectively). When subgroup analyses were reported, they included even fewer studies (Stewart et al., 2008), although it is not generally recommended to run summary effect size analyses with a very small number of studies (Borenstein, Hedges, Higgins, & Rothstein, 2009).

There was also significant variability in the way neuropsychological test scores were pooled into cognitive functions and reported as single, general scores (i.e. verbal, short-term memory, attention). Yet, current understanding of memory and attention is far more detailed than this (Strauss, Sherman, & Spreen, 2006). Such simplification of results, through the combination of very different measures, might influence the observed effect sizes, and the heterogeneity of results.

The present meta-analysis

The present meta-analysis is a synthesis of current literature (K=44) reporting cognitive functioning in adult cancer survivors treated with chemotherapy (described in Appendix 2). We examined the extent of cognitive impairment but, compared to previous meta-analyses, we also explored potential sources of methodological and clinical heterogeneity, which might have influenced the results obtained within the literature.

We pursued two types of subgroup analyses. First, we grouped test scores into constructs based on well-established guidelines (Strauss et al., 2006) with a clear distinction between different memory and attention types. Table 3 summarizes the tests

grouped within each neuropsychological function, as well as the number of studies (K) and effect sizes (N) included in the analyses.

Aggregate Constructs	Specific constructs	Tests used	K	N
Full scale IQ		Groeninger Intelligence Scale, MMSE, WAIS.	5	5
Memory		All memory tests regardless of retention interval (immediate or delayed), test format (free recall or recognition), and modality (visual or verbal).	37	189
Verbal memory		Verbal memory tests regardless of retention interval and test format (free recall or recognition).	31	122
Visual memory		Visual memory tests regardless of retention interval and test format (free recall or recognition).	20	57
Immediate free recall		Immediate memory tests regardless of modality.	26	47
Delayed memory		Delayed memory tests, regardless of modality and test format.	26	69
Delayed recognition		All recognition memory tests regardless of modality.	12	19
	Verbal immediate free recall	Logical memory I, CVLT/RAVLT/HVLT/Rey 15, WMS Verbal memory immediate, RBANS Immediate memory, VLMT 1-5, VSRT Short term, Encoding/recall correct.	24	48
	Verbal delayed free recall	Logical memory II, CVLT/RAVLT/15 Rey Delayed, RBANS Delayed memory, WMS Delayed recall, VSRT Delayed.	24	48
	Verbal delayed recognition	RAVLT/CVLT/Rey 15 recognition, HVLT Discrimination, Paired associates recognition.	9	21
	Visual immediate free recall	Logical memory I, variants of CVLT/RAVLT/HVLT/VLMT, RBANS Immediate memory, Encoding/Recall correct, WMS Visual memory immediate.	17	27
	Visual delayed free recall	Visual reproduction II, Family pictures II, ROCFT delayed, NVSRT delayed, WMS Visual memory delayed.	15	22
	Visual delayed recognition	Visual reproduction recognition, ROCFT recognition, Visual association test.	8	7

Attention		Includes all attention tests.	11	17
	Focused attention	Trails A, Stroop, Digit symbol, Symbol search, Symbol modalities, D2, Continuous performance tests, Visual search tests.	28	74
	Selective attention	D2, Fepsy binary, Go/No go selective attention, TEA Auditory/visual elevator, Ruff 2&7.	10	2
	Attention capacity	Letter-number cancellation/sequencing, PASAT, Digit span, Visual span Forward, Sentence repetition.	19	59
Executive functions		Stroop, Trail B, WCST, Tower of London, Consonant Trigrams, COWA or variants.	33	147
Verbal abilities		Lexical/Semantic search, Boston naming test, WAIS/WRAT Reading, RBANS Language.	8	15
Spatial abilities		Block design, ROCFT-Copy, RBANS Visuospatial (Figure copy and Line orientation).	15	18
Arithmetic		WAIS, WISC, WPPSI and any other mathematical achievement tests.	10	17
Motor functions		Pegboard, Fingertapping, Grip strength dominant and non-dominant.	16	45

Table 3. List of cognitive tests included in each function.

The number of studies (K) and effect size estimates (N) in analyses, before the multiple outcomes transformations. (MMSE=Mini Mental State Examination, WAIS=Wechsler Adult Intelligence Scale, WMS= Wechsler Memory Scale, WTAR= Wechsler Test of Adult Reading, CVLT= California Verbal Learning Test, RAVLT= Rey Auditory Verbal Learning test, HVLT = Hopkins Verbal Learning test, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, VLMT = Verbal Learning and Memory test, VSRT = Verbal Selective Reminding Test, NVSRT = Non-Verbal Selective Reminding Test, ROCFT = Rey-Osterrieth Complex Figure Test, TEA= Test of Everyday Attention, PASAT=Paced Auditory Serial Addition Test, WCST = Wisconsin Card Sorting Test, COWA = Controlled Oral Word Associations)

Second, we divided studies into subgroups based on their designs, as cross-sectional and longitudinal studies might have different sources of bias. For example, in cross-sectional studies, the effective matching between patients and controls is crucial to the identification of real impairments, while longitudinal designs are particularly

vulnerable to practice effects, both when tests have alternative formats and especially when they do not.

We further investigated the influence of two specific sources of bias, or moderators (Rosenthal & DiMatteo, 2001), which have not been considered by previous literature and could have influenced the observed effect sizes. The first is a methodological moderator, the quality of studies. The methods of conducting and reporting the results of primary studies, the quality of participant matching, the type of cognitive tests used, as well as availability of tests with alternative forms, are integral parts of their quality having a potential influence on the results of subsequent meta-analyses. Thus, we ran quality assessments of the studies and included the scores as potential methodological sources of heterogeneity.

The second sources of bias are clinical, related to the participant characteristics reported by primary studies and suggested by previous literature to have an impact on cognitive test results. These are the type of diagnosis, age of participants, and time since treatment. There could be several additional factors that might have had a significant impact, but those were either not reported (i.e. test results on treatment types or genders), reported inconsistently (i.e. types of treatments, time since diagnosis) or reported through different test scores (i.e. pre-morbid intelligence level of matched groups). The diagnosis was chosen as a proxy for the types of treatment and genders of the participants. The age of participants was chosen due to evidence from paediatric cancer studies that a younger age may be a vulnerability factor for cognitive impairments (von der Weid et al., 2003). Finally, evidence from breast cancer fMRI studies suggests that cognitive impairments may fade with time (Deprez et al., 2011). Consequently, the time lapsed from treatment to assessment might also be a significant factor influencing the cognitive test scores.

Our meta-analysis followed the robust and comprehensive guidelines of the Cochrane Collaboration (Higgins & Green, 2008) for conducting systematic reviews and meta-analyses. Additionally, due to the problems with methods such as the fail safe N, which assumes that the effect sizes of missing studies would be zero (Borenstein, et al., 2009), we performed a regression-based publication bias analysis using Egger's method to account for potentially unreported data (Egger, Davey Smith, Schneider, & Minder, 1997; Sterne, Gavaghan, & Egger, 2000)

2.2. Methods

Search strategies

The relevant literature was examined by one person (OL) through a search of the electronic databases (PubMed, Ebsco, Web of Science, PsychInfo, PRISMA, Cochrane) using the following search terms: (cancer OR chemotherapy) AND (cognition OR neuropsychology) AND (adults). We also conducted the search by replacing the words (cancer OR chemotherapy) with the names of chemotherapy drugs (i.e. doxorubicin, cyclophosphamide, etc.) and by replacing the words (cognition OR neuropsychology) with names of specific cognitive functions (i.e. attention, memory, verbal memory, executive functions, etc.). The reference lists of reviews were visually scanned and key journals of the International Psycho-Oncology Society, and conference proceedings were hand-searched for additional articles not detected by the literature search (list included in Appendix 2).

Inclusion and exclusion criteria

The study eligibility criteria are described in Table 4. They were driven by the participant – intervention – comparison – outcomes - study design elements (Higgins &

Green, 2008), while accommodating the ICCTF guidelines for studies in the field (Vardy et al., 2008).

	INCLUSION	EXCLUSION
Population	Patients exposed to chemotherapy.	Patients with central nervous system tumours.
Intervention	Patients exposed to chemotherapy.	Studies that test the effect of drugs other than chemotherapy (i.e. hormonal treatments). Patients exposed to CNS-directed radiotherapy.
Comparison/ Control group	Studies comparing patients to norms, healthy controls or cancer patients who were not treated with chemotherapy.	Studies that did not report results of any control group.
Outcomes	Articles reporting means and standard deviations of at least one neuropsychological test. See Table 3 for a description of the type of tests.	Duplicate results (i.e. articles based on dissertations) and studies only reporting changes in psychosocial functioning such as quality of life. Studies not reporting means and standard deviations on the tests.
Study design	Longitudinal and cross-sectional studies.	Case-studies were excluded because the design is rarely used to examine intended effects of a treatment.

Table 4. Criteria for including studies in the meta-analysis

Our search included all studies from 1980 to January 2011. We did not include unpublished data, or articles written in languages other than English. When studies did not report means and standard deviations, they were requested from the authors. If the data were not provided, we did not include the articles due to the nature of the software used for the initial analyses. Figure 4 depicts the search process that led to the inclusion of 44 studies.
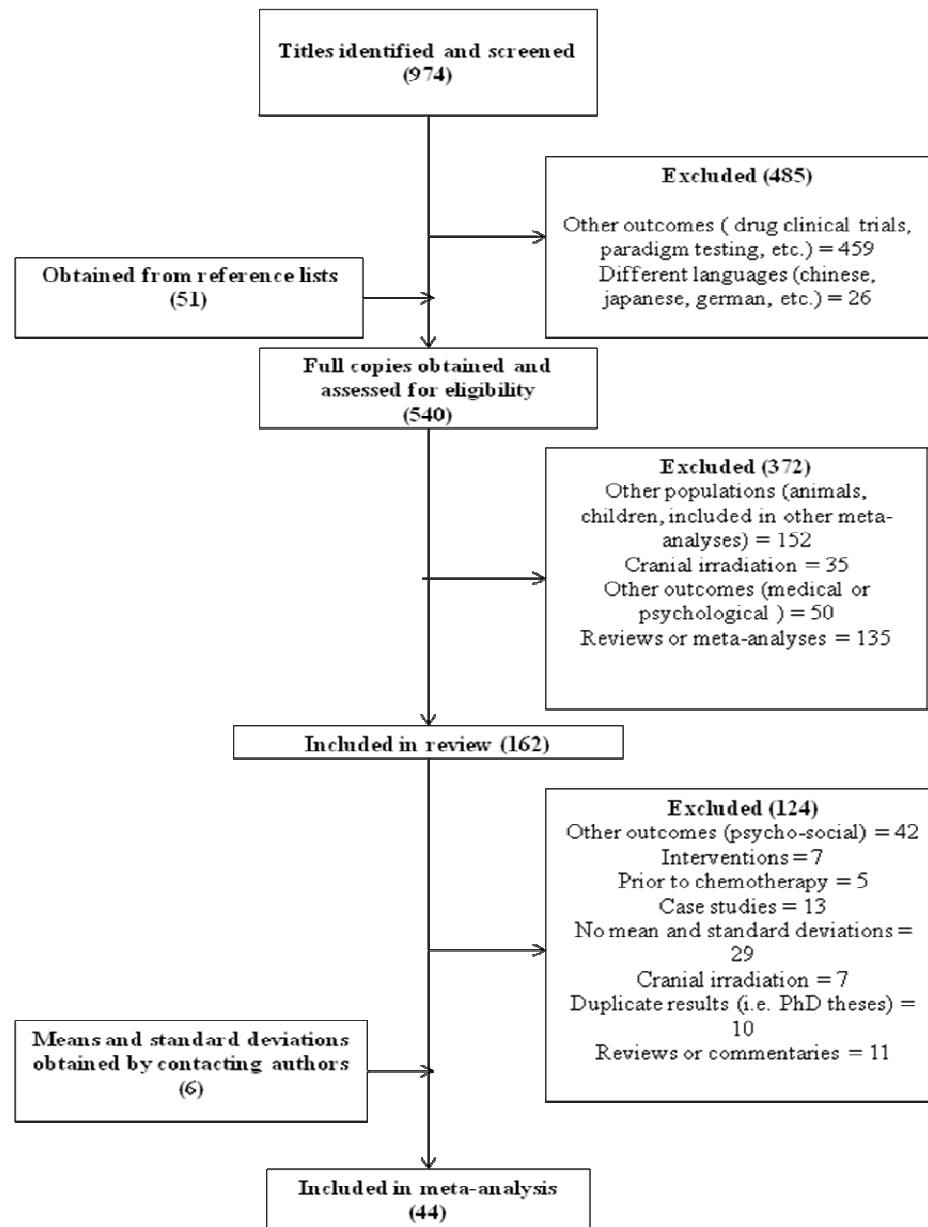
Figure 4. Study selection flow-chart.

Coding procedures

Means and standard deviations for all cognitive tests were recorded for each individual study, alongside the study quality and participant level moderators (cancer type, mean age, and mean number of years since treatment). The scores reported for each cognitive test were extracted from each article (i.e. Rey-Osterrieth Complex Figure Test-

Copy as a measure for visuospatial ability). These scores were then grouped within functions based on the guidelines suggested by Strauss et al. (2006).

The strengths and weaknesses of the studies included in the analyses were graded according to a quality assessment tool recommended by the Cochrane Collaboration. The Downs and Black scale (Downs & Black, 1998) contains 27 questions pertaining to both randomized and non-randomized studies and looks at all aspects of data reporting and analysis. Three questions, referring to the blinding of participants and experimenters, were removed due to the lack of suitability in the context of this research. Six additional questions were added to accommodate the ICCTF guidelines: whether any patients were exposed to local or cranial radiotherapy, had CNS malignancies, if a control group was present, and the inclusion of ICCTF recommended neuropsychological and self-assessment tools. Thus, each study received a score between 0 and 31.

The quality assessment was performed blindly by one master coder (OCL) and an independent researcher (DF). Disagreements about the scores were resolved by consensus. Following consensus, an interclass correlation was performed because the scores were measured on an interval scale; it yielded an inter-rater correlation of 0.97 ($p<0.001$), with scores ranging from 11 to 30.

Subgroup analyses

Most studies reported multiple outcomes and multiple time-points scores for each cognitive function. This facilitated the separation of the data into subgroups based on the types of designs employed by individual studies. The resulting subgroup analyses were:

- Post-chemotherapy cross-sectional studies: patients versus controls, after treatment.
- Patient longitudinal studies: patients at follow-up versus baseline.

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- Baseline cross-sectional studies: patients versus controls, before treatment.

- Control longitudinal studies: control participants at follow-up versus baseline.

The results of the first two analyses triggered the analyses pertaining to the performance of patients versus controls before chemotherapy and the performance of controls in longitudinal assessments. Their aim was to determine whether patients were impaired before chemotherapy and whether practice effects were present in both patients and controls evaluated multiple times. Each analysis was based on at least 4 individual study estimates, which is sufficient to perform a meta-analysis (Borenstein et al., 2009).

Effect size estimations

We used the random effects model for each level of the analyses, in order to account for the high variability of the data (Overton, 1998). We have computed Hedge's g standardized mean difference between groups as it provides a tighter estimate of the true effect size (Borenstein et al., 2009). Each study reported several scores for each cognitive test, for each comparison group, and for different time-points. Initially, we ran individual random model meta-analyses for all the data, and then in the four additional subgroups for each of the 26 cognitive functions. These initial analyses resulted in specific standard errors, and weights assigned to each outcome within each study. All of these calculations were run using Meta-Analyst (Wallace, Schmid, Lau, & Trikalinos, 2009).

In order to account for the dependency of data due to multiple outcomes and time points, we further calculated study-level composite effect sizes and variances for each set of outcomes reported by each study, per cognitive function. These were computed based on the formulas suggested by Borenstein et al. (2009). Finally, each study appeared once in the final summary effect size analyses. Studies reporting the same outcomes on different patient groups (i.e. lymphoma and breast cancer, (Ahles et al., 2002; Ahles et al., 2003),

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were analysed as two separate studies because of the importance of the differences between diagnoses.

Effect size integration

In order to create the random effects model summary effect sizes, we used an adapted version of the meta-analysis macros developed by Field & Gillett (2010) . This enabled us to use the composite effect sizes, and variances previously computed. Moreover, it helped us correct for unequal sample sizes by using the minimum weight received by each study in the initial analyses, and to compute the I^2 heterogeneity value.

The subgroup summary effect sizes are not directly comparable, thus they were interpreted as low if they were 0.2 or below, moderate between 0.2 and 0.5, and high above 0.8 (Cohen, 1992). However, as this is a general rule of thumb, effect sizes were also interpreted in the light of the specific literature on the topic of chemotherapy-induced cognitive impairments (Lipsey & Wilson, 2001), in which the effects are usually considered mild. For each analysis, we report the summary effect size, confidence intervals (*95% CI*), $I^2,$ and the overall significance level representing the null hypothesis that the treatment effect is zero (Borenstein et al., 2009). The negative or positive valence of effect sizes denotes the direction of the effect of chemotherapy on cognitive function: negative if suggestive of impairments, and positive if suggestive of performance increases in one group relative to the other.

Publication and selection bias

The publication bias for each main cognitive function was assessed through Egger's regression test (Egger et al., 1997). It estimates the asymmetry of the funnel plot due to under-reporting of data through a linear regression comprised of a normalized effect

size (divided by its standard error) and precision (inverse of standard error) We present the significance level of the intercept, which was considered to suggest publication bias if significant for *p*<.10.

Multilevel moderator analyses

Presently, there are two options available for conducting moderator analyses within a meta-analysis. The first, and most highly used method, was to run meta-regressions for each function, each design, and each moderator separately with the restricted maximum likelihood macros developed by Lipsey and Wilson (2001). The advantage of this method was that we could run specific analyses for each subgroup. However, this method can lead to a decrease in variance and a high likelihood of an increased Type 1 error when comparing multivariate effect sizes. Due to this reason and the presence of a categorical moderator (diagnosis) which requires dummy coding, we also pursued a multilevel model analysis for all effect sizes and moderators (Hox, 2002). We will briefly report the results of the classical meta-regressions, whilst focusing more on the results of the multilevel model approach.

The multilevel analyses were conducted with MLwin 2.1 (Rabash, Charlton, Browne, Healy, Cameron, 2009) with the restricted maximum likelihood procedure. We used a 3-level model with the study outcomes (summary effect sizes) as the first level, cognitive functions as the second level, and the studies as the third level. The moderators were the ones described above: study quality, diagnosis (coded as a dummy variable), age of participants, and time since treatment.

We will first report the intercept-only model, when no predictors are included. This is described by the equation:

$$ES_{ij} = \beta_{0j} + u_{0j} + e_{ij}$$

ES_{ij} refers to the effect size for outcome i from study j, β_{0j} is the value of the intercept (average effect size for an average outcome), u_{0j} is the random error at level 2, and e_{ij} is the random residual error at level 1. The variance of u_{0j} suggests the variability in effect sizes.

In the moderator analyses the equations take the form of:

$$ES_{ij} = \beta_{0j} + u_{0j} + \beta_1 Moderator_{ij} + e_{ij}$$

All the parameters represent the same values as in the empty intercept model, whilst the β_1 value represents the slope of the regression, suggesting the strength and direction of the change in effect size for a one-unit change of the moderator. All the analyses were run with predictors centred on their grand mean, to reduce the possibility of correlations between the intercept and predictors, as well as between the levels (Kreft & De Leeuw, 1998).

2.3. Results

2.3.1. Study characteristics

We analysed data pertaining to the neuropsychological evaluations of 1940 adult patients and 2000 controls. In total, 30 out of 44 studies (70%) included only breast cancer patients. The remainder included patients with testicular cancer, or lymphoma, or other haematological malignancies. Mean participant age was 51.57 (sd=6.29), and 75% of the studies included only female participants. All studies evaluated patients at an average of 2 years post-treatment (sd=2.52). In Appendix 2 we described the characteristics of each study included in our meta-analysis and the associated moderators.

2.3.2. Analysis of effect sizes across all subgroups

First, we compared the performance of all patients after chemotherapy to the performance of controls. Analyses were undertaken for all patients, irrespective of the comparison group – healthy controls or their own baseline performance – to allow comparison with previous meta-analyses. Effect sizes were small, had broad confidence intervals, and high heterogeneity (Figure 5). Patients had statistically significant performance increases (positive summary effect sizes) for visual memory and visual immediate free recall. Patients' performance was significantly reduced (negative summary effect sizes) only for selective attention.

Cognitive function	Effect size	CI lower	CI upper	I^2	p	K	Egger's
FSIQ	0.21	-0.21	0.64	0	0.32	5	0.27
MEMORY	-0.04	-0.16	0.07	19.05	0.45	36	0.35
Immediate	0.08	-0.03	0.19	37.33	0.15	27	0.27
Delayed	0.03	-0.14	0.2	20.66	0.72	26	0.4
Recognition	-0.13	-0.41	0.14	0	0.33	12	0.7
Verbal	-0.06	-0.19	0.06	0	0.32	31	0.88
Verbal immediate	-0.01	-0.14	0.12	12.23	0.86	24	0.12
Verbal delayed	-0.02	-0.22	0.17	0	0.8	24	0.13
Verbal recognition	-0.16	-0.42	0.09	0	0.22	9	0.58
Visual	0.2	0	0.4	55.8	0.04*	20	0.21
Visual immediate	0.22	0	0.45	39.31	0.05*	17	0.84
Visual delayed	0.15	-0.11	0.42	47.54	0.25	15	0.27
Visual recognition	0.03	-0.22	0.29	0	0.81	6	0.74
SPATIAL ABILITIES	-0.44	-1.33	0.44	0	0.32	14	0.11
ATTENTION	-0.09	-0.3	0.11	2.12	0.36	11	0.17
Focused	-0.02	-0.14	0.09	10.05	0.71	27	0.43
Selective	-0.26	-0.51	0	0.15	0.04*	10	0.87
Capacity	0	-0.06	0.06	0	0.94	20	0.09
EXECUTIVE FUNCTIONS	0	-0.11	0.11	0	0.95	34	0.4
VERBAL ABILITIES	0.12	0	0.23	0	0.03	10	0.2
ARITHMETIC	0.07	-0.06	0.22	0	0.27	10	0.69
MOTOR FUNCTIONS	0.11	-0.19	0.41	0	0.46	16	0.16

Figure 5. Forest plot of summary effect sizes in adult patients compared to any control group.

Note. We report the Hedge's *g* effect size, the *95% CI*, *I^2*, *p* as the significance level of the analysis, *k* as the number of studies in the analysis, and the significance level of the intercept in Egger's test. *p<.05

2.3.3. Analyses by study design

Cross-sectional designs

We performed separate analyses for cross-sectional studies, at post-treatment and baseline. Following chemotherapy, patients exhibited significant low to moderate impairments relative to controls (Figures 6 and 7). These were observed in memory, immediate free recall, delayed memory, delayed recognition, verbal memory, verbal immediate free recall, verbal delayed free recall, verbal delayed recognition, selective attention, and capacity of attention. Summary effect sizes of other cognitive functions did not reach statistical significance.

Cognitive function	Design		Effect size	CI lower	CI upper	I^2	p	K	Egger's
MEMORY	Cross-sectional		-0.23	-0.35	-0.11	44.29	<.001***	22	0.68
	Longitudinal		0.12	-0.05	0.3	41.51	0.16	18	0.64
Immediate	Cross-sectional		-0.1	-0.19	0	0	0.03*	15	0.41
	Longitudinal		0.3	0.1	0.49	36.09	<.01**	16	0.02
Delayed	Cross-sectional		-0.18	-0.34	-0.02	0	0.02*	14	0.07
	Longitudinal		0.2	-0.02	0.42	31.26	0.08	16	0.44
Recognition	Cross-sectional		-0.4	-0.75	-0.06	0	0.02*	8	0.27
	Longitudinal		0.07	-0.08	0.24	0	0.33	6	0.78
VERBAL	Cross-sectional		-0.2	-0.32	-0.09	0	<.001***	17	0.17
	Longitudinal		0.06	-0.14	0.26	0	0.56	18	0.55
Immediate	Cross-sectional		-0.16	-0.26	-0.05	0	<.01**	15	0.03
	Longitudinal		0.22	0	0.44	2.57	0.05*	13	0.03
Delayed	Cross-sectional		-0.15	-0.28	-0.02	0	0.02*	12	0.46
	Longitudinal		0.06	-0.23	0.36	3.99	0.65	15	0.23
Recognition	Cross-sectional		-0.47	-0.79	-0.15	0	<.01**	5	0.13
	Longitudinal		0.05	-0.15	0.27	0	0.59	4	0.09
VISUAL	Cross-sectional		-0.1	-0.24	0.03	0	0.15	12	0.2
	Longitudinal		0.52	0.24	0.8	60.7	<.001***	12	0.13
Immediate	Cross-sectional		0	-0.27	0.26	9.74	0.98	11	0.18
	Longitudinal		0.47	0.15	0.8	36.21	<.01**	10	0.2
Delayed	Cross-sectional		-0.21	-0.64	0.21	0	0.33	9	0.12
	Longitudinal		0.44	0.07	0.81	28.07	0.01**	10	0.12
Recognition	Cross-sectional		-0.28	-0.72	0.16	0	0.21	5	0.22
	Longitudinal		0.25	-0.22	0.74	0	0.29	3	0.36

Figure 6. Forest plot of longitudinal and cross-sectional study effect sizes in adult patients for memory functioning.

Note. *k*=number studies. Full diamonds - cross-sectional effect sizes; empty diamonds – longitudinal effect sizes. * p<.05, **p<.01, ***p<.001

Cognitive function	Design	Effect size	lower CI	upper CI	I²	p	k	Egger's
SPATIAL ABILITIES	Cross-sectional	-0.32	-0.76	0.11	0	0.15	7	0.55
	Longitudinal	-0.47	-1.92	0.96	0	0.51	9	0.22
ATTENTION	Cross-sectional	-0.14	-0.34	0.05	0	0.14	8	0.84
	Longitudinal	0.09	-0.18	0.37	23.39	0.5	11	0.48
Focused	Cross-sectional	-0.17	-0.38	0.03	0	0.1	14	0.02
	Longitudinal	0.09	0.01	0.17	1.31	**0.02***	18	0.84
Selective	Cross-sectional	-0.39	-0.73	-0.05	0	**0.02***	7	0.24
	Longitudinal	-0.04	-0.29	0.21	0	0.73	5	0.88
Capacity	Cross-sectional	-0.15	-0.23	-0.06	0	**<.001*****	13	0.37
	Longitudinal	0.1	0.03	0.17	0	**<.01****	11	0.2
EXECUTIVE FUNCTIONS	Cross-sectional	-0.21	-0.49	0.05	12.9	0.11	12	0.06
	Longitudinal	0.02	-0.16	0.21	43.24	0.82	17	0.64
VERBAL ABILITIES	Cross-sectional	-0.3	-0.89	0.29	0	0.31	4	0.23
	Longitudinal	0.14	0.02	0.26	0	**0.01****	6	0.25
ARITHMETIC	Cross-sectional	0.11	-0.1	0.32	0	0.31	6	0.57
	Longitudinal	0.13	-0.15	0.42	0	0.37	6	0.01
MOTOR FUNCTIONS	Cross-sectional	0.25	-0.28	0.78	11.75	0.35	12	0.09
	Longitudinal	0.11	-0.07	0.29	0	0.24	5	0.55

Figure 7. Forest plot of longitudinal and cross-sectional study effect sizes in adult patients for cognitive functions other than memory.

Note. *k*=number studies. Full diamonds - cross-sectional effect sizes; empty diamonds – longitudinal effect sizes. *p<.05, **p<.01, ***p<.001

At baseline, before chemotherapy, patients performed better than controls, across most cognitive functions (Figure 8). Effect sizes were moderate to high, and statistically significant, but had high heterogeneity values. Superior patient performance was observed in memory, attention, executive functions, spatial abilities, and verbal abilities. Due to an absence of reported outcome data, we could not compute cognitive function effect sizes for 12 functions. Results were not significant for the remaining four functions, two of which (verbal memory and attention capacity) had negative values, suggestive of potential impairments.

Cognitive function	Design		Effect size	lower CI	upper CI	I^2	p	k	Egger's
MEMORY			1.73	1.11	2.36	96.48	<.001***	10	<.001*
Verbal memory	Patients		-0.13	-0.28	0.02	30.8	0.06	29	0.59
Visual memory	versus		0.23	-0.14	0.6	14.68	0.22	8	0.1
ATTENTION	Controls		0.73	0.13	1.32	90.52	<.001***	10	0.01*
Capacity	before		-0.38	-0.93	0.16	5.43	0.37	5	0.11
EXECUTIVE FUNCTIONS	treatment		1.61	0.77	2.46	94.17	<.001***	7	<.01*
SPATIAL ABILITIES	(Baseline)		2.34	0.92	3.76	85.46	<.001***	6	<.01*
VERBAL ABILITIES			3.94	1.19	6.69	75.14	<.01**	5	<.01*
MOTOR FUNCTIONS			0.08	-0.1	0.33	17.58	0.25	16	0.16

Figure 8. Forest plot effect sizes of patients versus controls at baseline for all cognitive functions.

Note. We report the Hedge's g effect size, the *95% CI, I^2, p* as the significance level of the analysis, *k* as the number of studies in the analysis, and the significance level of the intercept in Egger's test. **p<.01, ***p<.001

To summarize the findings from cross-sectional designs, as expected, patients performed worse than controls after treatment. Contrary to expectations, patients performed better than controls at baseline, before treatment began. This pattern was observed across most cognitive functions, even in cases where it was not statistically significant. Figure 9 visually depicts the difference between our findings and what we predicted on the basis of available literature.

Figure 9. Pattern of results in cross-sectional studies.

Note. Straight line represents the relationship between effect sizes obtained by patients versus control at pre-treatment and post-treatment

Longitudinal designs

When longitudinal studies were analysed separately, there was a clear improvement in patients following chemotherapy, compared to baseline. This finding was true across most cognitive functions we were able to analyse (Figures 6 and 7). The improvements in performance were statistically significant for immediate free recall, verbal immediate free recall, visual immediate free recall, visual delayed memory, focused attention, capacity of attention, and verbal abilities. Effect sizes of other cognitive functions did not reach statistical significance. Notably, heterogeneity was higher in studies measuring longitudinal changes, than in cross-sectional studies.

Longitudinal data from healthy control participants were infrequently reported (Figure 10). As a result, effect sizes could only be computed for five of the 22 cognitive functions, each analysis including up to a maximum of seven studies. The analyses were restricted to those reporting patient and control comparison at different time points. Controls performed significantly better at follow-up than at baseline on memory and visual memory. In these analyses there was less heterogeneity, despite the smaller number of studies reporting longitudinal control results.

Cognitive function	Design		Effect size	lower CI	upper CI	I^2	p	k	Egger's
MEMORY			0.18	0.009	0.36	10.52	<.05*	6	0.48
Visual memory	Controls follow-up		0.23	0.05	0.41	0	<.01**	6	0.34
ATTENTION	versus		0.21	-0.19	0.62	80.41	0.3	7	0.66
Capacity	baseline		0.27	-0.24	0.79	76.69	0.3	7	0.7
EXECUTIVE FUNCTIONS			0.08	-0.01	0.19	0	0.08	6	0.92
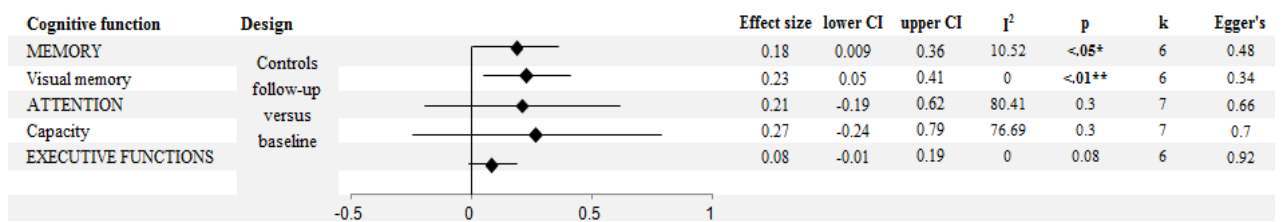
Figure 10. Forest plot effect sizes of controls at follow-up versus baseline for all cognitive functions.

Note. We report the Hedge's *g* effect size, the *95% CI*, I^2, *p* as the significance level of the analysis, *k* as the number of studies in the analysis, and the significance level of the intercept in Egger's test. **p<.01, * p<.05

To summarize the findings from longitudinal designs, contrary to expectations, patients performed better after chemotherapy than before. The only exceptions were spatial abilities and selective attention, which had negative values, but were not statistically

significant. Controls also improved, but the effect sizes were not as large as the ones estimated in patients. Because the two sets of effect sizes within the two subgroups are not directly comparable, we depict the expected versus observed values for controls and patients in longitudinal studies (Figure 11). For all other cognitive functions, which were not significant, patients' effect sizes were only negligibly reduced compared to those of controls (e.g. executive functions, patients $g=.02$ and control $g=.08$).
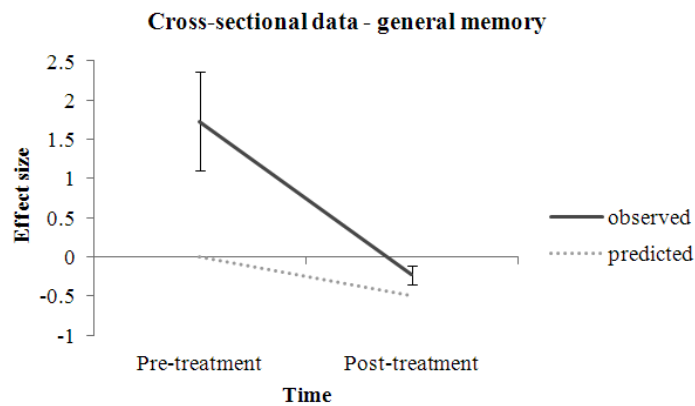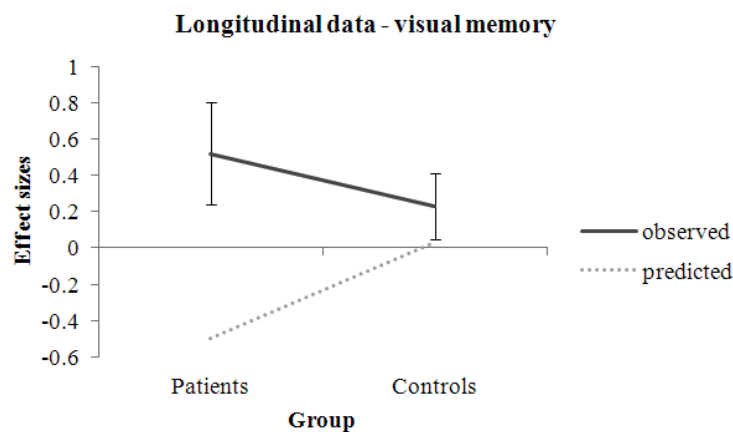

Figure 11. Pattern of results in longitudinal studies.

Note. Straight line represents the relationship between effect sizes obtained by patients at pre-treatment versus post-treatment, and separately for healthy controls

2.3.4. Moderator analyses

The classical moderator analysis, which was run using Lipsey and Wilson's (2001) macros, had the advantage of analysing the impact of each moderator on each function within the two designs. However, it had the disadvantage of comparing multiple effect sizes characterized by group dependencies, thus the variances of the results may have been underestimated and the significance values overestimated. Still, in R^2 values, the quality of the studies, age, and time since treatment significantly explained between 38% and 69% of the variance of effect sizes in cross-sectional studies, and between 16% and 66% of the variance in longitudinal studies. The most noteworthy results were those of the quality of

studies influencing up to 34% of motor function effect size variance in cross-sectional studies, and time since treatment explaining 56% of the visual immediate free recall variance in longitudinal studies (data not presented in paper, available upon request).

Our multilevel model did not have the advantage of analysing the results in subgroups, but for all available effect sizes. We will firstly report the result of the intercept-only model (see Tables 5 and 6 for all the coefficients). The first level was described by the summary effect sizes, the second level were the cognitive functions, while the third level was the study itself. The intercept only model, independent from variances at the third level was estimated at .18 (standard error =.07). Compared to the z-critical value for $p<.05$, the residual variance was significant, 3.10 (.17). In other terms, the overall mean effect size, irrespective of the type of design, functions, or variances at the third level was a low positive summary effect size, but there is a great amount of unexplained variance. When the intercept was set to vary at the study level, the average effect size decreased to .13 (.11). The between study variance of .24 (.10) was significant for $p<.05$ and the residual variance decreased but was still significant with 2.79 (.16).

Given the highly significant study level and residual variance, we carried on by including each of our moderators within the multilevel model. Compared to the results obtained in the classical meta-regression, none of the continuous moderators had a significant impact on the summary average effect size estimation. The slope for the quality of the studies was .05 (.03), for age .01 (.01), and for time since treatment -.04 (.04). The average effect sizes for the types of diagnoses were .18 (.12) for breast cancer, -.07 (.30) for testicular cancer, and .05(.27) for other diagnoses. The slopes had different orientations depending on the reference dummy-coded category. For all these results, both between

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study and residual variances continued to be significant and of roughly similar values (see

Tables 5 and 6 for details).

Moderator	β_0 (SE)	β_1(SE)	σ^2_u (SE)	σ^2_e (SE)	-2*loglikelihood	
Empty model (independent from Study)	.18 (.07)	NA	NA	3.106 (.17)	2377.67	
Empty model (dependent on Study)	.13 (.11)	NA	.24 (.103)	2.793 (.16)	2344.65	
Quality	.16 (.11)	.05 (.03)	.22 (.09)	2.791 (.16)	2341.55	
Age	.13 (.11)	.01 (.01)	.24 (.10)	2.793 (.16)	2343.56	
Time	.14 (.11)	-.04 (.04)	.23 (.10)	2.796 (.16)	2343.69	
					K=44	N=599

Table 5. Results of multilevel regression analyses for each continuous moderator.

Note. We report K as the number of studies in the analysis, N as the number of effect sizes included, β_0 as the value of the intercept, β_1 as the value of the slope associated with a certain moderator, the associated standard errors, σ^2_u as the variance associated with the study level, σ^2_e the variance of the random error, and the -2*loglikelihood values

β_0 (SE)	Breast cancer (β_1/SE)	Testicular cancer (β_1/SE)	Mixed diagnoses (β_1/SE)
.18 (.12)	Reference	-.25 (.32)	-.13(.30)
-.07 (.30)	.25 (.32)	Reference	.12 (.39)
.05(.27)	.13 (.09)	-.12 (.39)	Reference
K=44	N=599	$\sigma^2_u = 2.798$ (.16)	-2*loglikelihood = 2343.96
		σ^2_e=.27 (.02)	

Table 6. Results of multilevel regression analyses for each type of cancer.

Note. We report K as the number of studies in the analysis, N as the number of effect sizes included, β_0 as the value of the intercept, β_1 as the value of the slope associated with a certain moderator, the associated standard errors, σ^2_u as the variance associated with the study level, σ^2_e the variance of the random error, and the-2*loglikelihood values

2.3.5. Publication bias analysis

We performed publication bias analyses for each cognitive function examined. Some analyses were influenced by publication bias, thus should be treated with caution. When analysing the data irrespective of the type of control group, the intercept had a $p<.10$ only for capacity of attention. In the cross-sectional subgroup, verbal immediate free recall, delayed memory, focused attention, executive and motor functions, and had similar results. In longitudinal studies, the bias was present for immediate free recall, arithmetic, verbal free recall immediate, and visual free recall immediate. In the baseline subgroup, memory, executive functions, spatial, and verbal abilities were lower than .10 significance values, while the analyses of controls in longitudinal studies showed no influence of publication bias. Thus, these cognitive functions may have been reported more often in the literature if they showed impairments, while accounts of increases or lack of change might have been underreported.

2.4. Discussion

Our meta-analysis summarizes the findings from 44 studies examining an array of cognitive functions in adult cancer patients. Our primary objective was to identify which functions are impaired in each type of design. To that end, we divided studies into subgroups based on their design and calculated summary effect sizes for each type of cognitive function. The secondary objective was to identify potential factors that might explain the variability of results in previous literature. Thus, we analysed the impact of four moderating factors on all effect sizes.

When analysing all data, regardless of design and type of control group, only selective attention was impaired. Compared to previous meta-analyses, our effect sizes either did not reach statistical significance, or were very close to zero. Thus, pooling together a higher number of primary studies with inconsistent results, ultimately summed up to heterogeneous summary effect sizes, which did not distinguish between types of impairments (Rosenthal & DiMatteo, 2001).

Despite the influence of several confounding variables on the effect sizes, when patients were compared to controls at post-treatment, we observed small to moderate effect sizes, suggesting impairments in all aspects of verbal memory (immediate free recall, delayed free recall, and delayed recognition), in selective attention, and attention capacity. Furthermore, results in the cross-sectional subgroup analyses had lower heterogeneity values than those in other subgroups. This may suggest that cross-sectional studies are influenced by similar biases, whilst these might be more varied in longitudinal studies; but it may also be that the cross-sectional studies are generally influenced less by confounders. Irrespective of which hypothesis is true, they both suggest the need for better controlled studies to reduce subsequent heterogeneity (i.e. through proper participant matching).

Our cross-sectional analysis examining patients and controls at baseline investigated whether the patients' performance before exposure to chemotherapy. Patients performed strikingly better than the matched controls, for instance in their verbal (g=3.94) and spatial abilities (g=2.34).

The difference between the baseline and post-treatment results in patients and controls is depicted in Figure 9. This pattern contradicted our expectations based on previous literature. First, at baseline in cross-sectional studies, we would have expected patients to either perform worse than controls if the cancer itself would have had a

deleterious impact (Ahles et al., 2008), or at the same level as controls if participants had been matched accordingly on their educational and intelligence levels. This effect is not visible in our results. On the one hand, the high effect sizes at baseline clearly suggest that patients are not impaired before chemotherapy. They also question whether there were other factors that differentiated patients from controls from the start of the study, such as different education, socio-economic status, different intelligence levels, and even different motivation to perform well in testing. We note, however, that the two sets of analyses are not directly comparable, thus this is a relative comparison with the results one would expect based on previous literature reviews (Vardy & Tannock, 2007; Zachariae & Mehlsen, 2011). Post-treatment analyses are drawn mostly from cross-sectional studies, while the baseline analyses are only drawn from longitudinal studies in which patients were compared to control participants at baseline, and then at several time points post-chemotherapy. Thus, the potential poorer participant matching in the baseline assessments might stem from variability in longitudinal studies.

In longitudinal studies, patients performed better in follow-up evaluations than at baseline, with small to moderate effect sizes across multiple functions. Improvements between the first and second tests were also observed in control participants, for the limited set of cognitive functions we were able to analyse. These were lower and based on a smaller number of studies than the effects computed on patients, but were less heterogeneous than the patient analyses. Just as in the two cross-sectional subgroup analyses, the lower heterogeneity may be explained by the fact that the two sets of data were sourced from different articles, which may have been affected by confounders differentially. Despite this, the effect sizes of the patient group are still high, specifically for immediate free recall, and verbal immediate free recall.

The pattern of impairments in cross-sectional studies appears congruent with previous functional imaging studies. Compared to matched controls, breast cancer patients had significant left lateralized white matter decreases in the parahippocampal gyrus (de Ruiter et al., 2011; Inagaki et al., 2007; McDonald, Conroy, Ahles, West, & Saykin, 2010), and reduced activations in the left lateral posterior parietal regions and left dorsolateral prefrontal cortex (de Ruiter et al., 2011; Deprez et al., 2011; Koppelmans, de Ruiter, et al., 2012). The moderate impairments in selective attention may be associated with the decreased white matter in the superior fronto-occipital fasciculus and superior and medial frontal gyri observed in other imagining studies (de Ruiter et al., 2011, 2012; Inagaki et al., 2007; McDonald et al., 2010; Silverman et al., 2007). Despite the probable connection between these behavioural and imaging results, more studies are needed to confirm if these changes are related. Furthermore, the pattern of deficits in attention and memory makes it difficult to conclude whether the memory problems exhibited by cancer survivors are dependent on damage to the medial temporal lobes, or secondary to damage in frontal or parietal neocortical regions associated with attention performance. We hypothesise that some aspects of the memory impairments may be primary and others dependent on attention deficits, but further research is needed to address this issue.

The cognitive performance increases in patients in longitudinal studies are surprising, but may be linked to either additional sources of bias or genuine long-term improvements. Patients may be prone to a relatively stronger influence of practice effects due to certain characteristics that made them more motivated to take part in such studies, compared to control participants. Reasons could include the desire to perform well in the test, pre-existing knowledge that chemotherapy may be associated with cognitive impairment, and differential setting and framing of the tests for patients and control participants (Schagen, Das, & Vermeulen, 2012). However, some deficits may only be

short-lasting effects (McDonald et al., 2010; Silverman et al., 2007) or some participants may have higher cognitive reserves which allows the development of compensatory strategies in specific cognitive tasks (Ahles et al., 2010). Both these hypotheses warrant further investigation.

The multilevel analyses showed that neither of our chosen moderators explained the variance in effect sizes. This is a surprising result, given that it is unlikely that a different age, or a different time since treatment would not affect cognitive functioning. Some of our hypotheses regarding this non-significant result are that the multilevel model collapsed all summary effect sizes for all cognitive functions and all types of designs. If cross-sectional designs have negative summary effects, while longitudinal ones have positive summary effects, the resulting average effect size may very well approach zero.

A second potential explanation is the description of moderators. The quality of the studies was assessed on the best assessment scale recommended by the Cochrane Collaboration, but this may have been unsuitable for the types of studies conducted in this specific field, whilst there are no such tools available for the standard of neuropsychological studies. It may have been necessary to differentiate between specific aspects of quality, such as the presence of alternative-format tests, the reporting of certain test scores (i.e. full scale IQ), and the type of matching available in primary studies. The age of participants varied between 38 and 71, with an average of 51.57 (sd=6.29). The type of diagnosis is restricted to breast cancer in 70% of the studies, and the time since treatment in years varies between zero and 10 (m=2.09, sd=2.52). The non-homogenous samples in primary studies reflects the higher variance within the moderators, a reason why non-significant results are expected: there are not many studies conducted with people of exactly the same age, the same time since treatment, which may have led to non-significant

results when all effect sizes are collapsed together. We consider this aspect to warrant further examination in future meta-analyses.

Due to the multiple limitations of our meta-analysis (majorly due to the distribution of primary studies), we caution the interpretation of some of our results. First, our analyses show that our chosen moderators did not explain the heterogeneity of estimated effect sizes. Both between-study and residual variances remained high despite the inclusion of predictors. However, effect sizes in longitudinal studies are more heterogeneous than in cross-sectional studies, possibly due to additional factors which have not been measured, or have not been reported (e.g. impact of hormonal treatment, psychological co-morbidities, etc.). While many studies report matching on age and gender, intelligence is often a factor reported through various scores, ranging from the full scale IQ, to verbal or performance IQ. If the groups were not properly matched in primary studies, that would deem any meta-analytical results less trustworthy. To reduce such a possibility in future studies, intelligence should be measured and reported through the same measures (FSIQ). Throughout our analyses, we assumed the control participants and patients were matched on pre-morbid IQ, while this may not have been the case in all primary studies. For example, if patients' pre-morbid FSIQ were higher than controls', the observed deficits might not actually be mild, but severe for a highly functioning person. Due to this reason, the reporting of these scores in all future primary studies is warranted.

Second, the cancer diagnosis moderator was actually a proxy of treatment protocols and gender. While the type of treatment would be a valuable factor to analyse in relation to cognitive functioning, there is a high variability in the treatments reported, depending on the staging of the illness and patient-level medical characteristics. Importantly, the use of other classes of drugs such as corticosteroids, hormone antagonists or anti-emetics, may

also have influenced the results (Lupien et al., 2002), but these details are not always reported within the literature. Moreover, studies do not usually report the results of cognitive tests separately on the types of treatments.

As most studies with adults focus on patients with breast cancer, the diagnosis is also a proxy of the gender. Previous studies with paediatric cancer patients have shown that female gender may be a vulnerability factor to chemotherapy-induced changes (von der Weid et al., 2003). However, the results of cognitive tests were not reported separately in any of the studies including both males and females, thus gender would be a moderator to be accounted for in future studies.

Third, due to technical limitations, our review only included studies reporting means and standard deviations. Although we attempted to obtain this data from corresponding authors, this was not always possible, resulting in 23 studies being excluded. However, the Egger's values are only significant for four cognitive functions, thus most our analyses were not influenced by publication or selection bias. This relates to our fourth limitation - not adjusting for the publication bias found in these analyses. The distribution of our data within multiple subgroups, as well as the un-accounted between-study heterogeneity (Terrin, Schmid, Lau, & Olkin, 2003) would have resulted in inaccurate trim-and-fill results. However, there are only four specific results that should be treated with caution; specifically, in cross-sectional studies, delayed and verbal immediate memory, and, in longitudinal studies, immediate memory and verbal immediate free recall.

Finally, while heterogeneity was lower in cross-sectional subgroup analyses, it remained high in longitudinal studies. Our work should assist in reducing measurement noise in future empirical work. This should help minimize heterogeneity in future meta-

analyses, as well as reducing the number of confounding variables influencing results of primary studies.

2.5. Conclusions

The present paper summarizes research in the field of chemotherapy-induced cognitive impairments, while highlighting the nature, extent of impairments, and factors influencing their identification. Despite the considerable heterogeneity of data, the analysis of cross-sectional results could be considered the most reliable. With potentially less influence from additional variables, patients in cross-sectional studies performed worse than controls on tests of capacity of attention, selective attention, verbal memory, immediate, and delayed, in both free recall and recognition memory tasks. Although the interplay between attention and memory impairments remains a matter for future research, our results suggest that, the impairments might be linked to both frontal and medial temporal lobe dysfunction.

We have shown that cognitive performance prior to chemotherapy was higher in patients than in controls. That suggests that malignancy itself was not responsible for neuropsychological late effects, but it also casts doubt on the quality of participant matching and un-reported sources of bias in longitudinal studies.

Our moderator analyses were not significant, which is surprising given the plethora of factors that could influence cognitive data. This is the reason why, for the aid of future analyses on this topic, we suggest a number of guidelines that could be followed in the future studies:

1. The use of shorter neuropsychological batteries by focusing specifically on certain cognitive functions. This strategy would shorten the testing time and maintain

participants' interest active throughout the sessions. This option would contribute to minimizing the differences in participants' motivational levels during testing.

2. Longitudinal studies should only use cognitive tests with alternative formats, to avoid practice effects. Alternatively, when this standard cannot be achieved, only cross-sectional designs should be used.

3. If tests without alternative formats should be used, appropriate statistical techniques, accounting for practice effects, are warranted. These could include either the practice effects-adjusted Reliable Change Index or random effects/latent growth models centred on the average potential increase in performance due to practice effects (Ferrer, Salthouse, Stewart, & Schwartz, 2004; Small, Dixon, & McArdle, 2011; Wefel et al., 2010).

4. Avoiding the use of tests that are not sensitive to subtle cognitive impairments (i.e. MMSE or RBANS).

5. When using neuropsychological tests, striving to use very similar versions of the same cognitive tests between research groups, and reporting the same scores. This would promote a more consistent view of the impairments across studies. Examples of tests to be used would be the HVLT (and other similar versions, such as RAVLT or CVLT), the ROCFT (or other similar versions), any sections of the DKEFS (or similarly, the Stroop, Trail Making Test, and Controlled oral word associations), D2 (or Ruff 2&7), and Digit span for working memory.

6. Consistently grouping standardized groups of tests within the same cognitive functions, as the high number of neuropsychological tests variable method of clustering makes it difficult to understand whether two different results refer to the

same function. The present meta-analysis groups the tests within cognitive functions as suggested by Strauss et al. (2006).

7. Memory and attention have been consistently found impaired in many primary studies and meta-analyses, including our own. However, the links and mechanisms of these impairments are not yet explained. They could be investigated further through the development and administration of newly designed tests inspired by the neural mechanisms of these processes.

8. Reporting the pre-morbid intelligence levels, in a unitary fashion, as this is a key factor in matching controls and patients. This can be achieved by reporting the full scale intelligence quotient score as measured with the WTAR, NART, or other similar tests. These tests would correlate with most cognitive measures, unless the patients have very specific functional or structural brain changes due to treatment.

9. All cross-sectional studies should match participants closely on age, education, gender, and intelligence quotient, as all three of these variables could potentially change the whole interpretation of a cognitive dataset.

10. Results should be reported separately based on moderators that could introduce additional bias: gender, age of participants (if they vary between younger and older adults), relapses (as a potential factor relevant for the severity of impairments), types of diagnoses, and treatments.

11. Studies including control groups at baseline and follow-up could also report this set of data in the same table as the results of the patients.

While incorporating these conclusions and suggestions, future research should focus on the stability of these side effects, the link between memory and attention impairments, and

the treatments and clinical vulnerability factors that would predispose some participants more to impairments, rather than others. These future findings would inform the cognitive intervention strategies to help present and former patients cope with chemotherapy-induced cognitive impairments.

Chapter 3. Objectives and hypotheses

Based on the recommendations resulting from the meta-analysis, as well as the gaps in the literature, in the present chapter I will give a brief overview of the primary and secondary objectives and the hypotheses of each of the studies in this thesis. These are briefly described in the table below and will be detailed further in the corresponding chapters.

Chapter/Study	Objectives	Hypotheses
5. Neuropsychological difficulties in young adult post-treatment cancer patients	1. To describe the pattern of neuropsychological difficulties in post-treatment patients.	1. I expected decreases across attention, memory, executive functions, processing speed, relative to controls.
	2. To explore the relationship between potentially impaired functions, mood, fatigue, and cognitive complaints.	2. I expected a lower mood, higher fatigue and cognitive complaints. We did not expect any associations with cognitive deficits.
6. Pre-treatment neuropsychological profile of young adult cancer patients	1. To describe the pattern of neuropsychological difficulties in younger pre-treatment patients.	1. I expected decreases in attention and executive functioning tasks relative to controls.
	2. To describe the relationship between potentially impaired functions and mood, fatigue,	2. I expected non-significant associations with mood, fatigue, and cognitive complaints.

	and cognitive complaints.	
7. Acute memory deficits in chemotherapy-treated patients	1. To investigate if memory impairments are detectable immediately after the first treatment. 2. To evaluate whether there are selective impairments in encoding, consolidation, or retrieval.	1. I expected to identify memory impairments following chemotherapy. 2. I expected differences between patients and controls in all three mechanisms.
8. Subjective cognitive complaints, illness perceptions, and quality of life in post-treatment cancer patients	1. To describe the levels of distress, fatigue, cognitive complaints, type of illness perceptions and quality of life. 2. To describe the impact of distress, fatigue, cognitive complaints, and illness perceptions on patients' quality of life.	1. I expected post-treatment patients to have higher levels of distress, fatigue, cognitive complaints, and a lower quality of life compared to controls. 2. I expected illness perceptions to be associated with the level of distress, the latter to be associated with subjective cognitive complaints and all of the former to have a significant impact on quality of life.

Table 7. List of objectives and hypotheses for each study chapter.

Chapter 4. General methods

The *Participants*, *Instruments*, and *Procedures* sections of the studies share many similarities. Consequently, they will be described in more detail in this chapter, whilst the individual studies will only provide a brief review of the main points as a reminder.

4.1. Participants

All patients were recruited through NHS Trusts after receiving all necessary ethics approvals from the Greater Manchester North West Ethics Committee. Recruitment and accrual of all patients commenced on 22.11.2011 and ended on 21.03.2014. Control participants were recruited through local newspaper adverts and posters in local social venues (N=72), or were friends/family of the patient (N=2). They were considered an appropriate match to a patient if they perfectly matched them on gender, and final level of education attained and were maximum within a five-year age difference. The main decisions regarding inclusion and exclusion criteria were based on participant ages, types of diagnosis/treatment, stage within the treatment, and number of participants needed.

1. **Ages**

Based on the 5-year relative cancer survival statistics of the Office of National Statistics (ONS, 2011) by age at diagnosis, out of the 331,487 people diagnosed with cancer in 2010, 63% of the survivors were adults aged 15-59. These are all working age adults who may want to go back to work or into education following a successful treatment. Previous studies on the effect of chemotherapy on cognition have focused either on very young children diagnosed with leukaemia with ages ranging between two and 15 (*m*=9.7, *sd*=3.6) or older participants diagnosed with breast cancer, with ages ranging

between 38 and 71 (*m*=51.5, *sd*=6.29). These findings are informative regarding the cognitive consequences in children who had been treated very early within their development and the effects of breast cancer treatments in women usually over the age of 50. One of the main questions within this project was whether patients between the ages of 16 and 50 had similar deficits as those observed in prior studies with other groups.

The inclusion criteria were restricted to 16-50, both because this age group is under-represented in psycho-oncology research, and because it helped us reduce the variability in our sample. It is widely known that older age relates negatively to cognitive functioning, especially after the age of 50 (Verhaeghen & Salthouse, 1997). Cognitive functions are dynamic throughout the lifespan. For example, processing speed reaches its peak development around the age of 16, maintains a relative plateau between 20 and 30 years of age, after which it slowly declines. Poor cognitive performance is strongly related to age from 50 years onward, as processing speed relates to decreases in performance on other cognitive tests, such as episodic memory (Craik & Bialystok, 2006). Thus, neuropsychological results may be more heterogeneous in younger and older age compared to mid-adulthood, primarily because of the increased number of neural changes inherent to these periods (Van Petten, 2004). Due to this reason, as well as the underrepresentation of this group in psycho-oncology research, my studies only focused on young adults aged 16 to 50.

2. Diagnoses/treatment types

The first argument for the types of diagnoses included in the study was the key question of whether groups receiving treatments other than those for leukaemia and breast cancer exhibit similar cognitive impairments. If that were the case, it would suggest that all chemotherapy agents lead to a similar type of neurocognitive insult. By contrast, if the

results differed it would lead to the hypothesis that either the mechanisms (i.e. inhibitors of DNA replication via topoisomerase inhibition, such as anthracyclines, or via the crosslinking of the DNA such as alkylating agents) of specific drug groups and/or their respective metabolites may affect cognition in different ways. To be able to describe a picture of how different treatments may affect cognitive function the goal was to include several patients treated for the same malignancies with approximately homogenous treatments.

Because I was interested in the effects of chemotherapy on cognitive functioning, I aimed to recruit patients who were not administered CNS-directed treatments, and had a relatively good prognosis. Patients with metastatic cancer, and those who had received CNS-directed radiotherapy or chemotherapy were excluded. I focused on patients who received treatment for a primary, but not secondary malignancy and without a history of relapse, unless it was within 5 years of their initial treatment. Consequently, the patient groups consisted of:

1. Hodgkin's lymphoma patients who had been treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).

2. Breast cancer patients who had or were due to be treated with fluorouracil, epirubicin, and cyclophosphamide in addition to hormonal treatment with tamoxifen (FEC-T).

3. Germ cell tumour patients who had or were due to be treated with bleomycin, etoposide, and cisplatin (BEP).

4. Non-Hodgkin's lymphoma patients who had or were due to be treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone (RCHOP).

5. Ewing sarcoma patients who had or were due to be treated with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) and/or vincristine, actinomycin, and ifosfamide (VAI); osteosarcoma patients treated with high dose methotrexate, cisplatin and doxorubicin (MTX-CisDox); endometrial sarcoma patients treated with Doxorubicin alone.

3. Timings of recruitment and assessments

A group of patients was recruited before any chemotherapy in order to investigate potential pre-treatment neuropsychological deficits as suggested by previous literature (Ahles et al., 2008; Cimprich et al., 2010; Cimprich, So, Ronis, & Trask, 2005; Lange et al., 2014; Mandelblatt et al., 2014; Scherling, Collins, Mackenzie, Bielajew, & Smith, 2011, 2012; Schilder et al., 2010). This was also a group of interest for the investigation of the potential acute effects of chemotherapy on memory.

Post-treatment patients were recruited any time between six months and six years following the end of their treatment. The lower limit was chosen to ensure patients were well enough after the treatment to be able to dedicate their time to the study. The 6-year upper limit was decided to be able to focus on the short- to medium-term effects of chemotherapy while avoiding the additional heterogeneity that may be induced by extending our inclusion criteria to a longer time-range.

Based on these choices, the inclusion and exclusion criteria for both patients and controls were the following:

Criteria	Pre-treatment	Post-treatment	Controls
Between 16-50 years old			
Diagnosed with non-metastatic lymphoma, breast			

cancer, germ cell tumour, or sarcoma	X	X	
No previous history of chemotherapy	X		X
No prior history of malignancy*	X		X
Between 6 months and 6 years post-treatment		X	
No previous history of cranial irradiation or CNS-directed treatment	X	X	X
No previous history of brain injury	X	X	X
No previous history of mental health problems	X	X	X
No previous history of substance abuse	X	X	X
Not presently on drugs that may affect their mood (antidepressants, benzodiazepines, anticonvulsants)	X	X	X
Not presently on hormonal therapy**	X		X

Table 8. Inclusion and exclusion criteria for pre-, post-treatment patients and controls.

Note. Grey cells correspond to the group that had to meet that criterion to take part in the study. *To increase recruitment numbers the study included patients who had been treated for a relapse within 5 years of their previous treatment. **This exclusion criterion was applied to all groups other than breast cancer.

4. Patient accrual

A close investigation of the studies included in the meta-analysis revealed that the number of participants needed to obtain a moderate effect size was highly variable depending on the type of cognitive function and measures used. The studies examined in the meta-analysis included a median of 36 participants. The minimum number of participants in a study contributing to moderate effect sizes for a function was nine, while the largest number of participants for a similar effect size was 138. The minimum number of participants contributing to a large effect sizes was 14. Thus, the decision was made to recruit 15 patients for each diagnosis group in each of our studies. This would have translated in approximately 150 patients (75 post-treatment patients and 75 pre-treatment) and 150 control participants.

Although target accrual was achieved in post-treatment patients this was not the case in pre-treatment patients in whom the recruitment was seriously hampered by

logistical difficulties. Specific difficulties were present in recruiting pre-treatment patients and post-treatment sarcoma patients. At the same time, the post-treatment group was not as homogenously distributed as originally planned. Figure 12 depicts the total number of patients approached, of whom 41% consented to the study. Some participants did not complete all the instruments. In order to reach the target of 15 participants for each test, additional patients were recruited to replace missing data in respective groups. While there were no differences between responders and non-responders on any demographic variables, the number of participants included in the analysis of each neuropsychological test differed. These will be specified within each individual article.
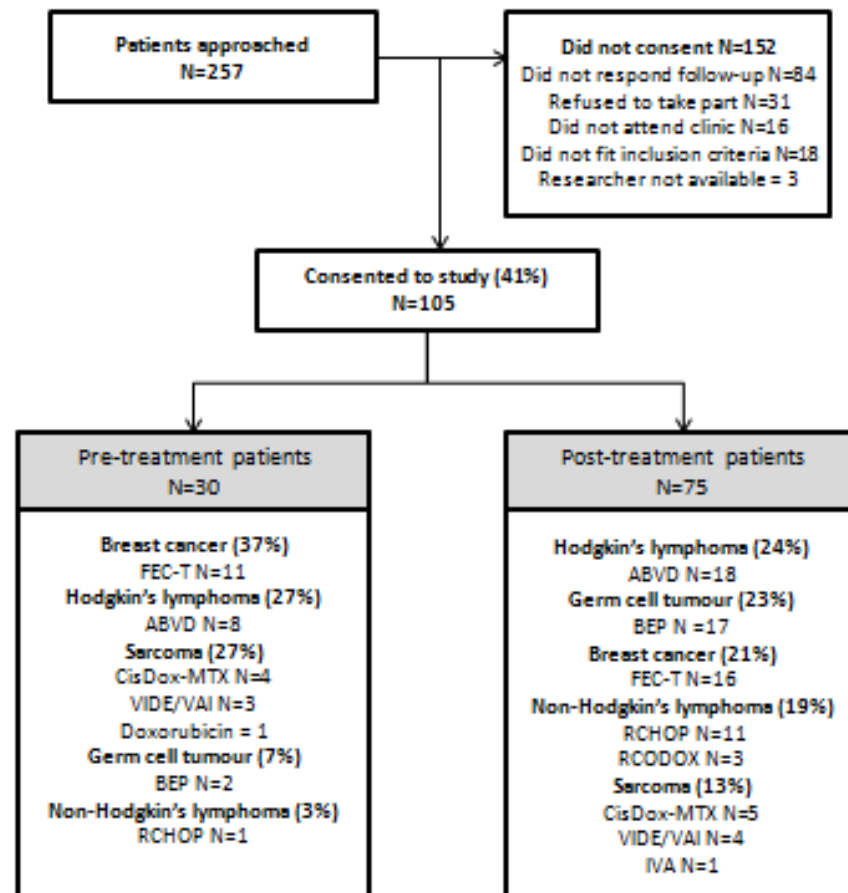
Figure 12. Flowchart depicting the number of patients approached and consented to the study.

4.2. Instruments

In this chapter, I describe the three classes of instruments I used, as well as the rationale for choosing them: a newly designed memory test, the neuropsychological battery, and a battery of self-assessment questionnaires. The order in which the tests are described reflects the order in which they were administered to all participants.

4.2.1. Memory test

The newly designed memory task was similar to classical list learning verbal memory neuropsychological tests (Geffen, Butterworth, Forrester, & Geffen, 1994). It involved the development of several lists of words, which the participants had to learn and recall three consecutive times (Figure 23, Chapter 7), on three consecutive days. Five word lists[1] were developed and their allocation to each day of testing was counterbalanced following a balanced Latin Square method (Bailey, 1996). They consisted of nouns depicting natural and man-made concepts (Animals and Vehicles, Fruits and Clothes, Vegetables and Kitchen objects, Four-legged animals and Musical instruments, and Birds and Toys) from the Snodgrass and Vanderwart (1980) database. The lists (Appendix 3) were equivalent in familiarity and Kucera-Francis frequency scores. All words were 4-10 letters in length. The first two letters of each word were unique, allowing the use of the first two letters as hints in a cued recall test. The 2-letter hints were displayed in a random order for each participant.

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[1] List A: Animals (19) and Vehicles (5); List B: Fruits (11) and Clothes (13); list C: Vegetables (9) and Kitchen objects (15); list D: Four-legged animals (15) and Musical instruments (9); list E: Birds (11) and Toys (13). The unequal distribution of the words in the lists was determined by the number of concepts in the database, which complied with our length, familiarity and frequency constraints.

Distracter task. Three spot-the-differences games were used, one game allocated to each session. Each game consisted of two versions of the same picture, containing 15 differences. Participants were asked to find as many differences as they could within the 2-minute timeframe. None of the participants identified all the differences on any of the pictures.

The test was administered before any other neuropsychological measures and in the same order to all participants. The first neuropsychological test that followed it on the first day of testing (Session 1) was the Wechsler Test of Adult Reading (The Psychological Corporation, 2001).

General test administration procedure. Each session lasted approximately 10-15 minutes. During study, words were presented on a screen for 2.5 seconds. Participants were asked to produce a sentence with the target word (e.g. "The **helicopter** is in the sky"), after which they pressed a key to proceed to the next word. Sentences were not recorded, but they had to be different for each word, whilst they could be the same for each study session. Recall sessions were not time limited, but they were terminated if participants stopped recalling items for more than 20 seconds. The experimenter recorded the words participants produced during each recall trial.

Testing flexibility. Given that the experiment took place at an extremely sensitive time for the pre-treatment patients, testing had to be flexible, while still maintaining an appropriate control of the experimental conditions. If patients could not make it to the hospital on Sessions 2 or 3, they could complete the task at home. When at home, participants were tested using a CD on their own computer, while speaking to the experimenter over the telephone. To access the program, participants were requested to fill in a dialogue box detailing their Participant number, the Session number and a Session

code which was unique to each day and formerly unknown to the participant. Controls were tested at university rather than at hospital, but the testing procedures were the same for each patient and their respective matched control (i.e. if a patient was tested at home in Session 2 they were matched to a control participant who was also tested at home).

In Session 1, which took place approximately 24 hours before the patients' first treatment, participants studied the first list of words (List 1), and were then asked to freely recall them in any order (FR11: the first number denotes the list, the second number the serial number of the test). The same study-recall procedure was administered a second time (FR12). Finally, participants studied the same list for the third time. In order to maximize the chance that items were retrieved from long-term memory, the third free recall test (FR13) was preceded by a 2-minutes activity filled delay during which participants performed the distracter task. The instructions for this part of the task were as follows:

"*On the screen you are going to see a list of words that I'd like you to remember. The list is quite long, so don't try to remember all the words from the start. We are going to go through the same list several times, for you to be able to remember more words each time. Whenever you see a word on the screen please tell me a sentence containing it. The sentence can be simple (such as "Cats have fur", if the word on the screen is "Cat"), but please make sure you use a different sentence for each word. After you see the entire list, I will ask you to tell me what you remember from it. The list of words for today will be made out of X and Y*".

After this instruction, participants saw the list and then given the following instruction:

"*Now tell me all the words you can remember*". They free recalled all the words they could remember at their own pace. If they paused for more than 20 seconds, they were asked: "*Is that all you can remember?*" If they confirmed, the next session begun:

"*Now we are going to go through the same list of words again just as we did before. Again, tell me a sentence with each word, you can use the same sentence as before*".

The same procedure as in Session 1 was repeated in Session 2 and the beginning of Session 3. Following the list presentation in Session 3, participants played the 2-minute distracter game:

"*Before you tell me what you remember, you will play a short game. On the screen, you are going to see two pictures and I want you to tell me how many differences you see between them. You will have 2 minutes to tell me as many differences as you can*". The experimenter recorded the differences spotted by the participants. At the end of the 2 minutes, participants were asked to recall the word list for the third time: "*Now tell me all the words that you can remember from the list*".

Session 2 took place the subsequent day. For patients, this was scheduled before they commenced treatment, while in hospital or before leaving home. Participants were first administered a surprise delayed free recall test (FR14) for the list they studied the day before, followed by a surprise cued recall test of the same list (CR15). Finally, they studied and recalled List 2 three times in a process identical to the previous day (FR21, FR 22, FR23). The instructions for this session were as follows:

"*First, could you tell me what words you remember off the list of X and Y you learned yesterday?*"

Participants were allowed to respond in the same manner as in the free recall trials in Session 1, following which the cued recall trial begun:

"*Now we are going to do something a bit different. On the screen, you are going to see the first two letters of each of the words you learned in this list, maybe they will help you remember a few more words. Don't think about it too much – if the word comes immediately to mind, tell me what it is. If it doesn't, just say Pass.*"

Following this trial, participants were presented with the second list of words, in a process identical to Session 1:

"*Now we are going to go through another list of words just as we did yesterday – three consecutive times and with sentences. This time the list of words that you will be learning is made out of X and Y*". The remainder of Session 2 had the same instruction as for Session 1, while Session 3 had the same instructions as Session 2.

Session 3 took place the following day, approximately 24 hours after the first chemotherapy dose. The procedure was identical to the second session: participants were tested on their memory for List 2 using free and cued recall (FR24, CR25), and then studied and recalled List 3 three times (FR31, FR32, FR33).

The procedure was first piloted on 40 university students. The goal of the pilot was to determine the type of stimuli (visual or verbal) and type of orienting task (shallow – naming the concept or deep – making up a sentence with the concept) that would be better suited for patient testing. Both factors can influence the strength of memory in an immediate or delayed retrieval task (Demb et al., 1995; Weldon, Roediger, & Challis, 1989; Wixted, 2004). Because I expected the memory impairment in the patients to be mild (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000) it was important that our task

would not favour floor or ceiling effects, would be feasible for several administrations, and that the cues provided additional support comparatively with the free recall trial.

The pilot demonstrated an effect of the type of stimuli (image or word) on the learning rate. Because the learning rate was steeper for image stimuli and we expected the memory impairment in patients to be mild, we decided to utilise the verbal stimuli. The orienting task did not influence the learning, forgetting, or retrieval rates. Because the use of sentences allowed us to gain insights on the strategy used by participants to commit the items to memory, we decided to employ the deep encoding task. Due to these reasons patients were administered the verbal deep encoding version of the tests.

4.2.2. Neuropsychological battery

Some of neuropsychological tests were included in the battery as suggested by the ICCTF (Stroop, Digit span, Verbal fluency, Trail Making Task, and a version of the List learning test), to maintain consistency between the data acquired in these studies and research pursued by other investigators. The battery aimed to be comprehensive, while keeping it as short as possible due to the logistical time constraints of a non-routine psychological evaluation. It also aimed to include tests that were most sensitive to mild cognitive impairments, while making sure each of them had alternative formats to increase the potential of running follow-up assessments with the same participants.

Wechsler Test of Adult Reading (WTAR, The Psychological Corporation, 2001) is a test for predicting intellectual functioning and memory abilities. It is co-normed with the Wechsler Adult Intelligence Scale and Wechsler Memory Scale, thus making it possible to predict the full scale IQ (FSIQ) and global memory functioning. It consists of a list of 50 words with atypical grapheme to phoneme translations. It takes approximately 5

minutes to administer and can assess intellectual functioning in people aged 16 to 89. This test was administered to all participants.

D2 Concentration-Endurance (Bates & Lemay, 2004) is a paper-pencil test evaluating sustained attention and concentration. In this test, participants had to cross out the letter "d" surrounded by two quotation marks (") either above, below, or with one mark below and one above. The distracter items are letter "d"-s surrounded by a different number of quotations and letter "p"-s. Participants are required to mark as many target items per line as possible within 20 seconds. The total length of the test is 4 minutes and 40 seconds.

Test of Memory Malingering (Rees, Tombaugh, Gansler, & Moczynski, 1998) evaluates memory effort using a forced-choice methodology. Participants are shown 50 line drawings, after which they are shown another set of drawings, two per page, one of them being one of the drawings shown previously, the other being a new one. They had to make a decision which of the two drawings they saw previously. The test has two trials, participants being shown and asked to recognise the target items on two separate occasions. The test also has an optional delayed trial (with no additional prior exposure to the target items), which was not administered in these studies. As per the test manual, the cut-off score for memory effort is 45 hit items. Participants' potential poor performance on the neuropsychological tests may have been considered to stem from a lack of appropriate effort if their scores were less than the 45 cut-off on both trials. The test takes approximately 5 minutes to administer.

The Stroop test (Golden, 1975) evaluates whether a person can hold a goal in mind while suppressing an automatic response to a stimulus in the favour of a newly learned rule. It starts with the person reading out names of randomized colours (blue, red,

green) written in black ink as quickly as possible (Word task). Off a separate page the participant points out the colour of the ink (Colour task), while on the last page names of colours are written in non-consonant ink (Colour-Word Task). There are 100 items to be read out per page and the participant has 45 seconds to read out as many as possible. The total time of administration is 2 minutes 25 seconds

Birt Memory and Information Processing Battery (BMIPB, Coughlan, Oddy, Crawford, 2007) is a collection of memory and speed of processing tests similar to the WMS, but normed on the British population and benefiting from 4 alternative versions. The total time of administration is 40 minutes. The battery contains a **Story memory** test in which participants are read out a short story, after which they have to remember it in as much detail as possible. Participants then have to remember the story again 40 minutes later. This serves as an immediate and delayed verbal memory test, and a retention score is calculated by dividing the number of items remembered on the delayed test from the ones on the immediate one and multiplying by 100. It is followed by a **Figure learning** test in which participants first have to copy a complex figure on a blank sheet of paper (Figure copy, as a measure of visuospatial performance). Then, they have to draw it again from memory immediately and 40 minutes later. This part serves as an immediate and delayed visual memory test and a retention score is computed by dividing the percentage of details recalled on the delayed version of the task from the ones recalled immediately, multiplied by 100.

The next test was **List learning,** focusing on verbal immediate memory. The experimenter reads out a list of 15 words (**List A**), which the participant has to remember. The reading-recall sequence is repeated 5 times or until the participant recalls the full list twice. Then the experimenter reads out a second list (**List B,** also called the interference

list) just once, and the participant is asked to recall as many words as possible. Finally, the participants are asked to recall List A again, without having it repeated to them. This part is followed by an immediate **Verbal recognition** task in which participants are shown pairs of words on a card. Out of each pair, one word had been learned in the previous test and one was new. They need to point out which of the words in the pair they learned previously and whether its source is List A (which had been repeated 6 times) or List B (only recalled once).

The fifth part was a **Design learning** task, focusing on visual immediate memory. Participants are shown a complex design (**Design A**) which they have to draw out of memory. The design is shown and recalled five consecutive times, or until the participant correctly recalls it twice. Participants are then shown a second design (**Design B**) just once, which they need to remember and draw. Following this, they are asked to draw Design A again, for the sixth time. This immediate visual memory test is followed by an immediate **Visual recognition** test in which participants are randomly shown images of Design A, Design B, and new designs from a 40-image booklet. Participants have to specify whether they had seen the design before or not, and to identify it as Design A or B.

Finally, the **Information processing** test requires participants to cross-out the second highest number out of rows of five two-digit numbers. They need to be as accurate and fast as possible, while crossing out as many numbers within 4 minutes. This test was followed by a **Motor speed** test; within 25 seconds, participants have to cross-out as many numbers "11" as possible, which are randomly assigned within rows.

Wechsler Adult Intelligence Scale - III - Digit span (Wechsler, 1997) is a short, 5-minute, working memory test with two parts. In the **Digit span-Forward,** which serves as a short-term memory test, the participant is read sequences of digits, which they then

have to repeat in the same sequence. An extra digit is added to the sequence after every two trials. In the **Digit span-Backward**, which serves as a working memory test, the participant is read similar digit sequences which they then have to repeat backwards (i.e. the experimenter reads "1-2-3" and the participant repeats it as "3-2-1").

Verbal fluency test (Henry & Crawford, 2004) is an executive function test evaluating the ability for quick response generation, self-monitoring, and mental set shifting. In the **Phonetic form** the participants had to generate as many words as possible beginning with three types of letters (F, A, and S) within 60 seconds. In the **Semantic form** participants were given a certain category (either Animals or Kitchen objects, counterbalanced on the basis of the category list used in the memory task with each participant at the beginning of the testing session) for which they had to generate as many exemplars as possible. The test takes 4 minutes to administrate and also benefits of additional equivalent alternative forms (Ross, Furr, Carter, & Weinberg, 2006).

The **Delis-Kaplan Executive Function System (DKEFS) Trail Making Task (TMT,** Delis, Kramer, Kaplan, & Holdnack, 2004) is another executive functioning test focusing on visual attention and task switching. It has five parts examining the participants' speed in visual scanning, processing of numbers, processing of letters, mental flexibility in connecting numbers and letters (1-A-2-B-3-C, etc), and motor speed. Separate contrast scores are computed by subtracting the time taken to complete each individual task versus the Number-Letter sequencing trial. It takes approximately 5 minutes to administer, depending on the participant's speed (Spreen, Sherman, Strauss, 2006).

All the raw scores obtained by participants on each test were transformed into standardized t-scores with a mean of 50 and standard deviation of 10. The transformation was based on the published normative data of each of the tests. The normative data either

accounted for the age, sex, and education of the participants (BMIPB, D2), age and education (WTAR, Stroop, Digit span), or solely the age of participants (Verbal fluency, DKEFS).

4.2.3. Psycho-emotional assessment

Cognitive performance can be influenced by a plethora of factors, which may need to be statistically controlled to avoid false positive neuropsychological results. At the same time, we were interested in the emotional functioning and level of subjective cognitive complaints in this group of participants, which is not very well known. In order to meet both goals the study included several self-assessment questionnaires, which were chosen based on whether they have been specifically designed for oncology patients or other clinical populations, their construct validity, and frequency of usage in other similar studies.

EORTC Quality of Life (QoL) version 3.0 (Aaronson et al., 1993) is a 30-item questionnaire, designed to assess the quality of life of cancer patients. The general version was used due to the mixed sample characteristics. The questions are divided into three main scales: functioning, symptoms, and global quality of life. Scoring was pursued based on the QLQ-C30 manual (Fayers, 2001). High scores on the functional and global quality of life scales represent a high/healthy level of functioning; a high score on the symptom scale represents a high level of symptomatology.

The Fatigue Questionnaire (Chalder et al., 1993) is an 11-item questionnaire that has been specifically designed for the assessment of fatigue in patients. It has been previously used with cancer and HIV patients. The questions can be summed into a total fatigue score, as well as divided into physical and mental fatigue scores (Dittner, Wessely, & Brown, 2004).

The Cognitive Failures Questionnaire (Broadbent et al., 1982) evaluates self-reported failures in memory, attention, perception, and motor functioning. It consists of 25 items, which can be rated from 4 (very often) to 0 (never). The total score is obtained by summing items, ranges between 0 and 100, with higher scores suggesting more failures.

The Illness Perception Questionnaire-Revised (IPQ-R, Moss-Morris et al., 2002) investigates patients' perception of their illness through various scales. The first one is the Identity scale in which participants state whether they had experienced 12 types of symptoms since the onset of their illness (i.e. pain, nausea, etc.) and whether they believe the symptom is related to the their illness. The sum of "yes" answers on the latter question is the level of illness Identity. The second part of the questionnaire evaluates the patients' view of their illness through 39 items which are rated between 0 (strongly disagree) and 5 (strongly agree). Some items have reversed scorings. This second part is scored and interpreted on seven separate scales: Timeline of the illness, its Consequences, Personal control and Treatment control of symptoms, Illness coherence, whether the illness is likely to be Cyclical, and its Emotional representation. A third part of the questionnaire investigates the patients' beliefs about the possible causes of their illness and is usually analysed separately in a qualitative manner. This part of the questionnaire was not included in the present analyses as it was beyond the scope of these investigations. Although the IPQ-R is generally used in an adapted form (i.e. by replacing the term "illness" with "cancer"), the questionnaire was administered in its original form. Patients were asked state their beliefs regarding their diagnosis since they finished treatment.

Hospital Anxiety and Depression Questionnaire (Zigmond & Snaith, 1983) is designed to identify anxiety and depression symptoms in clinical groups. It consists of two 7-item subscales (anxiety and depression), each item being rated between 0 (not at all) to 3

(very often). The minimum score is 0 and maximum for either anxiety or depression is 21, with a possible case cut-off score of 8+ for each scale (Bjelland, Dahl, Haug, & Neckelmann, 2002).

4.3. Procedure

In the following sub-chapters, I will describe the general strategies employed throughout the project in order to recruit and test participants.

4.3.1. Recruitment

For the whole project, we filed one ethics application (Appendix 4), which has undergone three amendments. The recruitment of both pre- and post-treatment patients was done through several NHS Trusts: The Christie NHS Foundation Trust, Royal Liverpool University Hospital, Royal Albert Edward Infirmary in Wigan, Macclesfield District General Hospital, and Great Western Hospitals NHS Foundation Trust in Swindon. Finally, patients in the NHS were recruited through two main strategies:

1. In the hospital, with the agreement of the patient's consultant, a member of the clinical care team outlined the study and gave potential participants a Participant Information Sheet and a leaflet (Appendix 4), specifically designed for this study. If they were interested in the study, the experimenter gave the patients more details about the study and exchanged phone numbers. After 24 hours, patients were contacted again to have any questions answered and to schedule an appointment in the hospital or the university building.

2. Through self-referral, with the aid of an advert that was published in the local newspapers, on the Cancer Research UK and Salford Citizen Scientist websites and other cancer-related forums (i.e. Macmillan Cancer Support) to enable potential participants to get in touch directly. This led to the recruitment of additional breast cancer post-treatment patients, some off the Greater Manchester Younger Breast

Cancer Network Facebook page (N=2) and some through adverts in newspapers (N=6).

Control participants were recruited through the following strategies:

1. All patients were asked if they had a friend or colleague who might agree to participate in the study as a control. Permission was asked to contact that person to describe the study, send out an Information sheet and schedule an appointment. This strategy led to the recruitment of two control participants.

2. Through adverts in local newspapers and posters in local social venues and cafes.

Patients and controls alike could ask for travel reimbursement for the participation in the first study. Due to the poor control participant accrual, the third amendment included the option of paying controls £10 for their participation.

4.3.2. Testing

The administration of the memory task and neuropsychological battery lasted one hour and a half. Participants had the option of either sitting the tests in one go, or those who were feeling unwell or could not undergo the whole battery due to other reasons, had the option to have the tests administered in three modules. One pre-treatment patient and one control participant chose to be tested on several days, while all other participants chose to undergo the whole testing at once. Regardless of this choice, tests were administered in the same order to all participants.

Pre-treatment and post-treatment patients, as well as controls and were evaluated in a quiet room in the hospital or university. The steps of the testing procedure were as follows:

1. Participants were asked to read and sign the consent form.

2. Participants underwent Session 1 of the memory test.

3. The neuropsychological tests were administered either together or divided in the three separate Modules. The timings for administering the modules were agreed together with the participant, making sure all the tests were administered within the same week and no later than just prior to the first treatment for pre-treatment patients.

4. At the end of the neuropsychological testing, participants received a self-addressed, pre-paid envelope containing a CD with the computerised memory test and the set of self-assessment questionnaires. A time was scheduled to run the additional memory tests over the telephone during the two subsequent days.

5. On the next two consecutive days, participants were contacted for Sessions 2 and 3 of the memory test. To be able to access the program on the CD the participants had to input a series of codes, which were only provided in the moment of the assessment. For most participants assessment went smoothly through this procedure. Unfortunately, due to technical issues a few participants (details provided in **Chapter 7**) could not access the computerized version of the test, and the assessment was administered verbally, omitting the 2-minute distracter task. Data from these participants was excluded to reduce variance.

6. Following Session 3 of the memory test participants were reminded to send the pre-paid envelope with the CD and questionnaires back to the experimenter.

The following chapters describe the rationale for each of the studies, as well as the respective methodology, results and their implications.

Chapter 5. Neuropsychological profile of young adult post-treatment cancer patients

Lindner, Mayes, McCabe, Wearden, Radford, Talmi. To be submitted to Journal of Clinical Oncology.

Abstract

Objective Cancer survivors exhibit post-treatment cognitive difficulties, but evidence to date is mostly limited to post-treatment breast cancer patients who are over 50 years old. This is the first study to explore the pattern of cognitive deficits in a mixed sample of post-treatment cancer patients who are under the age of 50, whilst accounting for the influence of other factors, such as subjective cognitive complaints, distress, and fatigue. *Method* Patients (N=75) who had been treated for sarcoma, lymphoma, breast cancer, and germ cell tumour were recruited and compared to healthy controls (N=74) matched on age, sex, and education. Participants were administered a comprehensive neuropsychological battery and several self-assessment questionnaires. *Results* Despite matching on education, groups differed on FSIQ. They also differed on anxiety, depression, fatigue, and cognitive complaints. After including these factors as covariates, patients performed worse than controls on executive functions, visuospatial abilities, and verbal memory. Lymphoma and germ cell tumour patients had a lower performance on most tests, compared to controls and other post-treatment groups. Visuospatial performance was related to verbal memory, and they were both related to the number of cognitive complaints, level of tiredness, and distress reported by patients. *Conclusions* Young adult post-treatment patients, who had been treated for several malignancies, exhibited difficulties in a number of cognitive functions that varied with treatment. We also demonstrated the importance of statistically controlling for covariates such as IQ, emotional distress and fatigue when determining the extent of cognitive difficulties.

chemotherapy, cognitive impairment, chemo-brain, young adults, cancer

5.1. Introduction

The presence of cognitive difficulties in cancer patients, demonstrated through several studies, extend to most cognitive functions (Ahles & Saykin, 2007; Kaiser, Bledowski, & Dietrich, 2014; Lindner et al., 2014), but tend to be highly variable, with 17% to 78% of patients being classed as impaired (Schagen & Wefel, 2013). The sources of variability are both methodological and clinical, but there are also suggestions that some patients may be more predisposed to difficulties than others (Ahles et al., 2012; Du, Cai, & Symanski, 2013; Koppelmans, Breteler, Boogerd, Seynaeve, & Schagen, 2013). However, it is still unclear if the cognitive impairments are related to potential clinical characteristics of patients that are also present before treatment and whether they are triggered primarily by chemotherapy or other factors.

Nevertheless, these behavioural results are further supported by imaging studies with breast cancer patients, identifying the neural correlates of the cognitive difficulties (Lepage et al., 2014; Simó, Rifà-Ros, Rodriguez-Fornells, & Bruna, 2013), as well as animal models outlining their potential mechanisms. After treatment, patients exhibited white and grey matter volume decreases in frontal and temporal regions (McDonald & Saykin, 2013), as well as abnormal brain activations during cognitive tasks in frontal, prefrontal, and parietal regions, compared to healthy controls (de Ruiter & Schagen, 2013; Simó et al., 2013). Proposed mechanisms are the induction of inflammation, oxidative stress, apoptosis, disruption of CNS blood supply, CFS composition, and inhibition of neuro- and gliogenesis (Ahles & Saykin, 2007; Minisini et al., 2004; Seigers et al., 2013).

To date, research has been polarized between studies of childhood leukaemia, and older patients treated for breast cancer. The first set of studies demonstrated that survivors of acute lymphoblastic leukaemia exhibited cognitive difficulties across all functions, as

well as significant IQ decline (Krull, Bhojwani, et al., 2013). It is unclear if these effects are primarily associated with chemotherapy, but it is known that leukaemia treatment is highly aggressive and CNS-directed, administered during a period when the latter is going through major developmental changes. These studies highlight that younger age and an increased survival time are predictors of chemotherapy-induced cognitive deficits, which may vary in severity depending on the malignancy and treatment. They also highlight the need for therapeutic strategies to ensure a higher quality of life for survivors of childhood cancers.

Historically, studies with adult patients have focused mainly on breast cancer survivors aged 50 or more (Kaiser et al., 2014; Lindner et al., 2014); recently, the effects of treatment for other malignancies have started to be given some, albeit limited, attention (Craig, Monk, Farley, & Chase, 2014; Cruzado et al., 2014; Wefel et al., 2014; Zimmer et al., 2014). While previous studies pinpoint the cognitive difficulties associated with breast cancer treatments, they also emphasize their large variability. The value of these studies for the understanding of the chronic effect of chemotherapy is limited in two ways. On the one hand, these patients received hormonal therapy and its effects on cognitive functioning are still a matter of debate (Jenkins et al., 2004; Ryan, Carrière, Scali, Ritchie, & Ancelin, 2009). On the other hand, the studies were mostly focused on older patients. Verhaeghen & Salthouse (1997) demonstrated strong negative correlations between age and processing speed, episodic, working memory and spatial abilities in participants over 50. They also describe processing speed as the main correlate of episodic memory; interestingly, this is one of the functions mentioned as impaired in other neuropsychological (Anderson-Hanley et al., 2003) and electrophysiological studies (Kreukels et al., 2005; Kreukels et al., 2006) and has been associated with interleukin-2 and interferon-alpha treatments (Capuron et al., 2001; Scheibel, Ph, Valentine, Brien, & Meyers, 2004). It is not yet known whether it may

drive the deficits observed in other functions, and whether these are only present in just a subgroup of patients.

To provide a more complete picture of the pattern of cognitive difficulties following chemotherapy, the present study explored the types and associations between potential deficits faced by a group that has yet to be extensively studied: post-treatment patients aged 16 to 50. The importance of focusing on this group is two-fold. First, cancer prevalence in this age range continues to increase (CRUK, 2014a; Maddams et al., 2009), and patients in this age group have a higher probability of long-term survival (ONS, 2011). Second, cancer survivors are known to have decreases in professional attainment and financial difficulties (Boykoff, Moieni, & Subramanian, 2009), and their subjective cognitive complaints are associated with a reduced quality of life (Hutchinson et al., 2012). Therefore, exploring the potential difficulties of young adult working age patients is paramount.

Previous studies have not usually found associations between cognitive deficits and levels of distress, fatigue, and cognitive complaints in cancer patients (Hutchinson et al., 2012). However, these factors need to be taken into account, both due to the effects of distress and fatigue on cognition (Burt, Zembar, & Niederehe, 1995; Dalgleish & Werner-Seidler, 2014; Jurado & Rosselli, 2007; Wearden & Appleby, 1996) and due to the higher incidence of these issues in cancer survivors (Linden et al., 2012; Seliktar, Polek, Brooks, & Hardie, 2014). Therefore, the second aim of the study was to explore how much of variance in neuropsychological performance may be explained by these factors.

5.2. Methods

5.2.1. Participants

Cancer patients in NHS Trusts in the United Kingdom were invited to the study if they were between 16 and 50 years old, and had been treated for sarcoma, lymphoma, breast cancer, and germ cell tumour (for the specific numbers of participants, see Figure 13). Patients included in the study if they were between 6 months and 6 years post-treatment. They were excluded if they had a previous history of CNS malignancies, cranial irradiation, a history of mental health problems, substance abuse, or previously exposed to mood altering drugs, or were not proficient in English. Seventy-five patients were included and were individually matched to healthy controls (N=74) on age, gender, and education. The latter were recruited through adverts in local newspapers, posters placed throughout social venues in the Greater Manchester area, or were friends/family of the patients. Recruitment and testing of both patients and controls commenced in November 2011 and ended in July 2014.

5.2.2. Instruments

Participants were tested using a neuropsychological battery, which included eight tests and resulted in 57 different scores. At the end of the appointment, they were offered a set of self-assessment questionnaires, which they had to complete at home. It included measurements of anxiety, depression, fatigue and subjective cognitive complaints. Table 9 describes the tests administered and the resulting scores.

5.2.3. Procedure

Patients were tested in a quiet room in the hospital at any time between 6 months and 6 years post-treatment, during a 90-minutes appointment. Control participants were evaluated either in a hospital office or university laboratory. The self-assessment

questionnaires were offered to all participants in a self-addressed pre-paid envelope, to complete at home. Tests were administered in the same order to all participants.

Cognitive function/ Norms	Test	Scores
Pre-morbid Full Scale IQ Age and education	Wechsler Test of Adult Reading (The Psychological Corporation, 2001)[1]	FSIQ
Attention Age, education, sex	D2 Concentration-Endurance[2] (Bates & Lemay, 2004)	Total number of items processed (TN) Total number of items minus errors (TNE) Omission errors Commission errors Percentage of errors (E%) Concentration performance (CP) Fluctuation rate
Executive functions Age, education	Stroop (Golden version, 1978)[3]	Word score Colour score Colour-Word Interference
Age	Delis-Kaplan Executive Function System Trail Making Task[9] (DKEFS, Delis et al., 2004)	Contrast scores between Number-Letter sequencing and Visual scanning (C1), Number sequencing (C2), Letter sequencing (C3), Number+Letter sequencing composite score (C4), Motor speed (C5).
Age	Verbal fluency[8] (Henry & Crawford, 2004)	Phonemic fluency: F, A, S Category fluency: Animals or Kitchen objects (counterbalanced)
Memory effort N/A	Test of Memory Malingering[4] (Rees et al., 1998)	Trial 1 and Trial 2, both with a cut-off of 45.
Memory Age, education, sex	Birt Memory and Information Processing Battery[5] (Coughlan, Oddy, Crawford, 2007)	Story memory – immediate and 40-minutes delayed recall Figure Copy Figure learning – immediate and 40-minutes delayed recall List learning: List A Total, List B, List A 6th recall Verbal recognition: words and list source Design learning: Design A Total, Design B, Design A 6th recall. Visual recognition: designs identified and source.
Speed of Information processing (SIOP) Age, education, sex	Birt Memory and Information Processing Battery[6] (Coughlan, Oddy, Crawford, 2007)	Total score Percentage of errors Motor speed Total score adjusted for speed
Working memory Age, education	Wechsler Adult Intelligence scale - III – Digit span[7] (Wechsler, 1997)	Forward Backward Total

Cognitive complaints	Cognitive Failures Questionnaire (Broadbent, Copper, Fitzgerald, Parkes, 1982)	Number of subjective cognitive complaints
Fatigue	Chalder Fatigue Scale (Dittner, Wessely, Brown, 2004)	Total fatigue score
Emotional distress	Hospital Anxiety and Depression Questionnaire (Zigmond and Snaith, 1983)	Anxiety Depression

Table 9. Cognitive tests, their respective norms and self-assessment questionnaires administered.

Note. Superscript numbers signify the order of the test within the battery.

Statistical analyses

Neuropsychological status of patients relative to norms. It is recommended that patients' performance should not be compared to norms alone (Collins, Mackenzie, & Kyeremanteng, 2013; Vardy et al., 2006) due to the heterogeneous nature of the patient group compared to that of controls used to create test norms and because the latter do not always account for all relevant factors – age, education, and sex. To explore the probability of a patient being classed with a lower than expected performance, the results of both patients and controls was evaluated against the test norms. If patients were not impaired, a similar percentage of patients and controls should have exhibited a poor performance (Crawford & Garthwaite, 2009). The 10th percentile represents those participants who perform at or below 1.28 standard deviations under the population mean. Thus, all those participants who performed at or lower than the 10th percentile were identified and the odds ratio was calculated (Altman, 1991), or the probability of identifying a patient or a control in their respective groups, with a similarly lower than expected performance on the specific test.

Neuropsychological status of patients relative to matched controls. Distributions of all variables were inspected, and when it was not normal either in skeweness or kurtosis, both

bootstrapped analyses of variance (ANOVAs) and Kolmogorov-Smirnov tests were run to facilitate the comparison between different scores (Tabachnick & Fidell, 2007). Because the results from these two methods overlapped, the results of parametric tests will be reported. The effect sizes were also calculated, as standardized Hedge's *g* scores and the corresponding 95% confidence interval (Borenstein et al., 2009). To account for the different distributions in the calculation of effect sizes, the bootstrapped standard error was used in the formula. Finally, focusing on the patient group, bootstrapped correlations were ran between all cognitive functioning scores that were found significantly different between the two groups, as well as distress, fatigue, and cognitive complaints, to help in the interpretation of the pattern of performance decreases.

5.3. Results

5.3.1 Participant recruitment and characteristics

Figure 13 details the recruitment process that lead to the inclusion of post-treatment patients. Out of the 197 patients who were approached by their clinical team, 38% (N=75) consented to the whole study, and data from this sample are analysed below. Out of this group, 10.6% did not complete all the tests in the battery. Two participants did not complete the Stroop due to colour blindness. Two other participants did not complete tests 6 to 8 from Table 9, due to lack of time. Twenty-five percent of the sample (N=18) did not return the completed questionnaires. All 75 patients were included even if they provided partial data. There were no differences between responders and non-responders on any demographic variables, thus the data are considered to be missing completely at random (Osborne, 2007).

Table 10 depicts the characteristics of participants included in the study. Patients were between 6 months and 6 years post-treatment (*m*=2.6 years, *sd*=1.9 years). There

were no differences between groups on any demographic variables, but they were

significantly different on FSIQ. Consequently, FSIQ has been added as a covariate in the

ANOVAs. Similarly, patients were more depressed, anxious, and reported higher levels of

fatigue and cognitive failures compared to their matched controls.

Group	Education %	Sex %	Age M (SD)	FSIQ M (SD)	Cognitive complaints* M(SD)	Fatigue* M (SD)	Anxiety* M (SD)	Depression* M (SD)
Patient (N=75)	5% general 21% college 74% degree	49 % women 51% men	35.4 (9.53)	103.05 (8.07)	46.48 (18.22)	16.35 (3.38)	8.52 (4.20)	4.70 (3.89)
Control (N=74)	20% college 80% degree	48% women 52% men	34.5 (9.84)	107.67 (4.82)	33.53 (13.35)	13.49 (2.92)	5.52 (3.29)	2.22 (2.55)
Differences			$p>.05$	$t_{147}=-4.24$, $p<.001$	$t_{117}=4.45$, $p<.001$	$t_{117}=4.95$, $p<.001$	$t_{117}=4.35$, $p<.001$	$t_{117}=4.15$, $p<.001$

Table 10. Characteristics of post-treatment patients and matched controls.

Note. *M* =mean, *SD*=standard deviation. The last row depicts the differences between patients and controls.

*Analyses based on 55 patients and 63 controls, given that some participants did not return the completed questionnaires
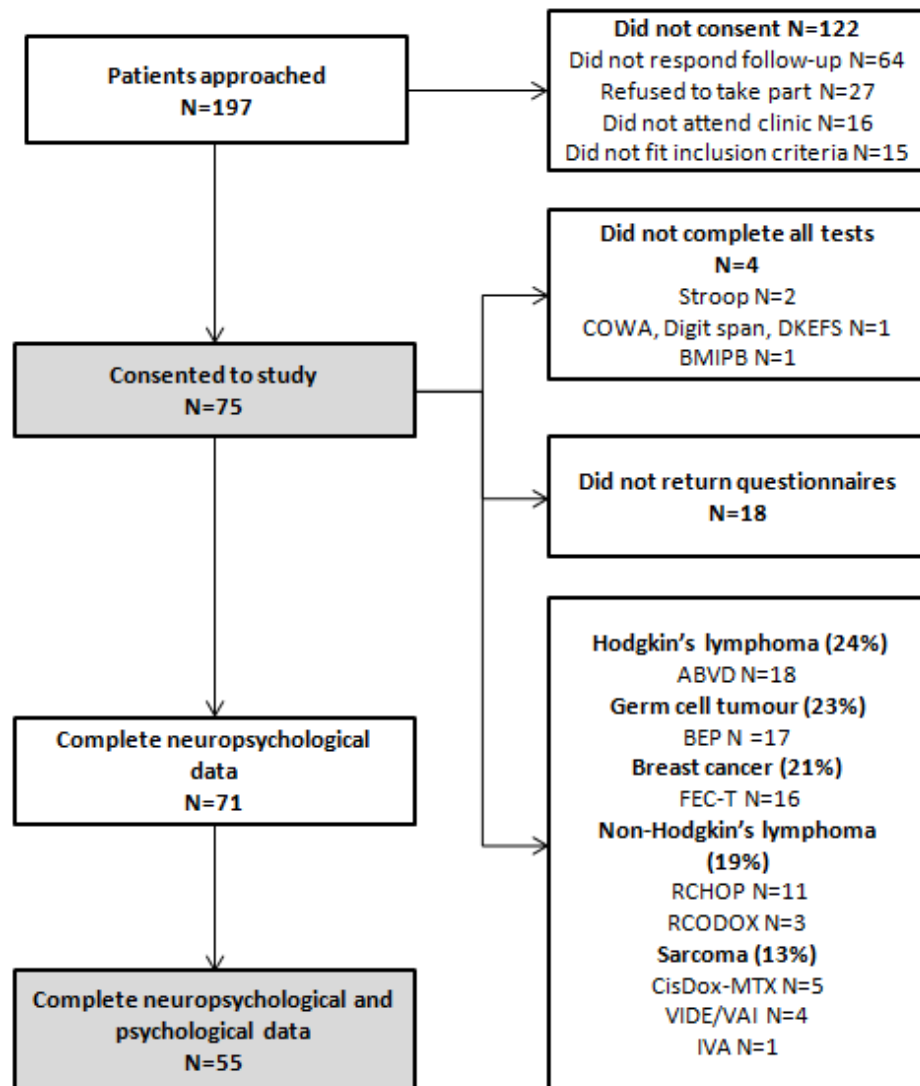
Figure 13. Patient recruitment flowchart.

Note. *ABVD= adryamicin, bleomycin, vinblastine, dacarbazine; BEP = bleomycin, etoposide, cisplatin; FEC-T= fluorouracil, epirubicin, cyclophosphamide, taxotere, RCHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, RCODOX = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, methotrexate, cytarabine, CisDox-MTX = cisplatin, doxorubicin, high dose methotrexate, VIDE/VAI= vincristine, ifosfamide, doxorubicin, etoposide, actinomycin, IVA= ifosfamide, vincristine, actinomycin.*

5.3.2. Neuropsychological status compared to norms

Compared to controls, patients had a higher probability to be under the 10th percentile on 13 of the 57 scores. There were significantly more patients than controls with lower performance on executive functions, immediate and delayed verbal memory (free recall and immediate recognition), visuospatial abilities, and speed of information processing. While there was a difference in the percentage of patients performing more poorly on the Verbal Fluency F-word production, this difference did not come across when analysing the other letters, or in the total FAS score. Analysing the rate of word-production separately on each letter suggests that while there is a difference between patients and controls on the first letter, patients benefit from practice with the task. Figure 14 depicts the percentage of patients and controls performing under the 10th percentile on each of these functions, and the odds ratios and corresponding 95% confidence intervals. Surprisingly, while 83% of patients performed at or lower than the 10th percentile on the Figure Copy test, a rather high percentage of controls also performed poorly on this task. That may potentially due to the similarity between groups in age and education, and the high sensitivity of the test in detecting subtle differences in visuospatial perception and organisation.
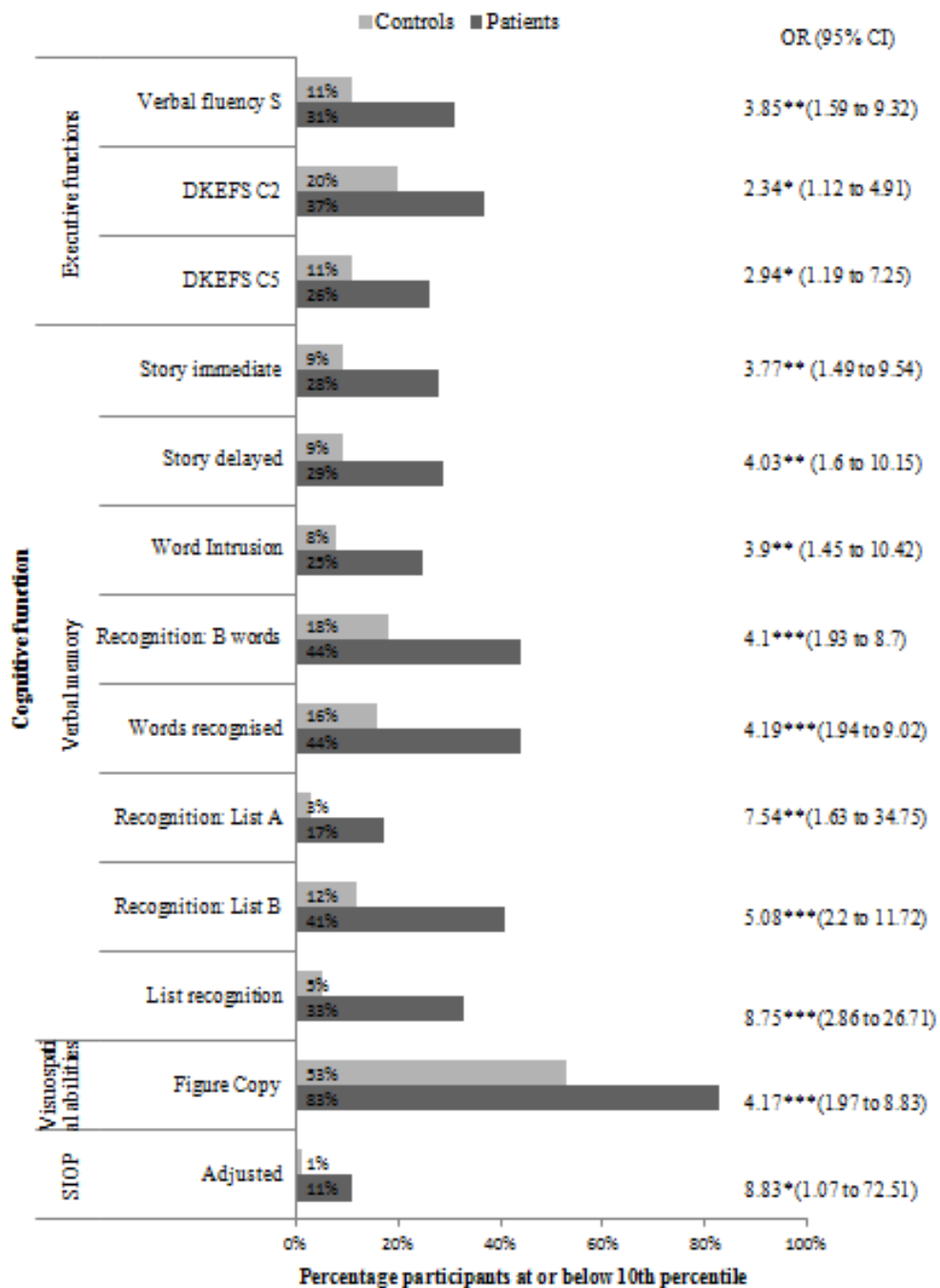
Figure 14. Percentage participants at or under the 10th percentile.

Note. Scores on which the odds ratios (OR) and 95% confidence intervals (CI) between patients and controls were significantly different. *p<.05, **p<.01, ***p<.001

5.3.3. Neuropsychological status relative to controls

Cognitive function	Score	Patient M (SD)	Control M (SD)	Effect size	95% CI Lower	95% CI Upper	FSIQ Variance
Attention	DTN	448.8 (93.87)	476.8 (78.46)	-0.32*	-0.64	-0.001	4.5%**
	DTNE	425.6 (87.64)	457.38 (80.10)	-0.37*	-0.70	-0.05	6.7%***
	Commission errors	2.64 (3.72)	1.5 (2.68)	0.34*	0.02	0.67	1.70%
	Concentration	169.3 (39.92)	185.8 (38.45)	-0.42**	-0.74	-0.10	9%***
Executive functions	Stroop Intrusions	50.83 (8.54)	54.32 (7.96)	-0.42**	-0.74	-0.09	4.4%**
	Verbal fluency F	13.21 (4.52)	15.62 (4.67)	-0.52**	-0.84	-0.11	10.7%***
	Verbal fluency A	11.02 (4.78)	13.42 (4.76)	-0.61**	-1.16	-0.07	16.1%***
	Verbal fluency S	15.24 (5.04)	17.85 (4.84)	-0.50**	-0.82	-0.17	14.4%***
	Verbal fluency Total (FAS)	13.16 (4.14)	15.58 (3.97)	-0.62***	-0.95	-0.29	18%***
	DKEFS C2	8.94 (1.79)	10 (1.99)	-0.55***	-0.85	-0.19	8%***
Verbal memory	Story immediate	24.85 (10.21)	28.94 (8.83)	-0.42*	-0.74	-0.10	7.6%***
	Story delayed	21.87 (9.03)	26.76 (8.14)	-0.56**	-0.89	-0.24	5.4%**
	Story retention	87.13 (12.73)	93.2 (11.95)	-0.48**	-0.81	-0.16	-0.01
	List B	6.4 (1.99)	7.26 (2.33)	-0.39*	-0.71	-0.07	10%***
	Recognition B words	11.74 (2.68)	13.58 (1.29)	-0.86***	-1.2	-0.53	5.8%**
	Word recognition	26.29 (2.94)	28.37 (1.54)	-0.87***	-1.21	-0.54	4%**
	List A recognition	14.18 (1.21)	14.79 (1.2)	-0.5**	-0.82	-0.17	6.6%**
	List B recognition	12.49 (2.85)	14.62 (1.8)	-0.88***	-1.22	-0.55	11.2%***
	List recognition	26.68 (3.2)	29 (1.37)	-0.93***	-1.27	-0.59	11%***
Visuospatial abilities	Figure Copy	83.55 (12.73)	92.71 (6.4)	-0.9***	-1.24	-0.57	0.10%

Table 11. Cognitive scores different between patients and controls before controlling for FSIQ.

Note. M=average, SD=standard deviation. Hedge's g effect sizes, corresponding 95% CI and the percentage of variance accounted for by FSIQ for each score, in R^2-adjusted scores. *$p<.05$, **$p<.01$, ***$p<.001$

Before controlling for FSIQ, patients performed more poorly than controls on 19 of the possible 57 neuropsychological scores (Table 11). These included attention, executive functions, most verbal memory tasks, and visuospatial abilities. FSIQ accounted for the variance in attention (4.5%-6.7%), executive functions (4.4%-16%), verbal memory immediate free recall (7.6%), learning of List B (10%), and verbal recognition memory (4%-11.2%).

After controlling for FSIQ, 10 of these scores remained significantly different between patients and controls, with moderate to large effect sizes (Figure 15). Post-treatment patients had deficits on executive functioning tests, free recall delayed verbal memory and retention (delayed memory divided by immediate memory multiplied by 100), verbal recognition memory, and visuospatial abilities.

The role of other covariates in explaining the remaining variance was examined. Depression explained part of the variance in executive functions, the performance on such tasks being lower in participants with higher depression levels, whereas subjective cognitive complaints explained part of the variance in word source recognition. This suggests that participants who performed poorly on the executive functioning had a lower mood and those who performed poorly on the word source recognition task reported more subjective cognitive complaints.

Cognitive function	Score		Patient M (SD)	Control M (SD)	Effect size	95% CI Lower	95% CI Upper	% Variance Complaints, Fatigue, Distress	B-coefficient	Group differences
Executive functions	Verbal fluency F		13.65 (4.59)	15.19 (4.59)	-0.33*	-0.65	-0.01	4%	Depression B=-.27*	HL<C*
	Verbal fluency FAS		13.68 (0.45)	15.06 (0.45)	-0.35*	-0.67	-0.03	5.2%*	Depression B=-.37*	(HL***, GCT*)<C
	DKEFS C2		9.09 (1.96)	9.85 (1.96)	-0.38*	-0.71	-0.060	3.70%	Depression B=-.14*	GCT<C**
Verbal memory	Story delayed		22.39 (8.75)	26.25 (8.83)	-0.43*	-0.76	-0.11	7.8%**		HL<C** HL<S*
	Story retention		86.64 (12.52)	93.68 (12.69)	-0.55**	-0.88	-0.23	6%*		GCT<C*
	Recognition B words		11.85 (2.22)	13.47 (2.23)	-0.72***	-1.05	-0.39	9.3%**		(GCT, Bcan)<C***
	Word recognition		26.37 (2.43)	28.29 (2.45)	-0.78***	-1.11	-0.50	8.8%**		(GCT, Bcan)<C***
	List A recognition		14.27 (1.27)	14.7 (1.27)	-0.33*	-0.65	-0.01	9.5%**		GCT<C***
	List B recognition		12.7 (2.44)	14.41 (2.44)	-0.69***	-1.02	-0.36	15.7%***	Complaints B=-.04**	(GCT***, Bcan**)<C nHL<C*
	List recognition		26.89 (2.54)	28.78 (2.54)	-0.73***	-1.06	-0.41	15%***	Complaints B=-.04**	(GCT***, Bcan**, nHL*, HL*)<C
Visuospatial abilities	Figure Copy		83.47 (10.41)	92.78 (10.39)	-0.89***	-1.22	-0.55	3.80%		(nHL***, HL***, S**)<C nHL<(GCT, Bcan)***

-1.5 -1 -0.5 0 0.5 1 1.5

Figure 15. Differences between patients and controls after controlling for FSIQ.

Note. Hedge's *g* effect size, and corresponding 95% *CI*; Amount of variance accounted for by distress, fatigue, and cognitive complaints (R^2-adjusted and corresponding bootstrapped *B*-coefficient); Group differences, Bonferroni-adjusted for multiple comparisons. C=control, HL=Hodgkin's lymphoma, GCT=germ cell tumour, Bcan=breast cancer, S=sarcoma, nHL=non-Hodgkin's lymphoma. *p<.05, **p<.01, ***p<.001

Next, the performance for each subgroup of diagnoses was compared to that of controls (Table 12). Former germ cell tumour patients, treated with BEP, performed worse than controls on eight scores, whereas former Hodgkin's lymphoma patients treated with ABVD had a lower performance on five scores compared to both controls and other cancer groups. The lower performance encompassed all target outcomes. Former breast cancer patients, who had been treated with FEC-T, had worse performance than controls on four cognitive function scores related to word and source recognition, but they performed better than germ cell tumour and lymphoma patients. Non-Hodgkin's lymphoma patients had a worse performance than controls on three scores, related to source recognition and visuospatial abilities; however, they performed less well than germ cell tumour, sarcoma, and Hodgkin's lymphoma patients on the Figure Copy task. Finally, sarcoma patients, performed less well than controls on word recognition and visuospatial abilities. Importantly, none of the participants (controls or patients) performed under the TOMM cut-off score of 45, on either trials.

Function	Test	Groups	Mean patient (SD)	Mean control (SD)	p
Executive functions	**Verbal fluency F**	HL<C	11. 31 (3.91)	15.61 (4.70)	0.02
	Verbal fluency FAS	HL<C	11.10 (3.08)		<.001
		GCT<C	12.17 (4.77)		0.03
	DKEFS C2	GCT<C	8.00 (2.39)	10.02 (2.04)	0.003
Verbal memory	**Story delayed**	HL<C	17.75 (8.69)	26.80 (8.30)	0.003
		HL<S	17.75 (8.69)	27.90 (8.53)	0.04
	Story retention	GCT<C	82.75 (12.21)	93.14 (11.87)	0.02
	Recognition B words	GCT<C	11.05 (2.35)	13.61 (1.41)	<.001

		Bcan<C	11 (3.91)		<.001
	Word recognition	GCT<C	25.71 (2.59)	28.41 (1.55)	<.001
		Bcan<C	25.62 (4.17)		<.001
	List A recognition	GCT<C	13.53 (1.73)	14.82 (1.23)	0.002
	List B recognition	nHL<C	12.43 (2.44)	14.61 (1.82)	0.04
		GCT<C	11.82 (2.87)		<.001
		Bcan<C	11.93 (3.64)		0.002
	List recognition	nHL<C	26.78 (2.77)	29.01 (1.39)	0.03
		GCT<C	25.35 (3.40)		<.001
		Bcan<C	26.50 (3.81)		0.005
Visuospatial abilities	**Figure copy**	HL<C	81.70 (12.86)	92.73 (6.32)	<.001
		nHL<C	72.70 (15.81)		<.001
		S<C	82.35 (12.72)		0.01
		nHL<GCT	72.70 (15.81)	89.44 (6.64)	<.001
		nHL<Bcan	72.70 (15.81)	90.62 (7.01)	<.001

Table 12. Descriptive table of means (M) and standard deviations (SD), and significance levels associated with differences between patient groups and control participants following Bonferroni adjustment for multiple comparisons.

Note. Scores were analysed in their standardized format, as described in Table 9 of the present chapter.Figure 16 depicts the associations between the 10 cognitive scores on which patients differed from controls, and depression, anxiety, fatigue, cognitive complaints, and age. Executive functions did not correlate with any other scores. Performance on visuospatial abilities only correlated positively with delayed free recall ($r=.21$, p<.05) and verbal recognition memory ($r=.21$, p<.05) and was associated with more anxiety symptoms ($r=$-

.21, p<.05) and a higher number of cognitive complaints (*r*=-.20, p<.05). Based on Cohen's (1988) interpretation of magnitude of correlations, distress, fatigue, and cognitive complaints had low to moderate associations with the verbal memory. This suggests that a low performance on the latter was related to higher distress, fatigue, and that a poorer cognitive performance is related to patients' subjective reports of cognitive failures.

Finally, age correlated significantly with the story retention score, number of words recognised off List B, and source memory, which suggests that young adult participants were generally better at retaining information over a delay and recognising the source of the information. A post-hoc analysis revealed that specifically List recognition correlated significantly with age in patients (r=-.35, p<.01), but not in controls (r=-.02, p>.05); when controlling for the differences in FSIQ, age accounted for 8.4% of the variance in this score in patients (p<.01).

		Executive functions		Verbal memory (free recall)		Verbal memory (recognition)					Visuospatial abilities	Psychological variables				Other
		Verbal fluency F	Contrast 2	Story delayed	Story retention	B words recognition	Word Recognition	List A recognition	List B recognition	List Recognition	Figure Copy	Complaints	Fatigue	Anxiety	Depression	Age
Executive functions	Verbal fluency F		0.09	0.17	0.09	0.14	0.15	-0.04	0.05	0.01	0.08	-0.03	-0.004	-0.15	-0.12	0.08
	Contrast 2			0.13	0.02	0.05	0.05	0.002	0.03	0.08	-0.05	-0.14	-0.01	-0.02	-0.11	-0.12
Verbal memory (free recall)	**Story delayed**				.36***	.25**	.32***	.18*	.22*	.32***	**.21***	**-.19***	**-.18***	**-.27****	**-.23***	-0.03
	Story retention					.23*	.31**	0.1	0.17	.27**	0.15	**-.20***	**-.27****	**-.28****	**-.26****	**-.32*****
Verbal memory (recognition)	B words recognition						.89***	0.16	.73***	.77***	0.15	**-.27****	**-.22***	**-.27****	**-.22***	**-.25****
	Word Recognition							.19*	.66***	.73***	**.21***	**-.23***	**-.24****	**-.27****	**-.25****	-0.15
	List A recognition								.41***	.31**	0.08	**-.24****	**-.29****	**-.28****	**-.21***	0.07
	List B recognition									.84***	0.18	**-.39*****	**-.26****	**-.27****	**-.23***	-0.17
	List recognition										0.14	**-.38*****	**-.25****	**-.28****	**-.26****	**-.19***
Visuospatial abilities	Figure Copy											**-.20***	-0.16	**-.21***	**-.18***	-0.07
Psychological variables	Complaints												.56***	.65***	.57***	.24***
	Fatigue													.53***	.56***	0.11
	Anxiety														.67***	0.15
	Depression															.18*

Figure 16. Bootstrapped correlations between scores, controlling for FSIQ.

Note. *$p<.05$, **$p<.01$, ***$p<.001$

When analysing the association between cognitive performance and age in more detail, there was only a marginal difference between patients at or under the age of 30 and their matched controls on List recognition ($F_{1, 56}$=3.93, p=.052), and a significant difference in those over 30 years old ($F_{1,86}$= 16.21, p<.001). This suggests that patients were more impaired relative to age-matched controls as they got older (Figure 17). There were no significant associations between any scores and time since treatment.
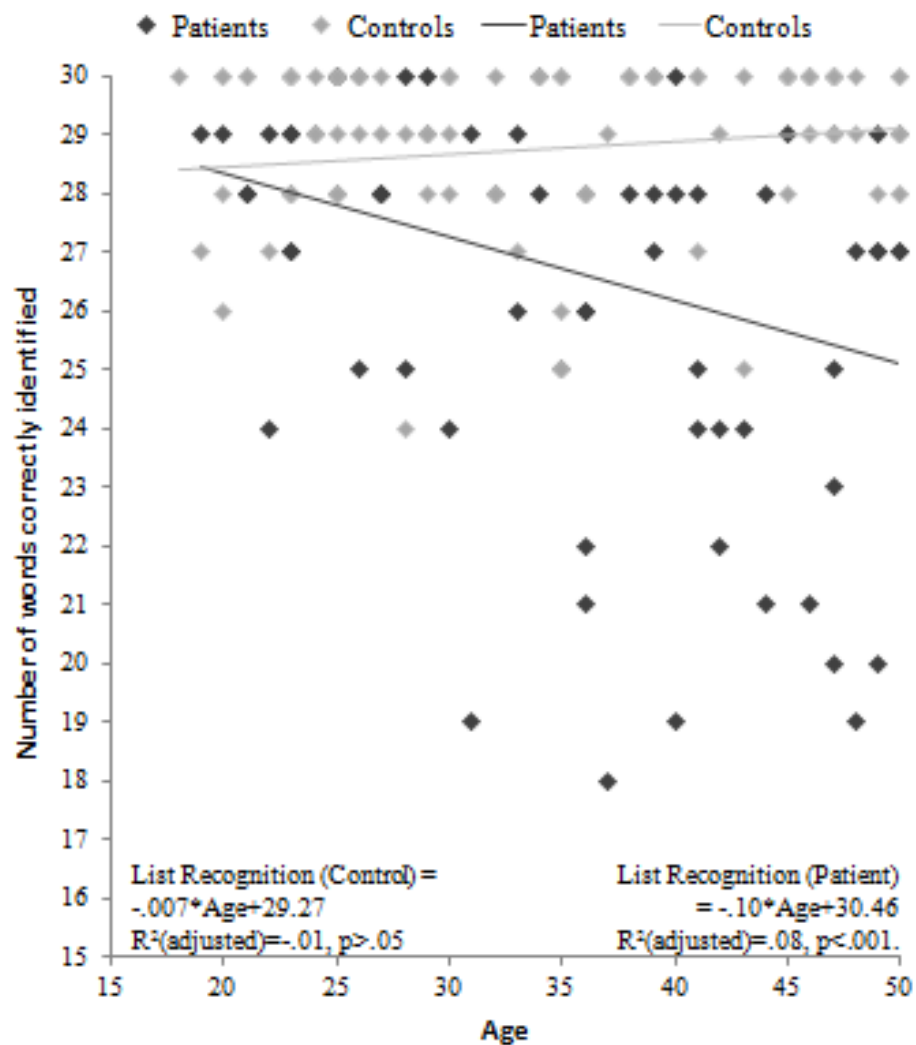

Figure 17. Regression slopes of the relationship between List recognition and Age in patients relative to controls.

5.4. Discussion

The present study provides evidence for cognitive difficulties in young adult post-treatment cancer patients. The study also emphasises the importance of exploring, reporting, and controlling for FSIQ, as the number of impaired cognitive functions significantly decreased when it was included as a covariate. While education is often used as a proxy (Neisser et al., 1996), this may not suffice in between-group cognitive studies (Deary & Johnson, 2010).

After controlling for FSIQ, patients performed worse on executive functions, delayed verbal memory, the amount of information retained over a delay, verbal recognition memory, and visuospatial abilities. The pattern of deficits was similar both when examining patients' results against test norms, and compared to healthy controls, but the latter comparison attenuated the magnitude of deficits.

Delayed free recall and recognition memory have been extensively associated with medial temporal lobe functioning (Eichenbaum, Yonelinas, & Ranganath, 2007; Frisk & Milner, 1990). Visuospatial abilities, are normally associated with frontal and parietal functioning (Melrose, Harwood, Khoo, Mandelkern, & Sultzer, 2013; Somerville, Tremont, & Stern, 2000), whereas the DKEFS and the Verbal fluency tests are associated with lateral prefrontal (Yochim, Baldo, Nelson, & Delis, 2007) and dorsal frontal functioning (Stuss et al., 1998). I will comment on each of these findings separately.

First, the deficits observed in verbal memory are consistent with previous findings of hippocampal volume decreases in breast cancer patients relative to controls (Bergouignan et al., 2011; Eberling, Wu, Tong-Turnbeaugh, & Jagust, 2004; Kesler, Janelsins, et al., 2013). However, the involvement of the medial temporal lobe, and specifically the hippocampus (implying an amnesia-like memory dysfunction), warrants

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further examinations, given that a set of studies found no changes in this structure (Koppelmans, de Ruiter, et al., 2012; McDonald & Saykin, 2013; Yoshikawa et al., 2005). It is possible that hippocampal changes only occur in a subgroup of patients.

Second, previous studies with breast cancer patients demonstrated grey matter decreases in frontal regions (Conroy et al., 2013; Hosseini, Koovakkattu, & Kesler, 2012; McDonald et al., 2010), which are consistent with the results obtained on executive functioning tasks by patients in this study. Frontal lesions are associated with deficits in free recall and source memory tests (Janowsky, Shimamura, & Squire, 1989), which are reversible if the level of demand on executive functions is decreased through the provision of additional organization strategies, such as clustering or cues (Gershberg & Shimamura, 1995). Thus, this could be a modality for future studies to test whether the nature of the deficits is frontal or amnesia-like.

Third, patients also exhibited visuospatial deficits, which were related to participants' performance on delayed memory and word recognition. Surprisingly, when comparing the performance of both groups to that of norms, a rather high percentage of patients and controls performed under the 10th percentile, specifically 53% of the controls and 83% of the patients. The overall the high percentage of low performers may be related to the means of the age and education-stratified norms, which have a high threshold. However, a high mean norm suggests that the details of the figure should have been a lot easier to identify by participants. It is possible that as a result of our matching on age, sex, and educational level, a lot more controls were prone to a lower attention to visuospatial details. The significantly higher number of patients performing poorly, as consistently depicted by both the odds ratio and analysis of variance comparisons strongly suggests difficulties in visuospatial processing in patients relative to controls. Visuospatial

processing has been associated with two major neural pathways, which project either dorsally or ventrally from the occipital lobe. Lesion studies in both human and primates have shown that disruptions to either of these pathways can produce distinct behavioural changes. The dorsal stream has been described to project from the occipitoparietal cortex to the posterior half of the inferior parietal lobule, towards the dorsolateral prefrontal cortex, either directly or via the posterior cingulate and retrosplenial areas. It was associated with impairments in tasks requiring accurate visual guided actions. Conversely, the ventral stream projects from the occipitotemporal cortex, towards the rostral inferior temporal regions and into the ventrolateral prefrontal cortex. Whilst motor accuracy is intact in lesion studies focusing on this area, patients had impairments in object perception (Kravitz, Saleem, Baker, Mishkin, 2011). The distinct functional roles of these pathways, and the structural changes in frontal, parietal, and cingulate areas in cancer patients (McDonald et al., 2010; de Ruiter et al., 2012; Conroy et al., 2013; McDonald et al., 2013) may suggest a specific pattern of impairments. Thus, a hypothesis that could be tested in future studies is whether the dorsal stream may be affected, as suggested by the reduced performance in accurately reproducing the details of spatial relationships in the Figure copy task.

Furthermore, the posterior parietal lobe is involved in the retrieval of episodic memory details and has been demonstrated to be hypoactive in breast cancer patients during memory encoding and executive functions tasks (de Ruiter et al., 2011; de Ruiter et al., 2012). Patients with parietal lesions have a normal performance in free recall, source memory, and item-recognition, but they are deficient in producing detailed and vivid memories (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). This predominantly suggests retrieval deficits, as opposed to encoding and consolidation. Although the Figure Copy test is underlain by both frontal and parietal functioning, the patients' immediate and delayed

retrieval were intact, whereas the processing of details during the examination of the figure was impaired. This would suggest a frontal/encoding deficit as opposed to a retrieval or consolidation issue.

It follows that evidence available thus far is not clear regarding the frontal-parietal-temporal involvement in chemotherapy-induced cognitive deficits. The group of patients included in this study, exhibited deficits on tasks often associated with all these regions. To differentiate between memory deficits due to medial temporal lobe or frontal and parietal involvement, future studies could focus on whether post-treatment patients exhibit mainly organizational encoding/retrieval or consolidation/storage deficits.

The study also explored if the pattern of impairments differed in patients as a function of specific malignancies, given that they received fairy homogenous treatments. Breast cancer patients exhibited deficits in the verbal memory tasks relative to controls, whereas patients treated with ABVD and BEP had performance decreases on most tests. To date, preclinical studies suggested that anthracyclines such as doxorubicin, which were administered to all lymphoma and sarcoma patients, are related to neural death, increase in inflammatory processes, oxidative stress, and impaired neurogenesis (Seigers et al., 2013). To the best of our knowledge, there have not been any studies investigating the effects of other drugs, which act in similar ways to doxorubicin, such as etoposide, epirubicin, or bleomycin. However, any conclusions at this stage regarding which drugs may have a stronger indirect neurotoxic effect, would be merely speculative. Future and better-powered studies with similarly homogenous groups will enhance our knowledge on the types of neural disruptive processes that could be prevented before and during treatment.

Memory and visuospatial performance, but not executive functioning, were related to the number of cognitive complaints, fatigue, and distress patients reported. Depression

accounted for part of the variance in executive functions, and cognitive complaints part of the variance in memory and visuospatial performance, but the direction of these relationships warrants additional investigations. It is possible that patients notice the cognitive deficits, which lead to higher levels of depression and fatigue due to the increased effort of performing well in demanding tasks. Importantly, additional exploratory analyses revealed that compared to age-matched controls, performance on verbal recognition memory tasks decreased, as patients grew older. Previous studies (Krull et al., 2013; Wefel et al., 2014) highlighted younger age as a predisposing factor to chemotherapy-induced deficits. In this group of cancer patients, the results suggest an exaggerated age-related deterioration, as performance decreased as patients got older, compared to their age-matched controls.

A limitation is that some patients who were included in the examination of cognitive deficits did not complete the questionnaires needed for the analyses exploring the relationships between the latter and distress, fatigue, and cognitive complaints. Attrition analyses focusing on demographic variables and neuropsychological differences between those who returned the questionnaires and those who did not revealed no differences. However, the possibility that responders and non-responders were different in their levels of anxiety, depression, fatigue, or cognitive complaints cannot be excluded. The study is informative regarding the differences between young adult patients and matched controls. Future studies should focus on whether the same differences are identified and have the same magnitude when patients are monitored longitudinally and compared to non-chemotherapy treated patients. The longitudinal perspective on the results would provide information on the stability of cognitive effects over time, whereas the comparison with non-chemotherapy treated patients would confirm if chemotherapy is the primary trigger of these changes.

5.5. Conclusions

The results propose that young adult post-treatment cancer patients have difficulties in executive functions, verbal memory, and visuospatial abilities after controlling for other group differences such as FSIQ, emotional distress, fatigue, and subjective cognitive complaints. Hodgkin's lymphoma and germ cell tumour post-treatment patients were more affected than the other three cancer groups tested.

Previous studies have not found associations between distress, fatigue, cognitive complaints and objective cognitive deficits. These were present in this group of patients, possibly due to differences in the prevalence of emotional distress among cancer groups (Lindnen et al., 2012). Future studies will focus on defining the direction of these relationships to investigate whether emotional distress triggers cognitive deficits (Burt, Zembar, Niederehe, 1995; Rock, Roiser, Riedel, Blackwell, 2014), or the awareness of difficulties that leads to anxiety and depression (Hutchinson, et al., 2012).

A key finding of this study was that younger patients who were on average 35-year old had moderate to high cognitive deficits, suggesting the involvement of fronto-parietal-temporal areas. Crucially, we do not yet know how these regions may relate to the behavioural results, nor which regions are more likely to suffer from long-lasting disruptions; it may be that some areas are more vulnerable to direct or indirect cytotoxic effects of chemotherapy.

Interventions focusing on improving patients' daily functioning following treatment through cognitive training, or preventing these effects pharmacologically, are still in the pilot stages (Fardell et al., 2011), with several questions yet needed to be answered. These questions refer to the relationships between potentially impaired cognitive functions, the

involvement of age and malignancy/treatment type in identifying higher risk groups, as well as whether deficits are transient or long lasting.

Nevertheless, to guide future interventions, it will be vital to differentiate between memory deficits underlain by the medial temporal lobe, versus those guided by frontal and parietal dysfunction. Similarly, future studies should investigate whether the same cognitive functions are impaired at baseline and post-treatment, to elucidate whether these observed impairments are related to chemotherapy, as opposed to between patient differences in age, FSIQ, and emotional distress.

Chapter 6. Pre-treatment neuropsychological profile of young adult cancer patients

Abstract

Objective Cancer survivors exhibit post-treatment cognitive impairments. However, cognitive difficulties have also been documented in patients before treatment. This raises the question as to what extent chemotherapy is the primary trigger of the cognitive deficits observed in post-treatment patients and whether these may be caused by other factors in addition to chemotherapy. Previous results are restricted to breast cancer patients over 50 years old and age has been discussed as a potential confounder. This is the first to explore pre-treatment cognitive performance in young adult pre-treatment cancer patients. Their performance is also investigated in relation to emotional distress, fatigue, and cognitive complaints. *Method* Patients under the age of 50, diagnosed with breast cancer, lymphoma, sarcoma, and germ cell tumour (N=30) were recruited. Patients were matched to healthy controls (N=30) on age, sex, and education. Participants were administered a comprehensive neuropsychological battery and self-assessment questionnaires. *Results* Patients performed worse than controls on several functions. However, despite matching on education, participants differed on full-scale IQ. After including it as a covariate, patients still performed poorly on tests of attention, executive functions, and visuospatial abilities. Distress, fatigue, and cognitive complaints did not differ between groups. *Conclusions* The results suggest impairments in attention, executive functions, and visuospatial abilities in a subgroup of young adult patients, before chemotherapy. Future studies should focus on the reasons for these impairments, as well as more precisely mapping the changes in disrupted cognitive functions during and after treatment.

neuropsychology, cognition, cancer, young adults

6.1. Introduction

Chemotherapy-induced cognitive impairments have been documented in patients who have undergone treatment for several non-central nervous system malignancies (Ahles & Saykin, 2007; Schagen & Wefel, 2014). Potential mechanisms have been suggested (Dietrich & Kesari, 2009; Kaiser et al., 2014) and research aiming to describe them is ongoing. However, there is also evidence that patients may exhibit a lower than expected performance before treatment (Ahles et al., 2008; Schagen & Vardy, 2007). Such findings raise the question whether chemotherapy is the primary factor associated with the post-treatment cognitive declines and to which extent other risk factors may predispose some patients to exhibit impaired cognitive functioning both before and after treatment.

There are presently nine studies detailing the cognitive status of cancer patients before treatment (Cimprich et al., 2005; Ahles 2008; Cimprich et al., 2010; Schilder et al., 2010; Scherling et al., 2011; Wefel et al., 2011; Scherling et al., 2012; Lange et al., 2014; Mandelblatt et al., 2014). The remainder of evidence originates from longitudinal studies (for examples see Wefel, Lenzi, Theriault, Davis, Meyers, 2004; Hermelink et al., 2007). Qualitatively reviewing the latter may point towards a reduced performance in pre-treatment patients compared to controls. However, a meta-analytical evaluation suggests that in longitudinal evaluations patients perform better than controls on several measures, but these results are highly heterogeneous, thus potentially influenced by other factors (Lindner et al., 2014). For example, longitudinal reports focus on those patients who were not lost to follow-up, thus the sample may have different self-selected characteristics compared to patients who were only included in pre-treatment studies (Matthews,

Chatfield, Freeman, McCracken, & Brayne, 2004). Consequently, the literature focusing on baseline evaluations will be briefly described.

There are nine reports of cognitive difficulties in pre-treatment patients, all apart from one, focusing on older breast cancer patients. Two studies described the cognitive status of patients aged >60 (Lange et al., 2014; Mandelblatt et al., 2014). In one of these studies, patients had deficits on 41% of the assessments, especially on episodic memory, compared to norms (Lange et al., 2014). The second study (Mandelblatt et al., 2014) found decreased executive functioning compared to controls, with the odds of identifying impairments being higher for older, less educated women, and for those with medical co-morbidities (diabetes and cardiovascular disease).

Six studies focused on patients who were approximately 50 years old (m=54.35; sd=7.28), demonstrating performance decreases in attention and working memory accuracy, reaction time (Ahles, 2008; Cimprich et al., 2010; Scherling et al., 2011; Scherling et al., 2012), executive functions and visual memory (Schilder et al., 2010), when patients were compared to controls. Two of these studies included fMRI measurements in which patients had increased activations in frontal and parietal regions (Cimprich et al., 2010; Scherling et al., 2012). One study found no differences when patients were compared to norms on test of attention and short-term memory (Cimprich, 2005). The last study focused on younger (mean age 31) patients due to be treated for germ cell tumour. Compared to norms, 37% of the group had deficits on verbal learning, and 21% in tests measuring executive functions and motor abilities.

Within these studies, several factors were demonstrated to have had an impact on the neuropsychological outcomes. These were older age (Cimprich et al., 2005; Schilder et al., 2010; Scherling et al., 2011), medical co-morbidities (Schilder et al., 2010; Cimprich,

2005), psychological co-morbidities (Scherling et al., 2011), lower education (Cimprich et al., 2005), and lower full-scale IQ (FSIQ; Schilder et al., 2010; Scherling et al., 2011). Ahles et al. (2008) reported reaction time deficits in patients who did not differ from controls on age and education, but FSIQ was not reported. Cimprich et al. (2010) reported slower and less accurate reactions in more demanding conditions of a working memory task, but patients were younger and less educated than controls, while FSIQ was not reported. While education and age did not influence the results in this group, it is uncertain whether the associated frontal hyperactivations would have been the same in a larger sample. Finally, Scherling et al. (2012) reported differences between patients and controls in a response inhibition task, but not on neuropsychological tests; while patients and controls did not differ on age, education, and FSIQ, patients were more depressed and anxious. Younger age and lower distress levels were associated with higher neuropsychological performance, while the response inhibition and activations in the cerebellar tonsil, left middle frontal, and cingulate gyri changed as a result of cortisol and days since surgery.

Thus, it becomes clear that frontal functions (attention, executive functions) are consistently reported as impaired in pre-treatment patients. However, there are several sources of heterogeneity in baseline neuropsychological assessments of cancer patients, of which the most commonly highlighted factor is age. This is not surprising, as it has been previously established that cognitive performance varies negatively with age, especially in healthy adults over 50 (Verhaeghen & Salthouse, 1997). It is unclear whether after chemotherapy more patients are impaired relative to their age, despite the confounding effect of this factor on cognitive functioning. Therefore, this is one of the first studies to describe the cognitive status of cancer patients under 50 years old, diagnosed with a range of non-CNS malignancies. If, as previously suggested (Ahles & Saykin, 2007; Ahles,

2008; Ahles, Root, Ryan, 2012), factors related to the biology of cancer are implicated in reducing cognitive performance, results similar to previous studies would be expected, namely performance decreases in tests related to frontal functioning, irrespective of age or other psychological factors.

Furthermore, lower performance on frontal tests influence performance on other measures, especially memory (Verhaeghen & Salthouse, 1997), both in aged adults, and in depressed individuals (Braw, Aviram, Bloch, & Levkovitz, 2011; Jurado & Rosselli, 2007; Nyberg et al., 2014). For this reason, the secondary aim was to explore the relationships both between potentially affected cognitive domains, and between other psychological variables such as distress, fatigue, and subjective cognitive complaints. If the phenomenological characteristics of the diagnosis itself were to be implicated in the potential cognitive differences between groups, we would expected much of the variance in cognition to be explained by distress and/or fatigue.

6.2. Methods

6.2.1. Participants

Cancer patients in NHS Trusts in the United Kingdom were invited to the study if they were between 16 and 50 years old, and had been diagnosed with breast cancer, lymphoma, sarcoma, and germ cell tumour (Figure 18). Participants were excluded if their diagnosis was a relapse, if they had a previous history of chemotherapy, cranial irradiation, brain injury, a history of mental health problems or substance abuse, had previously been exposed to mood altering drugs, or were not proficient in English. Control participants were individually matched to patients on age, gender, and education, the exclusion criteria being the same as for the patients. They were recruited through adverts in the local newspapers, and posters in local social venues.

6.2.2. Instruments

Participants were administered a battery of eight neuropsychological tests, resulting in 57 different scores. They also completed a set of self-assessment questionnaires, which included measurements of distress, fatigue, subjective cognitive complaints. Table 13 describes the tests administered and the resulting scores.

Cognitive function/ Norms	Test	Scores
Pre-morbid Full Scale IQ Age and education	Wechsler Test of Adult Reading (The Psychological Corporation, 2001)[1]	FSIQ
Attention Age, education, sex	D2 Concentration-Endurance[2] (Bates & Lemay, 2004)	Total number of items processed (TN) Total number of items minus errors (TNE) Omission errors Commission errors Percentage of errors (E%) Concentration performance (CP) Fluctuation rate
Executive functions Age, education	Stroop (Golden version, 1978)[3]	Word score Colour score Colour-Word Interference
Age	Delis-Kaplan Executive Function System Trail Making Task[9] (DKEFS, Delis et al., 2004)	Contrast scores between Number-Letter sequencing and Visual scanning (C1), Number sequencing (C2), Letter sequencing (C3), Number+Letter sequencing composite score (C4), Motor speed (C5).
Age	Verbal fluency [8](Henry & Crawford, 2004)	Phonemic fluency: F, A, S Category fluency: Animals or Kitchen objects (counterbalanced)
Memory effort N/A	Test of Memory Malingering[4] (Rees et al., 1998)	Trial 1 and Trial 2, both with a cut-off of 45.
Memory Age, education, sex	Birt Memory and Information Processing Battery[5] (Coughlan, Oddy, Crawford, 2007)	Story memory – immediate and 40-minutes delayed recall Figure Copy Figure learning – immediate and 40-minutes delayed recall List learning: List A Total, List B, List A 6th recall Verbal recognition: words and list source Design learning: Design A Total, Design B, Design A 6th recall. Visual recognition: designs identified and source.
Speed of Information	Birt Memory and Information Processing	Total score Percentage of errors

processing (SIOP) Age, education, sex	Battery[6] (Coughlan, Oddy, Crawford, 2007)	Motor speed Total score adjusted for speed
Working memory Age, education	Wechsler Adult Intelligence scale - III – Digit span[7](Wechsler, 1997)	Forward Backward Total
Cognitive complaints	Cognitive Failures Questionnaire (Broadbent, Copper, Fitzgerald, Parkes, 1982)	Number of subjective cognitive complaints
Fatigue	Chalder Fatigue Scale (Dittner, Wessely, Brown, 2004)	Total fatigue score
Emotional distress	Hospital Anxiety and Depression Questionnaire (Zigmond and Snaith, 1983)	Anxiety Depression

Table 13. Cognitive tests and self-assessment questionnaires administered.

Note. Superscript numbers signify the order of the test within the battery.

6.2.3. Procedure

Patients were tested in a quiet room in the hospital one week to a few hours prior to their treatment. Control participants were evaluated either in a hospital office or university laboratory. Tests were administered in the same order to all participants. Due to the logistical difficulties posed by the non-routine psychological assessment, some patients did not complete the entire neuropsychological battery. The self-assessment questionnaires were offered to all participants in a self-addressed pre-paid envelope, to complete at home.

Statistical analyses

Neuropsychological status of patients and controls relative to norms. It is recommended that patients' performance should not be compared to norms alone due to the lower variability of normative data in psychological and medical co-morbidities. In addition, not all norms consistently account for all demographic variables: age, sex, and education (Vardy, Wefel, Ahles, Tannock, Schagen, 2008; Collins, Mackenzie, Kyeremanteng, 2013). To explore the probability that a patient would be classed with a lower than

expected performance, both groups' scores were compared against test norms. If patients were not impaired, it was expected that a similar percentage of patients and controls to perform under a pre-defined level of performance (Crawford & Garthwaite, 2009). The 10th percentile represented those participants who perform at or below 1.28 standard deviations under the population mean. All participants who performed at or lower than the 10th percentile were counted to calculate the odds ratio (Altman, 1991), or the probability of identifying a patient or a control in their respective age-matched groups, with a similarly low performance on the specific test.

Neuropsychological status of patients relative to matched controls. Distributions of all variables were inspected, and some were normal, whereas other were not. In such situations, transforming and comparing variables becomes difficult (Tabachnick & Fidell, 2007). When distributions were not normal, bootstrapped ANOVAs and Kolmogorov-Smirnov tests were run to evaluate the consistency of results. Given that the results overlapped, the results of the parametric tests will be reported. The effect sizes, as standardized Hedge's *g* scores and the corresponding 95% confidence interval (Borenstein et al., 2009) were calculated by using the bootstrapped standard error. Finally, focusing on the patient group bootstrapped correlations were conducted between all scores that were found significantly different between the two groups, and distress, fatigue, and cognitive complaints.

6.3. Results

6.3.1. Participant recruitment

Figure 18 describes the recruitment process that lead to the inclusion of 30 pre-treatment patients between November 2011 and May 2014.
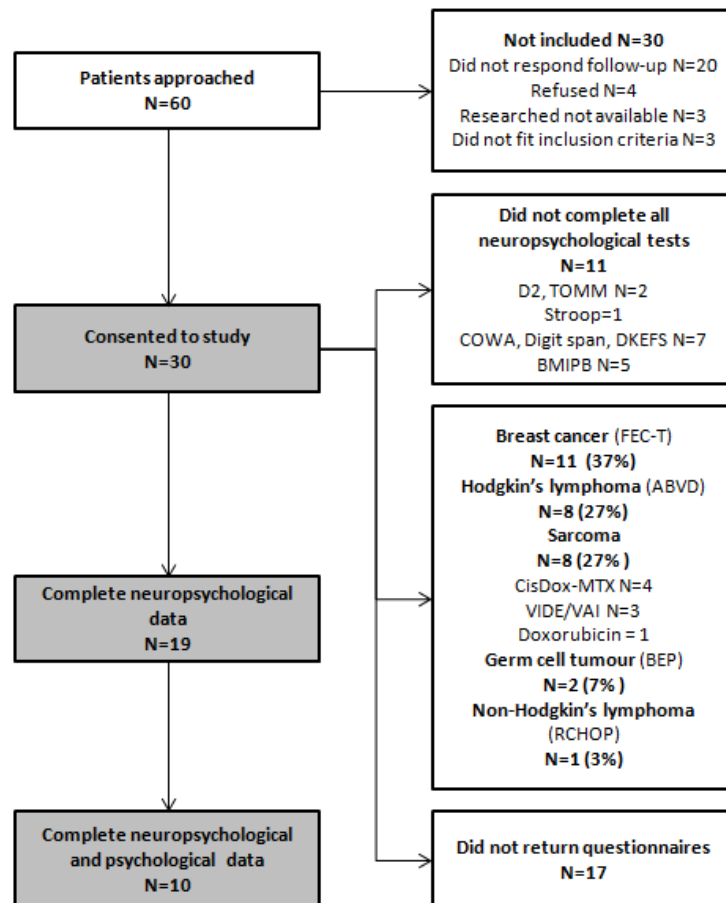
Figure 18. Patient recruitment flowchart.

Sixty patients were approached and invited to the study by their clinical teams. Half of them did not consent to participate. Of these, 67% had not replied to the follow-up call to set up the appointment; 15% declined due to poor health; 11% were missed due to unavailability of the researcher, and 7% were not included due to being outside of the inclusion criteria on either age, diagnosis, or treatment. Of the 30 participants who consented to the study, 56% completed the entire neuropsychological battery, and 43% completed all the questionnaires. Controls completed the entire neuropsychological battery, but 23% failed to return the completed questionnaires. There were no differences between responders and non-responders on any demographic variables, in either group.

Those who did not return the questionnaires were no different from the remainder of participants on any neuropsychological tests, and likewise, those who did not complete all the tests in the neuropsychological battery did not differ from the remainder on any self-assessment measures. Therefore, the data were considered to be missing completely at random (Osborne, 2007).

Table 14 describes the characteristics of patients and controls. The mean age in the groups was 32, most participants were women, and approximately half of them had a university degree. Patients and controls were not different on demographic or psychological variables; despite careful matching on educational level, they were significantly different on FSIQ. Consequently, it was included as a covariate in all analyses.

Group	Education %	Sex %	Age M(SD)	FSIQ M(SD)	Anxiety M(SD)*	Depression M(SD)*	Fatigue M(SD)*	SCC M(SD)*
Patient (N=30)	3% general 50% college 47% degree	73% women 27% men	32.10 (13.35)	100.24 (9.03)	7.4 (2.22)	3.73 (2.73)	16.12 (2.39)	37.85 (16.3)
Control (N=30)	3% general 47% college 53% degree	70% women 30% men	32.23 (12.80)	105.66 (4.81)	7.35 (2.64)	2.88 (2.42)	14.46 (2.41)	36.37 (13.71)
		Differences	p>.05	t_{58}=2.89, p=.006	p>.05	p>.05	p>.05	p>.05

Table 14. Characteristics of post-treatment patients and matched controls.

Note. *M* =mean, *SD*=standard deviation. The last row depicts the differences between patients and controls
*Analyses ran on subgroup of patients who completed the self-assessment measures (N=13) and their respective controls (N=13).

6.3.2. Neuropsychological status compared to norms

For most measures, there were an equal number of patients and controls performing in the lower 10% of the population, with the exception of executive functions (DKEFS Contrast 1 and Contrast 4; Verbal fluency F), verbal memory (number of intrusions in list learning and recognition of words in List B), and visuospatial abilities evaluated through the Figure Copy test (Figure 19).
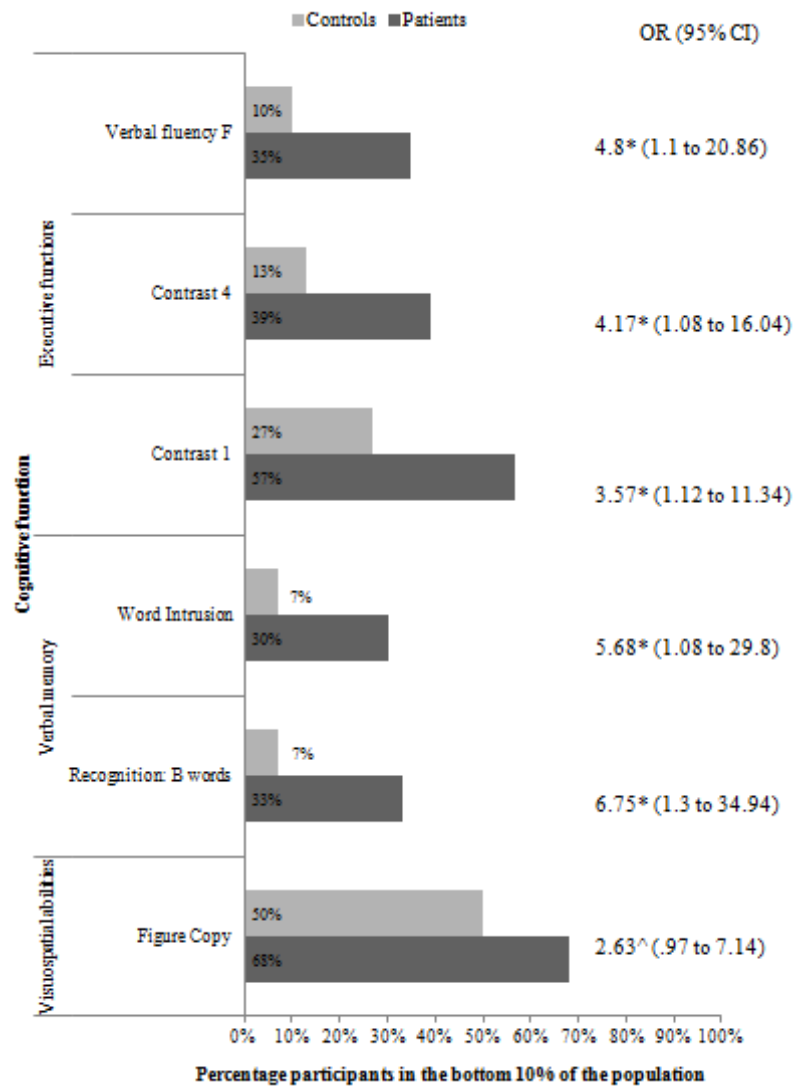

Figure 19. Percentage participants at or under the 10th percentile.

Note. Scores depicting OR (odds ratio) and 95%CI (confidence interval). * p<.05, ^p<.06.

6.3.3. Neuropsychological status relative to controls

Before controlling for FSIQ, patients were different from controls on 11 out of the 57 computed scores (Table 15). These included attention (TNE, CP, and omission errors), executive functions (DKEFS C1, Verbal fluency F, Verbal fluency summary score - FAS), working memory (Digit Forward), verbal recognition memory (recognition of words on List B, total word recognition), spatial abilities (Figure Copy), and visual memory (Design learning and number of intrusions).

Cognitive function	Score	Patient M (SD)	Control M (SD)	Hedge's g	95% CI Lower	95% CI Upper	FSIQ Variance explained
Attention	TNE	415.35 (72.01)	463. 63 (75.03)	-0.64*	-1.17	-0.13	0.05%
	CP	161.32 (39.84)	187.9 (37.52)	-0.77**	-1.29	-0.24	4.60%
	Omission errors	27.5 (29.05)	14.3 (11.55)	0.59*	0.07	1.11	7.6%*
Executive functions	DKEFS C1	8.43 (2.15)	9.76 (1.58)	-0.71*	-1.26	-0.15	1.60%
	Verbal fluency F	10.86 (3.02)	14.63 (4.38)	-0.96***	-1.53	-0.40	4%*
	Verbal fluency FAS	12.03 (0.76)	14.45 (0.67)	-0.66*	-1.21	-0.12	22%***
Working memory	Digit F	9.37 (1.61)	11.16 (2.79)	-0.75**	-1.30	-0.20	15.6%**
Verbal memory	Recognition: B words	12.66 (2.00)	13.79 (1.4)	-0.65*	-1.20	-0.11	6.7%**
	Word recognition	27.29 (2.79)	28.62 (1.40)	-0.61*	-1.16	-0.07	4%*
Visuospatial abilities	Figure Copy	86.74 (10.6)	92.94 (6.40)	-0.71*	-1.25	-0.17	0.07%
Visual memory	Design learning (A)	36.62 (6.56)	40.06 (5.36)	-0.57*	-1.11	-0.03	9.5%*
	Design intrusions	8.33 (6.36)	4.7 (5.25)	0.61*	0.08	1.16	12.3%*

Table 15. Differences between patients and controls before controlling for FSIQ.

Note. *M*=mean, *SD*=standard deviation. Hedge's *g* effect sizes, respective confidence intervals, and percentage variance accounted for by FSIQ based on the R^2 adjusted values. *p<.05, **p<.01, ***p<.001

However, the most important analyses were those accounting for the differences in FSIQ between groups, as seven of the formerly significant differences disappeared because of their associations with FSIQ. Specifically, patients' performance was no longer different

from that of controls on the Verbal fluency summary score, on the number of omission errors, working memory, verbal recognition memory, and visual memory. FSIQ accounted for 4%-6.7% of the variance in recognition memory, 7.6% in omission errors, 9.5-12.3% in visual memory, and 15.6% in working memory. After controlling for FSIQ, pre-treatment patients exhibited poorer performance on tests associated with frontal functioning (attention and executive functions) and frontal-parietal integrity (visuospatial abilities). All effect sizes were in the moderate range (Figure 20). Importantly, none of the participants (controls or patients) performed under the TOMM cut-off score of 45, on either test trials.
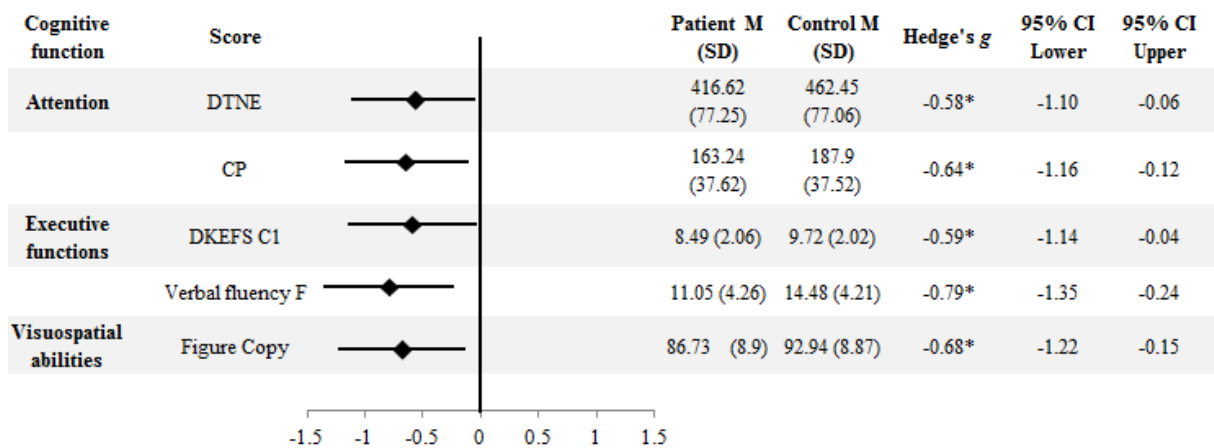
Cognitive function	Score		Patient M (SD)	Control M (SD)	Hedge's g	95% CI Lower	95% CI Upper
Attention	DTNE		416.62 (77.25)	462.45 (77.06)	-0.58*	-1.10	-0.06
	CP		163.24 (37.62)	187.9 (37.52)	-0.64*	-1.16	-0.12
Executive functions	DKEFS C1		8.49 (2.06)	9.72 (2.02)	-0.59*	-1.14	-0.04
	Verbal fluency F		11.05 (4.26)	14.48 (4.21)	-0.79*	-1.35	-0.24
Visuospatial abilities	Figure Copy		86.73 (8.9)	92.94 (8.87)	-0.68*	-1.22	-0.15

-1.5 -1 -0.5 0 0.5 1 1.5

Figure 20. Difference between patients and controls in means, standard deviations, after controlling for FSIQ.

Note. Hedge's g effect size and corresponding 95% *CI*. *p<.05

There were no significant associations between these aspects of cognitive functions, nor between them and depression, anxiety, fatigue, and cognitive complaints. A post-hoc analysis exploring the effect of age, revealed a negative correlation between age and performance on the DKEFS C1(r=-.48, p<.05), which was present in patients, but not in controls. This suggests that specifically older patients tend to have poorer results on this task. Follow-up analyses suggested that participants over the age of 30 performed more poorly than their matched controls ($F_{1,23}$=9.21, p=.01; g=-1.20, *95%CI*=-2.05 to -.36),

whereas patients at or under 30 did not have a significantly different performance relative to controls ($F_{1,26}$=1.02, *p*=.32, *g*=-0.37, *95%CI* = -1.10 to 0.35). In patients, age accounted for 20% of the variance on this test (Figure 21).
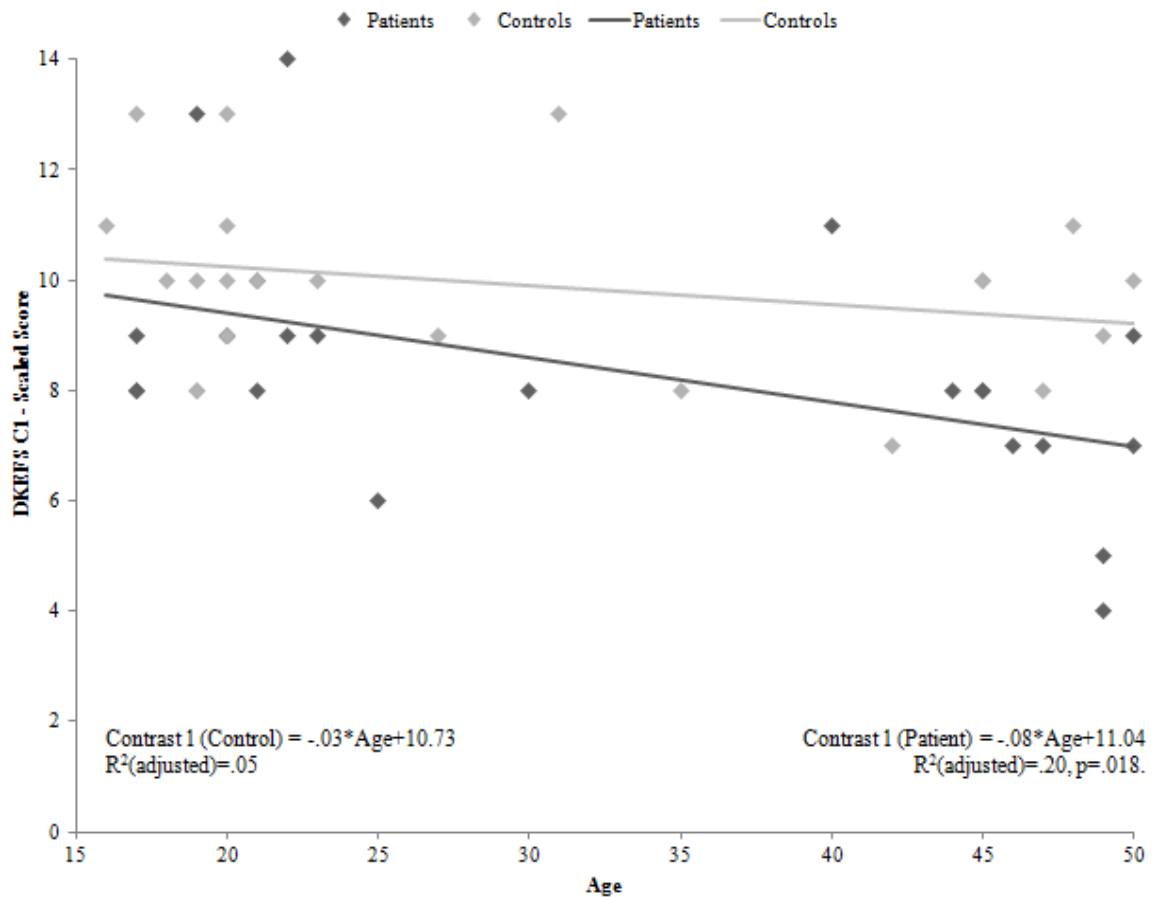

Figure 21. Regression slopes of the relationship between the DKEFS Contrast 1 score and Age in patients relative to controls.

6.4. Discussion

Given the impact of age on cognitive functioning, both in healthy adults (Verhaeghen & Salthouse, 1997) and cancer patients (Cimprich, 2005; Schilder et al., 2010; Scherling et al., 2011), the primary goal was to explore whether young adult cancer patients also exhibited cognitive difficulties prior to treatment. Critically, despite matching each patient individually to controls on education, the groups were still different on FSIQ. Pre-morbid intelligence has been demonstrated to be a predictor of neuropsychological

performance (Diaz-Asper, Schretlen, & Pearlson, 2004; Sheppard & Vernon, 2008). Thus, it was not surprising that controlling for it had an impact on the number of cognitive deficits observed. For example, differences in verbal and working performance ceased to be significant, which is unsurprising given that a high performance in these types of memory have been previously associated with higher FSIQ (Tremont, Hoffman, Scott, & Adams, 1998).

Confirming the initial hypothesis, irrespective of other variables, cancer patients under the age of 50 had a poorer performance in attention, executive functions, and visuospatial abilities. Consistent with previous studies, these findings continue to suggest that there may be other factors, apart from distress, that are involved in pre-treatment cognitive differences. In this context, a main question for future studies is whether these differences remain the same for the same group of patients during and after chemotherapy, and whether they become associated with the memory deficits observed at post-treatment.

When comparing both patients and controls to norms, patients had a higher probability of being in the lower 10% of the population on DKEFS, Verbal fluency, and Figure Copy. The only other tests on which ANCOVAs did not identify any differences, whereas these were present in norm comparisons, were the DKEFS C4, the number of intrusions on the list learning task, and the recognition of words on List B. It is possible that some of the discrepancies observed between the norm and group comparisons, specifically on the verbal memory measures, may have resulted from the differences in FSIQ, which were accounted for the in analyses of covariance, but not in the odds ratio calculations. The differences outlined by the norm comparisons may have also resulted from the different distribution of results in patients and controls. However, they are still relevant through their consistency with the other scores, and by highlighting a proportion

of patients who are indeed facing stronger difficulties. More surprising are those differences which were present in the group comparisons, but not in the norms, specifically in the attention scores. Odds ratio calculations do not take into account the variance of the results. A larger spread in patients' data distribution may have increased the between-group differences observed in the analyses of variance. Irrespective of their cause, these analyses emphasize the differences in interpreting cognitive results on the basis of norm versus group-level analyses. We suggest that both comparisons offer interesting frameworks to interpret cognitive difficulties, but matched-group comparisons should be predominantly used because they offer the possibility to control for additional covariates norms may not account for. Patients had a higher probability to make intrusion errors and had a lower speed on the Letter-Number sequencing task when compared to the separate composite score of the Number and Letter sequencing parts of the DKEFS. This suggests issues in mental flexibility when the task requires them to switch rapidly and sequence different types of stimuli.

This is a key finding, suggesting that prior to treatment, patients have cognitive difficulties that share certain commonalities. The TNE score provides a measure of speed and accuracy in the visual processing of highly similar items, as well as inhibitory control, while the CP score provides a measure of visual processing, without being skewed by arbitrary distortions in response style. Similarly, the DKEFS C1 score represents the speed of switching and sequencing numbers and letters, while parsing out visual scanning abilities. A poor performance has been associated with frontal lobe functioning, specifically in the lateral prefrontal regions (Yochim et al., 2007).

Patients were also significantly different from controls in generating words beginning with F on the Verbal fluency test. Differences in the word-generation fluency

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test have been associated with left frontal (especially dorsal) functioning in adults with restricted brain lesions, as well as healthy adults (Gourovitch et al., 2000; Strauss et al., 2006; Stuss et al., 1998).

Visuospatial abilities, as measured through the Figure Copy test, requires sustained attention, focusing on the features of the drawing (spatial positioning, orientation, size) and organising them in a correct manner, whilst trying to remember them for the subsequent memory test. Such demanding tasks have been previously associated with parietal and frontal functioning (Melrose et al., 2013; Somerville, Tremont, & Stern, 2000).

The conclusion is that there is a connection between the type of demand elicited by the tasks and their suggested neural underpinnings. Frontal, pre-frontal, and parietal regions seem to be particularly involved, which is similar to the parieto-prefrontal pathway which has been associated with spatial working memory (Kravitz, Saleem, Baker, & Mishkin, 2011). These results are also consistent with previous baseline imaging studies in cancer patients suggesting abnormal functioning of the same regions (Cimprich et al., 2010; Scherling et al., 2012). Future studies could examine the differential activations of this pathway, to confirm whether this is a potentially dysfunctional area in a subgroup of cancer patients.

Importantly, there were no additional associations between these impairments and distress, fatigue, and cognitive complaints. Interestingly, out of all the scores, the DKEFS Contrast 1 score was the most sensitive to the influence of age. Namely, age explained more of the variance in this test in patients, but not in controls. It follows that even if the sample is restricted to young adults, age may still have an important effect on certain cognitive scores, but it seems to play a more important role in its relationship to executive functioning in patients, rather than controls.

These results suggest that certain factors related to the symptoms of cancer may be involved in reducing performance in highly demanding tasks, before chemotherapy. Potential mechanisms related to cancer biology that will require further investigations are disruptions to the immune responses and inflammatory processes involved in tumour growth (Coussens & Werb, 2002; Rakoff-Nahoum, 2006). Whilst these are potential causes which require additional studies, the symptom with the highest prevalence in lymphoma patients that has also been associated with the presence of cognitive difficulties is anaemia (Beard, Kokmen, O'Brien, Anía, & Melton, 1997; Jacobsen et al., 2004; Katz, Beaston-Wimmer, Parmelee, Friedman, & Lawton, 1993; Peters et al., 2008; Shah et al., 2008). Such an idea is plausible, especially given that older cancer patients with cardiovascular and diabetes co-morbidities had a higher probability of lower cognitive performance in previous studies (Mandelblatt et al., 2013). It has a high incidence in cancer patients (Caro et al., 2001; Schwartz, 2007), but it can be present both because of the malignancy itself, and as an effect of chemotherapy. Hence, additional longitudinal studies will be needed to explore whether the level of blood oxygenation is a predictor of cognitive difficulties before, during, and after treatment in young adult patients. Other potential causes for the pre-treatment cognitive difficulties have been proposed (Saykin, de Ruiter, McDonald, Deprez, Silverman, 2013). These may be the stimulation of proinflammatory cytokines, which have been previously been associated with tumour growth (Ahles et al., 2008), as well as more subtle shared genetic predispositions to deficiencies in DNA repair mechanism which may increase the risk of both cancer and neurodegenerative disorders (Ahles & Saykin, 2007).

The study has certain limitations, mainly related to the patients or controls that did not complete the entire neuropsychological battery or did not return the self-assessment questionnaires. While the attrition in the patient sample reflects the difficulties in running

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non-routine assessments before commencing chemotherapy, it limited the possibility to generalize the non-significant associations between cognitive functioning, emotional distress, fatigue, and cognitive complaints. Re-sampling and sample size –tailored techniques have been used to account for this issue, and responders and non-responders did not differ on any variables, thus the data are considered to be missing completely at random (Osborne, 2007). However, it is possible that patients with a lower mood or a more significant level of symptoms did not return the questionnaires. Another limitation is the unequal number of patients with different malignancies. A preliminary analysis suggests that breast cancer patients performed significantly worse than controls on the DKEFS (p=.04), and that non-Hodgkin's lymphoma patients performed significantly worse than both controls (p=.02) and breast cancer patients (p=.02) on the Figure Copy task. However, these results are tentative and should be interpreted with caution given the very small sample size. Future studies could include a more homogenous number of patients to investigate whether there are cognitive differences on the same task as a function of diagnosis.

6.5. Conclusions

This is the first study to investigate the pattern of cognitive difficulties of cancer patients under the age of 50, before their treatment. Impairments were observed in attention, executive functions, and visuospatial abilities, which have been previously related to frontal, pre-frontal and parietal functioning. The possibility that these deficits may have been confounded by other factors, such as a low mood, fatigue and subjective cognitive complaints was explored. However, patients were no different from controls on any of these scores. Because the cognitive results were not significantly associated with these variables, the neuropsychological impairments may have been caused by malignancy-related symptoms, such as anaemia. However, interpretation of this result as

having a primary organic nature is restricted due to the small sample of participants who completed both neuropsychological and self-assessment questionnaires. The impact depression, anxiety, and fatigue will warrant further investigation in more highly powered future studies.

FSIQ had a major impact on the identification of a lower cognitive performance. As screening for FSIQ before including patients in a study is logistically difficult, education is frequently used as a proxy (Neisser et al., 1996). It has been previously demonstrated that this may not be sufficient in epidemiological studies (Deary & Johnson, 2010), and these results provide further evidence that this is the case in psycho-oncology studies. Consequently, it is paramount that future between-subject comparisons continue to report and control for pre-morbid IQ, given its major impact on differentiating between impairments.

The presence of cognitive difficulties in this patient sample highlights the importance of baseline and follow-up assessments. Patients may differ in performance at baseline, which may influence the trajectory of their cognitive status throughout and after their treatment in distinctive patterns. Examining patients' performance over time would inform future research in three ways. First, a clearer description of baseline performance would help differentiate between mechanisms of deficits related to the actual treatment versus physical and emotional side effects of malignancy. Second, establishing a baseline performance level would enable mapping the potential trajectory of declines. Some patients may not be affected at all, whilst others may have a normal status at the beginning, but deficits at post-treatment; some may have the same level of deficit at both time-points, whilst others may have deficits, which get worse at post-treatment. Each of these avenues would provide information whether the impairments are acute and transient, acute and

stable, or progressive and long lasting, which would suggest the involvement of different causes and mechanisms. Finally, it would inform us on the progression direction of specific types of impairments. For example, difficulties in executive functions before treatment may become stronger with treatment, triggering episodic memory deficits. Answering these questions will guide decisions regarding potential cognitive or pharmacological prevention strategies that could be implemented before or during treatment.

Chapter 7. Acute memory deficits in chemotherapy-treated cancer patients

Abstract

Background Studies with cancer survivors demonstrate that cancer treatments have lasting impairing effects on cognitive performance, including memory. They are generally complemented by changes in brain structure and function. Little is known about the potential acute effects of cancer treatment on patients' memory, hence this is the first study exploring whether memory disruptions are detectable immediately after the first treatment. The second objective was to investigate whether impairments are specific to encoding, consolidation, or retrieval. ***Methods*** The study measured the learning performance, forgetting, and retrieval rates in newly diagnosed young adult cancer patients before and immediately after the first treatment. Patients were compared to healthy controls, matched on age, gender, and education. Participants were administered a list learning task modelled after the Rey Auditory Verbal Learning Test, and a pre-morbid full scale IQ test. ***Results*** Patients had a poorer learning performance, which was accounted for by group differences in pre-morbid IQ. Immediately after treatment, they exhibited a faster forgetting rate compared to controls. The benefit of cues was not significantly different between groups and testing sessions. ***Conclusion*** This is the first study to provide a description of the type of mechanisms involved in chemotherapy-induced memory impairments. Specific faster forgetting rates were observed, while encoding and retrieval were numerically, but not statistically different between groups. The effect may be due to processes similar to protein synthesis inhibition or to increases in central nervous system inflammatory markers. Additional studies are needed to examine the brain regions affected, potential biological pathways involved, and clarify if the faster forgetting rate is due to a consolidation or retrieval deficit.

chemotherapy, memory, consolidation, chemo-brain, young adults

7.1. Introduction

Memory, especially for verbal information, is the cognitive function most frequently suggested to be affected in chemotherapy-treated non-central nervous system cancer patients (Lindner et al., 2014; Saykin, de Ruiter, McDonald, Deprez, & Silverman, 2013). In addition, imaging studies provide evidence for structural and functional brain changes in the parietal and medial temporal lobes, which relate to behavioural memory deficits (for reviews see de Ruiter & Schagen, 2013; Deprez, Billiet, Sunaert, & Leemans, 2013; McDonald & Saykin, 2013; Pomykala, de Ruiter, Deprez, McDonald, & Silverman, 2013).

Such studies compared structural MRI in breast cancer patients and healthy controls, or breast cancer patients who had not been exposed to chemotherapy. They showed decreases in hippocampal volume (Bergouignan et al., 2011; Eberling et al., 2004; Kesler, Janelsins, et al., 2013), grey matter in the left lateral posterior parietal cortex (de Ruiter et al., 2012), and grey and white matter in the parahippocampal, cingulate gyrus, and precuneus (Inagaki et al., 2007). Functional MRI studies showed hypoactivations in the prefrontal cortex (Kesler, Bennett, Mahaffey, & Spiegel, 2009), parahippocampal gyrus and posterior parietal areas during memory encoding (de Ruiter et al., 2011) and parietal, temporal, and frontal hyperactivations during memory retrieval tasks (Kesler et al., 2009).

Thus, previous studies provide extensive evidence for chronic effects of chemotherapy on memory. It is yet unclear if these memory deficits are due to an accumulation of side effects over the course of treatment, which can only be observed at later stages, or whether effects arise immediately after chemotherapy exposure. Answering

this question becomes is relevant for the timing and type of prevention strategies necessary to reduce or prevent memory declines in chemotherapy treated patients.

Evidence to date provides a descriptive account of the general memory deficits, but it focuses less on the potentially affected mnemonic processes. Consequently, this is the first study to explore whether memory deficits are characteristic of encoding, consolidation, or retrieval processes. A precise dissociation between the consequences of chemotherapy on the stages of memory processing is of particular importance for future descriptions of both potential regions and biological pathways associated with the long-term effects.

Furthermore, previous studies mainly focused on older breast cancer patients, making it unclear whether an older age may facilitate memory declines throughout treatment. As a result, this is also the first study to focus on memory performance decreases in a group of young adult cancer patients (17 to 46 years old) treated for several non-CNS malignancies.

Owing to the breadth of literature on the topic (McGaugh, 2002; Nadel & Moscovitch, 1997; Rubin et al., 1996), a straightforward way to describe the stages of memory processing is by first investigating memory consolidation. The concept is operationalized through the forgetting rate, or the proportion of words forgotten on a delayed retrieval trial versus a previous learning session (Averell & Heathcote, 2011; Wixted, 2004). The resulting hypothesis is that if chemotherapy induced disruptions to long-term memory storage pathways, faster forgetting rates should be observed at just one day following the first treatment.

A complicated issue is differentiating between disruptions in consolidation processes, as opposed to deficits in encoding and retrieval. Encoding is operationalized

through the learning performance over several presentations and immediate recall trials of the same stimuli (Craik, Govoni, Naveh-Benjamin, & Anderson, 1996). Consequently, if a person cannot withhold the presented information in short term memory, there will not be any information to consolidate or to be transferred into long-term memory. If encoding were affected, a difference in learning performance before and after chemotherapy should be observed, without any differences in the proportion of words forgotten. An additional analysis was included for the assessment of short term memory, through the inclusion of an activity filled 2-minute delay between the third study of the list of words and its recall. The difference between patients and controls before and after treatment would provide a measure of whether information fails to be stored in short term memory either before and/or after treatment.

Given that consolidation is measured through the amount of information that was not recollected, an increased forgetting rate may equally be a result of poor access to information, as well as due to a disruption in transferring it into long-term memory. If an individually- tailored retrieval strategy is absent, cued recall should aid by decreasing demands on recall processes, by providing an external "search and comparison" strategy. An analysis of the retrieval rate, operationalized through the proportion of items recalled at delay through cues compared to free recall, will clarify whether memory deficits are due to a poor ability to store information into long-term memory (consolidation) or a poor access to information that has been stored (retrieval) (Butler, Williams, Zacks, & Maki, 2001). The hypothesis is that if retrieval is affected, patients should benefit more from cues compared to controls following the first treatment. On the basis of these accounts, the study aims to describe the nature of chemotherapy induced memory deficits in young adult cancer patients, one day before and one day after their first treatment, compared to matched controls.

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7.2. Methods

7.2.1. Participants

Cancer patients were recruited through NHS Trusts in the United Kingdom. They were invited to the study by their clinical team if they were between 16 and 50 years old and had been diagnosed with sarcoma, lymphoma, breast cancer, or germ cell tumour. Participants were excluded if they had a previous history of cancer and/or chemotherapy, hormonal treatment, cranial irradiation, brain injury, a history of mental health problems or substance abuse, previously exposed to mood altering drugs, and if they were not proficient in English.

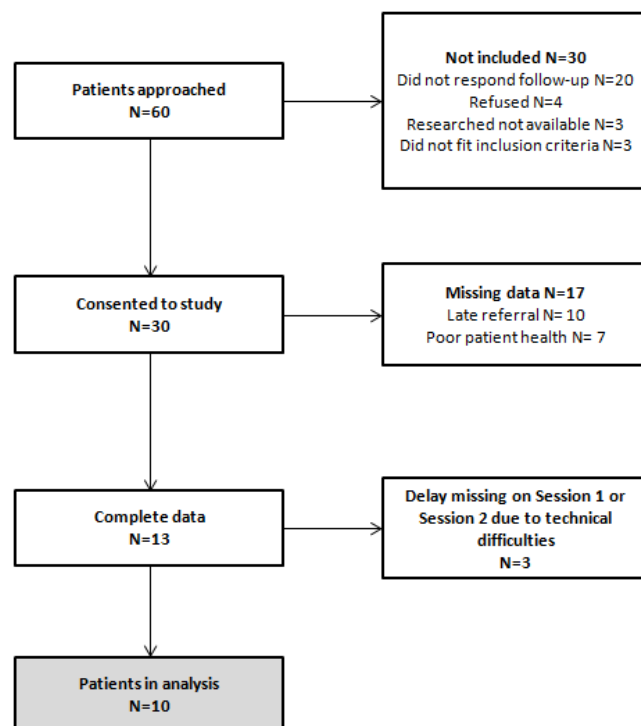**Figure 22. Flowchart of patients included in study and analyses**

Sixty newly diagnosed patients were approached and invited to the study by their clinical teams. Half of these participants consented to the study. Session 1 could not be administered to some patients due to late referral, while others were too unwell to pursue Session 3. Thirteen participants completed all the 3 days of testing. Due to logistical

difficulties three participants could not be tested using a computer in either Sessions 2 or 3, which prevented the use of screen-displayed verbal stimuli and the use of the distracter task aimed at clearing working memory. Consequently, these patients and their controls were removed from analyses. The final sample included ten patients (Figure 22). Four patients were treated for sarcoma, three for breast cancer, two for Hodgkin's lymphoma and one for germ cell tumour.

Control participants and patients were individually matched on education, sex, and age (+/- 5 years).They were recruited through newspaper adverts and posters placed in local social venues. The same exclusion criteria were applied to both patients and controls. There were no significant differences between participants on any demographic variables (Table 16).

	Newly diagnosed patients						Control participants			
ID	Diagnosis	Treatment	Age	Sex	Education	FSIQ	Age	Sex	Education	FSIQ
1	Ewing's sarcoma	VIDE	20	M	College	98	24	M	Degree	114
2	Osteosarcoma	CisDox	20	F	College	98.4	19	F	College	110
3	Germ cell tumour	BEP	30	M	Degree	97	30	M	Degree	108
4	Osteosarcoma	MAPDox	17	M	College	107	20	M	Degree	117
5	Hodgkin's lymphoma	ABVD	19	F	College	93	20	F	College	108
6	Ewing's sarcoma	VIDE	17	F	College	107	21	F	College	109
7	Breast cancer	FEC-T	46	F	Degree	98	46	F	College	109
8	Breast cancer	FEC-T	45	F	Degree	105	46	F	Degree	97
9	Breast cancer	FEC-T	45	F	Degree	110	46	F	Degree	110
10	Hodgkin's lymphoma	ABVD	22	F	Degree	92	20	F	College	103
M (SD) %	30% Breast cancer 40% Sarcoma 20% Hodgkin's lymphoma 10% Germ cell tumour		28.1 (12.44)	70% F 30% M	50% College 50% Degree	100.5 (6.26)	29.2 (12.01)	70% F 30% M	50% College 50% Degree	108.5 (5.48)

Table 16. Demographic details of participants included in the study and analyses

Note. VIDE=vincristine, ifosfamide, doxorubicin, etoposide; CisDox=cisplatin, doxorubicin,
BEP=bleomycin, etoposide, cisplatin; MAPDox=high dose methotrexate, cisplatin, doxorubicin; FEC-T=

fluorouracil, epirubicin, cyclophosphamide, docetaxel; ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine).

7.2.2. Instruments

Word lists. Five different lists of words were created. They consisted of concrete nouns describing items in the Snodgrass and Vanderwart (1980) database. To limit proactive interference and list confusion each list contained 24 words from two categories representing natural and man-made concepts. The lists were equivalent in familiarity and Kucera-Francis frequency (Appendix 3) and were counterbalanced between sessions, following a balanced Latin square method (Bailey, 1996). All words were 4-10 letters in length.[2] The first two letters of each word were unique within the list, allowing the use of the first two letters as hints in a cued recall test. The 2-letter hints were displayed in a random order for each participant.

Distracter task. Three spot-the-differences games were used, with one game allocated to each session. Each game consisted of two pictures with 15 differences each. Participants were asked to find as many differences as they could within the 2-minute timeframe. None of the participants identified all the differences on any of the pictures.

Additional tests. On the first day of testing, after the first session of the memory task, participants were also administered a neuropsychological battery. The first test in the battery was the Wechsler Test of Adult Reading (Psychological Corporation, 2001), and it was used to check whether, despite the careful matching on education level, there were differences between groups in full scale IQ (FSIQ). Given that the memory task was administered as part of a larger study, participants were also tested on various

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[2] List A: Animals (19) and Vehicles (5); List B: Fruits (11) and Clothes (13); list C: Vegetables (9) and Kitchen objects (15); list D: Four-legged animals (15) and Musical instruments (9); list E: Birds (11) and Toys (13). The unequal distribution of the words in the lists was determined by the number of concepts in the database, which complied with our length, familiarity and frequency constraints.

neuropsychological and psycho-emotional measures. However, these results do not form the purpose of the present report. Half of the patients included in the present study did not return the completed questionnaires, thus these scores could not be included in further analyses. There were no differences between responders and non-responders, in either demographic variables, or FSIQ.

7.2.3. Procedure

The following section will describe the method in which the memory task was administered, including the exact instructions specific to each testing session.

General procedure. Each session lasted approximately 10-15 minutes. During study, words were presented on a screen for 2.5 seconds. Participants were asked to produce a sentence with the target word (e.g. "The **helicopter** is in the sky"), after which they pressed a key to proceed to the next word. Sentences were not recorded, but they had to be different for each word, whilst they could be the same for each study session. Recall sessions were not time limited, but they were terminated if participants stopped recalling items for more than 20 seconds. The experimenter recorded the words participants produced in the free recall test.

Testing flexibility. Clearly, the experiment took place at an extremely sensitive time for the pre-treatment patients. They received their diagnosis shortly before Session 1, and were just about to commence a difficult course of treatment. This meant that testing had to be flexible, while still maintaining an appropriate control of the experimental conditions. The aim was for the task to be administered in the same fashion to all participants. However, if patients could not make it to the hospital on Sessions 2 or 3, they could complete the task at home. When at home, participants were tested using a CD on their own computer, while speaking to the experimenter over the telephone. To access the

program, participants were requested to fill in a dialogue box would appear on a screen requesting them to fill in their Participant number, the Session number and a Session code which was unique to each day and formerly unknown to the participant. Controls were tested at university rather than at hospital, but the testing procedures were the same for each patient and their respective matched control (i.e. if a patient was tested at home in Session 2 they were matched to a control participant who was also tested at home).

Memory task. A novel list learning task, modelled after the Rey Verbal Learning Test, was administered to participants over three sessions, on three consecutive days (Figure 23).
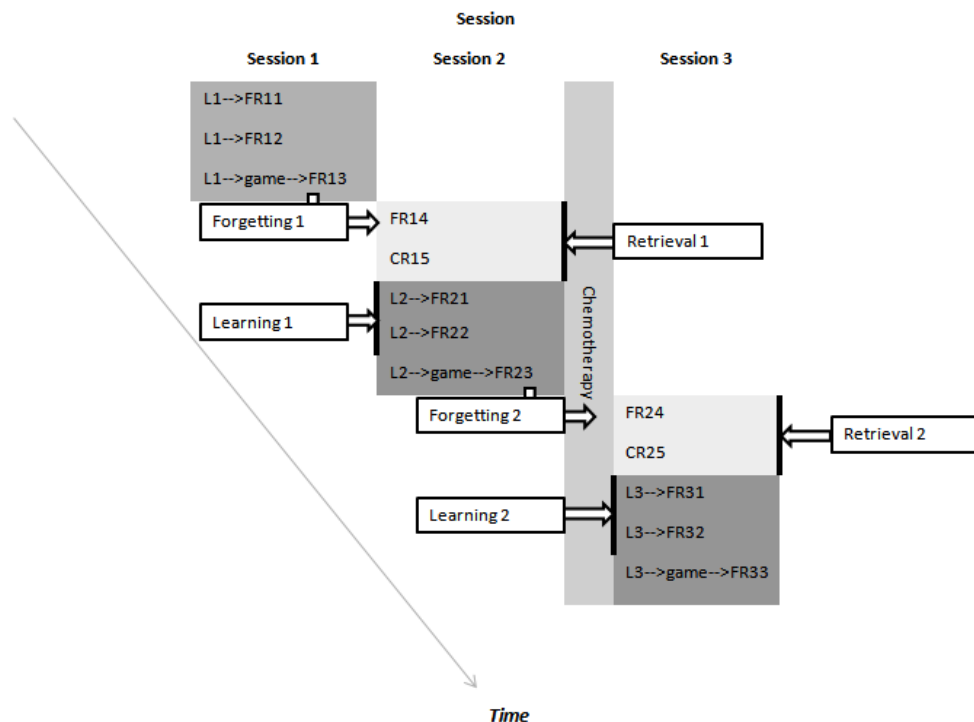
Figure 23. Memory task procedure.

Note. L1, L2, L3: Presentation and study of Lists 1, 2, 3. FR11, 12, 13, 14 : 3 immediate Free Recall Trials and a delayed free recall Trial of list 1. FR21, 22, 23, 24 : 3 immediate Free Recall Trials and a delayed free recall Trial of list 2. FR31, 32, 33, 34 : 3 immediate Free Recall Trials list 3. CR15, CR25: Cued recall trials of lists 1 and 2.

Session 1 took place approximately 24 hours before the patients' first treatment (range: 20-25 hours, *m=*23.20, *sd=*1.92). They studied the first list of words (List 1), and

were then reminded of the categories they had learned and asked to Free Recall them in any order (FR11: the first number denotes the list, the second number the serial number of the test). The same study-recall procedure was administered a second time (FR12). Finally, participants studied the same list for the third time. In order to maximize the chance that items were retrieved from long-term memory, the third free recall test (FR13) was preceded by a 2-minutes activity filled delay during which participants performed the distracter task.

The instruction relating to this session was the following:

"On the screen you are going to see a list of words that I'd like you to remember. The list is quite long, so don't try to remember all the words from the start. That is why we are going to go through the same list several times, for you to be able to remember more words each time. Whenever you see a word on the screen please tell me a sentence containing that word. The sentence can be simple (such as "Cats have fur", if the word on the screen is "Cat"), but please make sure you use a different sentence for each word. After you see the entire list I will ask you to tell me what you remember from it. The list of words for today will be made out of X and Y". After this instruction, participants went through the list of words and were then asked to remember the words. They were allowed to recall all the words at their own pace, but if they paused for more than 20 seconds they were asked: "Is that all you can remember?" If they confirmed, the next session begun:

"Now we are going to go through the same list of words again just as we did previously. Please tell me a sentence with each word; you can use the same sentence as before". The same procedure as in Session 1 was repeated for Session 2 and the beginning of Session 3. Following the list presentation in Session 3, participants played the 2-minute distracter game:

"Before you tell me what you remember, you will play a short game. On the screen, you are going to see two pictures and I want you to tell me how many differences you see between them. You will have 2 minutes to tell me as many differences as you can". The experimenter recorded all the differences spotted by participants. At the end of the 2-minutes participants were asked to recall all the words for the third time. **Session 2** took place the subsequent day. For patients, this was scheduled before they commenced treatment, while in hospital or before leaving home. Participants were first administered a surprise delayed free recall test (FR14) for the list they studied the day before, followed by a surprise cued recall test of the same list (CR15). Finally, they studied and recalled List 2 three times in a process identical to the previous day (FR21, FR 22, FR23). The instructions for this session were as follows:

"First, could you tell me what words you remember off the list of X and Y you learned yesterday?" Participants were allowed to respond in the same manner as in the free recall trials in Session 1, following which the cued recall trial begun:

"Now we are going to do something a bit different. On the screen you are going to see the first two letters of each of the words you learned in this list, maybe they will help you remember a few more words. Don't think about it too much – if the word comes immediately to mind, tell me what it is. If it doesn't, just say Pass." Following this trial, participants were presented with the second list of words, in a process identical to Session 1: *"Now we are going to go through another list of words just as we did yesterday – three consecutive times and with sentences. This time the list of words that you will be learning is made out of X and Y"*. The remainder of Session 2 has the same instruction as for Session 1, while Session 3 has the same instructions as Session 2.

Session 3 took place the following day, approximately 24 hours after the first chemotherapy dose (range: 23-29 hours, $m=25.13$, $sd=2.74$). The procedure was identical to the second session: participants were tested on their memory for List 2 using free and cued recall (FR24, CR25), and then studied and recalled List 3 three times (FR31, FR32, FR33).

Statistical analyses

They included two planned contrasts for each individual outcome, one focusing on the difference between patients before and after treatment, and a second one focusing on the difference between patients and controls following the second treatment.

Analysis of learning performance/Encoding. In Session 1, participants had not yet practiced the task, and had no previous exposure to similar word lists. To ensure that practice effects and proactive interference were equivalent between sessions, learning performance in Session 1 was not included in this analysis. The analysis compared the percentage of words recalled in the first two trials in Sessions 2 and 3 (FR21 and FR22 versus FR31 and FR32). The third recall tests (FR23, FR33) were not included in this analysis because its procedure differed from the procedure used in the first two free recall tests (retrieval based on working memory/recency effects was eliminated by using an activity-filled delay). However, these trials were examined separately to investigate potential short term memory differences between patients and controls prior and following treatment. It was expected that all participants would improve across the first two tests of each session, and would also perform better on the third trial irrespective of the distracter task. However, if chemotherapy impaired encoding, it was expected that patients would have a slower learning performance in Session 3 (both over the two learning trials and in FR3), both compared to controls and to their own performance on Session 2.

Analysis of forgetting rate/Consolidation. The proportion of information forgotten over 24 hours was calculated by comparing the percentage of words recalled in the delayed free recall test (FR14, FR 24) relative to the amount of information recalled on the third free recall trial of the previous session (FR13, FR23). Thus, the forgetting scores were computed as (FR13-FR14)/FR13*100 and (FR23-FR24)/FR23*100. While it was expected that all participants would forget a certain amount of information, we hypothesized that if chemotherapy impaired consolidation, patients would forget more after chemotherapy, both compared to their pre-treatment performance and to controls.

Analysis of retrieval rate. The outcome was the proportion of information retrieved in the cued recall task relative to the delayed free recall task. The retrieval rates were computed as (CR15-FR14)/FR14*100 and (CR25-FR24) /FR24*100. It was expected that all participants would gain benefits from cues relative to the free recall trial. However, if chemotherapy had an impairing effect on patients' retrieval, they would benefit more from the cues.

All results are depicted both as proportions and untransformed parameters following Tukey's corrections for multiple comparisons.

7.3. Results

7.3.1. Descriptive results

There were no differences in the timing of the tests between patients and controls on either day of testing (first delay, $t_{18}=1.95$, $p>.05$; second delay, $t_{18}=-.12$, $p>.05$). Despite employing an education matching strategy, which resulted in an equal number of controls and patients with college or university degree, patients had a lower FSIQ than controls

(t_{18}=-3.02, p<.01). Consequently, all the analyses included repeated measures ANOVA with FSIQ included in post-hoc covariate analyses.

7.3.2. Encoding

Free recall performance (depicted in Table 17) was analysed with a 2 (Group) x 2 (Session: before or after treatment) x 2 (Test: the first and second FR trial) ANOVA.

	Before treatment			After treatment		
	FR21	FR22	**FR23**	FR31	FR32	**FR33**
Patients M (SD)	47.50 (18.65)	64.17 (14.72)	68.33 (18.13)	48.33 (10.06)	60.00 (13.92)	61.67 (16.54)
Controls M (SD)	57.50 (13.29)	71.66 (14.00)	80.00 (15.69)	59.75 (11.62)	77.50 (8.83)	87.07 (11.53)

Table 17. Means (M), standard deviations (SD) in patients and controls on three immediate recall trials, before and after treatment

As expected, all participants improved across test trials $F_{1,18}$=146.15 (p<.001) on both sessions. Patients recalled fewer words over both trials and sessions compared to controls $F_{1,18}$=5.10, p=.03. There was a trend towards a significant interaction between group, session, and recall test, $F_{1,18}$=2.94, p=.10. There were no differences between groups over the three recall trials before treatment, whilst patients improved significantly less than controls over the three trials following treatment. Patients did not significantly improve their learning performance over the two days, whilst controls improved their trial-by-trial performance across the two testing sessions (suggesting practice effects). The difference between groups may suggests that encoding was impaired in the patients (Figure 24). However, including FSIQ as a covariate suppressed the difference between tests ($F_{1,17}$=1.20, p=.28) and there was a non-significant trend towards a group difference ($F_{1,17}$=4.29, p=.054) and for a Session*Trial*Group interaction ($F_{1,17}$=3.35, p=.08). The small sample size suggests that the non-significant effects should be interpreted with caution. To summarize, patients exhibited a slower learning rate compared to controls, but including FSIQ as a covariate suppressed this difference.

The additional analysis of learning performance on the third trial (following the 2-minute distracter task) when controlling for the difference in FSIQ, revealed a significant difference between groups ($F_{1,17}=5.14$, p=.02). The difference between participants was identified following treatment ($t_{17}=10.88$, p=.004), but not before treatment ($t_{17}=2.06$, p=.17), suggesting that after treatment patients remembered less words after a 2-minute delay compared to controls. This may suggest that short term memory processes may also be affected by the first chemotherapy dose.

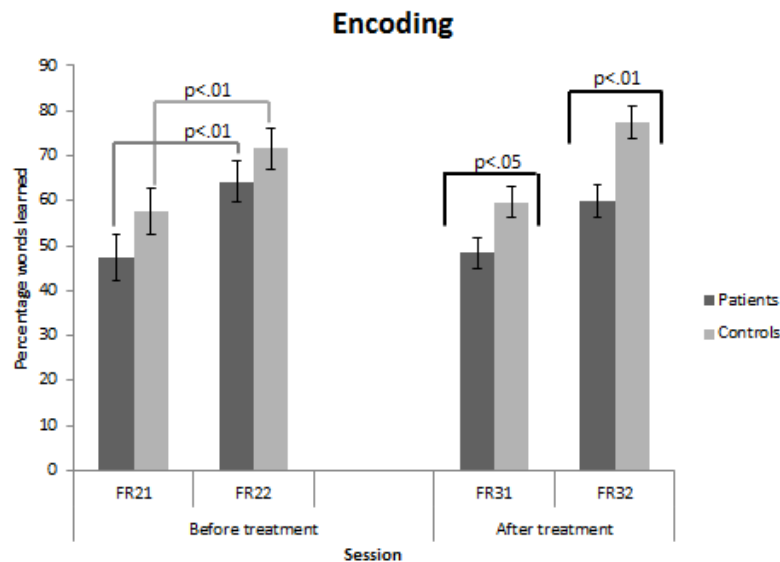**Figure 24. Difference in encoding between patients and controls before and after treatment.**

7.3.2. Consolidation

The percentage of words forgotten between the third immediate free recall trial and the 24-hour delayed free recall trial was analysed as raw values with a 2 (Group) x 2 (Session) x 2 (Trial) ANOVA (Table 18) and in proportional values (Figure 25) with a 2 (Group) x 2 (Session) ANOVA.

	Before treatment		After treatment	
	FR13	FR14	FR23	FR24
Patients M (SD)	66.25 (14.09)	52.08 (18.35)	68.33 (18.13)	42.91 (21.16)
Controls M (SD)	87.08 (9.91)	64.58 (11.83)	80.00 (15.69)	67.08 (17.73)

Table 18. Means (M), standard deviations (SD) in patients and controls on the immediate and delayed free recall trials administered before and after treatment.

Note. FR23 is the final immediate recall trial before treatment and FR24 is the delayed free recall trials taking place 24-hours later.

When analysing the results as percentages of information recalled, there was a significant effect of the test trial, suggesting that, as expected, all participant forgot information over the delay ($F_{1,18}$=76.18, p<.001), a significant difference between groups ($F_{1,18}$=8.44, p=.009), and a significant interaction between Session*Trial*Group ($F_{1,18}$=7.85, p=.01). These differences continued to be significant after including FSIQ as a covariate, specifically the interaction effect ($F_{1,17}$=12.83, p=.002) and the difference between groups ($F_{1,17}$=6.64, p=.02).

Given the difference between patients and controls in the learning performance on the third trial of the first day of testing, analysing these results as proportional values of information forgotten relative to the amount initially encoded is warranted. As a consequence of this transformation the difference between groups disappears ($F_{1,18}$=2.54, p=.13), whilst there is an interaction between Session*Group performance ($F_{1,18}$=7.00, p=.01) which continues to be significant after including FSIQ as a covariate ($F_{1,18}$=7.20, p=.01). Tukey post-hoc analysis revealed no difference between patients and controls in the forgetting rate before treatment (t_{18}=.47, p=.64, *g*=-.20, *95%CI*= -1.04 to .63), suggesting that after a 24-hour delay the two groups retained a similar proportion of the information. Compared to controls, patients had a faster forgetting rate following treatment (t_{18}=2.64, p=.01, *g*=1.13, *95%CI*=0.22 to 2.04). While controls did not show a difference in forgetting rate across the two sessions (t_9=1.58, p=.14, *g*=-.68, *95%CI*=-1.55 to .17),

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patients exhibited a non-significant trend towards a faster forgetting rate after treatment (t_9=2.11, p=.06, g=0.75, *95%CI*=-0.11 to 1.62). Hence, chemotherapy may have had an impairing effect on memory consolidation as early as 24 hours post-treatment.

Figure 25. Difference in consolidation in patients and controls before and after treatment.
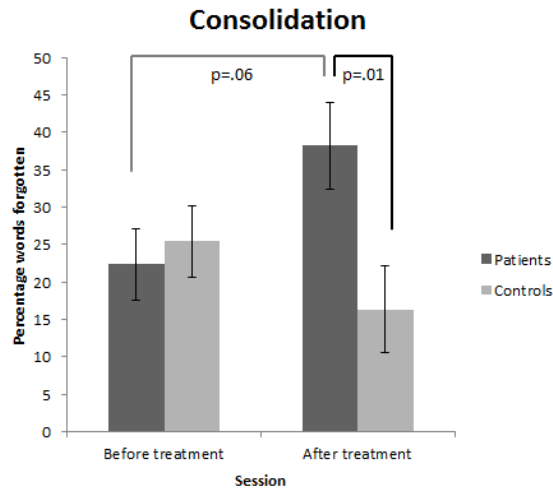
7.3.3. Retrieval

Just as with the other outcomes, we will first describe the analyses pertaining to the percentage of words recalled in the free delayed and cued delayed recall trials (Table 19), after which we will report the proportional retrieval rates.

	Before treatment		After treatment	
	FR14	**CR15**	**FR24**	**CR25**
Patients M (SD)	52.08 (18.35)	67.09 (18.05)	42.91 (21.16)	62.08 (26.39)
Controls M (SD)	64.58 (11.83)	76.67 (11.32)	67.08 (17.73)	75.00 (15.09)

Table 19. Means (M), standard deviations (SD), in patients and controls on the delayed free and cued recall trials, before and after treatment.

When analysing the difference between the two recall trials, between sessions and participants, there was a significant effect of the trial, suggesting that all participants improved their performance after being offered cues ($F_{1,18}$=24.04, p<.001) and a significant group effect, suggesting a difference between participants ($F_{1,18}$=5.50, p=.03). When

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including the FSIQ as a covariate, the significant difference between trials was suppressed, while the group effect continued to be significant ($F_{1,17}=5.12$, p=.03).

When analysing the same results as the relative retrieval benefit added by cues compared to the prior delayed free recall trial there was a non-significant trend towards a difference between groups ($F_{1,18}=3.01$, p=10), but the Session*Group interaction was not significant ($F_{1,18}=2.43$, p=.13). Specifically, the trend towards a difference between groups was driven by a marginally larger benefit from cues in patients ($t_{18}=-1.99$, p=.06) following treatment, whereas there was no such trend before treatment ($t_{18}=-.79$, p=.44). There were no differences in the retrieval rates between the two testing days in either participant groups. When including FSIQ as a covariate the trend towards a group effect was suppressed ($F_{1,17}=.65$, p=.43). These results suggest that the faster forgetting rate in patients may not have been due to a retrieval deficit (Figure 26), although the null effect should be interpreted with caution given the small sample size.
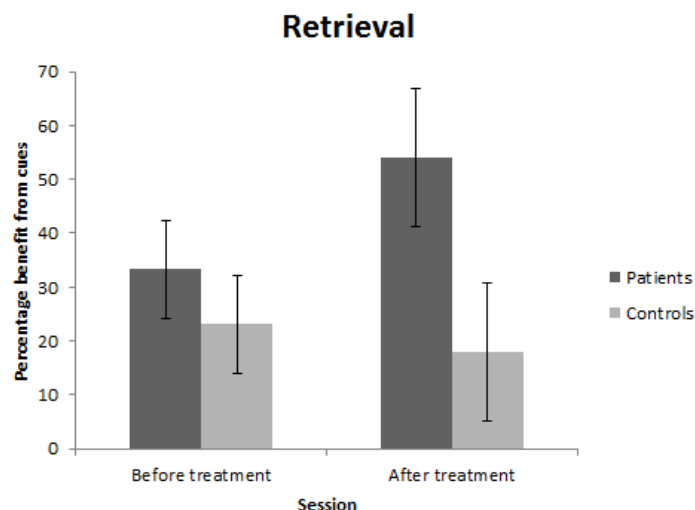

Figure 26. Differences in retrieval between patients and controls before and after treatment.

Note. Retrieval rates computed as (CR15-FR14)/FR14*100. Error bars represent the standard error.

7.4. Discussion

In recent years, there has been an increase in behavioural evidence for memory deficits in post-treatment cancer patient (Ahles, Root, Ryan, 2012; Lindner et al., 2014). These behavioural results have been associated with hippocampal volume decreases (Bergouignan et al., 2011; Eberling et al., 2004; Kesler, Janelsins, et al., 2013), and abnormal parietal and frontal activations during memory encoding and retrieval (de Ruiter & Schagen, 2013; Simó et al., 2013). Both pre-treatment and post-treatment patients have also been reported to experience attention and executive functioning issues (Ahles et al., 2008; de Ruiter et al., 2012; Conroy et al., 2013), making it unclear whether the memory deficits are underlain primarily by a lack of an ability to acquire, retrieve, or store information. Consequently, this was the first study aiming to differentiate between encoding, and retrieval, which are majorly underlain by frontal regions (Fletcher & Dolan, 1993; Nyberg et al., 2014), and consolidation which is usually related to medial temporal lobe functioning (Hardt, Nader, & Nadel, 2013).

Despite education matching to controls, and lack of further neuropsychological differences, our patients exhibited a lower pre-morbid IQ compared to controls, suggesting a performance disadvantage even before treatment; consequently we controlled FSIQ in all our analyses. This finding asserts the importance of pre-morbid IQ measurements when interpreting patients' cognitive performance.

First, we focused on encoding, or participants' ability to acquire new information. Patients' learning performance was lower than that of controls both before and after treatment. The treatment did not have a significant influence on this slower learning ability, but the difference between groups was reduced to a strong trend when controlling for FSIQ.

Second, we analysed forgetting rate, attempting to investigate potential direct effects of cancer treatment on long-term memory storage (Kandel, 2012). Our most robust finding demonstrates that patients' forgetting rate was faster after the treatment compared to controls, even after controlling for FSIQ.

Third, we asked whether the patients' retrieval abilities may be disrupted, by comparing the more effortful delayed free recall performance to a less demanding delayed cued recall session. Although suppressed when controlling for FSIQ, there was a trend in patients benefiting more from cues than controls, following treatment.

Our results suggest a faster forgetting rate in patients relative to controls, which was not explained by any other factors. Although our findings need to be confirmed with a larger and preferably more homogenous patient group, they demonstrate that patients forget more than controls following chemotherapy and have a strong tendency towards a slower learning. The trends towards lower learning and retrieval abilities suggest that the deficits we are observing may be due to frontal/executive type difficulties as well as medial temporal/consolidation disruptions. Additional imaging studies comparing immediate and delayed retrieval tasks in conditions of high and low demandingness would confirm whether the faster forgetting rate we observed is due to frontal, medial temporal damage or both.

The present study has certain limitations. First, given the logistical restrictions imposed by recruiting patients in a study shortly before and after their treatment, the study had a small sample size. The non-significant trends in encoding and retrieval should be interpreted with caution. However, while the sample size provided sufficient power to detect a faster forgetting rate, associated with a large effect size, it does raise the necessity for a replication. Second, studying patients in such trying circumstances represents a

challenge and there is a question as to whether our results may have been influenced by differences in distress and fatigue between groups. Most patients included in this particular study failed to return the self-assessment questionnaires aimed at controlling these variables, but the rest of the participants described in Chapter 6 exhibited no differences to controls in either in emotional distress or fatigue levels.

While conclusions regarding the involvement of various chemotherapy agents in these changes would be at best speculative, we note that most (N=9) participants had been treated with a protocol involving anthracyclines and topoisomerase inhibitors. Six patients received doxorubicin, one patient received etoposide, and remainder had been treated with fluorouracil, epirubicin, and cyclophosphamide. Doxorubicin, fluorouracil, and cyclophosphamide have been linked to apoptosis and inhibition of neuro- and gliogenesis through one of three mechanisms: disruption of the blood brain barrier, increase of CNS cytokine expression and/or oxidative stress (Johnston, 2014; Kaiser et al., 2014). Future studies focusing on which of these mechanisms is the first to be triggered at such a short time after the first treatment, will bring us closer to establishing strategies to prevent the long-term effects of chemotherapy on memory.

7.5. Conclusions

To conclude, we aimed to investigate if the memory problems frequently cited in the chemotherapy-induced cognitive changes literature are detectable immediately after the first treatment in a group of non-CNS cancer patients under the age of 50. A new memory task was specifically designed to define differentiate between the mechanisms that may underlie the memory deficits: encoding, consolidation, or retrieval.

Effectively storing informational content requires a persons' ability to attend and acquire that information; hence, our first analysis focused on learning performance, or encoding. Initial group differences identified both before and after treatment, were supressed by FSIQ control. The second analysis focused on patients' forgetting rate. Patients did not forget more compared to controls before the first treatment, but they forgot significantly faster after it. This effect was robust when controlling for FSIQ, suggesting that cancer treatment may have a detrimental effect on the storage of information in long-term memory. The third and last analysis focused on retrieval. Once information is attended, encoded, and stored, problems may arise with the strategy employed in retrieving it from memory. There was a trend towards a group difference in cue benefit, which was suppressed by the inclusion of FSIQ.

This is the first attempt to describe the pattern of cancer treatment-induced memory deficits as early as 24 hours following the first treatment. While differences were found in patients' forgetting rate, confirming whether cancer treatments predominantly affect frontal or medial temporal lobe functioning will require specifically designed imaging studies.

Chapter 8. Subjective cognitive complaints, illness perceptions, and quality of life in post-treatment cancer patients

Lindner, McCabe, Mayes, Talmi, Radford, Wearden (2014). To be submitted to Psychosomatic Medicine.

Abstract

Background Post-treatment cancer patients have objective cognitive difficulties, and they report high levels of anxiety, depression, fatigue, as well as subjective cognitive complaints, and a low quality of life. This cross-sectional study describes the psycho-emotional status of post-treatment cancer patients between the ages of 16 and 50, and examines the role played by subjective cognitive complaints, illness perceptions, distress, and fatigue in explaining their quality of life. ***Methods*** Young adult patients (N=57) were recruited between 6 months and 6 years following treatment for lymphoma, breast cancer, germ cell tumour, and sarcoma. They were individually matched to control participants (N=57) on age, education, and sex. Participants were administered self-assessment questionnaires examining illness perceptions, emotional distress, fatigue, subjective cognitive complaints, and quality of life. ***Results*** Patients had high distress and fatigue levels and a low quality of life. The associations between illness perceptions, fatigue and quality of life were partly mediated by cognitive complaints. Depression and anxiety largely mediated the relationship between cognitive complaints and quality of life. ***Conclusions*** This is the first study focusing on the relationship between illness perceptions, subjective cognitive complaints, and quality of life in young adult post-treatment patients. Results suggest that illness perceptions play an important role in triggering the impact of other psychological variables on quality of life. Thus, patients' illness perceptions should be explored in discussions during clinical visits.

illness perceptions, cognitive complaints, quality of life, chemotherapy, cancer, survivors

8.1. Introduction

Given the rise in cancer incidence (Maddams et al., 2009) and survival over 10 or more years (CRUK, 2014b), addressing the long-term side effects experienced by post-treatment cancer patients has become paramount. Two types of late effects, which have received increasing attention in recent years, have been the objective cognitive deficits and subjective cognitive complaints of these patients. The appropriate interventions for the two sets of symptoms may require different approaches, as the former may have a more organic nature (Fardell et al., 2011), while the latter may be primarily driven by emotional distress. Exploring potential options for each of them, becomes particularly important for the rising number of younger cancer survivors (ONS, 2011), whose quality of life could be hampered by a lower mood (Lindbohm et al., 2014; Short et al., 2005).

On the one hand, objective cognitive deficits following chemotherapy (Ahles & Saykin, 2007; Schagen & Wefel, 2013; Lindner et al., 2014) have been associated with a lower quality of life in cancer survivors (Fitch, Armstrong, & Tsang, 2008; Reid-Arndt, Hsieh, & Perry, 2010). However, the objective deficits are not usually correlated with fatigue and mood changes (Shilling et al., 2006; Vardy, 2009; Weis, Poppelreuter, & Bartsch, 2009). The fact that they are independent from emotional side effects may suggest that unlike in depression or chronic fatigue syndrome (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Rock, Roiser, Riedel, & Blackwell, 2013; Wearden & Appleby, 1996), in cancer patients objective cognitive deficits may be triggered primarily by factors other than distress and fatigue.

On the other hand, cancer patients report subjective cognitive complaints, which are related to a lower mood, higher levels of tiredness, and a low quality of life (QoL)

(Bower et al., 2000; Boykoff et al., 2009; de Jong, de Boer, Tamminga, & Frings-Dresen, 2014; Harrington et al., 2010; Husson, Mols, & van de Poll-Franse, 2011; Montazeri, 2009; Pullens et al., 2010; Reich, Lesur, & Perdrizet-Chevallier, 2008). The subjective complaints are independent from their results on neuropsychological assessments (Hutchinson et al., 2012). This pattern of results highlights the strong subjective nature of self-reported cognitive deficits, while raising the question whether they are triggered by distress or actual deficits. For example, in healthy older adults, such complaints were associated with higher levels of emotional problems (Kliegel et al., 2005; Slavin et al., 2010), whereas in other groups they were a relevant predictor of mild cognitive impairments (Mitchell, 2008). It is not yet known whether in cancer patients the subjective complaints are a result of an awareness of the objective impairment or primarily a result of fatigue and health-related anxiety. The lack of clarity regarding the aetiology of objective cognitive deficits still represents a challenge to the development of appropriate interventions to tackle them. By contrast, addressing the independent emotional consequences may be a first method of managing patients' psychological late effects, including subjective cognitive complaints.

Consequently, one of the goals of this study was to start by describing the psycho-emotional status of young cancer patients, who had been treated for several types of non-central nervous system malignancies. Akin to cancer groups investigated in other studies, the hypothesis was that this young adult group would experience higher levels of anxiety, depression, tiredness, and cognitive complaints, which would be associated with a lower QoL compared to healthy matched controls.

The second aim of this study was to offer a potential model of addressing the complex relationship between these markers of psychological adaptation, through the

illness perceptions (IP) held by patients. Illness perceptions (Weinman et al., 1996) represent the patients' personal beliefs regarding the symptoms, controllability, consequences, duration and causes of an illness.

Explaining the link between distress, fatigue, cognitive complaints, and their impact on QoL, may be facilitated by an understanding of their illness perceptions through the framework of cognitive behavioural therapies (Moorey & Greer, 2002). The rationale behind choosing this paradigm is its emphasis on the mediating role of cognitive interpretations in the relationship between an external event (such as cancer diagnosis or survivorship experience) and the psycho-emotional consequences (i.e. fatigue, anxiety).

The hypothesis was that there would be a potential pathway between IP and QoL, which would encompass mood, fatigue, and cognitive complaints. The arguments for proposing this model are three-fold. First, negative IP have been previously associated with higher levels of distress and a lower QoL in cancer patients (Millar, Purushotham, McLatchie, George, & Murray, 2005; Petrie et al., 2007). Second, based on the conclusions in Broadbent et al.'s classic paper (1982), subjective cognitive complaints do not result directly from stressful situations, but they facilitate the negative impact of other variables on quality of life. Third, the interactive model hypothesized (Figure 27), draws its influence from the Antecedent –Beliefs-Consequences paradigm of cognitive-behavioural and rational-emotive behavioural therapies (Butler, Chapman, Forman, & Beck, 2006; Ellis, 1991). Thus, it provides a structure with potential strong clinical applications.
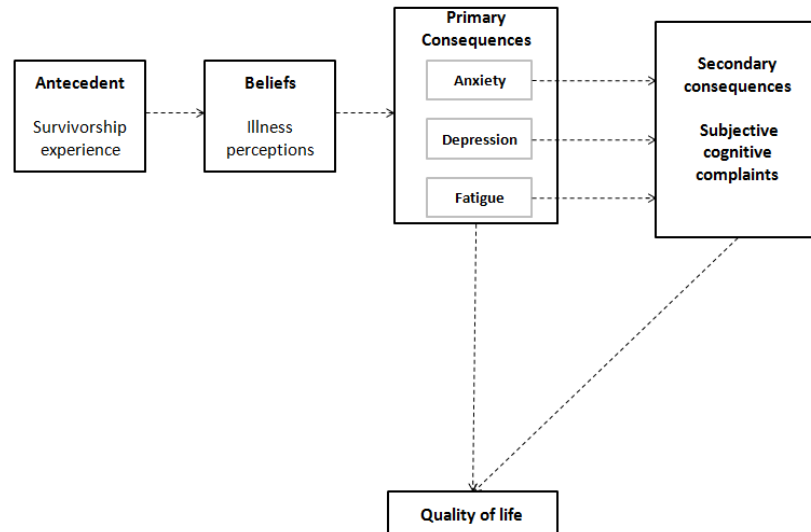
Figure 27. Potential explanatory model for the relationship between illness perception, distress and fatigue, subjective cognitive complaints, and quality of life.

Within this paradigm, the survivorship experience would be the **Antecedent** or the objective situation, which would generate personal illness perceptions or **Beliefs**. Negative illness beliefs would be associated with **Primary Consequences** such as anxiety, depression, and fatigue, which would in turn model patients' perception of their own cognitive functioning. Thus, anxiety, depression and fatigue would trigger **Secondary Consequences** – cognitive complaints or failures, potentially through attention and mnemonic biases (Dalgleish & Werner-Seidler, 2014; Hakamata et al., 2010). It follows that IP could decrease QoL by triggering higher levels of depression, anxiety, and fatigue and increasing the number of cognitive complaints. Consequently, in this model, QoL would receive a double influence, firstly from IPs via mood, fatigue, and cognitive complaints, and secondly, from mood and fatigue via cognitive complaints. This study aims to test this model using a step-by-step mediation approach.

8.2. Methods

8.2.1 Participants

Post-treatment cancer patients (N=75) were recruited through NHS Trusts in the United Kingdom by their clinical teams, during their follow-up visits. They were invited to the study if they were between 16 and 50 years old, and had been diagnosed with sarcoma, lymphoma, breast cancer, and germ cell tumour. Participants were excluded if their malignancy was a relapse or secondary effect of previous treatment, had been treated with cranial irradiation, had previously been affected by brain injury, had a history of mental health problems or substance abuse, previously exposed to mood altering drugs, and if they were not proficient in English. Control participants (N=74) were individually chosen to match patients on age, gender, and education. They were recruited through adverts in the local newspapers, posters, or were friends and family of the patients. The study was approved by the National Research Ethics Committee.

8.2.2. Instruments

Most of the administered self-assessment questionnaires can produce several scores. For the purpose of the present study, the model focuses on those scores from each questionnaire, which were relevant to the research questions.

The Illness Perception Questionnaire-Revised (Moss-Morris, et al., 2002) investigates patients' perception of their illness through by evaluating its identity (the number of symptoms participants perceive to be related to their illness), and seven constructs, measured using likert scale items. These were: timeline (the image of illness as acute or chronic), consequences (perception of the negative effects of the illness on personal, professional, and financial life), personal control (the belief the illness and symptoms can be controlled through one's behaviours), treatment control (the belief that

the illness and symptoms can be controlled by the treatment), illness coherence (whether patients believe they understand the diagnosis and treatment), timeline-cyclical (belief regarding the predictability and stability of symptoms), and emotional representation (whether thinking about the illness elicits negative emotions such as anxiety, anger and sadness). Although it was administered, the present study will not include the scale evaluating the perceived causes of the illness.

Hospital Anxiety and Depression Questionnaire (Zigmond and Snaith, 1983) is designed to identify anxiety and depression symptoms in clinical groups. It consists of two 7-item subscales (anxiety and depression), each item being rated between 0 (not at all) to 3 (very often). The minimum score is 0 and maximum for either anxiety or depression is 21, with a possible case cut-off score of 8+ for each scale (Bjelland et al., 2002).

The Fatigue Questionnaire (Chalder et al., 1993) is an 11-item questionnaire providing a continuous measure of fatigue, while determining a clinically significant cut-off. Items measuring physical and mental fatigue can be summed into a total fatigue score (Dittner, Wessely, Brown, 2004), which is focus of this report. Higher scores suggest higher fatigue levels.

The Cognitive Failures Questionnaire (Broadbent, et al. 1982) evaluates self-reported failures in memory, attention, perception, and motor functioning. It consists of 25 items, which can be rated from 4 (very often) to 0 (never). The total score is obtained by summing items, ranges between 0 and 100, with higher scores representing more self-reported failures.

EORTC Quality of Life (QoL) version 3.0 (Aaronson et al., 1993) is a 30-item questionnaire, designed to assess the quality of life of cancer patients. The general version was used due to the mixed characteristics of the patient group. There are three sub-scales

focusing on physical functioning and symptoms, and global quality of life. All scales will be discussed when reporting the psycho-emotional status of the patients, while the explanatory model will focus on the global quality of life. In accordance with the QLQ-C30 manual (Fayers et al., 2001), high scores on the functional and global quality of life scales represent a high/healthy level of functioning and a high score on the symptom scale represents a high level of symptomatology.

8.2.3. Procedure

Patients (N=75) and matched controls (N=74) were evaluated as part of the Chemotherapy-induced cognitive changes project, which involved a comprehensive neuropsychological assessment. At the end of the evaluation, participants were offered an envelope containing the five self-assessment questionnaires described above, to complete at home and then mail back to the researcher. Controls received the same measures, with the exception of the illness perception questionnaire. Although the Illness Perception Questionnaire did not undergo any adaptations, patients were asked to specify the perception towards their cancer in their present post-treatment status. Eighteen patients failed to return the questionnaires. There were no differences on any demographic variables between responders and non-responders. The final sample consisted of 57 patients and 57 individually matched controls.

Statistical analyses

Psycho-emotional status of patients relative to matched controls. None of the variables were normally distributed. Consequently, analyses included both bootstrapped analyses of variance and Kolmogorov-Smirnov tests. Given that the results were similar, only the results of the parametric tests will be reported. Effect sizes were also computed as standardized Hedge's *g* scores and corresponding 95% confidence interval for each of the

variables (Borenstein et al., 2009). The effect size calculations were based on the

bootstrapped standard error. For anxiety and depression, the odds ratios were calculated

(Altman, 1991) or the probability of identifying a patient or a control in their respective

groups, with a level of depression and anxiety score above the cut-off score.

Relationship between psycho-emotional variables. To evaluate the relationship

between IP, anxiety, depression, fatigue, cognitive complaints, and QoL bootstrapped

correlations were ran with all the variables. Following that, hierarchical regressions were

used to evaluate the percentage of variance in QoL explained by IP, distress, fatigue, and

subjective cognitive complaints. To define the proposed model, David Kenny's SPSS

macro (Kenny, 2011) was used to test the associations between IP, depression, anxiety,

fatigue, cognitive complaints, and QoL. Baron & Kenny's (1986) procedure suggests three

regression steps to assess a mediation. The first step tests whether the predictor is

correlated with the outcome (direct effect or path C'). The second step tests whether the

predictor is correlated with the mediator (path A). Thirdly, the association between the

mediator and outcome is tested (path B). The final step tests for the indirect effect, where

complete mediation would be suggested if the direct effect were zero unless the mediator is

included; if the relationship were more than zero, but less than the indirect effect, it would

be considered a partial mediation. The level of the indirect (or mediated) effect is

established by calculating C'+A*B. The predictors were, in turn, aspects of IP, depression,

anxiety, fatigue, and subjective cognitive complaints, whereas the outcome was QoL.

8.3. Results

8.3.1. Patient recruitment and characteristics

Figure 28 details the three-year recruitment process that lead to the inclusion of 57

post-treatment patients in the present study. Out of the 197 post-treatment patients who

were approached by their clinical team, 38% consented to the whole study. Out of this group, 76% returned the questionnaires.
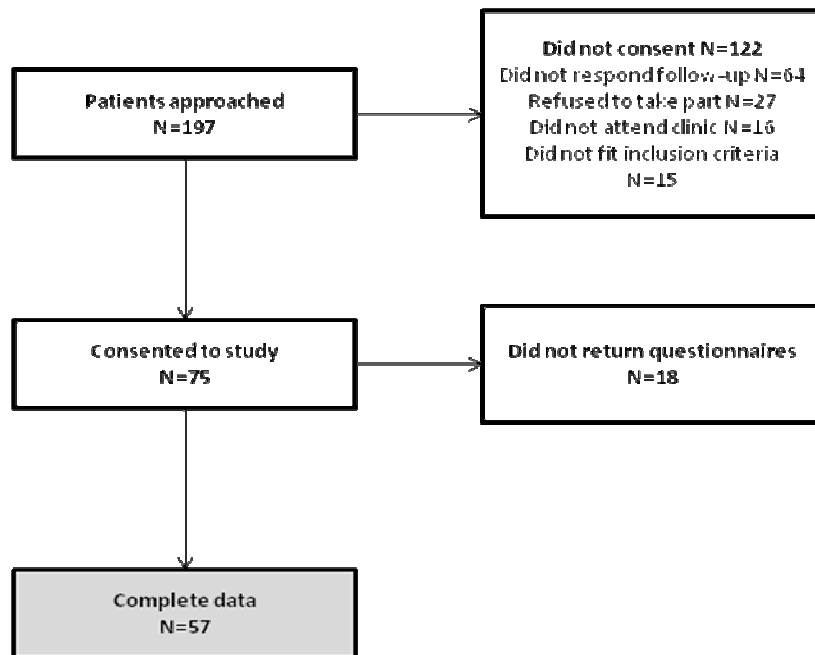
Figure 28. Study flow diagram.

Patients and controls were individually matched on age, education, and sex. The ages of the participants ranged between 19 and 50, approximately half of the sample consisted of women and most had a university degree (80% of patients and 75% of controls). Eighteen (31.6%) patients had been treated for Hodgkin's lymphoma (31.6%), fourteen for non-Hodgkin's lymphoma (24.6%), eleven for breast cancer (19.3%), nine for germ cell tumour (17.5%), and five for sarcoma (7%). All patients were between 6 months and 6 years post-treatment. Table 20 depicts the demographic details of the groups.

	Age M (SD)	Time since treatment M (SD)	Sex (%)		Education (%)		
			Women	Men	Higher general	College	University
Patients N=57	35.29 (9.79)	2.75 (1.87)	54.40% N=31	45.60% N=26	1.80% N=1	22.80% N=13	75.40% N=43

Controls **N=57**	36. 7 (9.01)	N/A	52.60% N=30	47.40% N=27	19.30% N=11	80.70% N=46

Table 20. Characteristics of post-treatment patients and matched controls

8.3.2. Psycho-emotional status in post-treatment cancer patients

Table 21 depicts the results of bootstrapped ANOVAs and associated effect sizes, which were in the moderate to high range. Compared to controls, post-treatment patients reported a lower level of physical functioning and QoL, and a higher level of symptoms. They also reported higher levels of depression, anxiety, fatigue, and subjective cognitive complaints. There were more post-treatment patients above the anxiety cut-off score (60%) compared to controls (32%) (OR=3.20, $95\%CI$: 1.48-6.91, p<.01). For depression, 21% of the patients and 9% of the controls were above the cut-off score, which was only marginally significant (OR=2.77, $95\%CI$: .90-8.47, p=.07). I will further examine the possible relationships between these variables.

	Patients	**Controls**	**p**	**Effect size**	**95 % CI Upper**	**95% CI Lower**
	Mean (SD)	**Mean (SD)**				
Quality of life	64.26 (19.7)	81.28 (13.89)	0.001	-0.99	-1.38	-0.60
Functioning	51.14 (22.64)	82.4 (17.74)	0.001	-1.53	-1.94	-1.11
Symptoms	27.04 (21.51)	7.62 (16.14)	0.001	1.18	0.79	1.58
Cognitive complaints	46.78 (18.19)	12.75 (15.71)	0.001	0.77	0.39	1.15
Fatigue (Total)	16.35 (3.24)	13.86 (2.11)	0.001	0.90	0.52	1.29
Fatigue (Physical)	10.26 (2.18)	9.07 (1.28)	0.001	0.66	0.28	1.03
Fatigue (Mental)	6.08 (1.81)	5.08 (0.98)	0.002	0.68	0.31	1.06
Anxiety	8.62 (3.85)	5.73 (3.32)	0.001	0.80	0.42	1.18

Depression	4.84 (3.92)	2.35 (2.56)	0.002	0.75	0.37	1.12

Table 21. Psycho-emotional status in young cancer post-treatment patients.

8.3.3. Relationship between psycho-emotional variables

Almost all variables correlated with each other in the expected direction (Table 22). The largest (>.50) correlations were between QoL, depression, cognitive complaints, and anxiety. Patients who reported more cognitive complaints had higher distress levels and a lower quality of life. QoL had a medium correlation (.30-.49) with illness identity and timeline; patients who attributed more symptoms to their illness and who perceive that it would be a chronic condition, also had a reduced quality of life.

Subjective cognitive complaints were highly related to patients' anxiety, fatigue, and depression and had a moderate correlation with the perceived illness timeline. Distressed patients had a negative emotional appraisal of the illness, a higher identity, and perceived their illness to have a cyclical or fluctuating course. Depression was highly correlated with illness identity and moderately with the perceived timeline. Thus, the perceived duration and cyclical nature of symptoms, and the perceived cognitive difficulties were related to higher distress and lower QoL.

	Function	Symptom	Cognitive complaints	Fatigue	Physical	Mental	Anxiety	Depression	ID	Time	Conseq.	Pers Ctrl.	Trt ctrl.	Coherence	Cycle	Emotion
QoL	.48**	-.72 **	-.66**	-.49**	-.39**	-.39**	-.61**	**-.71**	**-.45**	-.39*	-.32*	.09	.16	.22	-.26	-.30
Function		-.52**	-.40**	-.38*	-.39*	-.20	-.54**	-.51**	**-.43**	-.25	-.27*	.12	-.01	..20	-.29*	-.37**
Symptom			.48**	.48**	.42**	.35*	.55**	.64**	**.68**	.40**	.13	-.27*	-.22	-.31*	.09	.09
Cognitive complaints				**.56**	.41**	.49**	**.62**	.56**	.29*	**.38**	.24	-.20	-.23	-.05	.18	.22
Fatigue					.84**	.76**	**.53**	**.58**	.33*	**.36**	.15	.04	-.03	-.002	.15	.30*
Physical						.28*	.42**	.56**	.29*	.06	.16	-.02	-.14	.-13	.18	.25
Mental							.43**	.35**	.22	.57**	.08	.10	.12	.15	.06	.23
Anxiety								.67**	**.44**	.26	.29*	-.26*	-.22	-.19	**.44**	**.58**
Depression									**.49**	**.32**	.32*	-.19	-.16	-.10	.26*	**.39***
ID										**.34***	.07	-.28*	-.27*	-.33*	.08	.11
Time											.28*	-.03	.02	.004	.09	.23
Conseq.												-.30*	.02	-.03	.67**	.59**
Personal ctrl.													**.51**	.25	-.13	-.19
Treatment ctrl.														.44*	-.03	.07
Coherence															-.22	-.15
Cycle																.69**

Table 22. Bootstrapped correlations between quality of life, fatigue, cognitive complaints, mood, and illness perceptions in post-treatment patients.

Note. ID=identity, Time = timeline of the illness, Consq=consequences of the illness, Pers ctrl=personal control over aspects of the illness, Trt ctrl. = treatment control over aspects of the illness, Emotion = emotional response to illness. *p<.05, **p<.01, ***p<.001.

Before considering the potential causal pathways of these relationships, I first explored

which set of variables explained a higher percentage of variance in QoL (Figure 29).
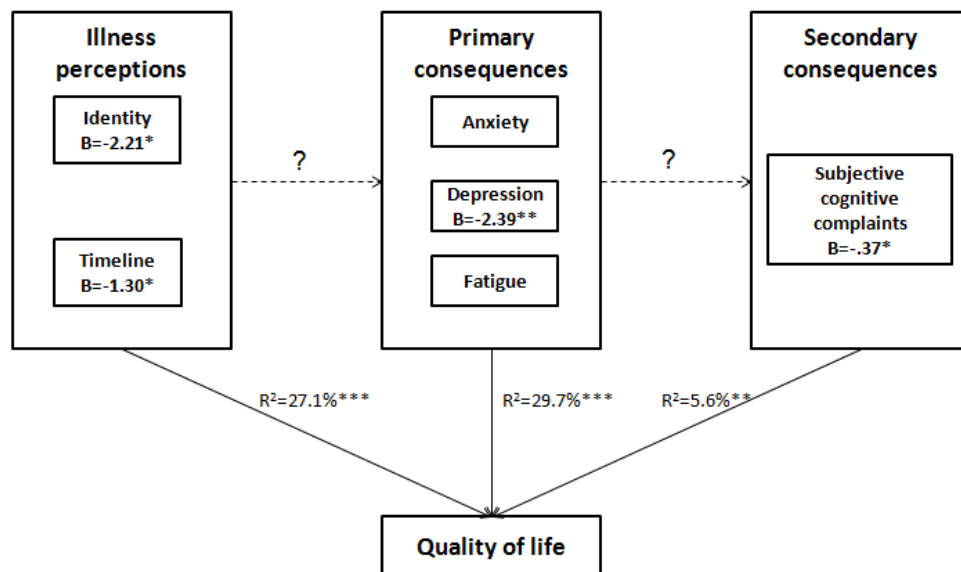

Figure 29. Hierarchical regression depicting variables accounting for the variance in quality of life.

Note. Results depict the R^2-change in quality of life and significant B-values of three types of predictors
(illness perceptions/anxiety, depression, fatigue/subjective cognitive complaints) on quality of life.
*p<.05,**p<.01, ***p<.001

This hierarchical regression revealed that when first including IP in the model, both

identity (B=-2.21, p<.05) and timeline (B=-1.30, p<.05) accounted for 27% of the variance

in QoL. In the second step of the regression, anxiety, depression, and fatigue explained an

additional 29.7% of the variance, but when they were included in the model alongside IP,

only depression (B=-2.39, p<.01) was still significantly associated with QoL. Finally, in

the third step, cognitive complaints explained an additional 5.6% of the variance. When it

was included in the model, only depression (B= -2.12, p<.01) and cognitive complaints

(B=-.37, p<.05) were still significantly associated with QoL. This suggests that each of the

three sets of variables contribute significantly to the variance in quality of life. However,

given the high inter-correlations between them, interpreting the findings of the hierarchical

model is not straightforward, nor does it provide information on the pathway between individual variables.

Consequently, to evaluate how these factors are connected, three mediation models were constructed (Table 23) to test the relationships between: IP and QoL via mood and fatigue; IP and QoL via subjective complaints; and between Mood/Fatigue and QoL via subjective complaints. First, I tested whether the primary consequences (anxiety, depression, fatigue) mediated the relationship between IP and cognitive complaints. Anxiety and depression, in particular, completely mediated the relationship between illness identity and subjective complaints, whereas fatigue mediated 60% of the same relationship. Similarly, the relationship between timeline and cognitive complaints was mediated between 38% and 41% by distress and fatigue. This suggests that the impact of illness perception on subjective cognitive complaints is primarily due to anxiety, depression, and fatigue.

	Direct pathway			Indirect pathway			
Relationship	Estimate	95% CI	Beta	Estimate	95% CI	Beta	% Mediated
IPs-Distress - SCC							
Identity - Anxiety - SCC	0.06	-1.23 to 1.36	0.01				95%
Identity - Depression - SCC	0.09	-1.32 to 1.50	0.01	1.60*	.19 to 3.01	0.29	94%
Identity - Fatigue - SCC	0.63	-.66 to 1.93	0.11				60%
Timeline- Anxiety - SCC	1.02*	.12 to 1.93	0.24				38%
Timeline - Depression - SCC	0.96	-.02 to 1.95	0.22	1.65**	.58 to 2.72	0.38	41%
Timeline - Fatigue - SCC	0.89	-.12 to 1.91	0.21				46%
Distress - SCC - QoL							
Anxiety-SCC-QoL	-1.64**	-2.86 to -.43	-.33	-3.00***	-4.05 to -1.95	-.61	45%

Depression - SCC - QoL	-2.56***	-3.66 to -1.46	-.49	-3.65***	-4.64 to -2.66	-.70	29%
Fatigue-SCC-QoL	-1.18	-2.70 to .32	-.20	-3.07***	-4.25 to -1.62	-.49	61%
IPs - Distress-QoL							
Identity - Anxiety - QoL	-1.56	-3.00 to -.12	-.25				47%
Identity - Depression - QoL	-1.05	-2.40 to .30	-.17	-2.97***	-4.44 to -1.50	-.47	65%
Identity - Fatigue - QoL	-2.17**	-3.62 to -.72	-.35				27%
Timeline - Anxiety - QoL	-1.21*	-2.23 to -.19	-.25				36%
Timeline - Depression - QoL	-.88	-1.83 to .06	-.18	-1.88**	-3.07 to -.70	-.40	53%
Timeline - Fatigue - QoL	-1.19*	-2.37 to '-.01	-.25				37%

Table 23. Direct and indirect pathways between each predictor, outcome and mediator.

Note. *p<.05, **p<.01, ***p<.001.

Second, the effects of anxiety, depression, and fatigue on QoL were significantly increased when cognitive complaints were added to the model. The last part of the model explored whether the primary consequences mediated the relationship between IPs and QoL. Anxiety, depression, and fatigue mediated this association between 27% and 65%. Depression, in particular, was the highest mediator of the association between illness identity and QoL.

The conclusion arising from these analyses is that in young adult patients a negative appraisal of their illness results in a lower quality of life, especially in the presence of subjective cognitive complaints, which are primarily triggered by emotional distress and fatigue.

8.4. Discussion

This is the first study focusing on young adult post-treatment patients' illness perceptions, and how they may be related to a poor quality of life due to the impact of emotional distress and subjective cognitive complaints.

First, I described the psycho-emotional status of patients relative to matched controls. Consistent with recent literature (Walker et al., 2014), these analyses revealed higher levels of anxiety, depression, and a low quality of life in young adult cancer survivors. Although patients were, on average, two and a half years post-treatment, they reported a lower physical functioning and more ongoing physical symptoms compared to their matched controls.

For the time being, there are no interventions to address patients' objective cognitive declines following chemotherapy. While clinical trials assessing pharmacological interventions are ongoing (Fardell et al., 2011; Lyons et al., 2011), the psychological impact of the survivorship experience on quality of life may be more readily tackled through psychological therapies (Sharpe et al., 2014). In order for such therapies to be maximally effective, the factors affecting QoL need to be understood, as well as the direction of the relationships between implicated factors. Given that mood, fatigue, and subjective cognitive complaints have been previously demonstrated to impact patients' quality of life (Hutchinson et al., 2012; Pullens et al., 2010), and given their potential highly complex associations, I chose to examine them through the Antecedents-Beliefs-Consequences framework. The Antecedent is the survivorship experience; the Beliefs are represented by the illness perceptions, and the Consequences are the levels of emotional distress and tiredness.

The tentative interpretation of the findings is that each of the factors contributes to a lower quality of life; however, the impact of illness perceptions (Beliefs) is mediated by an increase in the level of distress and tiredness, which is consistent with cognitive behavioural and rational emotive behavioural therapy formulations (Butler et al., 2006; Ellis, 1991; Moorey, Greer, 2002). For example, a patient who perceives a longer illness timeline, will assign a higher weight to any physical symptoms, irrespective of whether they are related to their diagnosis and treatment. The symptoms will be interpreted as an ongoing chronic illness, and will increase the levels of anxiety.

These analyses further revealed that subjective cognitive complaints are a secondary effect of negative illness perceptions through an increase in anxiety, depression and fatigue. Just as suggested by classical literature, in cancer patients, the subjective cognitive complaints do not relate to the objective cognitive deficits, but they facilitate the impact of other variables on quality of life.

Given the high prevalence of psychological co-morbidities in young adult cancer patients (Walker et al., 2014), as well as the rising number of cancer survivors (Maddams et al., 2009), there is a need for methods to ensure their higher quality of life, alongside a successful return into work and education (Short et al., 2005). Therefore, this complex model could be approached by eliciting and discussing negative illness perceptions, with a view to helping post-treatment patients reach a more adaptive model of their illness. Such an approach should aid in decreasing the levels of depression, anxiety, and subjective cognitive complaints. As a result, patients would see an increase in their quality of life. However, this hypothesis would need to be tested through appropriately powered controlled clinical trials. The way in which these factors relate to the objective cognitive

deficits, and whether reducing the level of distress would also change the prevalence of objective neuropsychological deficits, would be an issue to be tackled in future research.

Limitations of this study pertain to the fact that despite the several steps taken to demonstrate the validity of the model, there may be other factors that play a role, such as socio-economic status and employment history (Clegg et al., 2009), time elapsed since treatment (Massie, 2004), actual physical functioning, or sleep disturbances (Bardwell et al., 2006). Most patients included in the study were highly educated, thus this group may more readily monitor potential difficulties faced during demanding work tasks. Lastly, these assessments were part of a larger study focusing on chemotherapy-induced cognitive changes. In such studies, matching controls and patients on the emotional impact of the stressful life event on results can be more easily achieved if controls are friends or family of the patients. Consequently, some of the controls (N=3) were recruited in this manner, which means that the level of distress in the control group may have been slightly larger than in other studies. However, this aspect did not influence the power of the analyses, the effect sizes of the differences between patients and controls on most psychological variables being moderate to large.

8.5. Conclusions

Compared to matched controls, young adult cancer patients who had been treated for lymphoma, breast cancer, germ cell tumour and sarcoma had a lower quality of life, higher anxiety, depression, subjective cognitive complaints, and fatigue. None of the participants were actively receiving psychotherapy or counselling although most patients (60%) had anxiety levels above the Hospital Anxiety and Depression Scale cut-off (Bjelland et al., 2002)

Their lower quality of life received two main influences. The first was from illness perceptions through the level of depression, anxiety, and fatigue. The second was represented by depression, anxiety, and fatigue via the mediating influence of cognitive complaints. Finally, illness perceptions also trigger the subjectively reported cognitive deficits through the complete mediation of anxiety and depression.

These results suggest that young cancer patients have a lower quality of life than controls, as well as psychological co-morbidities. Given that none of the patients were under psychological care, it may be that their higher depression and anxiety levels were unrecognized at the time of this study. The relationships identified between the chosen variables suggest that interventions aimed at eliciting and attempting to modify negative illness perceptions during psycho-oncology appointments may have an impact on the number of reported cognitive failures, as well as their quality of life.

Chapter 9. General discussion

In the following chapter, I will summarize and interpret the main meta-analytical and empirical findings detailed in the thesis, through the framework set out by previous studies on chemotherapy-induced cognitive changes.

9.1. Meta-analytical findings

Chemotherapy-induced cognitive changes have been associated with both neuropsychological impairments and abnormalities in brain structure and functioning (Ahles & Saykin, 2007; Pomykala et al., 2013). However, despite the focus on specific types of malignancies, the incidence of these findings is highly variable. The meta-analysis described in Chapter 2 describes the types and extent of impairments experienced by post-treatment adult cancer patients, while highlighting the level of the heterogeneity within these studies.

When analysing both cross-sectional and longitudinal findings together, all effect sizes approached zero, were highly heterogeneous, and impairments could not be identified. This was surprising given the plethora of evidence pointing to the contrary. From a statistical point of view, such results could be classed as an example of Simpson's paradox (Julious & Mullee, 1994). This phenomenon appears when aggregating the results of datasets in which the outcome exhibit opposite effects. Given that the literature is methodologically divided between cross-sectional and longitudinal studies, the effects of chemotherapy on cognitive functioning were further analysed within these subgroups.

Cross-sectional studies had lower levels of heterogeneity and the effect sizes were small to moderate. Patients performed worse than controls on tests of capacity and

selective attention, and verbal memory (immediate, delayed, free recall and recognition). By contrast, in longitudinal studies, patients' effect sizes were close to zero, or they performed better following treatment compared to their baseline evaluation. Moderately high effect sizes, suggestive of improvements, were specific of tests evaluating the capacity of attention, verbal abilities, focused attention, verbal immediate memory (free recall) and immediate and delayed visual memory (free recall). Importantly, longitudinal studies were a lot more heterogeneous than cross-sectional studies, thus may have been influenced by additional factors. Interestingly, none of the chosen moderators (study quality, age, diagnosis, time since treatment) explained the heterogeneity within the estimated effect sizes. The result may point either towards the non-specificity of these moderators for this group of studies, or to another instance in which effect sizes with different potential directions (in this case, all cognitive functions) were pooled together.

Thus, the result of the meta-analysis does not exclude the possibility that these and other factors may still have an effect on the type and severity of neuropsychological difficulties identified. It just shows that the influence of factors, such as age or time since treatment, may depend on the type of cognitive function under investigation, and that there might be other factors influencing patients' performance in the long term. Figure 30 provides a summary of the complex structure of factors that may be implicated in the identification of mild cognitive impairments in non-CNS cancer patients. It builds onto the main elements necessary to define cognitive deficits and their potential predictors, which were specified in the introductory section.

For example, it has been demonstrated that some patients have cognitive issues before commencing treatment (Ahles et al., 2008), and there are many additional factors that could influence cognitive functioning in cancer patients, apart from chemotherapy

(Berman et al., 2014). Pre- and post-treatment differences between patients and controls may stem from population-level differences in cognitive performance due to age, education, socio-economical status and full scale IQ. For example, it is has been recently demonstrated that in older adults with a high life-time enrichment due to higher education and socio-economical status cognitive decline can be delayed for at least 8 years (Vemuri et al., 2014).
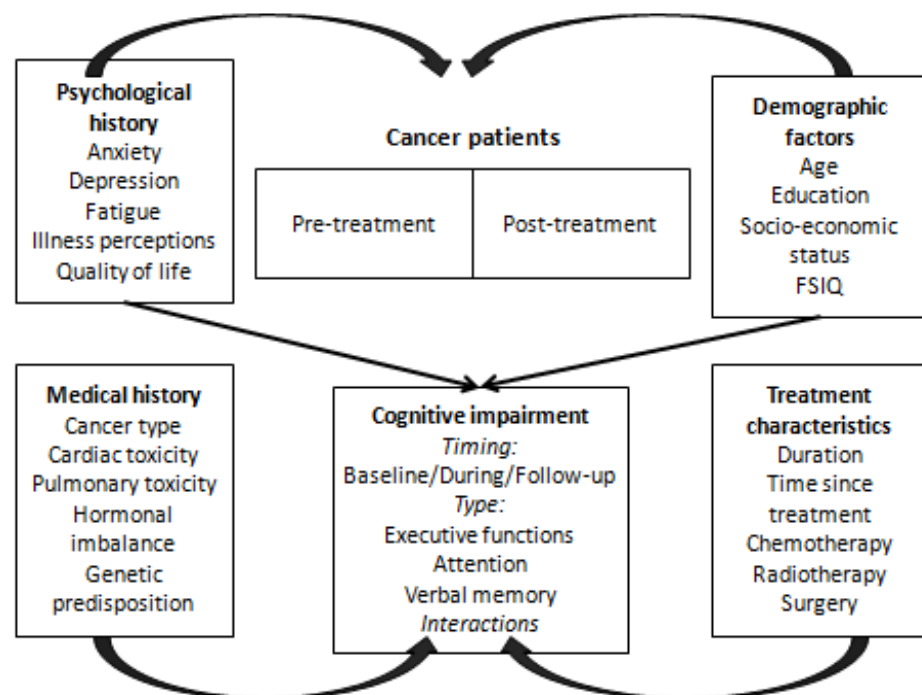
Figure 30. Main elements influencing the identification and development of cognitive changes in cancer patients.

Genetic predispositions may also play a role. Polymorphisms of the APOE 4 gene have been associated with cognitive declines in breast cancer patients (Ahles & Saykin, 2002). In Parkinson's disease, the same gene has been associated poor performance on similar tests to those identified in the young adult cancer groups included in the studies described in this thesis (delayed verbal memory, recognition, and executive functions as evaluated through list learning, the Letter-Number sequencing task and verbal fluency test,

Mata et al. (2014)). In leukaemia patients, polymorphisms of methionine synthase, glutathione S-transferase, and monoamine oxidase have been associated with attention deficits (Krull, Bhojwani, et al., 2013). These results may suggest that carriers of specific gene polymorphisms may be more predisposed to a poor performance in specific types of tests and it has been hypothesized that the presence of such polymorphisms may be related to both cancer onset and future cognitive declines due to poor DNA repair mechanisms (Ahles et al., 2012). While the presence of such connection has not yet been demonstrated, these independent variables may have a strong influence on both baseline cognitive assessments, performance fluctuations and decreases across the lifespan, and their effects may potentially be exacerbated by chemotherapy.

Other factors demonstrated to be important in determining cognitive status are medical and psychological co-morbidities. For example, cardiovascular risk (higher levels of resting blood pressure, fasting blood glucose, and total cholesterol) during mid-adulthood is associated with a faster cognitive decline over 25 years in the same participants (Yaffe et al., 2014). Depression has been associated with deficits in attention, executive functions, and memory similar to those identified in the cancer groups examined in this thesis (Rock et al., 2013; Snyder, 2013). However, some of these factors will be present at diagnosis, and will influence patients' responses to treatment (i.e. age, general health, genetic predisposition, baseline cognitive status), while others may develop patients without a previous history (for example, cardiac toxicity and depression).

In the next sub-chapter, I will describe the empirical findings relating to the cognitive function of a subgroup of patients who had been diagnosed or treated for various malignancies, but in whom the ages were younger than in previous research.

9.2. Empirical findings

9.2.1. Cognitive functioning in post-treatment patients

The first study examined cognitive functioning in post-treatment cancer patients who were on average 35 years old, and who had been treated for sarcoma, lymphoma, breast cancer and germ cell tumour. Performance on cognitive tests was compared both to that of matched controls from the general population and with published norms. The two sets of results were similar in terms of the pattern of cognitive domains impaired, but patients had more deficits when compared to norms rather than when compared to the matched controls. After controlling for differences between groups on FSIQ, patients performed worse than controls on tests of verbal memory (delayed free recall and immediate recognition), executive functions (Verbal fluency and DKEFS Trail Making Task) and visuospatial abilities (Figure Copy). Lymphoma patients treated on the ABVD protocol and germ cell tumour patients treated on the BEP protocol performed worse on a higher number of test scores compared to both controls and other cancer groups. These results are consistent with those obtained in older breast cancer patients, and young adult germ cell tumour patients. However, these are the first results suggesting that young adults treated for several malignancies may exhibit cognitive impairments.

Compared to previous studies, I found that differences mood, fatigue, and cognitive complaints explained a limited amount of variance in the neuropsychological tests. Specifically, they explained 4% of the variance in executive functions and 15% of the variances in source recognition. Of the three independent variables, depression had a significant explanatory value for the differences in DKEFS and Verbal fluency, suggesting that poorer executive control may be partly accounted for by mood. Similarly, cognitive complaints were the only significant predictor of the results in the source recognition task.

This may suggest that patients who reported more cognitive failures also had a poorer performance on that specific task. However, it cannot be specified whether depression and cognitive complaints trigger the objective neuropsychological deficits, or whether the objective deficits trigger a lower mood and are also being subjectively reported by patients. This result also suggest that emotional distress, fatigue, and cognitive complaints have a limited role in explaining post-treatment cognitive changes, and these may be accounted for by chemotherapy or other underlying medical vulnerabilities.

The fact that this study identified depression and cognitive complaints explaining some of the variance in cognitive functions, compared to previous studies, may be due to the prevalence of emotional issues varying across cancer groups (Lindnen et al., 2012). A better approach would have been to control and test for the different effects of depression, anxiety, and fatigue on each cognitive function within each group of patients, as for example lymphoma patients may have a different psycho-emotional status compared to breast cancer patients. However, due to the small number of participants in each group such an analysis would have not been possible due to lack of power.

Nevertheless, my study continues to point towards a frontal-parietal-temporal involvement in the chemotherapy-induced cognitive changes. It is also one of the first studies to highlight that some of these changes are in part influenced by depression and cognitive complaints. Future studies will be vital to investigate how structural and functional changes in these areas relate to the behavioural results I observed, and how their interaction may change from pre-treatment to months and years following treatment. What is more, compared to previous literature, this study suggests that some treatment groups may be more affected than others, and that future interventional trials should focus on executive functions and memory deficits to improve patients' daily functioning.

9.2.2. Cognitive functioning in pre-treatment patients

Because of the increasing number of studies reporting cognitive deficits in older patients before their chemotherapy, one aim of the research reported in this thesis was to evaluate whether young adult patients, who were on average 32 years old, exhibit similar deficits to those found in previous studies. The presence of some deficits before chemotherapy would make it more difficult to assign cognitive post-treatment effects solely to treatment as opposed to cancer symptomatology, depression and anxiety. After controlling for FSIQ differences, patients performed worse than matched controls on tests of attention, executive functions, and visuospatial abilities. These results are consistent with those in previous literature conducted with older breast cancer patients (Mandelblatt et al., 2014; Scherling et al., 2012). Importantly, comparing their performance to norms alone increased the number cognitive domains in which deficits were observed. Compared to previous studies (Cimprich et al., 2005), patients included in this examination were no different to controls in their levels of distress, fatigue and cognitive complaints, nor were there any associations between cognitive performance and these latter variables. However, I need to specify that this was a rather small group of patients (N=30), and only 13 them (43.33%) returned the self-assessment questionnaires. This may mean that the effects of anxiety or depression may have been missed in the non-responding group. Nevertheless, the neuropsychological results of the patients who were included were included in the analyses were not influenced by their psycho-emotional status.

The novel aspect of the results is that before treatment, young adults performed worse than their matched controls on cognitively demanding tasks associated with activity in frontal, prefrontal and parietal areas. The performance on executive functioning tasks decreased with age in patients, but not in controls, which may suggest that patients may be more predisposed to accelerated age-dependent cognitive declines even before treatment.

To test this hypothesis, future studies should focus on mapping the changes throughout treatment to examine whether they trigger additional long-term memory deficits.

What is more, because of the unequal numbers of patients with each specific diagnosis, further subgroup analyses were only tentative, for the sole purpose of hypothesis generation. The inclusion of larger number of pre-treatment patients would also facilitate further analyses on the influence of depression, anxiety, and fatigue on cognitive functioning within types of diagnoses. This further development would be guided by the differences in emotional distress prevalence between cancer groups, outlined in Chapter 8.

A smaller sample of these patients also took part in the third study that investigated the type of memory deficits that may be present immediately after the first chemotherapy dose. This is the first study to attempt to describe the potential pattern of memory impairments immediately following the first dose of chemotherapy. A part of this group had been treated on the FEC-T protocol, whereas the other part had been administered protocols that included anthracyclines. Compared to their matched controls, they had a faster forgetting rate after treatment, which would be consistent with memory consolidation problems. Differences were also observed in the learning rate, or encoding of information, but these appeared to be driven by the difference in FSIQ between groups. The lack of differences in encoding/retrieval suggests that the faster forgetting rate may be independent from attention/executive functioning impairments. However, because it was a small sample, the potential influences of attention/executive functioning deficits observed in the previous study could not be controlled. Consequently, this study would need to be replicated with a larger sample to reach a definite conclusion.

9.2.3. Psycho-emotional status of post-treatment patients

In the first empirical study, reported in Chapter 5, I observed that post-treatment patients had higher levels of anxiety, depression, fatigue, and cognitive complaints compared to their matched controls. These variables were included in analyses to investigate whether they accounted for any of the variance in cognitive functioning. Depression and cognitive complaints accounted for a part of the variance in executive functioning and verbal memory, respectively, but did not explain the full extent of differences in executive functions, verbal memory, and visuospatial abilities observed between the groups.

In the empirical study described in Chapter 8, I wanted to identify the exact extent of differences in depression, anxiety, fatigue, and cognitive complaints between patients and controls, as well as their association with illness perceptions and quality of life. Although none of the participants in the study was actively receiving any form of therapy, 60% had anxiety levels above the Hospital Anxiety and Depression cut-off score. This result is consistent with previous studies suggesting that emotional distress may be unrecognized in cancer patients (Kissane, 2014). Furthermore, patients reported negative illness perceptions. To explain the potential effects of illness perceptions, mood, fatigue, and cognitive complaints influence quality of life, I integrated all of these factors and their complex relationships within the Antecedent-Belief-Consequences model of cognitive-behavioural therapies. I observed that the illness perceptions regarding the identity and timeline of the illness were associated with patients' quality of life through their levels of depression, anxiety, and fatigue. These three factors, as well as the perception of symptoms and illness timeline were also associated with patients' quality of life through their subjective cognitive complaints. This is the first study to hypothesize an integrative model drawing together these factors and it is the first one to account for the role played by illness

perception. The conclusion was that illness perceptions play a role in triggering the impact of anxiety, depression, fatigue, and cognitive complaints on quality of life. Consequently, discussing the adaptive value of the patients' beliefs regarding their illness and the how illness perceptions drive the attribution of any physical symptoms to ongoing illness could reduce the impact of these variables on their quality of life. Future studies could examine how these variables also relate to the objective cognitive deficits. Specifically, they could analyse which of these factors - illness perceptions, mood, fatigue, or quality of life shape or are shaped by objective deficits in executive functioning or memory. The key question would be whether the presences of impairments, which are objectively observed and reported subjectively by patients, trigger ongoing negative illness perceptions and changes in mood, or whether the changes in illness perceptions and mood trigger and explain the cognitive deficits.

9.3. Future directions

The results obtained throughout this thesis are consistent in part with findings in previous studies, but also depict discrepancies. Specifically, previous longitudinal and cross-sectional studies describedifficulties in memory, processing speed, and executive functioning (Wefel, Vardy, Ahles, Schagen, 2011). Differences between the meta-analytical findings in cross-sectional studies and functions commonly cited as impaired, is solely the clustering of test scores within cognitive domains. Specifically, deficits were observed in Capacity of attention, which encompassed test scores such as Letter-number cancellation, Digit or Visual span, and PASAT. All of these tests could either be included under the proposed concept, or under the umbrella of executive functioning. Consequently, irrespective of the label assigned to the cognitive function under study, the pattern of deficits arises in the same types of tests as those depicted by the empirical studies in this thesis and by previous research.

There is an additional discrepancy between the moderator analyses in the meta-analysis and the results depicted in Chapters 5 and 6. In particular, age and diagnosis did not have a significant influence on the effect sizes, whereas both factors had an impact on the neuropsychological findings. Such discrepant results can be explained in two ways. A first explanation is the reduced specificity of these moderators in previous studies; as more than 70% of the studies included in the meta-analysis included breast cancer patients, and the age variance was small, there is a possibility that an impact of these moderators could not be identified. A second explanation is that all cognitive functions were pooled together in the multilevel model, whereas influences that are more specific may only have been obvious when analysing particular cognitive test scores (i.e. the relationship between the Trail Making Task and age observed in Chapter 6).

A final discrepant finding refers to the links between cognitive and psycho-emotional factors. Some of the previous pre-treatment studies found associations between these factors and cognitive functioning, whereas the studies in this thesis do not. One possible explanation is the unknown emotional characteristics of the patient non-responders included in Chapter 6. It may be possible that patients who were more distressed at the start of the treatment failed to return the self-assessment questionnaires. Finally, in the post-treatment group included in Chapter 5, there is an association between depression, cognitive complaints, executive functions and verbal memory, which was not highlighted by previous literature. This finding may be explained through the variable incidence of emotional issues in cancer patients treated for various malignancies (Walker et al., 2014).

Nevertheless, the pattern of cognitive difficulties in pre-treatment patients, suggests a frontal disruption, while in post-treatment patients, the cognitive deficits resemble a

frontal-subcortical profile, both consistent with previous research in the area. This is an interesting finding, given that the thesis focuses on younger patients, who were on average 35 years old and had been treated for various malignancies. The next steps suggested by the results presented in this thesis are: focusing on specific patient subgroups, making specific changes in the methods used, the inclusion of additional covariates, a more in-depth look at the mechanisms through which individual drugs may disrupt neural pathways, and intervention studies, which could be pursued through multicenter collaborations. I will briefly explain the reasoning behind each of these lines of work.

Patient groups

In Chapters 5 and 6 I observed that age accounted for 20% of the variance in pre-treatment patients' executive functioning and 8% of the variance in post-treatment patients' source recognition. Surprisingly, when dividing the groups further in those aged 16-30 and those aged 31-50, I observed that the latter group was more likely to have lower scores compared to their age-matched counterparts. While previous studies (von der Weid, et al., 2003; Wefel et al., 2014) suggest that younger age is related to cognitive deficits following leukaemia and germ cell tumour treatment, the reverse effect was found in the patients included in this study.

These results may be due to different development pathways disrupted between 16 and 50. A previous review (Ahles, Root, Ryan, 2012) suggests that chemotherapy may be associated with accelerated brain ageing, which means that the cognitive difficulties should be viewed within the context of normal ageing-induced cognitive changes. Craik & Bialystok (2006) suggest a model of cognitive ageing in which the stored informational representations, the access and ability to apply them to practice increase from childhood to maturity when they reach a plateau which is maintained into old age. However, control

processes (or frontal functions) reach a peak in adulthood, after which they decrease slowly as age increases. These changes are particularly obvious in demanding cognitive tasks, which elicit response speed decrements due to switch costs, such as the DKEFS Trail Making Task. While this pattern of age-related changes should be seen in both control participants and patients, the latter group had stronger deficits. Age-dependent performance decreases were observed in pre-treatment patients for executive functions, and in post-treatment patients for verbal recognition memory. It follows that for specific types of scores, patients within different age ranges will behave differently to their age-matched counterparts. Subsequently, to decrease heterogeneity, future studies should no longer focus on extended age ranges, such as 18 to 70 or 16 to 50, but could be restricted to specific age-ranges due to the dynamic particularities of cognitive status throughout the lifespan.

A second development in future studies would be to continue to focus on differences between homogenous groups of pre- and post-treatment patients. In Chapter 5, I observed that Hodgkin's lymphoma and germ cell tumour patients were more affected on most cognitive scores compared to the other cancer groups. Either particularities of the combination of drugs these patients receive or other underlying factors may exist that impact these patients' performance more. However, it is generally acknowledged that for multiple analyses of covariance the sample should include 10 participants for each covariate (Tabachnick & Fidell, 2007). Because of the small sample size, it would have been difficult to include other covariates such as depression, anxiety, and fatigue alongside multiple cognitive scores in the description of the pattern of impairment in each patient subgroup. Thus, larger collaborative studies are needed to explore these results further, as these two cancer groups seemed to have more deficits, which may place them at an increased risk of disruption to their daily activities after treatment.

Methods

The methods used in studies focusing on the cognitive changes induced by chemotherapy and their implications on patients' quality of life could be improved in two main ways. First, by integrating the results obtained throughout Chapters 5,6, and 7 it becomes clear that some patients have difficulties in executive functioning, attention, and visuospatial abilities prior to treatment. A smaller subgroup developed verbal memory consolidation deficits immediately after the first treatment, while patients treated at least six months previously had problems in executive functions, visuospatial abilities, and verbal memory. However, a major issue with interpreting the results in this simple manner is that the groups are not directly comparable. Hence, the first recommendation, which is vital for developing future interventions, is to map these differences in the same group of patients from a longitudinal perspective. The use of tests with alternative versions would minimize practice effects and the same group of patients could be monitored over a larger timeframe. Through the means of a larger groups of patient recruited through multicentre studies, the rest of the factors I outlined above could be included in the model to decrease the heterogeneity of results specific to longitudinal designs.

A second methodological issue is which instruments and neuropsychological assessments to use in future studies. There is increasing evidence that not all cognitive functions are impaired in adult age patients. Consequently, to increase the feasibility of non-routine neuropsychological assessments, especially in pre-treatment patients, shorter batteries could be used. They could be restricted to frontal, memory and visuospatial tests, which would decrease the timing of assessments from 90-120 minutes to a maximum of 40 minutes. Specifically, I suggest that based on the results obtained throughout this thesis, the most relevant tests would be the Verbal fluency, DKEFS-Trail Making Task, any list

learning task with free recall immediate/delayed trials, as well as a word and source recognition component, and a visuospatial abilities test. Tests that did not highlight any differences were the Stroop, TOMM, Digit span, the speed of information processing module, as well as tests of visual memory. An additional development would be to use internet-based cognitive assessments (Witt, Alpherts, & Helmstaedter, 2013). Although this approach would restrict the pool of participants to those owning a computer, it would be a feasible method to facilitate data collection from a large number of patients, whilst targeting the 16-50 age groups.

Inclusion of additional covariates

Apart from nominal, group-specific differences such as cancer diagnosis, and treatment Chapters 5, 6, and 7 have outlined FSIQ and age as continuous variables that have a major influence on the extent of cognitive differences between patients and controls. Longitudinal studies would not require the examination of FSIQ, but it becomes vital in cross-sectional designs. Importantly, Chapter 8 examines covariates such as mood, fatigue, cognitive complaints and quality of life. It is not yet clear whether cognitive deficits lead to mood changes and reductions in quality of life, or if the latter predispose patients to cognitive deficits following chemotherapy. This would be another aspect warranting further investigations.

Another factor, which I have suggested to have a significant impact, before, during, and after treatment, is anaemia. It has been previously shown that greater declines in haemoglobin over the course of treatment are associated with increases in fatigue (Jacobsen et al., 2004), anxiety (Vearncombe et al., 2009) and reductions in cognitive functioning. Patients with reduced haemoglobin levels also exhibit increases in the expression on IL-6 (Ershler, 1993; Maggio, Guralnik, Longo, & Ferrucci, 2006), and both

factors have been associated with cognitive deficits, especially in attention and concentration (Balducci, 2003). However, the direction of such relationships is yet to be demonstrated. Moreover, prior to treatment only patients with haematological malignancies would be more prone to anaemia.

Drug mechanisms of action

An additional development would be to continue to focus on the molecular mechanisms through which chemotherapy drugs may influence cognitive functioning. Chemotherapy drugs do not usually cross the blood brain barrier. Methotrexate and fluorouracil have been suggested to cross it to a limited extent (Muldoon et al., 2007; Neuwelt et al., 2008). One of the main hypotheses through which chemotherapy has been suggested to lead to cognitive impairments is through the insult created by increases in expression of cytokine markers (Seigers et al., 2013; Seigers & Fardell, 2011). Cytokines are known to cross the blood brain barrier, and their effects may be further increased by loss of the protective characteristics of the barrier (Banks, 2005; Pan et al., 2011). Both the direct influence of chemotherapy and its indirect influence through the increase in cytokines could have direct effects on the signal transduction cascades necessary for memory formation and storage. Such effects may be seen through deficits in short-term memory, or learning rates.

The formation of memories is based on molecular signalling and transcription factors (Kandel, 2012). Short-term memory requires minutes to hours and is only based on changes in synaptic communication between neurons. The exposure to a stimulus will trigger the production of neurotransmitters such as serotonin or dopamine, which are released into the synaptic junction and attach to the post-synaptic receptor. This process leads to the production of adenylyl cyclase, which is required to convert adenosine

triphosphate to cellular cyclic adenosine monophosphate (cAMP), marking the beginning of intracellular signal transduction. Elevated levels of cAMP have previously been associated with decreased levels of interleukins and TNF-α, which have been suggested to affect memory when present in high amounts (Chen, 1994; Cotman, Berchtold, & Christie, 2007; Kesler et al., 2013). Cyclic AMP recruits the cAMP-dependent protein kinase (PKA), which releases a catalytic subunit toward the pre-synaptic junction, stimulating the production of neurotransmitters in the post-synaptic neuron (i.e. glutamate).

The repeated exposure to a stimulus will maintain the production of cAMP, which will trigger transformations within the PKA catalytic subunit that was released towards the pre-synaptic neuron. The increase or dysregulation of interleukins may act in the period in which cAMP recruits PKA, which could lead to losses in short-term memory, and thus the induction of long-term memory processes may no longer take place (Gwosdow, O'Connell, & Abou-Samra, 1994; Ramos, Stark, Verduzco, van Dyck, & Arnsten, 2006). This one potential mechanism to be examined further.

A second potential mechanism would be represented by the transformations required in the nucleus of the cell to facilitate the formation of long-term memories. The catalytic subunit will recruit the mitogen-activated protein kinase (MAPK), which has a specific role in cell proliferation, survival, and apoptosis. At the nucleus level, MAPK and PKA are phosphorylated, bind to the cAMP-responsive element binding protein 1 (CREB 1) and stimulate transcription through the activation of immediate early genes which induce the creation of a new synapse. Immediate early genes known to be activated and involved in the formation of long-term memories are zif268 (Davis, Bozon, & Laroche, 2003) and Arc (Plath et al., 2006). It has been suggested that dysregulations involving the CREB family of transcription factors may lead to the inhibition of long-term memory

storage (Pittenger et al., 2002) and CREB activation has been associated with the suppression of IL-1 and tumour necrosis alpha (Zhao & Brinton, 2004).

The process described above is one of the most well described signal transduction pathways involved in memory formation (Abbott & Kandel, 2012; Kandel, 2012; Mayford, Siegelbaum, & Kandel, 2012). However, other pathways, such as the JAK-STAT pathway (Nicolas et al., 2012) may also play an important role in synaptic plasticity, thus may also be associate with memory storage and may become disrupted due to the direct or indirect effects of chemotherapy agents. Dysregulation of any of these pathways either through the increased influence of pro-inflammatory markers on brain cells or through the direct effects of chemotherapy agents may most likely lead to reduced cell proliferation and/or apoptosis (ELBeltagy et al., 2012; Mustafa et al., 2008). For example, the JAK-STAT pathway is also highly expressed in the brain, it is specifically activated by cytokines, and is involved in hippocampal NMDAR-mediated plasticity (Aaronson & Horvath, 2002; Nicolas et al., 2012) through the induction of long-term depression in the Schaffer collaterals and CA1 pyramidal neurons. The prolonged induction of long-term depression and inhibition of long-term potentiation through this pathway may also lead to long-term memory storage processes not taking place. Findings relating chemotherapy to deficits in long-term memory and an increased rate of forgetting may suggest that these are two of the mechanisms that may be disrupted.

Chemotherapy agents may be indirectly implicated in the disruption of any of these pathways, through interleukins. As an example, bleomycin, leads to increases in IL-1 and IL-18 which are associated with pulmonary injury in humans and rats (Hoshino et al., 2009). In mice, a single dose of doxorubicin can induce increases in the tumour-necrosis factor alpha and IL-1 (Ujhazy, Zaleskis, Mihich, Ehrke, & Berleth, 2003). Similarly,

rituximab and other monoclonal antibodies are known to induce cytokine-release

syndromes (Bugelski, Achuthanandam, Capocasale, Treacy, & Bouman-Thio, 2009) and

rituximab specifically has been demonstrated to inhibit the MAPK pathways through the

down-regulation of IL-10 (Vega et al., 2004). Critically, these examples of chemotherapy

agents which have also been administered to the patients included in the aforementioned

studies. While methotrexate and fluorouracil may have potentially had a more direct

effects on the CNS, it is probable that the other agents acted indirectly through the action

of interleukins on the CNS. The immediate effect on memory storage observed in Chapter

7 may have potentially been driven by the influence of cytokines on the memory formation

processes described above. While this hypothesis requires further preclinical examinations,

the associations between inflammatory markers and altered neurogenesis in the

subventricular zone and dentate gyrus, both in normal ageing and pathologies (Russo,

Barlati, & Bosetti, 2011), may suggest that pro-neurogenic interventions may potentially

prove useful in cancer patients. However, it needs to be specified that rituximab is a

successful medication in multiple sclerosis, by targeting specific subtypes of immune

responses (Linker, Kieseier, & Gold, 2008). Hence, not all cytokines and interleukins may

be associated with a detrimental influence on the central nervous system, and there is still a

lot that we do not know about their role in memory formation. Their influence may more

closely resemble an inverted-U shaped curve (Rostène et al., 2011), but this hypothesis still

needs to be tested in future studies.

Interventions

At present, based on both the results within this thesis and previous evidence, there

is no longer any doubt that chemotherapy has a negative influence on executive functions,

memory, and visuospatial abilities. However, studies to date, such as those included in this

thesis, have only provided snapshots of the influence or variance explained by each cluster of factors, based on the availability of resources in each institution and the openness to psycho-oncology research in different countries. Ultimately, answering the question of how much of the insult is due primarily to chemotherapy and how to counteract it, will only be possible through highly powered multicentre studies, taking into account all of these variables.

Nevertheless, because patients are affected by both emotional and cognitive problems, the information gathered so far already points towards the need for controlled trials focusing on intervention strategies to help patients' cope with these late effects. Furthermore, apart from benefiting patients directly, they could provide a method to differentiate between the potential cognitive deficits resulting from organic deficits versus those triggered primarily by mood. For example, neuropsychological tests could be administered before and after cognitive-behavioural interventions with or without a memory training component. This way, one could test for the differential changes in cognitive abilities due to decreases in depression/anxiety, versus the additional benefit of also including targeted cognitive training. However, any intervention will still need to encompass the holistic view of the patients, by integrating potential physical, psycho-emotional and cognitive consequences that may be interconnected.

In her 2003 American Cancer Society Award, Jimmie Holland outlined the main priorities to be addressed in psycho-oncology intervention research. Figure 31 is an adapted version of her suggested approach to psycho-oncology interventions, based on the interpretation of the results in this thesis.
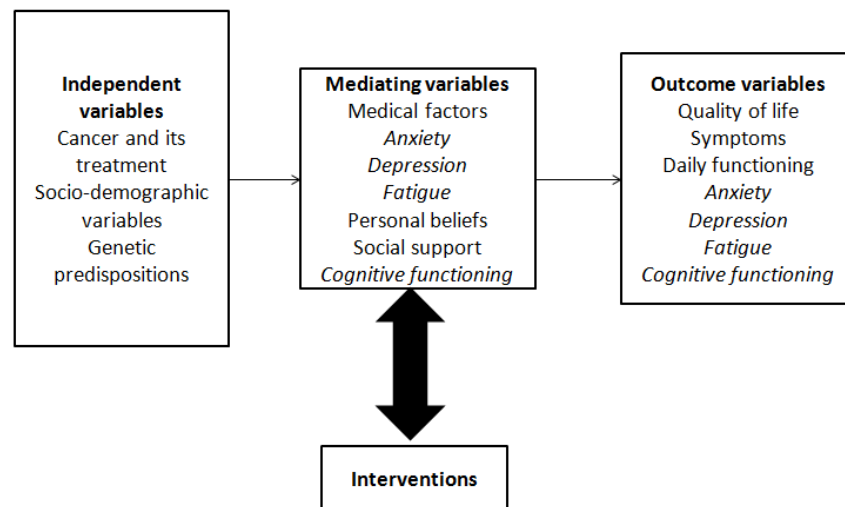
Figure 31. Factors involved in designing interventions in psycho-oncology

Note. Adapted from Holland (2003)

She highlighted that the connection between cancer and its treatment, patient-specific characteristics and outcomes such as quality of life is mediated by medical factors, mood, personal beliefs, or social support. However, in recent years we gained evidence that psycho-oncology should not only deal with the emotional and social burden of patients, but also with their cognitive side effects. Thus, the framework she proposed (Holland, 2003) can be adapted to that depicted in Figure 31. The independent factors, which should be defined in the context of interventions, are the characteristics of diagnosis, treatment, as well as the socio-demographic and genetic predispositions of patients. These would be linked to the mediating variables. In addition to the variables she proposed, the results presented in this thesis would suggest the addition of anxiety, depression, and fatigue, their importance being outlined in Chapter 8, as well as cognitive functioning, as outlined in Chapters 5 to 7. Given the limited amount of evidence on whether these are mediating variables of quality of life or consequences of other factors, I have added them all in *italics* both as mediators and as outcomes.

Specifying the contribution of each of these factors would enable the description of the neuropsychological status in subgroups of patients whilst reducing the high heterogeneity, which was described in the meta-analysis. Similarly, to the distribution of medical and psychological characteristics, some patients may have lower than normal cognitive functioning from baseline. Chemotherapy may have a role in increasing initial cognitive problems, as well as creating acute and/or long-lasting difficulties depending on the presence of underlying vulnerabilities. Following this, some problems may be transient in one group, long-lasting and stable in a second group, and long-lasting and progressive in a third group. These patterns have not yet been described, but the next step in studying chemotherapy-induced cognitive changes would be to map specific attention, executive functioning, and memory performance from the start of treatment to several years after it, whilst accounting for as many of these covariates as possible.

A method of investigating whether these factors have a mediating role or are outcomes of other predisposing factors would be to apply interventions and evaluate their consequences. It is very probable that, in reality, all the variables outlined in Figure 31 are actually inter-connected; for example, depression leads to a reduced quality of life, which will in turn lead to more depression symptoms. Describing the exact dynamic could only be done through longitudinal studies in which patients would be evaluated in a comprehensive and holistic manner (including cognitive functioning, mood, fatigue, quality of life, etc.) from their diagnosis, throughout their treatment, and following them up to a few years post-treatment. As demonstrated in Chapter 8, anxiety and depression are consequences of personal beliefs, which then lead to a reduced quality of life. Determining their relationship to cognitive functioning is yet to be examined, but would bridge the knowledge gap outlined by Figure 31.

There have been several pilot studies aiming to explore interventions that may be suitable for the cognitive changes associated with chemotherapy. These were cognitive-behavioural therapies with added psycho-education interventions (Ferguson et al., 2007; Kesler, Hadi Hosseini, et al., 2013; Schuurs & Green, 2013; Von Ah, Habermann, Carpenter, & Schneider, 2013; Weis et al., 2009) and they all had promising results. A very recent study evaluated the efficacy of using computerised cognitive training, such as Lumosity (Sternberg et al., 2013), in breast cancer patients. Lumosity is an internet-based intervention, which requires the user to play a few short games every day. These games do not last more than 10 minutes and are designed to train specific cognitive abilities such as task switching, and memory for words or faces. The task demands increase as the person gets proficient in completing them and the interface provides daily progress reports. The study found that training over 12 weeks resulted in improvements in cognitive flexibility, verbal fluency and processing speed, but improvements in memory were only marginal (Kesler, Lacayo, & Jo, 2011). In Chapter 5, when investigating the relationship between affected aspects of cognitive functions, there was only an average correlation between performance on delayed verbal memory and visuospatial abilities. However, there were no correlations between scores on executive functioning/verbal fluency and memory performance. The interventional results of Kesler et al. (2013) may be further evidence that the two classes of deficits are independent and may require different intervention strategies. Another vital question that arises is whether the effects of such interventions would be long lasting, or temporary over the course of the intervention and shortly after. In this context, future follow-ups are essential.

9.4. Reflection

Apart from addressing the crucial research question of whether working-age cancer patients experience neuropsychological difficulties, my project aimed to contribute to

raising awareness on this issue in the UK while giving patients a voice on this matter. Before this project, there were only a few studies on this topic in the United Kingdom, which mostly focused on the effects of hormonal treatments in breast cancer patients (for example, Jenkins et al., 2008, 2004; Shilling, Jenkins, Fallowfield, & Howell, 2003), the last study being published in 2008. Initially, the goal of the PhD project was to investigate memory deficits in the very acute stage of treatment and then follow-up these patients over six or more months.

A relative lack of awareness of these symptoms among treating clinicians, together with additional factors such as logistical difficulties of recruiting patients to clinical trials at a particularly vulnerable point in their treatment trajectory, has resulted in very poor initial accrual of pre-treatment patients. The challenges to recruiting pre-treatment patients would have led to a very small number of patients being included in any follow-up evaluations. These challenges were driven by a few factors.

First, healthcare providers had doubts regarding the necessity of neuropsychological testing, as complaints regarding the cognitive side-effects of chemotherapy were seen as purely anecdotal (Mitchell & Turton, 2011). Second, because the research committee was concerned about over-burdening patients with research that would not benefit them directly, the neuropsychological tests could only be administered to additional patients once the first 10 pre-treatment patients had signed up in the study. Third, the NHS has undergone major changes in the last years, which have resulted in many additional time pressures placed on staff responsible for identifying potential patients. These are additional potential causes, apart from the poor health of pre-treatment patients, which may have led to the initial poor accrual to the study, as well as last-moment referrals from clinical teams.

The mostly anecdotal label attached to this phenomenon may have also guided the attitude of the patients. Some patients considered they had no difficulties, but they may have been part of the group who does not experience them. Others connected it with the effects of stress or ageing:

Anonymous on Cancer forum: "Hard to tell if this is age or stress related but ever since I was ill I have had difficulty finding words, or saying the right thing..."

Others were thankful that research was ongoing:

Anonymous via email: "Thanks for doing this research, it is something my members and I talk about all the time"

and some felt they would have wanted to know about this potential effect:

Anonymous on cancer forum: "It would have been nice to have been better informed, or to have some wider acknowledgement".

Psychology specialists were also not aware of ongoing research on chemotherapy-induced cognitive changes, mirrored in the following excerpt from a BBC radio programme, Inside Health, which aired on 5th February 2013 (BBC Radio 4, 2013b):

" Mark Porter: Has much research been done into this area? Clinical Neuropsychologist: Not a lot I'm afraid. I think it's an area that really does cry out for proper research to be carried out so that we can actually disentangle all the various contributing factors."

The patient who raised the issue on this programme admitted to the distress associated with coming forward with these symptoms:

"I just try to cover it up (...) People think that because the treatment has finished, you are fine. That you feel lucky to be alive. They don't realise what you are still going through", while other patients considered it to be the first symptoms of dementia. Thus, apart from being a problem that is not acknowledged, patients who do have cognitive symptoms (or self-report cognitive failures) attach shame and fear to the cognitive symptoms.

After I contacted the programme to inform them of ongoing research at an international level, a new show was aired on 27th February 2013 (BBC Radio 4, 2013a). This time, the spouse of a patient knew about the cognitive side effects of chemotherapy and had sought help from NHS specialists. Despite them being sympathetic, the answer was that there is no available help:

"My wife had chemotherapy for breast cancer in 2008. She was given a leaflet, which mentioned possible memory problems as a side effect. A few months after successful treatment she had memory losses, which worsened. Although her NHS specialist sympathised and gave this the name "chemo-brain" she was unable to do more. After weeks of intensive internet research I discovered that chemo-brain is well known in the USA. In the end we saw a doctor in Maine who assessed her and offered cognitive therapy and agreed to work with a UK counterpart. This was adapted to CBT here and she learned strategies to cope with memory loss. These help her even now when her memory fails. Chemotherapy's prevalence suggests its side effects need more care and attention than a line in a leaflet."

Due to the mixed level of knowledge on this topic, as well as mixed attitudes towards the potential benefits of neuropsychological assessments, running a longitudinal study would have proven difficult. I hope that the studies enclosed within this thesis will

represent another step towards developing targeted interventions for cancer patients, within the framework of longitudinal studies. That is because the main purpose of the field of psycho-oncology is to address the aspects of suffering associated with the cancer diagnosis and treatment. Due to the continuously increasing number of patients successfully treated, the goal has moved beyond assuring survival to assuring the return to a normal quality of life following treatment. Cancer remains a life-limiting and life-threatening illness, thus assuring an adequate quality of life translates into make sure the physical, emotional, cognitive, and social needs of people affected by it are addressed.

Chapter 10. Appendices

10.1. Appendix 1 – Summary of research on paediatric cancers

No.	Article	Drug	Cancer (N)/Age (m)	Evaluation	Design	Quality
1	(Anderson, Smibert, Ekert, & Godber, 1994)	Methotrexate	ALL chemotherapy and cranial irradiation (100) ALL chemotherapy only (50) Healthy controls (100) Age=11.8	Minimum 2 years post-treatment.	Cross-sectional	20
2	(Ashford et al., 2010)	Methotrexate hydrocortisone, cytarabine, dexamethasone	ALL (97) -normal -leukoencephalopathy Age=10	2 years post-consolidation	Cross-sectional	18
3	(Brown et al., 1992)	Methotrexate, cytosine	ALL Recent diagnosis (19)	1-3 months post-diagnosis	Cross-sectional	20

			arabinoside, hydrocortisone, vincristine, prednisone, L-asparaginase, cyclophosphamide, 6-mercaptopurine	1 year post-diagnosis (16) 3 year course treatment (11) Healthy siblings (12) Age=6.9	1 year post-diagnosis 1 year post-therapy		
4	(Brown et al., 1998)	Methotrexate, vincristine, hydrocortisone, cytarabine, 6-mercaptopurine, prednisone	ALL (47) Age =11	2-7 years post-treatment	Cross-sectional	17
5	(Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman,	ALL: Methotrexate, prednisolone,	ALL (34) Wilms tumour (38) Healthy controls (151)	5 year post-treatment	Cross-sectional	17

	2005)	cytarabine, vincristine, L-asparaginase, 6-mercaptopurine, cyclophosphamide, daunorubicin. Wilms: vincristine, actinomycine, antracyclines, ifosfamide, etoposide, carboplatin	Age=10.7			
6	(Buizer, De Sonneville, van den Heuvel-Eibrink, Njiokiktjien, & Veerman, 2005)	Same drugs as previous study	ALL (36) Wilms tumour (39) Healthy controls (110) Age=10.7	6 years post-treatment	Cross-sectional	17

7	(Carey et al., 2007)	Methotrexate	ALL methotrexate over 24 hours (19) Methotrexate over 4 hours (13) Age=7.17	After induction therapy 1 year later	Cross-sectional	21
8	(Carey et al., 2008)	Not reported	ALL (9) Healthy controls (14) Age=15.2	Mean of 5 years post-treatment	Cross-sectional	19
9	(Copeland et al., 1985)	Not reported	ALL chemotherapy (24) ALL with cranial irradiation (25) – not included Mixed diagnoses no irradiation (25) Age=13.83	5 years post- treatment	Cross-sectional	22
10	(Giralt et al., 1992)	Cytosine arabinoside, methotrexate, cranial irradition	ALL chemotherapy (29) ALL with cranial irradiation (25) – not included Solid tumours (22)	3-10 years post- treatment	Cross-sectional	18

			Healthy siblings (24) Age=11.2			
11	(D E Hill, Ciesielski, Sethre-Hofstad, Duncan, & Lorenzi, 1997)	Methotrexate, vincristine, hydrocortisone, cyarabine, 6-mercaptopurine, prednisone.	ALL (10) Healthy controls (10) Age=10.2	3 years post-diagnosis	Cross-sectional	22
12	(Hill, Ciesielski, Hart, & Jung, 2004)	Cytosine arabinoside, hydrocortisone, methotrexate	ALL (10) Healthy controls (10) Age=7.5	Minimum 3 years post-treatment	Cross-sectional	19
13	(N. C. Jansen et al., 2005)	DCLSG ALL 9 Protocol	ALL (50) Healthy siblings (29) Age=7.4	2 weeks after the start of chemotherapy	Cross-sectional	25

14	(Kaemingk, Carey, Moore, Herzer, & Hutter, 2004)	Methotrexate, cytosine arabinoside, hydrocortisone	ALL (15) Healthy controls (15) Age=12.2	4 years post-treatment	Cross-sectional	17
15	(Kaleita, 2002)	Methotrexate, cytarabine, vincristine, prednisone, L-asparaginase, daunomycin, 6-mercaptopurine	ALL (30) Age=62 months	More than 4 years post-diagnosis	Cross-sectional	14
16	(Kingma et al., 2002)	Prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide,	ALL DCLSG-7 (20) ALL DCLSG-5 (17) Norms Age=3.6	2-4 years post-diagnosis	Longitudinal	24

		cytosine-arabinoside, 6-mercaptopurine, methotrexate, ifosfamide, mitoxantrone, dexamethoasone, doxorubicin, 6-thioguanine				
17	(Krappmann et al., 2007)	ALL BFM 95 COALL 06-97 Protocols	ALL (66) Age=7.9	Pre-treatment Post-reinduction	Longitudinal	23
18	(Lesnik, Ciesielski, Hart, Benzel, & Sanders, 1998)	Methotrexate, cytarabine, hydrocortisone	ALL (10) Healthy controls (10) Age= 6.8	At least 3 years post-treatment	Cross-sectional	20
19	(Lofstad, Reinfjell,	NOPHO-ALL	ALL (35)	4-12 years post-	Cross-sectional	21

	Hestad, & Diseth, 2009)	1992	Healthy controls (35) Age=11.5	diagnosis		
20	(Mennes et al., 2005)	Methotrexate, hydrocortisone, cytarabine (EORTC 58881 and 58951)	ALL (23) Healthy controls (23) Age=8.6	2-4 years post-diagnosis	Cross-sectional	18
21	(Moore et al., 2008)	Methotrexate	ALL (26) Low risk(7) Standard risk(13) High risk(6) Age=8.83	Beginning of remission 1 year post-remission	Longitudinal	18
22	(Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000)	Methotrexate, cranial irradiation	ALL with chemotherapy (20) With cranial irradiation (20) not included Healthy controls (21)	2-11 years post-treatment	Cross-sectional	19

			Chronic asthma (21) Age=10.8			
23	(Robinson et al., 2010)	Methotrexate, cytosine arabinoside	ALL (8) Healthy controls (7) Age=14.2	10 years	Cross-sectional	20
24	(Rodgers, Marckus, Kearns, & Windebank, 2003)	UKALL XI protocol	ALL (17) Healthy siblings (17) Age=10.6	5 years post-treatment	Cross-sectional	17
25	(Schatz, Kramer, Ablin, & Matthay, 2000)	Methotrexate common to all patients. Other agents not reported. Cranial irradiation	ALL chemotherapy (9) With cranial irradiation (18) Healthy controls (27) Age=14.1	Minimum 3 years post-treatment	Cross-sectional	18
26	(Schlieper, Esseltine, & Tarshis, 1989)	Methotrexate, cranial irradiation.	ALL chemotherapy (13) Cranial irradiation (17) not included	Minimum 4 years post-diagnosis	Cross-sectional	18

			Healthy controls (23) Age=15.4			
27	(Shah et al., 2008)	Not reported	Hematological malignancies (28) Healthy siblings (28) Age=7.8	1 year 3 years 5 years post-stem cell transplantation	Mixed	19
28	(Simms, Kazak, Golomb, Goldwein, & Bunin, 2002)	Chemotherapy and total body irradiation. Not reported.	Stem cell transplantation patients (47) Age=6.3	2-6 years post transplant	Longitudinal	25
29	(Spiegler et al., 2006)	Methotrexate, vincristine, daunomycin, L-asparaginase, prednisone,	ALL with chemotherapy (32) Cranial irradiation (25) not included Age=13.3	5 years post-diagnosis	Cross-sectional	24

		cytarabine, cyclophosphamide, 6-mercaptopurine, dexamethasone, 6-thioguanine, adriamycin, cranial irradiation				
30	(von der Weid et al., 2003)	Methotrexate, hydrocortisone, cytosine arabinoside, 6-mercaptopurine.	ALL survivors (132) Non-CNS tumour survivors (100) Age=5.1	2 years post-treatment	Cross-sectional	22

Table 23. Studies included in meta-analytical summary of paediatric studies.

10.2. Appendix 2 – Studies included in meta-analysis

No.	Article	Therapy	Cancer(N)/Age (m)	Evaluation	Design	Study quality
1	(Ahles & Saykin, 2002)	Cyclophosphamide, methotrexate, fluorouracil, vincristine, doxorubicin, prednisone, etoposide, carboplatin, procarbazine, bleomycin, etc.	Treated with chemotherapy (breast cancer = 35; lymphoma = 36). Without chemotherapy (breast=35; lymphoma=22) Age=56	5 years post-diagnosis	Cross-sectional	23

2	(Ahles et al., 2003)	Cyclophosphamide, methotrexate, fluorouracil, doxorubicin, vincristine, prednisone, vinblastine, thiotepa, halotestin, carboplatin, taxol.	Breast cancer (51) Lymphoma (29) Age=55.8	4-12 years post-treatment	Cross-sectional	24
3	(Castellon et al., 2004)	Cyclophosphamide, methotrexate, fluorouracil, doxorubicin, taxane, tamoxifen.	Breast cancer with chemotherapy (36) Breast cancer without chemotherapy (17) Healthy group (19)	2-5 years post-treatments	Cross-sectional	27

			Age=48.1			
4	(Collins et al., 2009)	Fluorouracil, epirubicin, cyclophosphamide, doxorubicin, cisplatin, taxols, hormonal therapy.	Breast cancer with chemotherapy (53) Breast cancer without chemotherapy (40) Age=57.7	1 year	Longitudinal	25
5	(Debess, Riis, Engebjerg, & Ewertz, 2010)	Cyclophosphamide, epirubicin, fluorouracil, tamoxifen.	Breast cancer with chemotherapy (75) With tamoxifen (26) Without chemotherapy (19) Healthy controls (208) Age=50.3	Pre-treatment 4 weeks post-treatment	Longitudinal	24
6	(Deprez et al., 2011)	Fluorouracil, epirubicin, cyclophosphamide,	Breast cancer with chemotherapy (17) Without chemotherapy (10)	80-160 days post-chemotherapy	Cross-sectional	23

		taxol, tamoxifen.	Healthy controls (18) Age=44.5			
7	(de Ruiter et al., 2010)	Cyclophosphamide, thiotepa, carboplatin, fluorouracil, epirubicin, tamoxifen	Breast cancer with chemotherapy (19) Without chemotherapy (15) Age=57.2	10 years post-treatment	Cross-sectional	21
8	(Eberhardt et al., 2006b)	Not reported	Younger patients (59). Age=45 Older patients (71). Age=69.1 Hematological or gastrointestinal malignancy	Pre-treatment After first course of chemotherapy (2-8 days after first chemotherapy)	Mixed	19
9	(Eberhardt et al., 2006a)	Not reported	Younger patients (43). Age=44.3 Older patients (34). Age=68.9	Pre-treatment 6 months after the	Mixed	19

			Hematological or gastrointestinal malignancy	start of treatment		
10	(Harder et al., 2002)	Cyclophosphamide, cytosine, etoposide, total body irradiation	Hematological malignancies (40) Age=40.8	22-82 months post-bone marrow transplant	Cross-sectional	19
11	(Hedayati, Alinaghizadeh, Schedin, Nyman, & Albertsson, 2012)	Fluorouracil, epirubicin, cyclophosphomide, doxetaxel, doxorubicin,, hormonal treatment.	Breast cancer with chemotherapy (18) With hormone therapy (45) No chemotherapy (14) Healthy controls (69) Age=56	Pre-diagnosis, post-surgery, pre-adjuvant treatment, 6 months into treatment, 3 months post-treatment	Mixed	24
12	(Hermelink et al., 2007)	Epirubicin, paclitaxel,	Breast cancer pre-treatment (109) Post-treatment (101)	Pre-treatment Towards the end	Longitudinal	30

		cyclophosphamide, methotrexate, fluorouracil, darbepoetin α.	Age=48.6	of treatment (21 days-6 months later)		
13	(Hess et al., 2010)	Not reported	Ovarian cancer pre-treatment (27) 3rd course (26) 6th course (23) Age=59.3	Pre-treatment 3rd course 6th course	Longitudinal	23
14	(Hurria et al., 2006)	Cyclophosphamide, methotrexate, fluorouracil, doxorubicin , paclitaxel, trastumab, hormonal therapy.	Breast cancer pre-treatment (31) Post-treatment (28) Age= 71	Pre-treatment 6 months post-treatment	Longitudinal	27
15	(Iconomou et al.,	Not reported apart	Mixed cancers: breast, coloreclat,	Pre-treatment	Mixed	26

	2008)	from epoetin alpha.	lung, genitourinary, other (50). Age=58.9	12 week later		
16	(Inagaki et al., 2007)	Doxorubicin, cyclophosphamide, methotrexate, fluorouracil, epirubicin, paclitaxel, doxifluridine, carmogur, tegafur/uracil, hormonal and radiation therapy.	One year study: Breast cancer with chemotherapy (51) Breast cancer without chemotherapy (55) Healthy controls (55) Three year study: With chemotherapy (73) Without chemotherapy (59) Healthy controls (37) Age=47.4	1 and 3 years post-treatment	Mixed	24
17	(Jacobsen et al., 2004)	Carboplatin, paclitaxel, doxorubicin,	Ovarian, lung, breast, endometrial, other cancer (77) Age=60	Pre-treatment Before fourth treatment cycle	Longitudinal	27

		cisplatin, docetaxel, etoposide, gemcitabine, cyclophosphamide, and others.				
18	(Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008)	Doxorubicin, cyclophosphamide.	Breast cancer pre-treatment (32) Post-treatment (30) Age=49.6	Pre-treatment 1 week post-treatment 6 months post-treatment	Longitudinal	27
19	(Jansen, Cooper, Dodd, & Miaskowski, 2010)	Doxorubicin, cyclophosphamide, taxane.	Breast cancer pre-treatment (71) 2 weeks post-chemotherapy (66) 1 week post-taxane (42) 6 months post-treatment (67) Age=50.3	Pre-treatment 2 week post-chemotherapy 1 week post-taxane 6 months post-	Longitudinal	28

				treatment		
20	(Jenkins et al., 2006)	Fluorouracil, epirubicin, cyclophosphamide, methotrexate, doxorubicin, paclitaxel.	Breast cancer with chemotherapy (85) With hormonal/radiotherapy (43) Healthy controls (49) Age=54.10	Pre-treatment 6 months post-treatment 18 months post-treatment	Mixed	24
21	(Jim et al., 2009)	Doxorubicin, cyclophosphamide, doxetaxel, paclitaxel, methotrexate, fluorouracil, epirubicin; hormonal treatment.	Ductal carcinoma or breast cancer (187) Healthy controls (187) Age=41-61	6 months post-treatment	Cross-sectional	24
22	(Kesler, Bennett,	Cyclophosphamide,	Breast cancer (14)	6 months post-	Cross-	21

	Mahaffey, & Spiegel, 2009)	methotrexate, fluorouracil, doxorubicin, taxol.	Healthy controls (14) Age=54.6	treatment	sectional	
23	(Kreukels et al., 2005)	Cyclophosphamide, methotrexate, fluorouracil, tamoxifen, radiotherapy.	Breast cancer with chemotherapy (26) Without chemotherapy (23) Age=52.3	3-5 years post-treatment	Cross-sectional	23
24	(Kreukels et al., 2006)	Cyclophosphamide, thiotepa, carboplatin, etoposide, fluorouracil, tamoxifen, radiotherapy	Breast cancer high dose (17) Standard dose (23) No chemotherapy (39) Age=51.9	4 years post-treatment	Cross-sectional	23
25	(Mehlsen, Pedersen,	Cyclophosphamide,	Breast cancer (34)	Pre-treatment	Mixed	23

	Jensen, & Zachariae, 2009)	epirubicin, fluorouracil, tamoxifen.	Cardiac patients (12) Healthy controls (12) Age=46.1	2-6 weeks post-treatment Cardiac: 3 months later Controls: 12-16 weeks later		
26	(Meyers, Byrne, & Komaki, 1995)	Cisplatin, ifosfamide, etoposide, radiotherapy	Small cell lung cancer with chemotherapy (25) Without chemotherapy (21) Age=54.8	Pre-treatment group Post-treatment and before cranial irradiation group.	Cross-sectional	23
27	(Pedersen et al., 2009)	Bleomycin, etoposide, cisplatin, radiotherapy	Testicular cancer chemotherapy (36) No chemotherapy (36) Age=40.1	2-7 years post-treatment	Cross-sectional	24
28	(Quesnel, Savard, &	Doxorubicin,	Breast cancer chemotherapy (41)	Pre-chemotherapy	Mixed	26

	Ivers, 2009)	cyclophosphamide, fluorouracil, etoposide, taxotere, hormonal therapy	No chemotherapy (40) Age=52.7	Pre-radiotherapy Post-treatment (34-38 days) 3 months follow-up		
29	(Reid-Arndt et al., 2010)	Doxorubicin, cyclophosphamide, paclitaxel, taxotere	Breast cancer: 6 months (39) 12 months (33) Age=53.3	6 months post-treatment 12 months post-treatment	Longitudinal	21
30	(Schagen et al., 1999)	Cyclophosphamide, methotrexate, fluorouracil, tamoxifen. radiotherapy	Breast cancer with chemotherapy (39) No chemotherapy (34) Age= 46.6	2 years post-treatment	Cross-sectional	24
31	(Scheibel et al., 2004)	Interferon alpha, cytosine	Chronic myelogenous leukemia (30)	Pre-treatment 14-43 weeks	Longitudinal	22

		arabinoside, hydroxyurea	Age=46	within treatment		
32	(Scherwath et al., 2006)	Epirubicin, cyclophosphamide, methotrexate, fluorouracil, thiotepa, mitoxantrone, tamoxifen	Breast cancer with chemotherapy (47) Without chemotherapy (29) Age=53.2	5 years post-treatment	Cross-sectional	24
33	(C. M. Schilder et al., 2009)	Doxorubicin, cyclophosphamide, tamoxifen, exemestane	Breast cancer with chemotherapy (80) Healthy controls (48) Age=58.8	2 years post-treatment	Cross-sectional	28
34	(V Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005)	Fluorouracil, etoposide, cyclophosphamide,	Breast cancer with chemotherapy (50) Healthy controls (43)	Pre-treatment 6 months post-treatment	Mixed	27

		methotrexate, doxorubicin, docetaxel	Age=51.7			
35	(Small et al., 2011)	Doxorubicin, cyclophosphamide, methotrexate, taxane, fluorouracil	Breast cancer with chemotherapy (72) Without chemotherapy (58) Healthy controls (204) Age=55.07	6 months post-treatment	Cross-sectional	25
36	(Stewart et al., 2008)	Fluorouracil, epirubicin, cyclophosphamide, doxorubicin, cisplatin, taxol, hormonal therapy	Breast cancer with chemotherapy (61) Without chemotherapy (51) Age=57.7	Pre-treatment 2 months post-treatment	Mixed	27
37	(Tager et al., 2010)	Doxorubicin, cyclophosphamide,	Ductal carcinoma or breast cancer with chemotherapy (30)	Pre-treatment 1 months post-	Mixed	25

		docetaxel/paclitaxel, cytoxan, methotrexate, fluorouracil, hormonal therapy	Without chemotherapy (31) Age=60.7	treatment 6 months post-treatment		
38	(van Dam et al., 1998)	Cyclophosphamide, epirubicin, fluorouracil, thiotepa, carboplatin, radiotherapy	Breast cancer with chemotherapy (70) Without chemotherapy (34) Age=46.5	2 years post-treatment	Cross-sectional	24
39	(Vearncombe et al., 2009)	Fluorouracil, epirubicin, cyclophosphamide, doxorubicin, methotrexate, taxol,	Breast cancer with chemotherapy (138) Without chemotherapy (21) Age=49.3	Pre-treatment 1 month post-treatment	Mixed	28

		taxotere.				
40	(Wefel et al., 2004)	Fluorouracil, doxorubicin, cycloposphamide, methotrexate, vinblastine	Breast cancer (18) Age=45.4	Pre-treatment 3 weeks post-treatment 12 months post-treatment	Longitudinal	29
41	(Wefel et al., 2010)	Fluorouracil, doxorubicin, cyclophosphamide, paclitaxel, radiotherapy	Breast cancer (42) Age=48.8	Pre-treatment 2 months post-treatment 7 months post-treatment 13 months post-treatment	Longitudinal	25
42	(Whitney et al., 2008)	Cisplatin, etoposide, radiotherapy	Non-small cell lung cancer (14) Age= 60.2	Pre-treatment 1 and 7 months post-treatment	Longitudinal	24

| 43 | (Wieneke & Dienst, 1995) | Cyclophosphamide, methotrexate, fluorouracil, doxorubicin, tamoxifen | Breast cancer (28) Age= 42 | 0.5 – 12 months post-treatment. | Cross-sectional | 20 |
| 44 | (Yoshikawa et al., 2005) | Cyclophosphamide, methotrexate, fluorouracil, tegafur/uracil, doxorubicin,doxifluridine, carmofur, tamoxifen, radiotherapy | Breast cancer with chemotherapy (44) Without chemotherapy (31) Age=48.2 | Assessed 3 years post-treatment | Cross-sectional | 11 |

Table 24. Summary of studies included in meta-analysis of studies with adults.

10.3. Appendix 3 - Characteristics of words used in memory task

List	Word	Familiarity	Kucera-Francis Frequency
Animals & Vehicles	Camel	421	1
	Helicopter	0	1
	Motorcycle	0	0
	Elephant	459	7
	Bicycle	0	5
	Butterfly	481	2
	Donkey	0	1
	Lion	511	17
	Train	548	82
	Plane	558	114
	Snail	489	1
	Rabbit	523	11
	Sheep	507	23
	Bear	526	57
	Ostrich	358	0
	Horse	560	117
	Sledge	0	0
	Squirrel	511	1
	Giraffe	381	0
	Swan	0	3
	Fish	548	35
	Kangaroo	0	0
	Goat	469	6
	Zebra	333	1
Fruits & Clothes	Dress	588	67
	Watermelon	0	0
	Mitten	0	0
	Jumper	0	1
	Strawberry	539	0
	Pear	567	6
	Apple	598	9
	Trousers	0	7
	Pineapple	489	9
	Orange	567	23
	Lemon	518	18
	Grapes	0	0
	Cherry	514	6
	Glove	575	9
	Necklace	536	3
	Banana	576	4

	Shoe	569	14
	Ring	589	47
	Belt	550	29
	Boot	566	13
	Skirt	551	21
	Sock	578	4
	Umbrella	511	8
	Tomato	574	4
Vegetables & Kitchen objects	Asparagus	534	1
	Carrot	539	1
	Spoon	612	6
	Fridge	0	0
	Corn	548	34
	Glass	611	99
	Table	599	198
	Iron	555	43
	Scissors	559	1
	Toaster	520	0
	Chiar	617	66
	Oven	577	7
	Mushroom	0	2
	Onion	550	15
	Pepper	554	13
	Potato	612	15
	Kettle	551	3
	Knife	573	76
	Ladder	507	19
	Bottle	591	76
	Pumpkin	0	2
	Broom	547	2
	Stool	531	8
	Lettuce	565	0
Four-legged animals and Musical instruments	Alligator	442	4
	Deer	509	13
	Frog	507	1
	Horn	498	31
	Leopard	431	0
	Violin	468	11
	Monkey	531	9
	Accordion	394	1
	Turtle	509	8
	Racoon	0	0
	Trumpet	490	7
	Bull	0	14

	Ferret	0	1
	Guitar	550	19
	Rhinoceros	400	3
	Flute	496	1
	Gorilla	554	0
	Seal	482	17
	Harp	430	1
	Piano	545	38
	Tiger	513	7
	Beaver	470	3
	Skunk	519	0
	Drum	506	11
Birds and Toys	Chicken	544	37
	Sailboat	0	0
	House	600	591
	Penguin	360	0
	Rooster	385	3
	Swing	0	24
	Sparrow	523	0
	Parrot	0	1
	Crow	490	2
	Wagon	443	55
	Football	565	36
	Eagle	465	5
	Skate	534	1
	Duck	529	9
	Dove	415	4
	Whistle	505	4
	Balloon	520	10
	Cannon	498	7
	Clown	511	3
	Stork	393	0
	Kite	481	1
	Truck	620	57
	Pigeon	499	3
	Snowman	0	0

Table 25. Characteristics of words used in memory task.

10.4. Appendix 4 - NHS Ethics approvals

10.4.1. Research ethics committee – Study approval letter

23 May 2011

Dear Ms Mereuta

Study title: **Chemotherapy-induced changes in cognitive function in young adults**

REC reference: **11/NW/0185**

Thank you for your email dated 06 May 2011 responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter	1	14 March 2011
Covering Letter	Email	06 May 2011
Evidence of insurance or indemnity	University of Manchester	16 March 2011
GP/Consultant Information Sheets	3	22 March 2011
GP/Consultant Information Sheets	2 - Letter	22 March 2011
Investigator CV	Oana Mereuta	16 March 2011
Investigator CV	Deborah Talmi	
Letter from Sponsor	University of Manchester	16 March 2011
Other: Explanation of point 4 in Prov Op	1	04 May 2011
Participant Consent Form: Patients	4	04 May 2011
Participant Consent Form: Controls	5	04 May 2011
Participant Information Sheet: Patients	5	04 May 2011
Participant Information Sheet: Controls	6	04 May 2011
Protocol	2	14 March 2011
Questionnaire: Wechsler Adult Reading Test	Validated	
Questionnaire: WAIS-Digit Span	Validated	
Questionnaire: D-KEFS Trail Making Test	Validated	
Questionnaire: Stroop	Validated	
Questionnaire: COWA	Validated	
Questionnaire: D2 Concentration-Endurance	Validated	
Questionnaire: BMIPB-Memory Test	Validated	
Questionnaire: TOMM - Effort Test	Validated	
Questionnaire: HADS	Validated	
Questionnaire: IPQ	Validated	
Questionnaire: FQ	Validated	

| REC application | 3.1 | 16 March 2011 |
| Response to Request for Further Information | 1 | 06 May 2011 |

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

> Notifying substantial amendments
> Adding new sites and investigators
> Progress and safety reports
> Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

| **11/NW/0185** | **Please quote this number on all correspondence** |

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Peter Klimiuk

10.4.2. Research ethics committee approval – Amendment 1

Dear Ms Mereuta

Study title: Chemotherapy-induced changes in cognitive function in young adults

REC reference: 11/NW/0185

Amendment number: 1

Amendment date: 10 April 2012

 The above amendment was reviewed by the Sub-Committee in correspondence.

Changes to Protocol to increase recruitment, add new participant groups and extend the

end of the study

Ethical opinion

 The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

 Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	1	10 April 2012
Summary of changes	1	20 February 2012
Protocol	3	20 February 2012
Participant Information Sheet: Survivor	1	02 March 2012
Participant Information Sheet: Controls	5	02 March 2012
Participant Consent Form: Survivor	1	02 February 2012
Participant Consent Form: Controls	3	21 February 2012
Questionnaire: Cognitive Failures	Validated	
Questionnaire: EORTC INFO25	Validated	
Questionnaire: EORTC QOL Core	Validated	
Advertisement	1	05 April 2012
Leaflet	1	02 March 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/NW/0185:   Please quote this number on all correspondence

10.4.3. Research ethics committee approval – Amendment 2

11 October 2012

 Dear Ms Mereuta

Study title: Chemotherapy-induced changes in cognitive function in young adults
REC reference: 11/NW/0185
Amendment number: 2 (Modified)
Amendment date: 19 September 2012

Thank you for submitting the above amendment, which was received on 21 September 2012. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 30 August 2012 refers).

The modified amendment was reviewed by the Sub Committee in correspondence. A list of the members who took part in the review is attached.

Ethical opinion
 I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents
The documents reviewed and approved are:

Document	Version	Date
Covering letter	Email	21 September 2012
Protocol	4	19 September 2012
Participant Information Sheet: Consultant	4	19 September 2012
Participant Information Sheet: Control	7	19 September 2012
Participant Information Sheet: Post Treatment	2	19 September 2012
Participant Information Sheet: Pre Treatment	6	19 September 2012
Participant Consent Form: Control	6	19 September 2012

Participant Consent Form: Post Treatment	2	19 September 2012
Participant Consent Form: Pre Treatment	5	19 September 2012
Advertisement	1	19 September 2012
Modified Amendment 2 (Modified)		19 September 2012

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/NW/0185:   Please quote this number on all correspondence

10.4.4. Post-treatment Participant Information Sheet

Project no
11/NW/0185

VERSION 2, 19 September 2012

Title of Project: Chemotherapy-induced changes in cognitive function

Researcher: Oana Mereuta

We would like to invite you to take part in a research study that is conducted at the University of Manchester. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully, and ask us if there is anything that is not clear or if you would like more information. Talk to others about the study if you wish, and take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of this study?

Some previous studies have shown evidence that some chemotherapy drugs may affect memory. However, it is not very clear yet which drugs are responsible and there have never been any studies done in young adults. This study is trying to work out if the chemotherapy you received has any effect on your memory. Memory can be affected by many things so in order to do the study properly we also need to assess such things as your ability to concentrate and to solve problems.

Why have I been invited?

We are inviting cancer patients, survivors, and healthy people of the same age to take part in this study.

As a former cancer patient, you must:

- Be between 16 and 50 years old;

- Have been diagnosed with a sarcoma, lymphoma, breast or germ cell tumour;

- Have finished treatment between 6 months and 5 years ago;

- Have no previous history of brain injury, mental health problems, or substance abuse;

- Be a proficient English speaker.

You will NOT be able to take part if you:

- Received radiotherapy to your brain or hormonal therapy (other than the oral contraceptive pill);

- Are taking drugs that may affect your concentration or mood (e.g., antidepressants, benzodiazepines, anticonvulsants);

- Have a history of brain injury, mental health problems or substance abuse;

- Are not a proficient English speaker.

Because of the different treatment protocol, former breast cancer patients will be able to take part even if they received endocrine therapy on the course of the treatment, as long as it did not include cranial radiation.

If you agree to take part the researcher will ask you if you have a friend, relative or colleague of a similar age who might agree to take part in the study as a 'control' who is has not received chemotherapy. With your permission he/she will be contacted to ask if he/she would like to take part in the study.

Do I have to take part?

You do not have to take part in the study. If you decide to take part and then later change your mind, either before you start the study or during it, you can withdraw without giving your reasons.

What will happen to me if I take part?

If you agree to participate the following will happen:
1. We will ask for your consent to this study and answer any of your questions while you are in hospital. We will ask for your consent to this study and answer any of your questions while you are in hospital. For patients who are not in the hospital consent will be obtained either at the university or at home.
2. We will test your memory by showing you a set of words and asking you to recall them immediately and then again 24 hours later. We will do this on 3 separate occasions, 24 hours apart. You can either be at home, hospital, or come to the university building for these tests. Each test will take approximately 10 minutes.

3. Your memory can be affected by many other things such as anxiety, emotions, or how tired you are. To make sure that your memory test has not been affected by these factors we will carry out a variety of other tests, looking at things like your anxiety level, your emotional state, your attention, and how tired you are. All the tests take about 90 minutes, but they can be divided into 3 sessions (modules).

The first module will be given to you when you agree to take part in the study. The other 2 modules will be planned at a time of your convenience. You are free to take breaks between any parts of these modules and if you find them too much effort to complete at the time, they can be organized for a later date, or cancelled.
It is preferable these tests take place in the hospital or in the university building, but if needed the chief investigator can also administer these tests at your own home.

We will also ask a member of your clinical team to give us information on your diagnosis and on your treatment regime.

Expenses and payments

You will not receive any money for your participation. However, if you need to be in hospital on additional days to carry out the tests we will reimburse you for your travel. For this, you will need to provide the receipts of the travel expenses.

What are the possible benefits of taking part?

You are not likely to benefit directly as a result of taking part in this study. However, it is important for us to find out if your chemotherapy regime has a tendency to affect memory so that we and others can begin to explore how such effects could be reduced for future patients.

What are the possible disadvantages and risks of taking part?

It is possible that you feel too tired we can reschedule the testing for a later time when you are feeling better. Some of the information we are collecting related to your emotional status might feel too sensitive. If that is the case, you are free to refuse completion of the test; however your results will remain confidential.

Will my taking part in the study be kept confidential?

Your name and contact details will appear only on the consent form, which will be stored in a locked office at the University of Manchester, separately from all other data you provide. Once you sign consent we will allocate you a study number and all other data obtained as part of the study will be linked to your study number. Only the research team will be able to link your identifiable data to your study number. No identifiable data will appear in any publications.
The data will be accessible only to the research team, but may also be looked at by individuals from the University of Manchester, and regulatory authorities, for monitoring and auditing purposes, and this may well include access to personal information.

What happens when the research study stops, and what will happen to the results?

The results of this study will be published in peer-reviewed scientific journals, but you will in no way be identifiable from such publications. When the results are published we would be happy to send you a copy of the publication if you wish.

Who is organising and funding the research?

The research is organized and funded by the Medical Research Council.

Who has reviewed the study?

The study has been reviewed and approved by the National Research Ethics Service Committee North West – Greater Manchester North, REC reference 11/NW/0185.

What if there is a problem?

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact the University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to research-governance@manchester.ac.uk

Further information and contact details

For further information please contact Oana Mereuta, School of Psychological Sciences, University of Manchester, Oxford Road, M139PL, Manchester. Email: oana.mereuta@postgrad.manchester.ac.uk. Telephone: +44 (0)1612752692.

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