Lifting the fog on ‘chemobrain’: 
a prospective cohort study of chemotherapy-related 
cognitive changes in women with early breast cancer.

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Declaration

This thesis is an account of research undertaken at the Research School of Psychology, the Australian National University. Unless otherwise stated, the work presented in this thesis is my own.

Rachel Lacey
February 2014
Acknowledgements

In a clinical PhD journey as long as this one, there are many people who I need to acknowledge for their contributions at different stages of this journey.

Sixteen years ago I was working at the ACT Cancer Society in my last trimester of pregnancy when, in the tearoom, I was laughing at the number of pens I had mislaid that week. Women from the breast cancer support group shared some of the memory changes they had experienced following chemotherapy. One younger woman told me she had forgotten to pick up her children from school; something she would never have done before. They related how their doctors had mainly been dismissive of these concerns. While this memory loss may have been due to distress, it struck me as not your everyday 'pen' type of forgetting, and prompted me many years later to want to investigate these problems. I would like to sincerely thank these women for sharing their personal stories.

I want to deeply thank all the women who participated in this study and gave so generously of their time at such a difficult period in their lives and who trusted me with their assessment and experiences and who, against all odds, kept coming back. This research could not have been done without their amazing effort. I also believe their perspective played no small part in making me remember to hold on to what was important throughout the challenges of a clinical PhD so that I have a family still talking to me at the end of it.

I would also like to acknowledge all the surgeons, oncologists, clinical nurse consultants and cancer care staff who gave thoughtful advice, patiently answered questions, responded enthusiastically and provided referrals. Especially notable support came from Dr Desmond Yip, Dr Noel Tait and the Calvary breast care nurses (Beth, Bethany and Melva).

I am indebted to my primary clinical supervisor, Professor Don Byrne, for his consistent support, his heroic efficiency with feedback and his astute advice. I would also like to thank my prodigal neuropsychological supervisor, Dr Anne Aimola Davies, for her invaluable input and insights and for returning home to Oz after four years in Oxford. I understand this thesis was not part of the decision-making equation but it was much appreciated nonetheless. I would like to express my appreciation to my statistical advisor,
Pauline Ding, for her guidance and for reminding me that I was not doing a statistics PhD whenever I strayed off course.

This research could not have been conducted without the financial assistance provided by the Research School of Psychology. I also appreciate the travel support, along with the financial assistance from Hurricane Voices, which allowed me to participate in the Venice workshop and meet other researchers in the field, a highlight in this journey. I have to acknowledge those who gave advice in the early stages, including Professors Michael Smithson and Robin Stuart Harris, as well as those who helped along the way with their neuropsychological expertise, Dr Phillipa Butcher and Vanessa Rawson.

I am lucky to have such wonderful friends and family who have kept up a supply of Tim Tams or words of support in the last months. This thesis ended up being written after work surrounded by the noise, love and demands of family and many a time I wondered whether there was such a thing as 'thesisfog'. It made me appreciate, if chemotherapy can affect cognitive functioning, how exponentially harder it would have been, not only to complete this, but to respond to the demands of everyday life. I am thankful for the love of our wonderful children, Liam, Seamus, Tegan and Emily, and their partners, Kirsty, Carla, Brody (and b/f Morgan!), and for our first beautiful grandchild, Eva. I am so proud of you all and thankful to have shared in all the milestones in your lives during this journey, including first relationships, heartbreaks, first jobs, study, graduations, travel, university, moving out of home (and back again), work, friends, love, career changes, marriage and starting a family. I want to thank my daughter, Emily, for brightening this journey at all the darkest points and for being such a grounding influence. I appreciate her asking me in the harrowing first months of juggling coursework, clinical internship and research, if I could make "a time to play" on the weekend. It made me put on the brakes and try to make this a more balanced journey. Recently she asked to make a time to go on a roadtrip, which has made me put on the accelerator to finish!

I want to thank my extraordinary parents for their lifetime of love and support and for their tireless proofreading; and for probably being two of the few people who will ever read this thesis in its entirety. Bless you!

Finally, I want to profess my profound gratitude and love to my wonderful, steadfast and loving husband, David, for his continuous encouragement, tireless support, his humour throughout the years of study and for holding the fort at home (and the 30 pieces of ceiling!) in these last months. This could not have been done without you.
Abstract

The purpose of this prospective study was to evaluate whether women treated with chemotherapy for early breast cancer would show significantly poorer cognitive functioning following treatment than women not treated with chemotherapy. A comprehensive clinical neuropsychological assessment designed to be sensitive to mild cognitive impairment and change in six cognitive domains was conducted in order to uncover any profile of chemotherapy-related cognitive impairment.

Women with early breast cancer scheduled to receive adjuvant chemotherapy completed a detailed assessment: before commencing chemotherapy (Time 1: n = 30); after completing chemotherapy (Time 2: n = 30); and again 9 months later (Time 3: n = 29). A control group of women with early breast cancer not receiving chemotherapy were tested at matched timepoints (Time 1: n = 15; Time 2: n = 16; Time 3: n = 16).

Prior to the group analysis, a multivariate statistical approach called Principal Components Analysis (PCA) was used to examine the entire set of relationships among neuropsychological outcome measures within a cognitive domain. This enabled the underlying dimensions that explain the correlations among the set of measures to be identified. From this a smaller set of neuropsychologically meaningful summarized outcome measures were derived, using the first principal component summary score, for use in subsequent analyses involving ANOVA and regression.

Two approaches were used for the analyses of individual deficits. For the first, individual test scores were screened for 'cognitive complications' at each timepoint, defined as a score of more than 2 standard deviations (SD) below the mean of age-standardized normative data for each test. An overall 'lower than expected performance' score was also calculated for each individual from the mean of all scores that were ≤1.5 SD below their estimated premorbid intelligence.

Findings from the group analyses provided limited support at the 95% confidence level for the hypothesis that women treated with chemotherapy would demonstrate significantly worse cognitive functioning over a 9-month post treatment follow-up period relative to women not treated with chemotherapy for breast cancer. Only verbal recall discriminability, derived from new more sensitive measures of verbal recall accuracy and
discrimination, displayed a significant interaction effect. However, when groupings with interaction effects that showed trends towards significance were examined, a subtle profile of chemotherapy-related cognitive impairment was revealed within verbal learning and memory, and executive functions. This trend was not found at the domain level of executive functions but was revealed at the nested subgroup level, namely in verbal fluency, flexibility and reasoning, and visual cognitive flexibility. Factors that increased the vulnerability of women to decline at Time 3 included lower premorbid IQ, clinical anxiety or mood disorders at Time 1, hormonal therapy following chemotherapy, and chemotherapy-induced adverse events, such as neutropenia.

For the first time in a prospective study the results of the group analyses were supported by the findings from the individual analyses.

The current study unveiled a complex interaction of pre-treatment cognitive reserve and cognitive resilience with chemotherapy-related cumulative threshold effects on cognitive outcome following chemotherapy. The cognitive reserve threshold appears to be lowered by the cumulative effects of chemotherapy and acute adverse events, like neutropenia, and hormonal therapy, but individual threshold differences are moderated by cognitive reserve and cognitive resilience.
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## Glossary

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<th>Name</th>
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<tbody>
<tr>
<td>AC</td>
<td>Doxorubicin/ cyclophosphamide</td>
</tr>
<tr>
<td>AI</td>
<td>Aromatase inhibitor</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>CAF</td>
<td>Cyclophosphamide/ doxorubicin/ 5-fluorouracil</td>
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<tr>
<td>CANTAB</td>
<td>Cambridge Neuropsychological Test Automated Battery</td>
</tr>
<tr>
<td>CFT</td>
<td>Complex Figure Test</td>
</tr>
<tr>
<td>CMF</td>
<td>Cyclophosphamide/ methotrexate/ 5-fluorouracil</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COWAT</td>
<td>Controlled Oral Word Association Test</td>
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<tr>
<td>D-KEFS</td>
<td>Delis-Kaplan Executive Function System</td>
</tr>
<tr>
<td>DSSP</td>
<td>Digit Supraspan</td>
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<tr>
<td>FEC</td>
<td>5-Fluorouracil/ epirubicin/ cyclophosphamide</td>
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<tr>
<td>HVLT</td>
<td>Hopkins Verbal Learning Test</td>
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<tr>
<td>HRQL</td>
<td>Health-related Quality of Life</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NART-2</td>
<td>National Adult Reading Test – Second Edition</td>
</tr>
<tr>
<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
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<tr>
<td>PCA</td>
<td>Principal components analysis</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>RAVLT</td>
<td>Rey Auditory Verbal Learning test</td>
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<tr>
<td>TAC</td>
<td>Docetaxel / doxorubicin/ cyclophosphamide</td>
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<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
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<tr>
<td>VPA&lt;sub&gt;n&lt;/sub&gt;</td>
<td>Verbal Paired Associates (names)</td>
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<tr>
<td>WAIS-III</td>
<td>Wechsler Adult Intelligence Scale – Third Edition</td>
</tr>
<tr>
<td>WCST</td>
<td>Wisconsin Card Sorting Test</td>
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<tr>
<td>WRAT</td>
<td>Wide Range Achievement Test</td>
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Chapter 1

Introduction

1.1 Background

Breast cancer is the most common cancer diagnosed among adult Australian women\(^1\). An average of 37 women are diagnosed every day in Australia with breast cancer\(^2\) and 1 in 11 women will be diagnosed with breast cancer before the age of 75 [Australian Institute of Health and Welfare [AIHW], 2012]. Between 1982-2008 the number of new breast cancers more than doubled from 5310 new cases to 13,567. The increase in the age-standardized breast cancer rate among all Australian women from 81 per 100,000 in 1982 to 115 per 100,000 in 2008 is likely due to the introduction of the national breast-screening program (known today as 'BreastScreen Australia'). With an increasing and ageing population, the number of women diagnosed with breast cancer is expected to rise in the future, with a projected 17,210 new breast cancer cases in 2020, equating to 47 women being diagnosed each day.

Although the incidence of breast cancer is increasing, the age-standardized mortality rates are declining, from 31 deaths per 100,000 women in 1988 to 22 deaths per 100,000 women in 2007. Between 1982-1987 and 2006-2010, the 5-year relative survival increased significantly from 72% to 89% (AIHW, 2012). These gains are associated with a combination of widespread mammographic screening improving early detection coupled with the initiation of adjuvant systemic therapies that have reduced the risk of recurrence and improved disease-free survival. At the end of 2008, 159,325 women in Australia were alive who had been diagnosed with breast cancer in the previous 27 years. Breast cancer survivors are now one of the largest survivor groups in the cancer community. As a result, the traditional goal for treatment to achieve a reduction in short-term mortality has been challenged. The new challenge is what survival from breast cancer means and whether cancer care management would change if more were known about survivors' long-term outcomes and quality of life (QOL) (Ebbs, Fallowfield, Fraser, & Baum, 1989; Fallowfield, 2002; Fallowfield, Hall, Maguire, & Baum, 1990).

---

1 Based on AIHW (2012) review of registrable cancers. This excludes non-melanocytic skin cancer as incidence data is not routinely collected.
2 Based on statistics from the AIHW (2012) reporting approximately 13,500 women are diagnosed with breast cancer in one year (2008).
With the more widespread use of chemotherapy as a systemic adjuvant treatment for breast cancer, there have been increasing numbers of complaints from women with breast cancer of memory and concentration problems during, following and even years after completion of treatment (Tannock, Ahles, Ganz, & Van Dam, 2004). These complaints have been coined 'chemofog' or 'chemobrain' by breast cancer survivors (Raffa et al., 2006; Wefel et al., 2004). The problems being reported are mainly in word-retrieval, memory loss, lack of concentration and multi-tasking. With increasing numbers of newly diagnosed breast cancer patients receiving adjuvant chemotherapy and becoming long-term breast cancer survivors, more emphasis is being placed on recognizing and reducing side effects associated with treatment that may affect long-term QOL. Cognitive functioning is closely connected with the central dimensions of QOL, such as independence and social functioning, and over the past two decades studies have begun to systematically investigate these complaints.

1.2 Definitions

1.2.1 Health-related Quality of Life

Quality of life (QOL) is rooted in the World Health Organization definition, which specifies "health is a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity\(^3\)" (World Health Organization [WHO], 1948). Spilker (1996) suggested that QOL is a multidimensional concept comprising five major domains:

- Physical status and functional abilities;
- Psychological status and well-being;
- Social interactions;
- Economic and/or vocational status and factors; and
- Religious and/or spiritual status.

As this conceptualization of QOL is broad, health care researchers commonly restrict their focus to the first three of these dimensions, using the term 'health-related quality of life' (HRQL). Health-related quality of life has been defined as the extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition.

---

\(^3\) Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19 June - 22 July 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.
or its treatment (Cella, 1995). The physical domain contains physical complaints, and the capability to perform activities. Complaints can be symptoms (pain, nausea), whereas activities concern a wide range of aspects like mobility and eating. Cognitive functioning (memory, orientation) and emotion (anxiety, depression) are elements of the psychological domain. The extent and quality of social contacts and activities (work, hobbies) are aspects of social function. While HRQL was first advocated as a relevant primary endpoint in late-stage or palliative cancer (Tannock, 1987), it is only in the last decade, as the ranks of long-term breast cancer survivors increase, that attention is being directed to the study of factors related to treatment that might compromise QOL.

1.2.2 Early breast cancer

Early breast cancer refers to breast cancer in the early, operable, non-metastatic stages. It has been defined as tumours of not more than 5 centimetres in diameter, with either impalpable or palpable but not fixed lymph nodes, and with no evidence of distant metastases (T1-2, N0-1, M0) (Haskell & Berek, 2001). Prior to adjuvant chemotherapy, surgery (either lumpectomy and/or mastectomy) has been performed and there is no detectable cancer present. In this thesis, where participants are described as women with early breast cancer this refers to women having been diagnosed and treated for early breast cancer.

1.2.3 Adjuvant therapy

Adjuvant therapy is any treatment given after primary treatment to reduce the risk of recurrence and increase the chance of long-term survival. Primary treatment is the main therapy used to reduce or eliminate the cancer. Surgery is the primary treatment for early breast cancer. Adjuvant therapy for early breast cancer includes radiation therapy, chemotherapy and/or hormonal therapy. Oncologists review prognostic factors, including age, cancer pathology, hormone receptor status and surgical margins, in order to provide recommendations regarding whether and which adjuvant treatment would likely have added benefit.

1.2.4 Local and systemic therapies/treatment

Breast cancer treatments are defined as local/localized or systemic. Surgery and radiation therapy are considered local therapies because they directly target the tumour, breast, lymph nodes or other specific regions. Drug treatments are systemic because they use substances that travel through the bloodstream to affect the whole body. One of the most
important advances in breast cancer control has been its treatment as a systemic disease. The use of systemic adjuvant therapy involves chemotherapy and/or hormonal therapy after surgery to treat any undetectable remaining cancer. These drugs work in different ways. Hormonal therapy uses drugs that manipulate hormone production in the body in order to deprive breast cancer cells of the hormone oestrogen, which many breast cancers need to grow. Chemotherapy uses cytotoxic drugs that kill faster growing cells, like cancer cells.

1.2.5 Adjuvant chemotherapy

Adjuvant chemotherapy is the use of cytotoxic drugs administered after surgery to help eliminate any residual undetectable cancer cells and reduce the risk of recurrence. Evidence has shown that combination chemotherapy (chemotherapy with multiple drugs used in combination) is more effective than single chemotherapeutic agents alone (National Health and Medical Research Council [NHMRC], 2001). Adjuvant chemotherapy is now offered to a significant proportion of women with early breast cancer, especially those with higher risk of recurrence, such as node-positive disease. This is a rapidly evolving area of knowledge and many new chemotherapy agents are in trial or are being used in different combination regimens. Standard-dose chemotherapy regimens used for early breast cancer over the course of the study are presented in Table 1.1.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Abbreviation</th>
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<tr>
<td>Cyclophosphamide/ methotrexate/ 5-fluorouracil</td>
<td>CMF</td>
</tr>
<tr>
<td>5-Fluorouracil/ epirubicin/ cyclophosphamide</td>
<td>FEC</td>
</tr>
<tr>
<td>Doxorubicin/ cyclophosphamide</td>
<td>AC</td>
</tr>
<tr>
<td>Cyclophosphamide/ doxorubicin/ 5-fluorouracil</td>
<td>CAF</td>
</tr>
<tr>
<td>Docetaxel / doxorubicin/ cyclophosphamide</td>
<td>TAC</td>
</tr>
<tr>
<td>Doxorubicin/ cyclophosphamide -&gt; paclitaxel/ docetaxel</td>
<td>AC -&gt; P; AC -&gt; T</td>
</tr>
<tr>
<td>AC based regimen -&gt; trastuzumab (Herceptin)³</td>
<td>-&gt; H</td>
</tr>
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</table>

³ Only used for HER2-positive breast cancers.

Major changes have taken place in the chemotherapeutic treatment of patients with early breast cancer in recent years based on systematic reviews of clinical trials and clinical practice guidelines. There are surprisingly few data available on the numbers or trends in the use of specific types of chemotherapy regimens administered for early breast cancer.
One study from the Netherlands examined trends in chemotherapy regimens from 2000-2008 for early breast cancer patients from a data linkage project between the Eindhoven cancer registry and the worldwide PHARMO database network (van Herk-Sukel et al., 2013). The use of CMF (cyclophosphamide/ methotrexate/ 5-fluorouracil) decreased from around 90% in 2000 to almost none since 2005. Administration of regimens that included anthracyclines (doxorubicin or epirubicin) showed a reverse trend. There was an increasing use of new taxane-containing regimens since 2005. This is consistent with trends from data collected by the ACT Breast Cancer Treatment Project over the same period (report in preparation). The use of taxane (docetaxel or paclitaxel) and trastuzumab (Herceptin) containing regimens (with or without anthracyclines) significantly increased from 2006 in Australia, when they were made available on the Pharmaceutical Benefits Scheme. In approximately 20-25% of breast cancers, the cancer cells make too much of a protein called human epidermal growth factor receptor 2 (HER2). These HER2-positive breast cancers tend to be more aggressive or faster growing. Herceptin has been shown to dramatically reduce the risk of recurrence.

While the physical side effects of chemotherapy are well known (e.g., myelosuppression, hair loss, nausea/vomiting, fatigue, mucositis, diarrhoea, appetite/weight change, constipation, amenorrhoea, peripheral neuropathy, febrile neutropenia), a relatively under-researched area is the effect on cognition. Clinical trials have tended to focus on disease-free survival outcomes or toxicity outcomes that affect the ability to tolerate prescribed doses, such as nausea/vomiting or serious haematological toxicities like neutropenia.

Cognitive function has mainly been examined in cancers that are:

- known to affect the central nervous system (CNS) such as brain tumours (for review see Taphoorn & Klein, 2004);
- involving treatments that appear to affect the CNS such as cranial irradiation, bone marrow transplant and intrathecal or high-dose chemotherapy followed by stem-cell transplantation (e.g., Booth-Jones, Jacobsen, Ransom, & Soety, 2005; S. R. Jacobs, Small, Booth-Jones, Jacobsen, & Fields, 2007; Raber, 2010);
- late stage or terminal cancer (e.g., R. S. Wilson, Segawa, Hizel, Boyle, & Bennett, 2012); or
- childhood cancers, where treatment or cancer is thought to affect the CNS (e.g., Butler & Copeland, 2002).
While there have also been a number of studies of cognitive impairment associated with chemotherapy in small-cell lung cancer (e.g., Kanard, Frytak, & Jatoi, 2004), the interpretation of the results may be confounded by the tumour secretion of cytokines found in lung cancer and the link (1:10) between lung cancer and secondary brain metastases (Haskell & Berek, 2001).

1.3 Cognitive impairment as a side effect of chemotherapy

Central nervous system toxicity has been thought not to occur in standard-dose chemotherapy regimens due to the mechanism of an intact blood-brain barrier limiting entry of cytotoxic agents to the brain. This is the reason why cancers of the nervous system, including brain and spinal metastases, do not respond to standard-dose chemotherapy. However, a number of lines of evidence began to suggest that standard-dose chemotherapy might disrupt cognitive function. Firstly, complaints of memory loss or difficulty concentrating were one of the most common side effects reported by cancer patients following chemotherapy (Griffin et al., 1996). Secondly, clinical case reports of adverse events in cancer patients were reviewed across a range of commonly used chemotherapy drugs where neurological symptoms, including delirium and confusion, were reported (Silberfarb, 1983). This provided evidence that chemotherapy may directly or indirectly affect cognition. Finally, studies began to demonstrate evidence of objective impairment in patients who had been treated with chemotherapy. In a study of cancer patients, Silberfarb et al. (1980) found that patients treated with chemotherapy demonstrated a significantly lower level of cognitive functioning than patients not treated with chemotherapy. While provocative, this study involved significant heterogeneity clouding interpretation of findings, with: different cancer groups, including cerebral metastases; different disease severity; different risks of secondary brain metastases; different types of chemotherapeutic agents and possible brain irradiation.

Subsequently, a study using objective measures of cognitive functioning found significantly poorer cognitive functioning in women treated with standard-dose adjuvant chemotherapy for early breast cancer over a range of functions compared to matched normative data as well as expected ability, based on estimated premorbid intelligence (Wieneke & Dienst, 1995). Moderate cognitive impairment was identified in 75% of these breast cancer survivors and was related to treatment duration but was unrelated to anxiety or depression or other treatment variables. This study did not include a pre-treatment baseline or a control group of women not treated with chemotherapy but it did
provide preliminary support for the presence of possible neurocognitive impairment from standard-dose chemotherapy for early breast cancer.

1.3.1 The study of cognitive effects of chemotherapy in women with early breast cancer

Since the original study by Wieneke and Dienst (1995), cognitive impairment as a potential side effect of standard-dose and high-dose adjuvant chemotherapy for early breast cancer has received increasing attention. A number of studies that examined HRQL outcomes indicated that more women reported cognitive deterioration following adjuvant chemotherapy for early breast cancer or considered it one of the most troublesome side-effects (e.g., Boykoff, Moieni, & Subramanian, 2009; Kohli et al., 2007; Shilling & Jenkins, 2007). Furthermore, evidence began to emerge from cross-sectional studies of objective and diffuse neuropsychological impairment in breast cancer survivors often many years after the completion of adjuvant standard-dose or high-dose chemotherapy treatment (e.g., Ahles et al., 2002; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995). Unexpectedly, subjective complaints were unrelated to objective impairment but were related to measures of psychological distress.

Results have been mixed for standard-dose regimens, hampered by methodological limitations and variation. The incidence of women displaying cognitive impairment following standard-dose chemotherapy has ranged widely, from 13% (Scherwath et al., 2006) to 75% (Wieneke & Dienst, 1995). The majority of studies have used cross-sectional designs without a pre-treatment baseline assessment, where it is not possible to conclude that chemotherapy itself reduces cognitive function. Prospective studies that have included a control cohort are appearing but findings have been inconclusive. A number of these studies have not found evidence of chemotherapy-related impairment at the group level, while others have found only subtle domain-specific changes (e.g., Ahles et al., 2010; Vearncombe et al., 2009), in contrast to the retrospective studies. These domain-specific cognitive changes can represent the no-chemotherapy group improving over time, consistent with a practice effect found on repeated exposure to a test, while the chemotherapy group does not improve or shows less benefit from practice. Findings at the individual level of analysis have suggested there is a subgroup of women who, when exposed to chemotherapy, exhibit impairment. However, a number of prospective studies have found evidence of cognitive impairment in women with breast cancer at baseline following surgery and prior to chemotherapy, calling into question whether ‘chemobrain’ exists or should be renamed (Hurria, Somlo, & Ahles, 2007).
Specific risk factors have not yet been determined and the extent, duration, and underlying aetiology of cognitive changes associated with adjuvant chemotherapy are not yet well understood. Women with early breast cancer have increasingly good long-term survival outcomes so the claim that chemotherapy can detrimentally impact on cognitive functioning is a significant issue for long-term QOL. More carefully designed prospective controlled studies are needed to build a clearer understanding of the extent, profile, duration and mechanisms for chemotherapy-related cognitive impairment.

1.4 Scope and purpose of this study

The current thesis is limited in scope to the study of the cognitive effects of standard-dose chemotherapy used as an adjuvant treatment in women diagnosed with early breast cancer.

The purpose of this study was to evaluate whether cognitive functions vary significantly over time between women with early breast cancer who receive adjuvant chemotherapy as compared to women with early breast cancer who do not receive chemotherapy.

A secondary aim was to determine whether a comprehensive clinical neuropsychological assessment in the context of a prospective cohort design could uncover a profile of impairment associated with exposure to chemotherapy.

1.5 Research questions

The main hypothesis was that women treated with chemotherapy would show significantly poorer cognitive functioning following treatment than women not treated with chemotherapy (i.e., significant Group × Time interaction effects).

A secondary hypothesis was that women treated with chemotherapy would be significantly more likely to experience more cognitive complications (z-scores < -2) over time and/or demonstrate significantly lower than expected cognitive performance, based on premorbid intelligence, than women not treated with chemotherapy.

If so, the following questions would need to be addressed:

- Is there a profile of cognitive impairment or decline?
- What is the duration and course of impairment?
- Does cognitive impairment occur in women with breast cancer prior to chemotherapy?
1.6 Outline of the thesis

Chapter 2 presents an overview of the current literature on the impact of chemotherapy on cognitive functioning in women with breast cancer. Findings from cross-sectional, longitudinal and prospective studies including objective neuropsychological assessments, as well as from neuroimaging and animal studies are presented. The impacts of different designs, assessments and definitions of impairment are reviewed.

In Chapters 3 and 4 the methods and procedures used in the current study are outlined, including details of: the design; the participants; the measures; the setting; the materials and process for gaining informed consent; and the procedure for conducting the clinical and neuropsychological assessments.

Chapter 5 presents descriptive results relating to the recruitment and flow of participants through the current study, as well as comparing participant, cancer and treatment characteristics for each treatment group at baseline. Chapter 6 outlines the statistical methodology for the group analyses and individual analyses.

Chapters 7 to 11 present the results of the group analyses and compare the cognitive performance of the chemotherapy and no-chemotherapy treatment groups over time within six cognitive domains. Chapter 7 reports the results of the assessment of Language, Motor and Visuoconstruction skills. Chapter 8 presents the results for Attention and Speed of Processing; Chapter 9 for Learning and Memory; and Chapter 10 for Executive Functions.

The final results chapter, Chapter 11, presents the results of the individual deficits analyses by examining the incidence of cognitive complications and comparing lower than expected cognitive performance over time between groups.

Chapter 12 presents a general discussion of the results and interpretation of the findings in light of the aims of the thesis and their consistency with the literature.

Chapter 13 presents the main conclusions of the study. Limitations of the study are discussed as well as recommendations for future research and implications for clinical practice.
Chapter 2

Literature Review

This chapter reviews the current literature on evidence for the possible effects of adjuvant chemotherapy for early breast cancer on cognitive functions. Section 2.1 introduces the literature with studies of subjective reports of cognitive changes in women with breast cancer treated with chemotherapy. Section 2.2 provides an overview of the number of publications concerning chemotherapy-related cognitive dysfunction in breast cancer by year and type of study. Section 2.3 to 2.4 examines the evidence from studies of objective cognitive impairment in women with early breast cancer treated with chemotherapy, including neuropsychological and neuroimaging assessments.

Studies of chemotherapy-related cognitive impairment are presented and reviewed by type of study design (2.3 - cross-sectional or 2.4 - longitudinal) and baseline assessment timepoints (pre- or post-chemotherapy). The results of retrospective studies are reviewed in section 2.3.1 and prospective studies in section 2.4.2. The effect of other methodological issues are examined, such as the type of control group, nature of neuropsychological assessment, definition of impairment and the assessment of possible moderators and mechanisms for impairment. Section 2.4.4 reviews the findings regarding the relationship of subjective impairment and psychological distress to objective impairment. Section 2.5 examines the meta-analyses in the field. Finally, Section 2.6 reviews the findings from animal studies on the effects of breast cancer chemotherapy on neural changes in rodents for discussion of possible mechanisms.

2.1 Self-reported complaints

Complaints of poorer cognitive function in cancer survivors after chemotherapy are a frequent topic of cancer support groups, including web chatting and blogging. They became referred to as 'chemobrain' or 'chemofog' (Argyriou, Assimakopoulos, Iconomou, Giannakopoulou, & Kalofonos, 2010; Tannock, et al., 2004).

Women treated with adjuvant chemotherapy report cognitive problems more than breast cancer survivors not treated with chemotherapy (Kohli, et al., 2007; Shilling & Jenkins, 2007). Approximately 50% (Hurria, Goldfarb, et al., 2006) to 83% (Shilling & Jenkins, 2007) of women report memory problems following chemotherapy for breast cancer. Cognitive changes are commonly reported in word-finding, concentration, memory.
prospective memory (e.g., forgetting to do something) and multi-tasking, and they continue to be of concern to around 40% of women 12 months after completion of chemotherapy (Shilling & Jenkins, 2007).

2.2 Overview of literature by year and study type

Even though chemotherapy has been used as a treatment for breast cancer since the 1950s, it is only in the past 15 years that studies have begun to examine the degree of neuropsychological impairment through standardized neuropsychological testing methods. There have been over 160 papers published since 1995 on chemotherapy-related cognitive dysfunction in early breast cancer patients indicating an increasing interest in this area (see Figure 2.1). There was a peak in published papers in 2009, with 40% of published papers being reviews and 30% being retrospective studies.

![Figure 2.1. Published papers per year on chemotherapy-related cognitive dysfunction in breast cancer patients (from Web of Science and Scopus as at May 2013).](image)

When all published papers were examined by type of publication (see Figure 2.2), around half were reports of studies and half were review papers. For some examples, see recent reviews (Ahles, 2012; O’Farrell, MacKenzie, & Collins, 2013; Scherling & Smith, 2013; Walker, Drew, Antoon, Kalueff, & Beckman, 2012; Wefel & Schagen, 2012). Of the published studies to May 2013, 60% have been cross-sectional in design, 8% longitudinal with a post-chemotherapy baseline, 25% involved prospective designs and the rest (7%) have been animal studies. There is a large variation in methodology across patient studies,
including sample sizes, consistency of assessment timing, the nature and scope of the neuropsychological assessment, criteria for impairment and the inclusion and type of control group.

Figure 2.2. Published papers on chemotherapy-related cognitive dysfunction in breast cancer patients by type of paper (from Web of Science and Scopus as at May 2013).

Results of objective neuropsychological assessments have been inconsistent, generating debate over whether 'chemobrain' exists or should be renamed (Hurria, et al., 2007; Taillibert, 2010). In the current literature review, studies are examined based on overall study design: cross-sectional designs (post-chemotherapy, pre-chemotherapy); longitudinal designs (with post-chemotherapy baseline); and prospective studies (with pre-chemotherapy baseline). The effect of other methodological issues are examined, such as the inclusion and type of control group, nature of neuropsychological assessment, profile and definition of impairment and the assessment of possible moderators and mechanisms for impairment.

### 2.3 Cross-sectional findings

Cross-sectional designs involve observations of different groups at a single assessment or timepoint. The benefit of this type of research design is that many variables can be compared at that point of time in relation to the event of interest (e.g., chemotherapy). Cross-sectional studies in the field can be divided into those conducted following chemotherapy treatment (retrospective), or prior to treatment (pre-chemotherapy). Findings from these types of cross-sectional studies will be considered separately.
Some studies involved women tested prior to or during chemotherapy compared to women who had completed chemotherapy. These are sometimes called quasi-longitudinal designs but, as they do not involve repeated measurements, cognitive changes within the same individuals along with changes in possible confounding factors cannot be assessed. They cannot provide information on cause-and-effect relationships.

Studies using cross-sectional designs for the neuropsychological assessment of chemotherapy-related cognitive dysfunction in breast cancer patients have been reported in around 50 published papers to date (Abraham et al., 2008; Adams-Price, Morse, Cross, Williams, & Wells-Parker, 2009; Ahles, et al., 2002; Ayala-Feliciano, Pons-Valerio, Pons-Madera, & Acevedo, 2011; Baxter, Durham, Phillips, Habermann, & Virning, 2009; Brezden, et al., 2000; M. S. Brown et al., 1995; Castellon et al., 2004; Cimprich et al., 2010; Cimprich, So, Ronis, & Trask, 2005; de Ruiter et al., 2012; de Ruiter et al., 2011; Debess, Riis, Pedersen, & Ewertz, 2009; Deprez et al., 2011; Desai et al., 2005; Donovan et al., 2005; Du, Xia, & Hardy, 2010; Ferguson, McDonald, Saykin, & Ahles, 2007; Freeman & Broshek, 2002; Inagaki et al., 2007; Jim et al., 2009; Kesler, Kent, & O’Hara, 2011; Koppelmans, Breteler, et al., 2012; Koppelmans, de Ruiter, et al., 2012; Kreukels et al., 2008; Kreukels et al., 2006; Kreukels et al., 2005; Kreukels, van Dam, Ridderinkhof, Boogerd, & Schagen, 2008; Lopez Zunini et al., 2012; Mar Fan et al., 2005; B. C. McDonald, Conroy, Ahles, West, & Saykin, 2010; B. C. McDonald, Conroy, Smith, West, & Saykin, 2013; Mehnert et al., 2007; O’Shaughnessy, 2002; Reid-Arndt, Yee, Perry, & Hsieh, 2009; Saykin, Ahles, & McDonald, 2003; Schagen et al., 2000; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001; Schagen, et al., 1999; Scherling, Collins, MacKenzie, Bielajew, & Smith, 2012; Scherwath, et al., 2006; Schirmer et al., 2009; Servaes, Prins, Verhagen, & Bleijenberg, 2002; Silverman et al., 2007; Tchen et al., 2003; van Dam, et al., 1998; Von Ah et al., 2009; Wieneke & Dienst, 1995; Yamada, Denburg, Beglinger, & Schultz, 2010).

The majority (around 80%) have been retrospective studies conducted after the completion of chemotherapy but a few have involved studies where patients were assessed during their chemotherapy regimen, using brief cognitive screening tests (e.g., Brezden, et al., 2000; Tchen, et al., 2003). Several cross-sectional studies have been conducted prior to chemotherapy. Findings from retrospective studies and those conducted prior to chemotherapy will be considered separately.
2.3.1 Retrospective studies

The original study

The original study of neuropsychological performance in women with early breast cancer treated with standard-dose adjuvant chemotherapy was conducted by Wienelke and Dienst in 1995. They found that 21 of 28 women (75%) displayed moderate cognitive impairment when tested an average 6 months (range 0.5 - 12 months) following completion of chemotherapy. This was defined as 2 standard deviations (SD) below normative test data on at least one test measure in addition to mild impairment (≥1 SD below norms on two or more tests). The battery was designed to be comprehensive, lasting around 3 hours, with neuropsychological tests selected that were sensitive to mild cognitive impairment, assessing eight cognitive domains, including premorbid intelligence.

Average group performance was significantly below age-, education- and gender-corrected norms on multiple test measures (11/20 at p < 0.05 and 8/20 at p < 0.01) with a diffuse profile of impairment across all cognitive domains, apart from Abstract/Conceptualization. Three tests (the Paced Auditory Serial Addition Test [PASAT], the Rey Complex Figure Test [CFT] - Copy and Delay correct) displayed the most impairment relative to test norms.

Average premorbid intellectual functioning was estimated to be in the High Average range (M FSIQ = 113) for the group as a whole. Average test performance was at least 1SD below average estimated premorbid functioning on all tests except Similarities and the Controlled Oral Word Association Test (COWAT), measures of abstract reasoning and verbal fluency.

Cognitive impairment was unrelated to demographic variables, type of chemotherapy, time since last treatment and depression. Overall cognitive impairment was significantly related to duration of chemotherapy (range 3 - 18 months). Chemotherapy regimens included conventional CMF, CAF or sequential CMF+CAF regimens. Standard chemotherapy regimens for early breast cancer, such as CMF, usually involve six cycles every three weeks over approximately four months. Chemotherapy of longer duration, such as 12 - 18 months, is likely to affect health and QOL, so it is hard to compare regimens of such varying duration. It is not clear whether this finding indicates a possible dose-response curve or whether longer treatment duration is associated with other pre-treatment factors, such as the cancer itself, that could indirectly have an effect on cognitive functioning. Although 39% (n = 11) of women were taking tamoxifen at the time of testing.
the role of hormone treatment was not explored. The authors readily noted the possibility of biased inclusion of women who had already complained to physicians about their cognitive functioning. The advantage of this study was the comprehensive neuropsychological assessment. The shortcomings were that it was retrospective, small, included widely different durations of chemotherapy and did not include a control group. While the study design did not enable conclusions to be drawn that cognitive impairment was directly attributable to chemotherapy, the findings were provocative and provided justification for further research.

**Other retrospective studies**

Retrospective designs have been employed in around 40 studies, where patients were assessed after the completion of chemotherapy. Times after the completion of chemotherapy have ranged from 1 month to 21 years, with the majority of studies assessing women within two years of completing therapy. Long term deficits have been found up to 21 years after the completion of chemotherapy, unrelated to anxiety and depression (Koppelmans, Breteler, et al., 2012). They have been found over 10 years post-treatment in both middle aged (Ahles, et al., 2002) and elderly survivors (Yamada, et al., 2010). The most common domains affected include attention and processing speed, verbal learning and memory, and executive functions. This raises important questions about the effect of adjuvant chemotherapy on survivor’s long term HRQL. Most of these studies, though, compared breast cancer survivors to healthy controls, which does not isolate the effects of chemotherapy. The study that used a local treatment control group also included male survivors of lymphoma, and the control group was assessed significantly longer since treatment than the study group (Ahles, et al., 2002). Other studies, conducted five years or more following the completion of chemotherapy, that included only breast cancer survivors and a local therapy control group, did not report any significant differences in average cognitive performance across domains between those that had received chemotherapy and those that had not (Scherwath, et al., 2006) or found only poorer executive functioning ($p < 0.05$) in chemotherapy-treated survivors 10 years post-treatment (de Ruiter, et al., 2011). This highlights the challenges of comparing studies in the field where methodological variation, including the degree of homogeneity of study groups, type of control groups, comparability between study and control groups, and time since treatment, make findings difficult to compare and limit generalizability.

Sample sizes of retrospective cross-sectional studies have varied from 10 (Abraham, et al., 2008) to 62,585 (Du, et al., 2010). The former was a neuroimaging study and the latter
was a population-based study. These types of studies will be considered separately to clinical studies.

a. Population-based studies

Population-based studies have generally focused on whether there is an increased risk of cognitive dysfunction or dementia in cancer patients compared to healthy controls (e.g., Braun, Rao, & Pirl, 2012; Buckwalter, Crooks, & Petitti, 2005; Heflin et al., 2005) but only a few population-based cohort studies have examined the effects of chemotherapy treatment in breast cancer survivors (Baxter, et al., 2009; Du, et al., 2010; Koppelmans, Breteler, et al., 2012).

The results regarding whether there is an increased risk of dementia in cancer patients have been mixed. Two studies have used telephone-administered cognitive screening tests to assess risk of dementia in cancer survivors as part of larger population studies (Buckwalter, et al., 2005; Heflin, et al., 2005). One conducted as part of the Women's Memory Study used a telephone interview of cognitive status to assess differences in cognitive performance between 541 elderly cancer survivors and 3,123 elderly women with no history of cancer (Buckwalter, et al., 2005). They found no significant differences between groups on this screening test. However, when this interview has been compared to an in-person neuropsychological assessment, findings demonstrated that the telephone interview should be used with caution in the detection of dementia and was not able to reliably discriminate mild cognitive impairment (Knapman et al., 2010).

The second study involved a population twin study of 486 twin pairs aged 65 and older in Sweden, where the cognitive function of cancer survivors were compared with that of their cancer-free twin, also using a telephone cognitive screen for dementia (Heflin, et al., 2005). They found cancer survivors overall were significantly more likely to have dementia than the cancer-free co-twins. Cancer survivors were twice as likely to be diagnosed with dementia as their co-twins, although this odds ratio did not reach statistical significance. No comparison was made of cognitive functioning among cancer survivors who received different treatments, which may mean the cognitive risk reported is an overestimate for some cancer survivors and an underestimate for others based on cancer treatment.

There are only a few population-based cohort studies that have examined the relationship between chemotherapy use and cognitive impairments in women with breast cancer. One study reviewed Medicare claims data in over 21,000 older breast cancer survivors to determine whether the risk of dementia was related to having received adjuvant
chemotherapy (Baxter, et al., 2009). They found having received chemotherapy was not associated with a greater risk of dementia diagnosis over time. Another study examined the risk of dementia diagnosis in 62,565 older breast cancer survivors based on chemotherapy use (Du, et al., 2010). Women who received chemotherapy were 8% more likely to have developed drug-induced dementia compared to women who did not receive chemotherapy, but this was not significant after adjusting for patient and tumour characteristics, such as age, education and cancer severity. Unexpectedly, the risk of developing Alzheimer’s dementia, vascular dementia or other dementias was significantly lower in women who had received chemotherapy.

In contrast, a population study of cognitive ageing found evidence of cognitive impairment in breast cancer survivors treated with chemotherapy compared to healthy controls (Koppelmans, Breteler, et al., 2012). They compared neuropsychological performance in breast cancer survivors \((n = 196)\) 21 years after the completion of CMF chemotherapy to a population-based sample of women with no history of cancer \((n = 1509)\). Women exposed to cancer and chemotherapy performed significantly worse on measures of motor speed, speed of processing, verbal memory, and executive function, but experienced fewer symptoms of depression.

These population findings have been inconsistent, likely due to variation in methodology, indicating that greater sample size does not always resolve the issue. Proxy measures such as dementia claims data or telephone screening for dementia are limited and not designed to assess for mild cognitive impairment and are not equivalent to an in person comprehensive neuropsychological assessment. In the only study (Koppelmans, Breteler, et al., 2012) that conducted a neuropsychological assessment as part of a population study of cognitive ageing, breast cancer survivors treated with CMF chemotherapy more than 20 years previously performed significantly worse than population controls never diagnosed with cancer in a range of cognitive domains, including processing speed, verbal memory and executive functioning. Unfortunately, this study did not compare performance to a breast cancer no-chemotherapy control group. It suggests, however, that a more detailed differential diagnosis may only emerge with more comprehensive clinical neuropsychological assessments.

b. Clinical studies

The majority of cross-sectional retrospective studies in the area of chemotherapy-related cognitive dysfunction in breast cancer have been smaller clinical studies involving a cognitive assessment using standardized neuropsychological tests, although the scope of this assessment has varied. The two most commonly assessed domains were attention and
memory with almost 90% of studies assessing these domains. Most did not assess premorbid intelligence (IQ) although this has been found to affect cognitive performance and to be both a protective (higher IQ) and vulnerability factor (lower IQ) following neurotoxic exposure and brain injury (Lezak, Howieson, Bigler, & Tranel, 2012). Around half did not assess fundamental motor function, language or visual spatial skills. Furthermore, while around three-quarters of these studies included at least one test of executive functions, such as verbal fluency, the majority did not conduct an assessment of different executive functions, including abstract reasoning, planning, problem solving, strategy, cognitive flexibility and inhibition.

Age in retrospective study participants has ranged from 30 to 79 years, with an average age of 50-55 (M SD = 9). Most studies applied an age limit around 65 years to reduce the risk of age-related mild cognitive impairment complicating the results. Only a couple of studies have studied the effect of adjuvant chemotherapy on women over 65 years. One examined the effects of age and treatment in younger and older breast cancer survivors and found an interaction effect where only older chemotherapy patients performed significantly poorer on a visual speed of processing task compared to healthy controls (Adams-Price, et al., 2009). However, this may have been influenced by the apparent ceiling effect on the test. The average performance of younger participants in the study, both in the chemotherapy and control group, was close to the fastest possible speed (16 milliseconds) on the Useful Field of View test, a brief test of visual processing and attention used to predict driving ability in older adults. Selecting tests that do not have ceiling effects and are sensitive to mild impairment in middle aged adults are critical in this field.

Sample sizes have ranged from 17 (Freeman & Broshek, 2002) to 374 (Jim, et al., 2009). There has often been an inverse correlation between study sample size and the scope of the neuropsychological assessment, with studies using larger samples employing a brief screening assessment (e.g., Brezden, et al., 2000; Mar Fan, et al., 2005; Tchen, et al., 2003) or a restricted range of tests (e.g., Von Ah, et al., 2009). Larger studies have been more likely to use test administration practices that may compromise the reliability of the results, such as telephone administration (Von Ah, et al., 2009), or use of survivor-nominated controls, whose performance may be biased by relationship to the survivor (e.g., Tchen, et al., 2003).

Smaller studies have generally used more comprehensive batteries of neuropsychological tests across a range of cognitive domains. However, even some smaller studies have employed tests that are not sensitive to mild cognitive impairment, such as the Clock
Drawing test (O'Shaughnessy, 2002), or a restricted range of tests that did not assess various cognitive domains (Servaes, et al., 2002).

**Group comparisons of neuropsychological performance**

The majority (about 80%) of retrospective studies have found significantly lower cognitive performance in women who have received chemotherapy compared to a variety of controls. Clinical studies that have used standard neuropsychological tests to assess at least three cognitive domains are presented in Table 2.1. As can be seen, the profile of impairment is diffuse rather than domain-specific but also variable as it does not readily implicate a specific cognitive domain.

Women treated with chemotherapy have demonstrated significantly poorer performance compared to controls or norms on cognitive tests but these findings do not provide a consistent profile within any domain across studies. Significantly lower performances have been found in motor function, language, visuospatial skills, verbal and visual learning and memory and executive functions compared to controls. However, the research has yielded an ambiguous mix of results within cognitive domains across studies. Some are decidedly significant, some suggestive and some are convincingly null. While there is diversity in the tests being used to assess cognitive functions, there is also not a reliable neuropsychological test pattern across studies. Possible explanatory variables such as age, education, anxiety, depression, fatigue and hormonal status have been unrelated to test performance.

In several studies, significantly poorer performance was found in women who had received chemotherapy compared to age-matched normative data, healthy controls, and early breast cancer survivors who did not receive chemotherapy or were treated only with local therapies (see Table 2.1). However, other studies did not find any significant differences in performance between women who had received chemotherapy compared to controls (no-chemotherapy; local therapy; high-dose chemotherapy; or healthy controls).

One study compared women who had received chemotherapy 6-12 months previously with women who were over midway through their chemotherapy treatment (Freeman & Broshek, 2002). They found no significant differences in motor function, language, attention, and learning or memory performance between the two groups. They did find that women who had completed chemotherapy performed significantly better on a task of visuospatial construction but were significantly slower on two conditions of the Stroop test, word reading speed and inhibition. This suggests that any problems in visuoconstruction experienced during chemotherapy are transient. Stroop interference
scores were inversely correlated with depression scores which might mean that reduced cognitive efficiency is frustrating and lowers mood or that depression affects the ability to inhibit an automatic response. However, this was a very small study with a sample size of 17.

Table 2.1

Average Performance in Women Following Chemotherapy Compared to Controls from Retrospective Studies by Cognitive Domain

<table>
<thead>
<tr>
<th>Study</th>
<th>Time since last chemotherapy</th>
<th>Comparison group</th>
<th>Language</th>
<th>Motor</th>
<th>Visuospatial construction</th>
<th>Attention and Speed of Processing</th>
<th>Verbal Learning / Memory</th>
<th>Visual Learning / Memory</th>
<th>Executive Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wieneke et al. (1995)</td>
<td>6-12 m</td>
<td>N</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Van Dam (1998)</td>
<td>2 y</td>
<td>LT</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Schagen (1999)</td>
<td>2 y</td>
<td>LT</td>
<td>X</td>
<td>X</td>
<td>N.S.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ahles (2002)</td>
<td>3 y M = 10 y</td>
<td>LT</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
<td>X</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freeman (2002)</td>
<td>6-12 m</td>
<td>Cx (cyc 4+)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
<td>X</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
</tr>
<tr>
<td>Castellon (2004)</td>
<td>2-5 y</td>
<td>LT</td>
<td>X</td>
<td>X</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
</tr>
<tr>
<td>Donovan (2005)</td>
<td>6 m</td>
<td>LT</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
</tr>
<tr>
<td>Scherwath (2006)</td>
<td>5 y</td>
<td>LT</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
</tr>
<tr>
<td>Jim (2008)</td>
<td>6 m</td>
<td>HC</td>
<td>X</td>
<td>N.S.</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Reid-Arndt (2009)</td>
<td>1 m</td>
<td>N</td>
<td>N.S.</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Yamada (2010)</td>
<td>10+ y M = 16 y</td>
<td>HC</td>
<td>N.S.</td>
<td></td>
<td>X</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
</tr>
<tr>
<td>De Ruiter (2011)</td>
<td>9.5 y</td>
<td>NC</td>
<td>N.S.</td>
<td></td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Koppelmans (2012)</td>
<td>21 y (CMF)</td>
<td>HC</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ayala-Feliciano (2011)</td>
<td>5.5 y</td>
<td>HC+NC</td>
<td>X</td>
<td>N.S.</td>
<td>X</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^Studies are identified by first author and year of publication. m = month; y = year; Cx = During chemotherapy, from at least cycle 4. X Chemotherapy group < control group. Significance level = p < 0.01; X Significance level = p < 0.05; X Chemotherapy group > control group. Significance level = p < 0.01. N.S. Not significant. Cx = During chemotherapy; N = Norms; NC = No chemotherapy; H = Hormonal therapy; HC = Healthy controls; HD = High-dose chemotherapy; LT = Local therapies (surgery ± radiation therapy)
A larger study compared the cognitive performance of women currently receiving chemotherapy \((n = 31)\) with women who had completed chemotherapy two years previously \((n = 40)\), and healthy controls \((n = 36)\) did not find any significant difference between the current and post-chemotherapy groups (Brezden, et al., 2000). Women who were receiving chemotherapy did perform significantly worse than healthy controls. However, this study used a cognitive screening assessment rather than a comprehensive neuropsychological assessment, making the findings difficult to compare.

The possibility of a dose-response neurotoxic effect on cognitive performance has been studied (high dose vs standard dose) (e.g., Mehnert, et al., 2007; Scherwath, et al., 2006; van Dam, et al., 1998). High dose treatment groups displayed significantly poorer performance on reaction time tests compared to normative data (Scherwath, et al., 2006) or local therapy controls (van Dam, et al., 1998). The risk of overall cognitive impairment was eight times higher for women with breast cancer in the high-dose chemotherapy group and three times higher in the standard-dose chemotherapy group than for patients not given chemotherapy (van Dam, et al., 1998). This provides some evidence for a dose-response curve. However, while the risk of impairment was elevated in both groups, the risk was only statistically significant for the high-dose group in comparison with the local therapy control group. Moreover, other possible explanatory variables, including fatigue and depression scores, were higher in the women who received high-dose chemotherapy. No differences were found in cognitive test performances between the standard-dose chemotherapy group and controls, or between the chemotherapy groups, apart from in reaction time. The case for a dose-response effect was equivocal.

Some of the larger studies that have conducted a comprehensive assessment across multiple cognitive domains did not find any significant differences in average performance between breast cancer survivors who had received chemotherapy and those that had not (Donovan, et al., 2005; Scherwath, et al., 2006; van Dam, et al., 1998). Interestingly, one of these studies attempted to control for selection bias innate in retrospective designs where women who experience more cognitive problems may be more likely to be recruited (Donovan, et al., 2005). This study recruited women prior to chemotherapy but tested them following the completion of treatment, and found those treated with chemotherapy were indistinguishable from controls.

Clearly these overall findings are not consistent. However, the diffuse profile of impairment found across domains is consistent with a meta-analysis of studies of chemotherapy-related cognitive impairment in women with breast cancer that examined cross-sectional studies, all retrospective, separately (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005). The meta-analysis found very small (Cohen's \(d = -0.03\)) to moderate
Cohen’s $d = -0.51$ effect sizes across, in increasing order of effect size, attention, memory, executive function, language, spatial ability and motor function. Apart from attention, the extent of cognitive impairment across domains was similar. *Time* since last receiving chemotherapy was negatively associated with study effect size, indicating that the magnitude of impairment lessened over time following treatment. However, only five studies were included with different types of comparison groups.

Profiles of diffuse impairment, accompanied by mild to moderate cognitive impairment, are associated with conditions such as early Parkinson’s disease, multiple sclerosis, chronic fatigue syndrome, mild traumatic brain injury and major depression (K. Zakzanis, Kaplan, & Leach, 1999). These profiles vary. Major depression is associated with a diffuse profile where fairly flat performance is demonstrated across tests, especially on effortful tasks. A profile of diffuse but variable impairment is found in patients with multiple sclerosis associated with white matter changes (Rao, Leo, Haughton, St Aubin-Faubert, & Bernardin, 1989; K. K. Zakzanis, 2000). The clinical presentation in multiple sclerosis is highly variable owing to distribution of lesions scattered through the central nervous system white matter. Research in this field often yields a mix of results similar to the research profile of chemotherapy-related impairment.

On the basis of cross-sectional studies conducted after chemotherapy, there is evidence in most studies (about 80%) of diminished cognitive performance in women who had received chemotherapy compared to controls. The profile of impairment has been diffuse and does not readily implicate a specific cognitive domain or test. Deficits have been found many years after treatment. However, some larger studies using comprehensive assessments did not find any differences between women treated with standard-dose chemotherapy and controls. Age, education, anxiety, depression, fatigue and hormonal status have been unrelated to performance. Definite conclusions on the role of chemotherapy cannot be drawn due to methodological limitations.

### Prevalence of overall cognitive impairment

In the event that group mean values may obscure cognitive impairment evaluation at the level of the individual, these retrospective studies have also examined the prevalence of individual overall cognitive impairment between groups. Different methods have been used to define overall cognitive impairment affecting the observed rates of impairment.
Overall cognitive impairment has been defined as:

- \( \leq 1\, SD \) below test norms on 2+ test scores (mildly impaired) plus \( \geq 2\, SD \) on 1 test measure (‘moderately impaired’) (Wieneke & Dienst, 1995). Rate of moderate impairment was 75% in breast cancer patients treated with chemotherapy.

- \( \leq 2\, SD \) below control group mean on 3+ tests (i.e., \( \leq 5^{th} \) percentile of control group test performance) (Schagen, et al., 2000; Schagen, et al., 1999; van Dam, et al., 1998). The rate of cognitive impairment was 32% in high-dose chemotherapy patients vs 17% in standard-dose FEC and 23% standard-dose CMF chemotherapy patients vs 9% in local therapy control group;

- \( \leq 2\, SD \) below the relevant test norm (Donovan, et al., 2005). No significant difference was found between prevalence of impairment between groups;

- \( z \leq 1.4\, SD \) below published test norm (for function and domain specific impairment) on 4+ parameters (i.e., \( \leq 5^{th} \) percentile of comparison group) (Mehnert, et al., 2007; Scherwath, et al., 2006). Global impairment: 8% high dose vs 13% standard dose vs 3% control. No significant between-group differences were found;

- \( \leq 1.5\, SD \) below the normative mean on 2+ tests (Jim, et al., 2009). Overall impairment: 34% chemotherapy vs 23% healthy controls. No significant between-group differences were found;

- Lower quartile of each domain score (pooled tests in each domain) in 4+ domains (Ahles, et al., 2002). Low performance: 39% chemotherapy vs 14% local therapy and chemotherapy group had significantly higher rate of impairment;

- Individual composite domain score (average of test z-scores within each domain) \( \leq 1\, SD \) below estimated premorbid IQ (Reid-Arndt, et al., 2009). Lower than expected performance was found in 41% of chemotherapy-treated women on verbal fluency, associated with decreased productivity in social roles but unrelated to depression;

- \( \leq 7^{th} \) percentile of healthy control group test performance (Von Ah, et al., 2009). The rate of cognitive impairment for breast cancer survivors was 17% for verbal learning and delayed recall;

- General Neurocognitive Performance (GNP) score (mean of the eight neurocognitive domain z-scores defined in relation to the healthy control group) (Castellon, et al., 2004). Women treated with chemotherapy scored significantly
lower on their GNP than women who received local therapy only \( (p = 0.01) \) but neither group scored significantly differently from healthy controls; and

- Normal, Borderline, Abnormal (mild, moderate, severe) used by screening test to classify performance (Brezden, et al., 2000; Tchen, et al., 2003). Significantly more chemotherapy patients were classified with moderate to severe impairment than healthy controls (33% \( v \) 4%; and 16% \( v \) 4% respectively).

Prevalence of overall cognitive impairment in breast cancer survivors following standard-dose chemotherapy has ranged from 13% to 75%, as compared to 3% to 18% in local therapy controls and 4% to 23% in healthy controls. It appears that a subset of women are cognitively affected following chemotherapy, although rates are influenced by the criteria being used and may be influenced by a biased inclusion of women who have already complained about their cognitive functioning. This issue of definition is not as critical in a between groups comparison.

There is little consistency in the way that cognitive impairment is defined or calculated. One study examined data from breast cancer patients post-chemotherapy and healthy controls and analyzed it using seven different methods, each taken from a different research paper in the field (Shilling, Jenkins, & Trapala, 2006). Not surprisingly, the extent of cognitive impairment was dependent on the method of analysis. Prevalence of cognitive impairment from the same data ranged from 12% to 68.5% in the chemotherapy group and 5% to 64% in the healthy control group, depending on criteria being used. This made the risk of being classified as impaired 1.21 to 3.68 times more likely for chemotherapy participants depending on the criteria. This study used methods based on single test scores rather than domain scores. The authors recommended further consideration of the use of domain scores. By dividing measures into domains and calculating a composite score within that domain, classification of impairment would be less likely to be influenced by performance on a single test.

Whilst these studies have differed in their methodologies, impairment has been found in most retrospective studies in both poorer average performance of women treated with chemotherapy compared to controls and higher prevalence of impairment, although the extent depends on the criteria used for impairment. The profile of impairment has been diffuse and variable. Deficits appear to manifest only in some patients while others seem relatively unaffected. Impairment has not been related to age, education, anxiety, depression, self-report, fatigue, time since treatment or menopausal status but only to chemotherapy treatment, including treatment duration (Ahles, et al., 2002; Wienke & Dienst, 1995) or dose (van Dam, et al., 1998). Some important moderator variables, such
as premorbid intelligence, have often not been assessed. Various adjuvant chemotherapy regimens have been used, including traditional CMF and anthracycline-based regimens, but no relationships have emerged to indicate that cognitive impairment relates to any particular cytotoxic drug or combined regimen. However, these studies have been limited methodologically by not including a pre-treatment baseline against which to assess post chemotherapy deficits, so it is not possible to determine whether deficits are the effect of chemotherapy or whether they existed prior to chemotherapy.

2.3.2 Neuroimaging studies

Several retrospective studies have used brain imaging or physiological measures of brain functioning to examine effects of chemotherapy on the brain and cognition (Abraham, et al., 2008; M. S. Brown, et al., 1995; M. S. Brown et al., 1998; de Rover et al., 2011; de Ruiter et al., 2012; de Ruiter, et al., 2011; Deprez, et al., 2011; Ferguson, et al., 2007; Inagaki, et al., 2007; Kesler, Bennett, Mahaffey, & Spiegel, 2009; Kesler, et al., 2011; Kreukels, et al., 2006; Kreukels, et al., 2005; Kreukels, van Dam, et al., 2008; Saykin, et al., 2003; Schagen, et al., 2001; Silverman, et al., 2007).

The Netherlands group conducted neurophysiological studies in a subset of women who were part of earlier studies from the high-dose, standard-dose chemotherapy, and control groups (Kreukels, Hamburger, et al., 2008; Kreukels, et al., 2006; Schagen, et al., 2001). Significantly more patients (n = 7) in the high-dose group had an asymmetry of the alpha rhythm of 0.5 Hz, indicating some cortical and subcortical dysfunction, than patients treated with standard-dose chemotherapy (n = 2) or local therapy controls (n = 0). There was no relationship between neurophysiological measures and neuropsychological performance (Schagen, et al., 2001).

High-dose chemotherapy has been accompanied by changes in cerebral white matter (M. S. Brown, et al., 1995; M. S. Brown, et al., 1998) and abnormal metabolic activity in the dorsolateral prefrontal cortex and in Broca’s area (Silverman, et al., 2007). It is not clear, however, whether the effects of high-dose regimens can be extrapolated to standard-dose regimens, or whether there might be a threshold for toxicity, as high-doses regimens have been shown to have significant neurotoxic side-effects not accompanying standard-dose regimens (e.g., acute cerebellar syndrome, somnolence; seizures; coma, leucoencephalopathy) (M. S. Brown, et al., 1995; M. S. Brown, et al., 1998; Silverman, et al., 2007).

The Netherlands group also studied reaction times during electroencephalography (EEG) registration and examined an event-related potential component (P3) in women who had
received standard-dose chemotherapy or local therapy 3–6 years previously. For women treated with chemotherapy, the P3 component peaked significantly earlier (by some 60 ms) and had significantly smaller peaks, especially in more difficult conditions (Kreukels, et al., 2005). Reaction times correlated negatively with P3 amplitude in both groups and P3 latency in the local therapy control group. The authors concluded that the earlier P3 peaks suggested the duration of evaluation processes is shorter post chemotherapy and may indicate a rushed evaluation and subsequent compensation at insufficient depth, requiring more response-related processes (reminiscent of double-checking). The smaller P3 peaks indicated more problems with information processing post chemotherapy.

Long term differences in structural brain functioning have been found in women following chemotherapy compared to controls. Studies using PET scans conducted on breast cancer survivors 5–10 years post chemotherapy found significantly altered cerebral blood flow in the frontal cortex and cerebellum compared to controls, that was correlated with short term memory performance (Silverman, et al., 2007). Another study using voxel-based morphometry reported smaller neocortical grey matter and cortical and subcortical white matter 5 years or more post chemotherapy in breast cancer and lymphoma survivors compared with healthy controls (reported in Saykin, et al., 2003). These studies of long term effects are supported by another structural imaging study showing decreased volume in the parietal and occipital cortex and cerebellum, and reduced tissue integrity in women exposed to chemotherapy nearly 10 years previously compared to matched controls (de Ruiter, et al., 2012). A large study using structural magnetic resonance imaging (MRI) found smaller total grey matter volume and total brain volume in breast cancer survivors who had been treated with chemotherapy 21 years previously ($n = 184$) compared to healthy controls ($n = 368$) (Koppelmans, de Ruiter, et al., 2012).

Ferguson et al. (2007) used functional MRI to investigate differences in brain structure in a pair of monozygotic twins, one of whom had been treated for breast cancer with adjuvant chemotherapy, while the other had no cancer. The twin exposed to chemotherapy had greater white matter lesion volume than the untreated twin and demonstrated broader activation in bifrontal and biparietal regions associated with increasing load in a working memory task. Objective neuropsychological test performances were not significantly different. The authors suggested that this may indicate more neural network is needed following chemotherapy to accomplish performance similar to an equivalent other who has not been not exposed. They reported they had detected this compensatory pattern in other disorders, such as multiple sclerosis, traumatic brain injury and mild cognitive impairment.
A large study reviewed a MRI database and examined regional brain volume differences between breast cancer survivors exposed to chemotherapy \((n = 124)\) and those not exposed \((n = 114)\) within one year or over three years post-surgery (Inagaki, et al., 2007). Significantly smaller grey matter and white matter were found in the chemotherapy survivors in the one year study in the prefrontal, parahippocampal, cingulate gyrus and precuneus. The volumes were significantly associated with indices of attention and visual memory. No significant differences were observed between breast cancer treatment groups in the three year study, suggesting these differences resolve in the longer term. This is contrary to findings of long-term effects from other neuroimaging studies (e.g., Koppelmans, de Ruiter, et al., 2012; Saykin, et al., 2003). No significant differences were found in volumes between cancer survivors who had received only local therapies and healthy controls at 1 year or 3 years, suggesting that differences were not explained by cancer itself.

Other studies, however, suggest cancer may play a role on brain dysfunction. One study found a negative relationship between cancer severity and neural activity (Kesler, et al., 2011). Breast cancer survivors demonstrated reduced activation in the left middle dorsolateral prefrontal cortex and premotor cortex, irrespective of their treatment history, compared to healthy controls. Women who had been treated with chemotherapy demonstrated reduced left caudal lateral prefrontal cortex activation and increased perseverative errors on a test of executive functioning, a measure that is highly sensitive to impairments in cognitive flexibility (WCST perseverative errors). This reduced activation was also associated with higher disease severity and subjective executive dysfunction. Age and education were associated with perseverative errors. In the chemotherapy group, women who were older or who had received a lower level of education were associated with increased perseverative errors on this task. This suggests that the negative effects of chemotherapy may be moderated by individual pre-treatment factors like age and education, a proxy measure of cognitive reserve.

These findings provide evidence for structural and functional abnormalities associated with chemotherapy-related cognitive deficits; however, the lack of pre-chemotherapy baselines make it impossible to assess whether observed abnormalities were present prior to chemotherapy.

### 2.3.3 Cross-sectional findings – pre-chemotherapy

Several studies have examined the cognitive performance of breast cancer patients prior to chemotherapy to determine whether deficits are already present, comparing performance to normative data (Cimprich, et al., 2005; Wagner et al., 2005; Wefel, Lenzi,
Theriault, Buzdar, et al., 2004) or to healthy controls (Ahles et al., 2008; Cimprich, et al., 2010; Debess, et al., 2009; Desai, et al., 2005; Scherling, et al., 2012; Tager & McKinley, 2004). Some of these were conducted as the baseline assessment of a longer-term prospective study but were analyzed and published separately as a cross-sectional comparison, and included in the analysis women who were examined at baseline but were later lost to follow-up (Ahles, et al., 2008; Wefel, Lenzi, Theriault, Buzdar, et al., 2004).

Assessments were mainly conducted post-surgery, ranging from 3 to 42 days prior to the commencement of chemotherapy. One study tested breast cancer patients before surgery using a brief evaluation of attention and memory (Cimprich, et al., 2005). The performance of breast cancer patients was generally within the normal range for healthy adults compared to age-matched normative data. Age, education, presence of a chronic health problem and menopausal status were all associated with cognitive performance.

A number of studies conducted following surgery found that breast cancer patients displayed significantly lower average neuropsychological performance compared to controls prior to the initiation of chemotherapy (Ahles, et al., 2008; Cimprich, et al., 2010; Wefel, Lenzi, Theriault, Buzdar, et al., 2004) although others, including a population-based study, did not find any significant differences (Cimprich, et al., 2005; Debess, et al., 2009). The functions affected mainly involved attention and speed of processing, although results were variable. Slower reaction times (Ahles, et al., 2008) and task performance (Wefel, Lenzi, Theriault, Buzdar, et al., 2004) were found in two studies but only decreased accuracy in another (Cimprich, et al., 2010), with no significant differences in speed of processing or accuracy in a fourth (Scherling, et al., 2012).

The prevalence of overall cognitive impairment in individuals ranged from 7% - 40% depending on the criteria being used (z ≥-1.5 on 3+ tests or z= ≥-2 on 2+ test; or z = >-1 on 2+ tests, respectively). The pattern of differences between impaired versus non-impaired breast cancer survivors was more diffuse, including visuospatial, motor, attention, memory and executive functions (Desai, et al., 2005; Tager & McKinley, 2004). Slower speed of processing could explain problems in multiple domains but this was not examined. Cognitive impairment was independent of age, education, hormonal status, stage of cancer, surgery, length of general anaesthesia, self-reported complaints, depression, anxiety, fatigue or biological markers, including haemoglobin levels in most studies.

Two studies using functional neuroimaging during an attention, working memory or an executive function task found different patterns of brain activation in women with breast cancer prior to chemotherapy (Cimprich, et al., 2010; Scherling, et al., 2012). Breast
cancer patients were less accurate and slower in the high demand condition of a verbal working memory task and displayed increased activity in the prefrontal cortex and in additional recruitment during more demanding tasks compared to healthy controls (Cimprich, et al., 2010). The other study found less neural activity in the left cerebellar 'tonsil', important in impulsivity control, in pre-chemotherapy patients compared to healthy controls. This was significantly correlated to response inhibition performance, a task that can be affected by problems in speed of processing or executive control (Scherling, et al., 2012). This reduced activity was not associated with cortisol levels but was significantly associated with days since surgery. This showed that it is premature to attribute chemotherapy as the sole mechanism for impairment, as there are pre-chemotherapy differences that could relate to surgery or anaesthesia, or other factors such as pain, fatigue or psychological distress.

These studies highlight the importance of obtaining baseline assessments of breast cancer patients before treatment in order to gain a clearer picture of the nature and course of impairment and the contribution of chemotherapy. However, these studies do not answer the question of whether problems found prior to treatment are further exacerbated by chemotherapy, and whether the pattern of deficits is different. Furthermore, while women with nonmetastatic breast cancer are not expected to experience cognitive dysfunction, so their performance is expected to be similar to age-matched normative data or healthy controls, these cohorts fail to control for potential differences related to the cancer itself, surgery or the psychological impact of diagnosis. The inclusion of a control group of breast cancer patients not receiving chemotherapy, as well as the prospective evaluation of cognitive change before and after treatment, is more able to help clarify the nature and mechanisms for impairment.

2.4 Longitudinal findings

Longitudinal designs involve observation of the same cohort over time, using repeated measurements. The benefit of this type of research design is that it allows an examination of changes over time at both a group and individual level. Longitudinal studies in the field can be divided into those with: baselines conducted during or following treatment; or prospective studies where baselines were conducted prior to the commencement of chemotherapy. Prospective studies enable the assessment of cognitive changes associated with exposure to treatment.
2.4.1 Longitudinal studies with post-chemotherapy baseline

A number of groups that had previously conducted cross-sectional studies during or post-chemotherapy, conducted follow-up studies on some or all of these participants to examine the course of cognitive dysfunction over time in breast cancer survivors (Kreukels, Hamburger, et al., 2008; Kreukels, et al., 2006; Mar Fan, et al., 2005; O'Shaughnessy, 2002; Reid-Arndt, et al., 2009; Schagen et al., 2002; Schilder et al., 2009; Vardy et al., 2006; Weis, Poppelreuter, & Bartsch, 2009). Some involved the same neuropsychological assessment, and therefore continued to use screening measures (Mar Fan, et al., 2005; O'Shaughnessy, 2002). These studies in general have shown neuropsychological deficits during or after chemotherapy, with improvement in performance over time.

One study investigated the cumulative impact of chemotherapy and differential hormonal treatment as part of randomized trial of hormonal treatments in post-menopausal survivors who had completed AC chemotherapy treatment two years previously (Schilder, et al., 2009). The study found that the sequential use of chemotherapy and hormonal treatments was associated with lower verbal fluency and information processing compared to healthy controls.

The Netherlands group examined reaction time and P3 amplitude and latencies on breast cancer survivors around 5 years post-chemotherapy who had been originally assessed one to two years following the completion of standard dose (Kreukels, van Dam, et al., 2008) or high dose chemotherapy regimens (Kreukels, et al., 2006). They found that women who had been assessed as cognitively impaired one year following standard-dose chemotherapy had significantly longer P3 latencies, lower P3 amplitudes and slower reaction times with less accuracy when assessed five years following completion of standard dose chemotherapy, compared to women who were assessed as cognitively unimpaired one year post chemotherapy (Kreukels, van Dam, et al., 2008).

However, without a pre-chemotherapy baseline and appropriate control group, it is not possible to determine from these studies whether cancer and the development of cognitive problems share common risk factors, whether the cognitive deficits found after chemotherapy can be ascribed to those found prior to chemotherapy or whether women with cognitive deficits before chemotherapy are more vulnerable to the effects of chemotherapy. Nevertheless, to understand the cognitive effects of chemotherapy, it is
necessary to measure pre-treatment functioning and to examine changes following treatment by using a prospective study design.

2.4.2 Prospective studies (pre-chemotherapy baseline)

Early prospective studies used small heterogenous samples to assess the effects of chemotherapy on cognitive function with a limited range of tests. One early study examined ten patients (60% with breast cancer) before and after chemotherapy (24 hours and 1 month) on four subtests (Oxman & Silberfarb, 1980). There were no significant differences found after chemotherapy but this was a small heterogenous sample tested three times over a month using a brief assessment, where the effects of practice were not controlled. Further studies were recommended that examined more consistent regimens in homogenous populations (i.e., patients with the same cancer).

The first prospective study of women with early breast cancer

The first published prospective study of women with breast cancer was conducted using a small sample \( N = 18 \) tested before and after chemotherapy (3 wks, 6 months and 1 year post-chemotherapy) (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Three subjects (17%) did not complete the long-term assessment. There was no significant deterioration in average group performance between baseline and follow-up. In fact, performance on all cognitive measures either remained constant or significantly improved. However, without a control group it cannot be ruled out that the improvement on retesting may be explained by practice effects, a limitation of repeated cognitive testing.

Approximately one-third of women exhibited cognitive impairment prior to chemotherapy (defined as z-score \( \leq -1.5\) SD below age-adjusted test norms on 2+ tests, or z-score \( \leq -2\) SD on 1 test) that was not associated with mood, demographic characteristics or clinical factors. Immediately post-chemotherapy 61\% \( (n = 11) \) of women exhibited a decline relative to baseline in one or more domains, with almost half \( (n = 5) \) of these improving by a year after chemotherapy, whereas half remained below baseline (prechemotherapy) performance.

The interpretation of these results is complicated not only by the small sample size and the lack of an appropriate comparison group to control for effects of distress, disease and practice, but also because half the sample went on to have a further four cycles of chemotherapy (methotrexate/vinblastine) between the ‘post-chemotherapy’ short and long term follow-up. Furthermore, the probability of false-positive classification increases with the number of measures used and normal test-retest variability means it is likely that
an individual will display a poorer re-test score on at least one of 15 tests without it representing an underlying deficit. Interestingly, the authors determined that nearly half the sample would not have been classified as having experienced a decline in cognitive function based on post-chemotherapy evaluations alone had they not undergone baseline cognitive assessment. The significance of the claim that chemotherapy can impair cognitive function underscores both the need for pretreatment assessment in determining the impact of treatment on cognitive functions but also the need for methods that account for normal variability over time.

Other prospective studies

More recently, a number of prospective studies evaluating patient's performances before and after chemotherapy have been published. Some of these studies did not include a control group or used only normative data for comparison (Gottschalk, Holcombe, Jackson, & Bechtel, 2003; Hurria, Zuckerman, et al., 2006; Iconomou, Mega, Koutras, Iconomou, & Kalofonos, 2004; Rolfe, Mengersen, Vearncombe, Andrew, & Beadle, 2011; Ruzich, Ryan, Owen, Delahunty, & Stuart-Harris, 2007; Vardy, et al., 2006). Some studies included a breast cancer control group (Ahles, et al., 2010; Bender et al., 2006; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009a; Hedayati, Alinaghizadeh, Schedin, Nyman, & Albertsson, 2012; Hermelink et al., 2008; Mehlsen. Pedersen. Jensen. & Zachariae. 2009; Quesnel, Savard, & Ivers, 2009; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006; Stewart et al., 2008; Tager et al., 2010; Vearncombe, et al., 2009) and/or a healthy control group (e.g., Collins, MacKenzie, Tasca, Scherling, & Smith, 2013; Debess, Riis, Engebjerg, & Ewertz, 2010). One included a cardiac patient control group to attempt to control for the effects of surgery (Mehlsen, et al., 2009). Breast cancer control groups included those: receiving local therapy (surgery and radiation therapy only); hormonal therapy only; not receiving chemotherapy; and high risk patients receiving high-dose chemotherapy. Most controlled for gender but one study compared an all female breast cancer study group with males in the control groups including an all male cardiac control group in an attempt to control for the effects of surgery (Mehlsen, et al., 2009). Using such a comparison group can make findings difficult to interpret, not only because cardiac surgery involves a risk of hypoxia unlike breast cancer surgery, but also because some neuropsychological tests are susceptible to the influence of gender (Lezak, et al., 2012).

Assessment points have ranged from pre-diagnosis (Hedayati, et al., 2012) or pre-surgery (Hermelink, et al., 2008) to 18 months following the completion of chemotherapy (Ahles, et al., 2010; Rolfe, et al., 2011). Most baseline assessments, though, were conducted prior to chemotherapy and post-surgery. One study conducted a mixed pre- and post-treatment
baseline, assessing some cancer patients first prior to chemotherapy and others, who were younger, after the first cycle of chemotherapy, combining these in the analysis as the baseline evaluation (Eberhardt et al., 2006). This is not considered a pre-treatment cognitive baseline and are not considered here as prospective studies. Around one-third of final assessments were conducted immediately following the completion of chemotherapy so they assessed only short-term effects and three-quarters of final assessments were conducted within 6 months following the completion of chemotherapy, assessing short to medium-term effects. Most studies assessed the control group at similar timepoints and intervals between assessments but some did not (Quesnel, et al., 2009; Schagen, et al., 2006; Vearncombe, et al., 2009).

Some studies relied on very brief cognitive screening tests, such as the Mini-Mental State Examination, that was designed to screen for substantive impairment such as dementia (Iconomou, et al., 2004), or new tests that do not have established validity (Gottschalk, et al., 2003), or a restricted range of tests (e.g., Hedayati, et al., 2012; Rolfe, et al., 2011). Some included tests susceptible to practice effects but did not include parallel or alternate forms to minimize these effects (e.g., Stewart, et al., 2008). Even the assessments that included a broader range of cognitive domains conducted less detailed assessments than those in cross-sectional studies, with around eight tests. Neuropsychological tests frequently yield multiple outcome measures that help to differentiate impairment in different processes or functions. Concerns that multiple measures increase the chance of false positive (Type I) errors appear to have led more often to the selection of a single test score to represent a domain. Ahles et al (2008 & 2010) instead applied a well-established multivariate method, Principal Components Analysis (PCA), to their neuropsychological assessment data to derive a smaller number of linearly independent components that explained as much variance in the data as possible. These were identified as representative of nine cognitive domains. The nine domain summary scores were then used in further analysis. PCA has great potential in neuropsychological research to help reduce the dimensionality of rich test outcome data and decrease the chance for Type 1 error.

Several studies did not report details of the testing environment (Bender, et al., 2006; Collins, et al., 2009a; Iconomou, et al., 2004; Stewart, et al., 2008; Wefel, Lenzi, Theriault, Davis, et al., 2004), making it impossible to determine if test administration was conducted in an appropriate, standardized setting. Of those that did, some reported using different convenience settings for assessments (e.g., hospital or patient’s home) (e.g., Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005; Vearncombe, et al., 2009) which can compromise the reliability and interpretability of the test results. In hospital or a home,
the examiner has little to no control of the test environment, including lighting, temperature, background noise or interruptions, which can all affect performance on a test. Testing an individual in such settings is dramatically different from the standardized, quiet, controlled test environment in which the normative test data are typically obtained. Environmental factors like noise, heat and indoor lighting have been found to negatively effect cognitive performance (Hygge & Knez, 2001). Uncontrolled environments can threaten test result reliability not only between subjects but within subjects. It is nearly impossible to determine if there has been any change in the subject’s cognitive functioning if the testing conditions were different between assessments or to determine whether differences in test performances between individuals are due to cognitive or environmental differences.

Ages of participants ranged from 25 to 84, although most studies used an age cut-off of around 65 to reduce the risk of mild cognitive impairment or dementia associated with ageing confounding interpretation of the results. However, some studies have specifically focused on the cognitive effects of chemotherapy in postmenopausal (Stewart, et al., 2008; Tager, et al., 2010) or older women (Hurria, Zuckerman, et al., 2006). While postmenopausal chemotherapy patients performed within the normal range, they were found to be 3.3 times more likely to show reliable decline than hormonal therapy patients (Stewart, et al., 2008). The mechanism may not be a direct effect of treatment as chemotherapy patients that declined were less educated and had higher depression scores at baseline than those that did not.

Sample sizes have ranged from 12 (Gottschalk, et al., 2003) to 177 (Ahles, et al., 2010) to a population-based study with a sample size of 328 (Debess, et al., 2010). Attrition rates have been variable ranging from 8% (Hedayati, et al., 2012) to 52% (Bender, et al., 2006) with studies showing high rates of attrition (≥30%) having longer lengths of follow-up (≥ one year post-chemotherapy).

Baseline comparisons

In some prospective studies there was evidence of cognitive impairment in women with breast cancer before the start of chemotherapy, either in lower group performance or in the proportion of individuals showing impairment (22 - 50% depending on criteria used) (Ahles, et al., 2008; Hedayati, et al., 2012; Hermelink, et al., 2008; Quesnel, et al., 2009; Rolfe, et al., 2011; Ruzich, et al., 2007; Tager, et al., 2010; Vardy, et al., 2006; Wefel, Lenzi, Theriault, Buzdar, et al., 2004). Impairment was most consistently found in the domain of speed of processing (Ahles, et al., 2008; Hedayati, et al., 2012; Rolfe, et al., 2011; Ruzich, et al., 2007). This is consistent with cross-sectional pre-chemotherapy neuropsychological
and neuroimaging studies (e.g., Cimprich, et al., 2010). Some studies found declines in other functions or domains, such as working memory, attention, learning and memory or executive functions (Ruzich et al., 2007; Hermelink et al., 2007; Tager et al., 2010). Poorer performance on these tests may be an effect of slower speeds of processing but this was not explored. While the observed impairments have been unrelated to depression, anxiety, fatigue or surgical factors, there has been no definitive explanation. Some candidate mechanisms that have been used to explain these results include: cancer or neuroimmunological characteristics, general anaesthetics or elevated cytokines (proteins released by the immune system that play a key role in immune response) (e.g., Miller, et al., 2008; Vardy et al., 2007).

However, some of the larger prospective studies found no significant differences between the neuropsychological performance of women with breast cancer and healthy controls prior to chemotherapy (Schagen et al., 2006; Jenkins et al., 2006). It is not clear what accounts for this discrepancy in findings between studies; whether it is due to the nature of the assessment, differences in assessment time points or methods that take more account of normal variability in test performance over time.

Importantly, two studies found cognitive performance in breast cancer patients below normative means or healthy controls before definitive cancer diagnosis (Hedayati et al., 2012) or surgery (Hermelink et al., 2008) that was unrelated to anxiety or depression scores, suggesting deficits may be related to the cancer itself. Performance was poorer on tests of processing speed or response speed (Hedayati et al., 2012; Hermelink et al., 2008) and sustained attention and cognitive flexibility (Hermelink et al., 2008). Average cognitive performance did not decline in women after diagnosis and surgery in either of these studies. However, approximately one-quarter of women showed a decline in cognitive performance, with no consistent pattern of deficits. The influence of treatment-induced menopause was investigated and found to be unrelated to cognitive decline. There was a significant interaction effect found in the study which used a control group (Hedayati et al., 2012). Attentional performance improved on retest after surgery in women who had undergone a diagnostic lumpectomy but did not receive a breast cancer diagnosis, while women recently diagnosed and surgically treated for breast cancer did not improve. Therefore, the failure to attain a practice effect may be an indicator of cognitive deterioration that is only evident with a control group. Deficits found prior to cancer surgery raise the question of whether there is a shared biological mechanism contributing to the development of cancer and cognitive decline; or inflammatory effects associated with the cancer; or whether psychological mechanisms have been adequately assessed.
In studies that found evidence of impairment post-surgery and prior to chemotherapy, three found significant deterioration in average verbal memory performance immediately following chemotherapy (Shilling et al., 2005; Ruzich et al., 2007; Vearncombe et al., 2009) which returned to baseline at six months following the completion of chemotherapy (Ruzich et al., 2007; Vearncombe et al., 2009). Declines or poorer performance were also found in either verbal ability summary performance (Ahles et al., 2010), verbal working memory (Shilling et al., 2005) or verbal abstract reasoning (Vearncombe et al., 2009) following chemotherapy. One study used Bayesian growth models to assess the degree of recovery in verbal learning and memory in women receiving chemotherapy (Rolfe et al., 2011). They found a near complete recovery for learning and around 60% recovery for verbal memory at 18 months post-chemotherapy, indicating a prolonged period of reduced functioning. Other studies found only transient decline immediately following the completion of chemotherapy and significant improvement in other domains, such as language, visual recall and executive functions (e.g., Ruzich et al., 2007), or no further evidence of decline in average performance at the group level (e.g., Wefel, Lenzi, Theriault, Davis, et al., 2004). However, repeated administration of many neuropsychological tests lead to improvement in performance due to the effects of practice and the lack of a control group does not account for these effects.

When performance following treatment has been compared to baseline, women treated with chemotherapy have shown declines in isolated abilities that improve over time, while other functions remain the same or display improvement. While the results are mixed there is some suggestion there may be a transient impact of chemotherapy on verbal functions. This picture could be obscured by the possibility of practice effects in repeated neuropsychological assessments. Comparisons of cognitive change between groups over time can help to take account of the confounding effects of practice.

**Group comparisons of neuropsychological performance over time**

Comparison of cognitive performance or change between groups following treatment has presented a different profile from prospective studies compared to retrospective studies. Results of published prospective studies are presented in Table 2.2 that analyzed differences in group performance following standard-dose chemotherapy. Studies are included where neuropsychological tests covered at least three cognitive domains. Where results were published regarding the same study at different stages (e.g., Shilling et al., 2005 & Jenkins et al., 2006; Stewart et al., 2008 & Collins et al., 2009) only the final results are presented.
When cognitive performance is compared over time between women that have been treated with chemotherapy and those that have not, the profile of impairment is more limited in scope than from retrospective studies (see Table 2.2). Verbal abilities, verbal working memory and verbal fluency were substantially poorer in women following chemotherapy in some studies compared to women not treated with chemotherapy or healthy controls. These changes can be subtle with simply a failure to show benefit from practice indicating impairment.

Table 2.2

*Differences in Average Performance in Women Following Standard-dose Chemotherapy Compared to Controls as found in Prospective Studies by Cognitive Domain*

<table>
<thead>
<tr>
<th>Study</th>
<th>Time since last chemotherapy</th>
<th>Loss to follow-up</th>
<th>Comparison group</th>
<th>Language</th>
<th>Motor</th>
<th>Visuocognition</th>
<th>Attention and Speed of Processing</th>
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1 Studies identified by first author and year of publication.

w = week; Dro = month; y = year; Cx = During chemotherapy, after each cycle of treatment; PC= post-chemotherapy.

X Chemotherapy group < control group. Significance level = p < 0.01; X Significance level = p < 0.05;

X Chemotherapy group > control group. Significance level = p < 0.01; N.S = Not significant.

NC = No chemotherapy; HT = Hormonal therapy; HC = Healthy controls; LT = Local therapies (surgery ± radiation therapy); Car = Cardiac patients post-surgery; CIM = Chemotherapy-induced menopause.

T2 = Time 2 – first assessment following chemotherapy; T3 = Time 3 – second assessment following chemotherapy.

* time intervals between assessments differ to study group. nr = not reported.
One study found that women who were not exposed to chemotherapy and the healthy control group improved significantly over time on Verbal Ability. However, women exposed to chemotherapy failed to improve shortly following chemotherapy but improved at the following timepoints (Ahles et al., 2010).

Subtle differences have also been found in processing speed, verbal working memory and visual memory (Bender, et al., 2006; Collins, et al., 2009a). Bender et al. (2006) examined cognitive performance in chemotherapy patients who were receiving or not receiving hormonal therapy. They found even poorer verbal working memory and visual recall in those receiving hormonal therapy, suggesting there may be an interactive effect.

Some prospective studies have reported chemotherapy-related cognitive impairment in executive functions, namely verbal fluency or abstract reasoning, following chemotherapy (Quesnel et al., 2009; Vearncombe et al., 2011), while several other studies have found no differences in executive functions between groups. One found the chemotherapy group performed better than healthy controls (Collins et al., 2009).

These findings are far from consistent. For each significant finding within a domain there are many more non-significant results reported in the same domain. In a number of studies the standard-dose chemotherapy group did not perform significantly worse than the control group/s following the completion of chemotherapy on any test (Jenkins, et al., 2006; Mehlsen, et al., 2009; Schagen, et al., 2006; Wefel, Lenzi, Theriault, Davis, et al., 2004) or actually performed better. This has been found in other studies as well (Debess et al., 2010; Rolfe et al., 2011; Hermelink et al., 2008). This has cast doubt on whether chemotherapy has any negative effect on cognitive function.

A recent study assessed women before treatment and then after each cycle of chemotherapy (Collins, et al., 2013). After controlling for baseline performance, women showed a significant progressive decline over the course of chemotherapy treatment compared to a healthy control group. Decline was found in overall cognitive performance, as well as domain-specific summary scores. The greatest decline was found in working memory and processing speed, followed by verbal memory and visual memory. This provides support for a dose-response relationship, but does not provide any information on the duration or course of impairment following chemotherapy.

Schagen et al. (2006) conducted a large prospective study of high risk breast cancer patients who were randomly assigned to receive standard-dose FEC chemotherapy or high dose CTC chemotherapy. Their performance was compared to local therapy or healthy controls before and 6 months post treatment. More women in the high-dose
Chemotherapy group showed a deterioration in performance over time, with the strongest effects found in executive functions. However no such differences were observed between the standard-dose chemotherapy group and the no-chemotherapy group or the healthy controls. Details on the tests used in this study and the test results were not reported so it is still not clear whether this provides evidence of a dose-response effect but the tests were not sensitive to subtle changes associated with exposure to standard-dose chemotherapy.

Prevalence of individual decline between groups

When the incidence of cognitive decline or impairment has been examined, a proportion of women have demonstrated cognitive decline following chemotherapy. The incidence of decline or impairment found following the completion of chemotherapy has ranged from 17% (Vearncombe et al., 2009) to 66% (Wefel, Lenzi, Theriault, Davis, et al., 2004) depending on the criteria used (reliable decline using reliable change indices with correction for practice effects on 2+ measures; or decline relative to baseline in 1+ tests, respectively). In most studies the proportion of breast cancer patients found to decline was small (around 20-25%) and found on multiple measures with improvement generally at longer term follow-up. Again, findings are not consistent. Other studies, in contrast, have found that the prevalence of individuals showing impairment or decline did not differ significantly between those who received standard-dose chemotherapy and control groups (Jenkins et al., 2006; Mehlsen et al., 2009; Schagen et al., 2006; Hermelink et al., 2008). Schagen et al. 2006 found that significantly more women receiving high dose chemotherapy experienced decline in cognitive performance over time compared to healthy controls, with measures of executive functions showing the strongest effects.

Predictors of cognitive decline after chemotherapy

Overall decline or impairment has been unrelated in most studies to self-report, demographic variables (e.g., age, education), psychological variables (e.g., anxiety, depression), QOL, health/disease characterisitics (e.g., haemoglobin levels, biological markers, cancer), treatment characteristics (e.g., surgery/anaesthesia, chemotherapy or hormonal treatment), menopausal status or treatment-induced menopause. Individual studies, however, have found associations between cognitive decline and: age, estimated IQ or lower education (Ahles et al., 2010; Debess et al., 2010; Stewart et al., 2008); baseline depression scores (Stewart et al., 2008; Vearncombe et al., 2009); increased anxiety and reductions in haemoglobin levels (Vearncombe et al., 2009); treatment-induced menopause (Jenkins et al., 2006); higher chemotherapy dose (Schagen et al., 2006); and the cumulative effects of hormonal therapy following chemotherapy (Ahles et
al., 2010; Bender et al., 2006; Collins et al., 2009). The effects of specific mechanisms, such as treatment-induced menopause, have been examined directly. One study examined treatment-induced menopause as a result of pre-operative chemotherapy, surgery or hormonal therapy and found that it did not negatively affect cognition (Hermelink et al., 2008). Instead, treatment-induced menopause favourably influenced a Letter Fluency/ Switching condition in a test of cognitive flexibility.

Some candidate mechanisms have been proposed such as differences in cognitive reserve that predispose patients to poorer performance under cognitive load both prior to and after completion of treatment (Ahles & Saykin, 2007). A large study examined the impact of cognitive reserve (measured by estimated premorbid IQ) and age on cognitive change in women being exposed to chemotherapy compared to those not exposed to chemotherapy and healthy controls at 1, 6, and 18 months after treatment (Ahles et al., 2010). A significant interaction effect was only found in Verbal Ability summary performance, with poorer performance observed shortly following chemotherapy. However, when the interaction of treatment group and age and/or premorbid IQ was examined it was found that women who were older (60-70) and/or had lower estimated premorbid ability (WRAT-3 < median) performed significantly worse on Processing Speed following chemotherapy compared to controls. This was unrelated to self-report or other possible explanatory factors, such as menopausal status, depression, anxiety or fatigue. This suggests that pre-treatment cognitive reserve and age could influence outcomes from chemotherapy treatment.

These studies raise methodological issues specific to repeated neuropsychological assessments involved in prospective designs that can confound inferences about the presence of change. Most neuropsychological tests have been designed for the purposes of a single assessment and they can be vulnerable to practice or learning effects on repeated administration or can even fail to assess the same function, as in tests that assess planning and response to a novel task. Without a control group it cannot be ruled out that the improvement on retesting are explained by practice effects and a lack of improvement may indicate an impairment.

They also raise issues regarding the use of control groups that may not be appropriate for the comparison of cognitive performance. In treatment studies that include a control group drawn from a similar population who do not receive the study intervention, assessed at the same times on the same tests under the same conditions, practice effects and other disease-related factors can be accounted for to some extent. To date, a consistent profile of chemotherapy-related cognitive impairment has not emerged. This is likely related to methodological shortcomings. This means an appropriate control cohort
needs to be examined at the same timepoints and intervals and neuropsychological assessments need to be comprehensive covering multiple domains. Neuropsychological tests need to be selected that are designed to be able to detect mild cognitive impairment and measure change, including using alternate forms where the test is susceptible to practice effects.

2.4.3 Neuroimaging studies

Neuroscientists have been making progress in identifying underlying brain structures that change after administration of chemotherapy. Both structural and functional imaging have been used to compare women with breast cancer receiving chemotherapy to those not receiving chemotherapy and healthy controls before and 1 month and/or 1 year following chemotherapy or at similar time frames (Conroy, McDonald, Ahles, West, & Saykin, 2013; B. C. McDonald, et al., 2010; B. C. McDonald, Conroy, Ahles, West, & Saykin, 2012; B. C. McDonald, et al., 2013). Cancer patients displayed baseline group differences showing more activity in the bilateral frontal lobes, with pre-chemotherapy patients displaying more activity in the right inferior frontal lobe (B. C. McDonald, et al., 2012). There were no performance differences found between groups on the fMRI working memory task, yet the chemotherapy group showed a deterioration in high task load conditions 1 month following chemotherapy compared to baseline. Both breast cancer groups showed grey matter declines at 1 month post-chemotherapy compared to healthy controls, but with a different profile of results. Chemotherapy treated patients showed decreased grey matter particularly in frontal regions, some of which recovered at one year post-chemotherapy. A further larger study found frontal grey matter changes shortly following chemotherapy were associated with self-reported executive changes (B. C. McDonald, et al., 2013), while another found increased activation in women who experienced chemotherapy-induced menopause suggestive of effective compensation (Conroy, et al., 2013). Another prospective study also found baseline differences, with pre-chemotherapy patients showing less activation of the anterior cingulate than controls on a verbal recall task (Lopez Zunini, et al., 2012). There were also changes in brain activation following chemotherapy but not in controls. Importantly days since surgery, fatigue, anxiety and depression accounted for some of these differences, especially prior to chemotherapy, but after controlling for these variables, they found chemotherapy played a significant part in changes in brain activation.

One study imaged breast cancer patients before and 3-4 months after chemotherapy treatment (Deprez et al., 2012). Deterioration was evident in several white matter tracts, including the corpus collosum, which connects the left and right hemispheres, the superior
longitudinal fasciculus, which carries neuronal traffic between the frontal and parietal cortices, needed for execution of executive function tasks; and the ‘forceps major’, which connects the occipital lobes. Brain alterations in these areas were significantly associated with changes in attention and verbal learning and memory. They did not find significant differences in baseline performance between the chemotherapy group and healthy control group after controlling for premorbid IQ and depression. However, when the covariate for depression was removed, significant differences in attention were found. This may indicate that impaired scores pre-chemotherapy are related to emotional processes.

Prospective studies using structural and functional imaging are relatively recent and have revealed further empirical evidence of a significant impact of chemotherapy on neural structure and function. The direction of this activation is varied, though, with some studies showing increased activation and others showing decreased activation compared to controls or over time. These studies again highlight the importance of baseline assessments of patients before treatment in order to determine any changes to cognition associated with exposure to chemotherapy and of assessing confounding or moderating variables such as days since surgery, fatigue, anxiety and depression that may contribute to cognitive problems at different stages.

### 2.4.4 Relationship to self-report and distress

A consistent finding across studies has been that self-reported cognitive problems are unrelated to objective tests of cognitive function, but are significantly associated with psychological distress, including anxiety and depression. This suggests that the perception of cognitive problems may not be a good indicator of actual impairment but more likely reflects emotional distress.

Most subjective measures of cognitive function have items that focus predominantly on memory and concentration problems. These are also the domains on which most objective testing has focused. If both subjective and neuropsychological batteries focus on memory or concentration functions but do not assess and differentiate other cognitive functions it is harder to establish any relationship between subjective and objective impairment.

Other psychological mechanisms may moderate perceived cognitive problems, such as expectations of impairment. Studies of health-related expectations, including placebo studies, indicate that the expectation of side effects before taking medication can contribute to perceived symptoms after treatment (Barsky, Saintfort, Rogers, & Borus, 2002; Flaten, Simonsen, & Olsen, 1999). Cancer chemotherapy side effects are highly variable and for any group of patients receiving identical regimens, only some will
experience the toxicities associated with that regimen. Pretreatment expectation of
toxicity has been associated in a number of studies with perceived toxicities post-
chemotherapy, although findings relating to vomiting have been inconsistent
(Andrykowski & Gregg, 1992; Cassileth et al., 1985; Roscoe, Hickok, & Morrow, 2000). One
study that examined a wider range of chemotherapy toxicities, including problems with
concentration, found a strong association between pre-treatment expectations of toxicities
and post-chemotherapy experiences of cognitive problems (Olver, Taylor, & Whitford,
2005). Patients with pre-existing knowledge of chemotherapy-associated cognitive
complaints also reported significantly more cognitive complaints than those without this
knowledge and priming of the ‘chemobrain’ schema significantly increased reporting of
complaints in women without a history of chemotherapy (Schagen, Das, & van Dam,
2009).

While chemotherapy-related cognitive impairment or decline has overwhelmingly not
been associated with psychological distress, including anxiety or depression scores, there
have been individual studies that have found associations with baseline depression scores
and anxiety scores (e.g., Vearncombe, et al., 2009); emotion-focused coping strategies
(Ayala-Feliciano, et al., 2011) or amount of intrusions, using a posttraumatic stress
disorder checklist (Schirmer, et al., 2009). However, the direction of cause-and-effect in
these relationships is not clear from these studies. Cognitive decline related to
chemotherapy could be a cause of distress.

The assessment of depression and anxiety in cancer patients is problematic as most
surveys of anxiety and depression rely heavily on somatic symptoms (e.g., weight or
appetite changes, insomnia, fatigue, loss of energy, racing heart, sweating, nausea,
dizziness, shortness of breath, diarrhoea) that can relate to the disease process in cancer
or treatment side-effects. This reduces the sensitivity of many survey measures to detect
depression or anxiety in this population. Most of the measures of depression and anxiety
that have been used in the field include physiological or somatic symptom items, such as
the Centre for Epidemiological Studies Depression Scale (CES-D), the Beck Depression
Inventory (BDI) or the State-Trait Anxiety Inventory (STAI). Higher scores do not then
necessarily reflect psychological distress or higher anxiety or depressive symptoms due to
the lack of specificity of somatic items. Surveys that do not include somatic items, such as
the General Health Questionnaire (GHQ) and the Hospital Anxiety and Depression Scale
(HADS), are more appropriate for assessing levels of psychological distress in cancer
patients. The HADS was recommended by the British Medical Council’s Cancer Therapy
Committee Working party on QOL for use in cancer studies (Maguire & Selby, 1989).
The role of clinical anxiety and depression in cognitive impairment warrants further investigation because clinical levels of anxiety and depression are known to decrease performance on neuropsychological tests, as well as increase vulnerability to stressors and brain injury (Lezak et al., 2012). Only the initial study by Wiencke and Dienst included a structured clinical interview to assess clinical anxiety and mood disorders in order to examine their relationship to objective impairment.

2.5 Meta-analyses

Meta-analyses can help integrate findings from published studies to assess the nature and severity of neuropsychological impairment observed in cancer patients treated with adjuvant chemotherapy. Some meta-analyses have been conducted to date that have studied the neuropsychological effects of chemotherapy or systemic cancer treatment with either a broader or more restrictive scope.

Anderson-Hanley et al. (2003) evaluated 30 studies that examined the cognitive effects of various systemic cancer treatments in a range of cancers (e.g., breast, lung, prostate) in adult populations. Almost all effect sizes across cognitive domains were in the negative direction indicating a general trend towards decrements in functioning in cancer patients who had received systemic cancer treatments, although these effect sizes ranged from negligible to large. Moderate to large negative effect sizes were found across normative and control group comparisons for motor function, verbal memory and executive functions. In contrast, baseline comparisons yielded no significant effects across the seven cognitive domains. The heterogeneity of cancer diagnoses and treatments makes interpretation of these analyses difficult. Jansen et al. (2005) evaluated 16 studies of the effects of chemotherapy alone on cognitive function in various cancers and again calculated effect sizes for each test by method of comparison (normative data, baseline data, or control group). Only one domain, visual memory, demonstrated significant impairment across all comparison types. When compared with normative data, significant effect sizes were also found in speed of processing, verbal memory and executive functions. When compared with healthy controls, small significant effect sizes were found in language and verbal memory. Most deficits ranged from small to moderate but three-quarters of studies were retrospective cross-sectional designs. Hodgson et al. (2013) included 13 studies of the cognitive effects of chemotherapy in a range of cancers where subjects were without current anxiety or mood disorders and had not had radiation or hormonal treatment. Nearly three-quarters of the sample were women with breast cancer. They found evidence for cognitive impairment following chemotherapy in executive functioning and memory, although the effect size was small. No relationship was found
between cognitive functioning and time since treatment but there was a significant negative relationship with treatment duration. A limitation of these meta-analyses is their non-specificity with respect to a particular cancer diagnosis or treatment.

Only three meta-analyses have examined the cognitive effects of adjuvant chemotherapy in women treated for breast cancer alone. Falleti et al. (2005) identified six studies (five cross-sectional and one prospective) meeting criteria. Small to moderate effect sizes were found in the cross-sectional studies indicating poorer average performance across domains in women who had received chemotherapy for breast cancer compared to controls, with effect sizes negatively associated with time since last chemotherapy treatment. Small to large effect sizes were found in the one prospective study, indicating improvements in cognitive function from the beginning of chemotherapy to three weeks and one year following treatment, indicative of practice effects. Methodological limitations were noted in the research, including the lack of a control group and alternate forms in the prospective study to control for practice effects. Stewart et al. (2006) identified seven studies, including the same one prospective study, and found similar results.

Finally, Jim et al. (2012) conducted a meta-analysis of 17 studies of breast cancer survivors in the post-chemotherapy period who had been treated with chemotherapy at least six months previously. These included findings from retrospective and prospective studies. Women who had been treated with chemotherapy performed worse than healthy controls on tests of verbal ability and worse than breast cancer survivors not treated with chemotherapy on visuospatial ability, although the effect sizes were small. This finding is in marked contrast to previous meta-analyses where impairments were found in multiple domains, including memory and executive functions. Eight of the 17 studies included a pre-chemotherapy baseline, but only four of these included a control group. Small to no differences were found in women following chemotherapy compared to their own pre-chemotherapy baseline. However, many of the individual tests used to create the effects sizes are known to be susceptible to practice effects on repeated assessment using the same form (e.g., WCST, COWAT, CVLT, RAVL, HVLT, Logical Memory, Complex Figure test, Visual Reproduction, Block Design). A longitudinal study of the effect of repeated assessments on 25 commonly used tests of cognitive functioning found clinically relevant ceiling and practice effects in most tests, with the most pronounced improvement from baseline to the second testing timepoint (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). The most pronounced score increases were found in executive functions and learning and memory, whereas changes in visuospatial performance failed to reach significance, pointing to a ceiling effect. Language showed evidence of both
practice and ceiling effects. As the reliability of a meta-analysis depends on the reliability of the data it includes, this might explain the difference in findings.

Meta-analyses have indicated that chemotherapy-treated patients perform poorer across several cognitive domains than normative or study control groups. However, a direct neurotoxic effect of chemotherapy is unclear given that women who receive chemotherapy can have more advanced cancers, longer surgery, more general anaesthetics and also receive radiation and/or hormonal therapy.

In contrast, no such effect has been found from baseline comparisons most likely due to practice or ceiling effects in repeated measurement. These meta-analyses have all pointed out methodological limitations in the research in this area, including non-equivalence of groups at baseline, the lack of comparability of treatment and control groups, the lack of control of practice effects and the inconsistent time between retesting.

2.6 Animal studies

One of the greatest gaps in knowledge is a lack of understanding of the mechanisms that could account for observed changes. Despite the protection of the brain by the blood brain barrier, many mechanisms have been suggested for observed cognitive dysfunction, including direct neurotoxic injury and white matter changes, microvascular injury, deficits in DNA-repair mechanisms, immunological or (neuro)inflammatory processes, neurochemical changes, cerebral blood flow changes, inhibition of neuronal production, oxidative stress, stress-related, hormonal processes or cancer itself (Ahles & Saykin, 2007; Kannarkat, Lasher, & Schiff, 2007). Animal studies can be helpful in shedding light on cellular biological changes in the nervous system associated with toxic drug exposure and allow a systematic study of potential mechanisms in the absence of patient or cancer confounds.

The first animal study of the cognitive effects induced by chemotherapy agents cyclophosphamide or 5-fluorouracil in female rats did not find evidence of impaired learning and memory performance in maze tests or neuronal synaptic function in the hippocampus seven weeks following treatment (G. Lee et al., 2006). Instead, learning performance and long-term potentiation in the hippocampus showed transient improvement, which the authors suggested may be due to the oestrogen cycle and the effects of treatment-induced menopause which can have a positive effect on learning behaviour in rats. However, there was evidence of neuronal dysfunction in the hippocampus during cyclophosphamide treatment. A growing body of experimental animal studies have found that many chemotherapy agents, including cyclophosphamide, methotrexate, 5-fluorouracil, and doxorubicin, especially in combination, are associated
with adverse effects on neurobiology and cognition (for reviews see Monje & Dietrich, 2012; Seigers & Fardell, 2011).

A study examining the effects of methotrexate and 5-fluorouracil on retrieval in mice in a conditioned retrieval task found that exposure to 5-fluorouracil alone led to significantly slower speed of retrieval by day 2, without change to response rates or motivation, and that the combination of both chemotherapy agents produced significantly greater delays than either agent alone (Foley, Raffa, & Walker, 2008).

Studies of exposure to common chemotherapeutic agents or regimens in rats, including methotrexate (Seigers et al., 2008; Seigers et al., 2009), cyclophosphamide and doxorubicin (Christie et al., 2012), and combined CMF (Briones & Woods, 2011), have shown decreased cell proliferation in the hippocampus, a brain region involved in neurogenesis, a process by which neurons are generated from neural stem and progenitor cells. Progressive damage has also been found to white matter tracts (Seigers et al., 2009). These neurological changes have been associated with deterioration in spatial memory performance on a water maze task, independent of the effects of physical activity. One study also found rats treated with methotrexate failed to distinguish a novel object from a familiar one (Seigers et al., 2008).

There has been only one animal study conducted of the newer chemotherapeutic agent, paclitaxel (Taxol). It was found to induce signs of peripheral neuropathy in rats 24 hours after administration but did not impact negatively on speed of processing as measured by a 5-choice reaction time task (Boyette-Davis & Fuchs, 2009). It is possible that treatment-induced CNS damage may only become apparent with time, or may affect other cognitive functions, or behave differently in combination with other drugs.

Decreased hippocampal neurogenesis and damage to subcortical white matter in rodents resulting from exposure to chemotherapy drugs if translated to humans, offers a plausible explanation of cognitive side effects of chemotherapy. However, this does not account for the cognitive impairment found in cancer patients before the onset of chemotherapy.

Animal experiments have made use of healthy animals to test the effects of chemotherapeutic drugs on cognition and biological processes. Yet, these are prescribed as an adjuvant treatment for cancer. One study has found that the presence of a tumour in rats reduced the number of proliferating cells in the hippocampus compared to healthy controls (Seigers et al., 2010). Methotrexate treatment caused a similar decrease in cell proliferation in animals with a tumour and healthy rats. The presence of a tumour did not further enhance the negative effect of methotrexate on hippocampal cell proliferation.
This suggests that while cancer may affect brain function in patients, chemotherapy contributes independently to impairment.

Recent studies have explored possible strategies to prevent or ameliorate the cognitive adverse effects of chemotherapy that also suggest possible mechanisms. Ginsenoside Compound K, a metabolite with anti-tumour and anti-inflammatory properties, has been found to ameliorate the decrease of neurogenesis in the hippocampus in mice following cyclophosphamide exposure (Hou et al., 2013). N-Acetyl cysteine, an antioxidant, has been shown to prevent cognitive decline in rats after combined cyclophosphamide and doxorubicin, suggesting oxidative stress may play a causal role in cognitive impairments (Konat, Kraszpulski, James, Zhang, & Abraham, 2008). Rodent studies have found that fluoxetine, a selective serotonin reuptake inhibitor (SSRI) anti-depressant, increases cell proliferation and neurogenesis in the hippocampus and improves spatial memory performance (Marcussen, Flagstad, Kristjansen, Johansen, & Englund, 2008). A recent study demonstrated that fluoxetine prevented cognitive deterioration and damage to cell proliferation in the hippocampus in rats associated with 5-fluorouracil chemotherapy when administered before and during treatment, but not after (Lyons, ElBeltagy, Bennett, & Wigmore, 2012).

There is evidence that exercise improves cognitive function, by improving mood and by affecting the neural systems that appear to be targeted by chemotherapy, such as cell proliferation in the hippocampus (van Praag, Christie, Sejnowski, & Gage, 1999) and white matter integrity (Marks et al., 2007). A recent study found that the combination of 5-fluorouracil and oxaliplatin chemotherapy had a significant impact on spatial memory and novel object recognition in rats (Fardell, Vardy, Shah, & Johnston, 2012). However, rats who exercised for four weeks post-chemotherapy had improved cognition compared to rats who did not exercise following chemotherapy. This suggests that exercise may prove useful in ameliorating the cognitive effects of chemotherapy. This is supported by a study of a 3-month post-operative resistance training exercise program in a small group of breast cancer patients which found that the exercise group performed significantly better on cognitive tasks at the end of the program than the control group (Baumann et al., 2010).

Reminding strategies by re-exposure to the task appear to re-activate spatial memory traces or help develop compensatory skills. Rats who demonstrated impaired spatial memory performance four months after methotrexate chemotherapy treatment, were able to perform at a similar level to controls after two retraining trials were given (Fardell, Vardy, Logge, & Johnston, 2010). While cognitive retraining is a promising avenue for intervention in cancer patients (e.g., Ferguson et al., 2012), this also suggests that using
the same test on repeated administration is not likely to be sensitive to underlying
impairment and that tests with parallel or alternate forms should be selected wherever
possible.

2.7 Chapter summary

The first study by Wiencke and Dienst in 1995 found 75% of women who had been
treated with chemotherapy for early breast cancer displayed moderate cognitive
impairment. Results of subsequent studies have been mixed and prevalence of impairment
has not replicated the rates of the original study. These studies of chemotherapy-related
cognitive impairment highlight that different neuropsychological pictures emerge from
different study designs. From cross-sectional retrospective studies a profile of diffuse
impairments appear in studies of women who had previously received chemotherapy in
contrast to age-matched normative data or healthy controls. These neuropsychological
impairments are found years after the completion of chemotherapy, and are supported by
structural changes in brain function compared to controls using neuroimaging.
Longitudinal studies examining cognitive change following chemotherapy, using baseline
assessments conducted during or post-chemotherapy, suggest a different picture, with
poorer cognitive function during or immediately following chemotherapy, compared to
control groups, but with performance improving over the year following chemotherapy.
Without a pre-chemotherapy baseline it is not possible to conclude from these studies that
chemotherapy itself disrupts cognitive function. This was supported by the evidence that
women with breast cancer display cognitive deficits, mainly in speed of processing, prior
to the commencement of chemotherapy. While this may be due to the effects of surgery or
general anaesthesia or to psychological distress, two studies found deficits prior to
surgery, unrelated to anxiety or depression.

Neuroimaging studies have confirmed pre-chemotherapy impairments. Some role in
impairment may relate to the disease itself and this is supported by a neuroimaging study
indicating disease severity associated with decreased neural activity. There may be a
complex, multifactorial process with factors such as disease severity, surgery,
chemotherapy and distress playing roles at different stages.

More prospective studies are needed but these are more demanding, costly and take
longer to conduct. Results have been reported recently from prospective studies and
results have been mixed, with some showing impairments in the performance of women
prior to chemotherapy and further deterioration associated with chemotherapy and
others, including larger studies with control groups, have not. The profile of impairment
found following chemotherapy has been more limited and domain-specific, in contrast to
the diffuse profile found across cognitive domains in retrospective studies. However, methodologies have varied. Some have used small samples tested multiple times while others have used larger samples tested once before and once immediately after chemotherapy. Some have included a control group of women with breast cancer not receiving chemotherapy but others have not recruited a control group. Some have not tested the study and control group at the same interval between assessments or included variable test conditions or non-standardized administration. A neuropsychological assessment can be expensive and time consuming, so about half the clinical studies have used simpler but less informative screening measures. These do not enable the examination of a profile of impairment and change across different cognitive domains and functions. There has been an inadequate use of neuropsychological tests sensitive to mild impairment with equivalent alternate forms, particularly in the domain of executive functions.

Most studies have attempted to determine the impact of important explanatory variables, including age, education, fatigue, anxiety, depression, disease severity, type of surgery, hormonal status, hormonal therapy and type of treatment. Most found these variables did not remove or significantly account for the cognitive declines identified in their samples. Many studies have not assessed important moderator variables such as premorbid IQ. Subjective and objective cognitive impairment have been unrelated but subjective cognitive impairment has been associated with psychological distress. It is unclear whether this is due to a lack of sensitivity in the measures being used. Most studies have not used domain-specific subjective measures of cognitive problems. They have often not used tests of anxiety and depression that have adequate sensitivity and specificity in cancer patients or assessed clinical levels of mood disturbance. High rates of attrition have affected many longer term follow-up studies and this can influence the power to detect changes, or introduce bias, affecting the generalizability of the results.

There have only been a few prospective studies using neuroimaging conducted to date and results have been mixed. There has been some evidence of structural changes including deterioration in grey and white matter and pathways associated with executive functioning following chemotherapy. These changes have correlated with deterioration in attention and verbal learning and memory. Retrospective studies have revealed that reductions in grey matter in women following chemotherapy were associated with poorer executive functioning performance.

Most of the animal studies have found that chemotherapeutic drugs are associated with cognitive dysfunction, with more marked effects in combination, although a few studies have failed to find any cognitive effect. Differences in experimental design likely account
for these discrepancies. Despite this, some possible pathways that may contribute to cognitive impairment include inhibition of neurogenesis, white matter damage and oxidative damage. However, it is still too early to conclude whether these pathways are directly affected by treatment or indirectly affected by changes. Overall, the results of human research regarding the effects of chemotherapy on brain functioning are largely consistent with the findings of animal studies.

2.8 Rationale for the current study

The field is developing rapidly in the quality, quantity and diversity of approaches to the topic but results need to be interpreted cautiously because of a variety of methodological limitations, including inadequate research designs or selection of tests. Undoubtedly, given the literature available to date, there is sufficient evidence to be concerned about the possible functional impacts of exposure to standard-dose chemotherapy and further study of neuropsychological changes in women with early breast cancer treated with adjuvant chemotherapy is warranted.

Given processing speed impairments found prior to chemotherapy and the diffuse and variable profile of impairment found following chemotherapy in retrospective studies, there is a need for more well-designed prospective studies using comprehensive neuropsychological assessments. Studies are needed that include a comprehensive clinical neuropsychological assessment sensitive to mild cognitive impairment and decline across a range of cognitive domains, with an appropriate control cohort tested at similar timepoints in a standardized setting, with an adequate assessment of anxiety and depression, as well as possible moderating variables, and follow-up longer than immediately following the completion of chemotherapy. This was the rationale for this study.

This thesis describes a prospective study of cognitive functioning over time in women with early breast cancer receiving chemotherapy compared to those not receiving chemotherapy, using a comprehensive clinical neuropsychological assessment that was designed to be sensitive to mild cognitive impairment in a range of cognitive domains, including executive functions, and minimize ceiling and practice effects.

The following two chapters outline the methods and procedures used in the study, including details of: the design; the participants; the measures; the setting; the materials and process for gaining informed consent; and the procedure for conducting the clinical and neuropsychological assessments.
Methods and Measures

The aim of the study was to assess the impact of adjuvant chemotherapy treatment on cognitive function in women with early breast cancer. This study used a prospective, cohort design to compare changes in cognitive function in women who were receiving chemotherapy with women who were not receiving chemotherapy, following surgery for early breast cancer. This chapter describes the design, the pilot study development, the participants and the final measures used in the study.

3.1 Research design

The randomized controlled, pre-post repeated measures experimental design is argued to be the most reliable and sensitive design to reduce experimental error and threats to internal validity, and provide the highest level of evidence or ‘gold standard’ for clinical trials (NHMRC, 1999). While a randomized controlled prospective study on healthy subjects (with no cancer) allocated to treatment groups (chemotherapy, no chemotherapy) would provide the highest level of evidence for answering the research questions, it is not ethical to treat healthy subjects with chemotherapy regimens solely on the basis of research design. Even a randomized controlled prospective study using women diagnosed with early breast cancer is not ethically justified, as to allocate or withhold adjuvant breast cancer treatment, which may impact on long-term survivorship, cannot be justified solely on the basis of study design. Adjuvant treatment is recommended where there is significant added benefit to reducing the risk of recurrence or improving survivorship. Such recommendations are made by the treating oncologist based on a number of factors, including the age and menopausal status of the patient, the size and pathology results of the tumour and the surgical margins achieved.

The prospective cohort design is the most appropriate and sensitive design for naturally occurring groups, when the comparison group is matched as closely as possible on all but the variable of interest. This design allows for pre-post comparisons within and between groups in order to examine the impact of the variable of interest, taking account of the effects of practice and moderating variables. It is more powerful than retrospective designs but it also takes longer, both to recruit and to collect data, and it carries a higher risk of attrition. Since the studies that had been conducted at the time of the study proposal had been retrospective or had not included an appropriate control group, it was
considered that the prospective cohort design would provide the most sensitivity to answer the research questions, as well as add to knowledge in the field.

Chemotherapy regimens are most commonly used for the treatment of cancer. Cancer incidence increases with age, as does the incidence of dementia. The age range in this study was restricted to 65, in order to reduce the risk of dementia. In the target age group (<65) breast cancer is the most common cancer treated with chemotherapy. There are approximately 100 reported cases of breast cancer diagnosed in the ACT each year (Breast Cancer Treatment Group [BCTG], 2004). Almost all cases (>99%) are in women. Women with early breast cancer have good survival rates and low risk of secondary brain tumours. They are also treated with fewer types of chemotherapy regimens than in some other cancers. Women with early breast cancer receiving adjuvant chemotherapy following surgery were selected as the target group.

It is important in selecting a comparison group to match it as closely as possible to the target group. For this reason women with early breast cancer not receiving chemotherapy were chosen to compare to the target group over time. Both groups are the same gender, have experienced a recent cancer diagnosis, similar cancer staging, breast surgery and other adjuvant treatment. This enables an examination of the cumulative impact of chemotherapy and other adjuvant treatment on cognitive function in the longer term compared to women receiving other adjuvant treatment. Using a control group of women with early breast cancer who were not undergoing any adjuvant treatment was considered, but these women generally have earlier stage cancers, are older, and have only one surgery (involving breast conservation) (BCTG, 2004). Originally, a second control group was planned involving age-matched women who did not have cancer but who recently had breast surgery, to control for the effects of surgery and anaesthesia. However, only one woman was recruited to this group so it was discontinued.

By using standardized z-scores based on age-adjusted normative test performance, the neuropsychological test performance of both groups could also be compared to age-matched healthy, normal populations.

### 3.1.1 Variables in the quantitative analysis

The research question predetermines a set of variables for this study. The relevant treatment group membership of women diagnosed with early breast cancer is in one of two groups, i.e., Chemotherapy or No-chemotherapy. This was a prospective repeated measures study and the assessment of change was measured over Time. Thus, there were two independent variables:
• Group was a categorical variable with two levels (Chemotherapy and No-chemotherapy); and

• Time was a categorical variable with three levels, the three timepoints for assessment (Time 1, Time 2, Time 3). The first two timepoints were event based, as seen in Figure 3.1. Time 1 was pre-chemotherapy (post-surgery); Time 2 was shortly post-chemotherapy (around 6 months from Time 1); and Time 3 was 9 months following the completion of chemotherapy (around 15 months from Time 1).

![Diagram showing event-based timepoints]

**Figure 3.1.** Time diagram for the study.

The dependent variables were Cognitive function, comprising of multiple continuous outcome measures derived from neuropsychological tests in different cognitive domains.

Selected variables that may affect cognitive performance were identified through the literature (Chapter 2). These variables included: individual characteristics, such as age, education and premorbid IQ; psychological wellbeing characteristics, including depression and anxiety; self-reported cognitive changes, QOL and social support; and cancer pathology and treatment characteristics (including adverse events). If impairment was found they were assessed as possible explanatory variables in further analysis of possible mechanisms for impairment.

### 3.2 Pilot studies

#### 3.2.1 Development of a comprehensive neuropsychological battery – defining the features

The aim of the neuropsychological battery was to comprehensively assess changes in cognitive function in women diagnosed with early breast cancer related to chemotherapy treatment. The battery was designed primarily to assess the domains of attention and speed of processing, learning and memory, and executive functions, taking into account...
any underlying impairment in the primary domains of language, motor and visuoconstruction. As previous studies have not established consistent results, tests from different modalities (verbal, visual, spatial) were included in the assessment of higher-order domains to help determine any profile of cognitive impairment. The battery was also designed to assess executive functions in a more comprehensive manner than had been done previously, and with consideration of the difficulties in repeated testing, in order to examine any role they might have in chemotherapy-related cognitive dysfunction.

The criteria that were used to evaluate candidate tests were consistent with those used to evaluate the adequacy of tests for detecting mild and diffuse impairment in multiple sclerosis and cognitive changes in clinical drug trials in this population (Benedict et al., 2002). These included consideration of:

- Reliability, especially test-retest reliability (TRR). A figure of 0.8 is often cited as acceptable test-retest reliability. However, neuropsychological tests with TRR of 0.8 or more are relatively rare (Paulo, 1998). Paulo introduced a categorical system of TRR coefficients, declaring 0.8 or higher to be 'good', 0.6-0.79 to be 'fair' and scores of <0.6 to be poor. Data pertaining to internal consistency and inter-rater reliability may be available but were less critical;

- Validity. Tests needed to demonstrate that they measure what they purport to measure with reasonable specificity and be sensitive enough to detect mild impairment;

- Adequate range, especially in regard to being free of ceiling effects in order to detect change in high functioning adults;

- Normative data, preferably on a large sample of healthy normal adults in the target population age range (<65);

- Standardized materials and administration;

- Parallel forms of equivalent difficulty, where the test was sensitive to practice effects;

- Practical, including being time efficient, easily administered, user friendly, easily available and within budget; and

- Parsimonious. The optimal battery should provide a comprehensive, yet efficient, neuropsychological assessment (around 2.5 hours).
Tests that were considered for inclusion were:

- Behavioural Assessment of the Dysexecutive Syndrome (BADS) (B. Wilson, Alderman, Burgess, Emslie, & Evans, 1996);
- Boston naming test (Kaplan, Goodglass, & Weintraub, 1983);
- California Verbal Learning Test (I and II) (D.C. Delis, Kramer, Kaplan, & Ober, 1987; D.C Delis, Kramer, Kaplan, & Ober, 2000);
- Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, 2005);
- Complex Figure tests (CFT): Rey CFT (Meyers & Meyers, 1995); modified Taylor CFT (Hubley & Tremblay, 2002); Mack CFT (Frazier, Adams, Strauss, & Redline, 2001);
- Delis-Kaplan Executive Function System (D-KEFS) (D.C. Delis, E. Kaplan, & J. H. Kramer, 2001a) (Color-word interference, Verbal fluency, Tower, Proverbs, Word context, Letter-number sequencing, Sorting);
- NART-2 (Nelson & Willison, 1991);
- Paced Auditory Serial Addition Test (2.6, 2.0, 1.6, 1.2 sec presentation format) (Gronwall, 1977) and (3- and 2-sec format) (Rao & Society., 1990);
- Speed and Capacity of Language Processing tests (SCOLP) (Baddeley, Emslie, & Nimmo-Smith, 1992);
- Test of Everyday Attention (TEA) (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994)(Elevator counting with distraction, Visual Elevator, Elevator counting with reversal, Telephone search, Telephone search while counting);
- WAIS-III (Wechsler, 1997a)(Symbol search, Matrix Reasoning, Information, Picture completion, Vocabulary, Digit Span, Coding, Similarities and Block Design);
- Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001);
- Wisconsin Card Sorting Test (Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1993); and
3.2.2 Development of a comprehensive neuropsychological battery – pilot study 1

After reviewing the psychometric properties and practicality (e.g., duration, cost of response sheets) some tests were excluded. Potential neuropsychological tests were pilot tested on healthy women (postgraduate students), age range 25-50, to check for ceiling effects, user response and construct validity.

Tests that were identified as having ceiling effects included: the Boston naming test; the WTAR; WAIS-III/ WMS-III (Verbal paired associates, Visual reproduction, Digit span); TEA (Lottery and Elevator counting). Tests sensitive to practice effects that did not include a parallel or alternate form included: WAIS-III (Information, Vocabulary, Picture Completion); WMS-III (Logical memory I and II; Verbal Paired Associates); and the Wisconsin Card Sorting test.

Tests having problems with construct validity were: WMS-III Verbal paired associates (visual strategies reported to aid recall); WMS-III Family Pictures; Visual reproduction (visual memory tests that were easy to verbalize); and CANTAB Verbal recognition memory (verbal memory test administered visually). Tests that were highly stressful for respondents were: CANTAB Delayed matching to sample; and the PASAT (2.6, 2.0, 1.6, 1.2 sec presentation format).

3.2.3 Extension or modifications of tests – pilot study 2

Testing the limits of Digit Span – Digit Supraspan

As some pilot subjects reached the ceiling of the WAIS-III Digit Span test, it was decided to extend the test in order to test the limits and minimize the risk of ceiling effects. The Digit Span forwards test was extended to 13 digits and the Digit Span reverse test was extended to 11 digits. This was pilot tested on eight postgraduate women and no one reached the limits of the test. More detailed information regarding the rationale and development is provided in 3.4.7e Attention: Digit Span.

Verbal paired associates (names)

In the pilot study, a number of subjects received the maximum score on the WMS-III Verbal Paired Associates test (Wechsler, 1997b) on the first or second trial. Most voluntarily admitted to using visual strategies to aid recall of the unrelated words. For example, if the word pair was ‘elephant – glass’, they described imagining an elephant holding a glass. As the battery already included a sensitive measure of visual paired
associate learning, it was considered important to include a paired associate learning task that was not as readily visualized. The WMS-III Verbal Paired Associates administration format was used but the stimuli were modified to eight name pairs. This was pilot tested in three phases. For more details regarding see 3.4.7e Learning and Memory: Verbal Paired Associates (names).

### 3.2.4 Development of a comprehensive neuropsychological battery – pilot study 3

The draft neuropsychological battery in the proposed test order was pilot tested on four women in the appropriate age range to assess the battery, gain feedback and measure times. Final modifications were made to the battery and order in response to feedback and observations and revisions were made to ensure regular breaks and a balanced test order. The complete assessment was pilot tested on four women in the relevant age range (range 37-64) who were comparable to the target group (i.e., had experienced cancer or a chronic illness). After the first two trials, the clinical interview was moved to earlier in the assessment rather than last, in response to feedback. Otherwise feedback was positive. The complete assessment in the final test order was pilot tested on the final two women. Feedback was positive.

### 3.2.5 Appropriate setting – pilot study 4

At the study design stage it was suggested by medical staff that testing could be conducted in the hospitals at the time of a routine medical visit or possibly while chemotherapy was being first administered, as this can take a couple of hours. Although convenient, this was discounted as being a stressful experience and not prior, but during, the initial administration of chemotherapy. Potential testing environments were visited at the hospitals for consideration with a sample test being conducted in them with a volunteer staff member. They were judged to be less than optimal conditions for a neuropsychological assessment, as there was little control over noise, interruptions and distractions in the hospital environment and testing conditions would vary between patients and assessments. Furthermore, some women reported they felt anxious even approaching the hospital where they had treatment. It was decided to create a testing room in the Research School of Psychology at the university, where the testing conditions could be controlled and be consistent, even though this meant willing participants would have to travel to the university for the assessments. Some funds were provided by the department for travel expenses incurred over the course of the assessments ($20 per participant).
3.3 Participants

3.3.1 Sampling procedure

The total population of interest were women, aged between 18 and 65 years, in the Australian Capital Territory, who had recently been diagnosed with early breast cancer and could be assessed prior to commencing post-operative adjuvant chemotherapy. The control cohort group were women, aged between 18 and 65 years, in the Australian Capital Territory, who had recently been diagnosed with early breast cancer, who were not receiving post-operative adjuvant chemotherapy and could be assessed initially at a similar time from diagnosis or surgery. The group was made up of a convenience sample from these women.

Patient information leaflets were developed by the investigator and revised using feedback from cancer care staff and cancer patients. The investigator met with the ACT breast cancer nurses prior to the study commencing to seek advice regarding the best options for providing information regarding the study to the target group. Patient information leaflets were included in all breast cancer patient information packs post-surgery by the breast care nurses, with ethics approval. Contact details for the investigator were provided on the leaflet so that interested women could either contact the investigator directly or speak to their breast care nurse or specialist who could provide a referral to the investigator, who would then contact the patient directly.

Some women who contacted the investigator had already commenced chemotherapy. They advised the investigator that they had not had time to read their information pack, which included the study leaflet, within the short timeframe for individual recruitment (i.e., prior to chemotherapy or matched time). All breast cancer surgeons, medical oncologists, oncology registrars, radiation oncologists, breast care nurses and head nurses from the hospital oncology departments were contacted by the investigator to introduce the study and seek help with providing information to relevant patients. Regular (monthly) contact was made to update and remind these sources of the recruitment status. The investigator also gave a presentation to the oncology network and spoke to cancer support groups about the study. Patient leaflets were updated with numbers needed to complete recruitment and provided to all of these potential referral sources. The investigator also attached leaflets, with prior approval, to information display boards in oncology and radiology departments.
3.3.2 Sample size and power

There were too few prospective studies, using variable measures with such variable results, to provide the data needed in advance to calculate the required sample size for adequate statistical power. Effect sizes for impairment (Cohen's d) in various cognitive domains have ranged from large (1.09) in the domain of attention to small (0.11) in motor function.

Power calculations were derived using appropriate binomial, geometric and exponential distribution models based on normative test parameters for tests within the neuropsychological test battery. The worst-case power calculations apply to the binomial and geometric tests, and of these the geometric tests need a larger sample to enjoy adequate power to detect a difference between groups.

Thirty participants from the ACT were required to complete the study in the target group (chemotherapy) to achieve sufficient power to detect a difference between two groups, with 95% confidence limits, using the least sensitive test in the test battery. Allowing for 15% attrition, 36 women with early breast cancer about to undertake post-operative chemotherapy were originally going to be recruited in the target group, but this number was revised to account for low attrition.

3.4 Measures

3.4.1 Screening measures

Brief measures were conducted on all participants at baseline to screen for possible dementia and visuoperceptual deficits that would exclude them from the study. Because the Color-Word Interference test (D.C. Delis, et al., 2001a) as well as a number of the CANTAB visual tests (Cambridge Cognition, 2005) involved the discrimination of colours, participants were also screened for colour blindness.

Mini-mental state examination (MMSE)

The Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) is one of the most frequently used screening instruments in the evaluation of mental state in both clinical practice and research (Lezak, et al., 2012). It consists of 11 items that permit a rapid screening of a restricted set of cognitive domains, including orientation, encoding, attention, recall, language, reading, writing and drawing. The total MMSE score is out of 30 points. In the original standardization sample, none of the 63 normal adults, aged 55 and over, scored below 24. A score of <24 differentiated 206 hospitalized patients with
cognitive impairments, including dementia and delirium, from those who were cognitively intact with 87% sensitivity and 82% specificity (Folstein, et al., 1975). The MMSE was administered as part of the structured clinical interview (CIDiv2). None of the participants failed the screening test.

**Visual Object and Space Perception (VOSP) Screening test.**

The VOSP (Warrington & James, 1991) is a widely used and standard test of visual perception. The initial screening test in the VOSP battery was used to ensure participants had adequate visual sensory capabilities. This involves a test of visual shape detection where the subject has to identify whether there is an embedded 'X' on 20 black and white pattern sheets. A score of 13 or lower is the cutoff for those unable to complete the battery. None of the participants failed the screening test.

**Ishihara color blindness test – vanishing number plates**

The Ishihara color blindness test (Ishihara, 1983) includes pseudoisochromatic plates, each composed of a circle filled with differently sized and coloured dots. In the vanishing numeral plates, a number is embedded within the pattern of dots, visible to those with normal colour vision. To a person with a red-green colour vision impairment all the dots appear similar or the same and the number is not visible. The vanishing numeral plates were used as a screening test. None of the participants failed the screening test.

### 3.4.2 Demographic measures

Demographic information was collected from participants on their age (date of birth), dominant hand, years of education, highest qualification, employment status and occupation. Information regarding marital/relationship status, number of children and cohabitation status were also collected.

Information regarding ethnicity was based on: indigenous (ATSI) status and country of birth. Where the country of birth was from a non-English speaking country, language was examined, including the age the participant started speaking English and whether they usually speak English at home.

Alcohol risk was assessed with two questions: asking the participant the usual number of standard drinks they consumed in a day and the maximum number of standard drinks they had consumed in 24 hours over the past year. One standard drink contains 12.5ml of alcohol. The first measure was designed to measure long-term risky alcohol consumption based on the 2001 national health guidelines for women: from (0) Non-drinker to (3)
'High risk' (5 or more standard drinks per day) (NHMRC, 2001). The second was designed to capture short-term risky alcohol consumption based on the NHMRC's 2001 guidelines for women: from (0) Non-drinker to (3) 'High risk' (7 or more standard drinks on any one day).

**Menopausal symptoms, sleep quality, fatigue and perceived interference**

Menopausal status was assessed based on the questions used by the Australian Longitudinal Study of Women's Health (ALSWH) (C. Lee et al., 2005). These included: Have you ever had a hysterectomy or oophorectomy? Are you currently on hormone replacement therapy (HRT) or taking the oral contraceptive pill (OCP)? Have you had a period or menstrual bleeding in the last 12 months? In the last 3 months? Compared with 12 months ago are your periods: 1) less frequent; 2) about the same; 3) more frequent; or 4) changeable?

Women who had undergone surgical menopause were defined as post-menopausal. The menopausal status of women who were currently using HRT or OCP could not be defined. Menopausal status categories for all other women who had not undergone surgical menopause were based on the definitions recommended by the ALSWH, based on Guthrie and colleagues (Guthrie, Dennerstein, & Dudley, 1999). Women were defined as pre-menopausal if they had menstruated in the last 3 months and reported no change in menstrual frequency in the past 12 months; peri-menopausal if they reported changes in menstrual frequency or 3-11 months of amenorrhea; and post-menopausal if they reported amenorrhea for 12 months or more.

The self-reported frequency (average number over 12 hours) and intensity of vasomotor symptoms i.e., hot flushes and night sweats, were recorded for each on a 4-point scale from (0) None to 3 (Severe). Perceived interference from menopausal symptoms was also collected and assessed by the question "In general, how much do menopausal symptoms interfere with your day to day activities?" rated on an 8-point scale from (0) No interference to (7) Extreme interference.

While fatigue symptoms were assessed elsewhere in a self-report survey, the perceived interference from fatigue was assessed by the question "In general, how much do fatigue symptoms interfere with your day to day activities?" rated on an 8-point scale from (0) No interference to (7) Extreme interference. Sleep quality was also assessed over the past four weeks on a 5-point rating scale from (1) Very sound to (5) Very restless.
ECOG Performance status

Current performance status was assessed based on the participant's reported functioning over the past week using the performance status categories developed by the Eastern Cooperative Oncology Group (Oken et al., 1982). For live patients these range from (0) Fully active, able to carry out normal activities without restriction to (4) Completely disabled; totally confined to bed/chair; not capable of any self-care. These scales and criteria are commonly used by doctors and researchers in oncology, to monitor disease progress, toxicity and treatment response, based on the impact on activities of daily living.

Prescribed and non-prescribed medications

The participant was asked whether they were taking any prescribed medications and non-prescribed medications currently (yes/no) and these were recorded.

3.4.3 Self-reported Quality of life measures

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, version 3 (EORTC QLQ-C30)

The EORTC QLQ-C30 was first developed in 1987 for evaluating the QOL of patients participating in cancer clinical trials and was the product of more than a decade of collaborative research (Aaronson et al., 1993). The EORTC QLQ-C30 was later revised and EORTC QLQ-C30 version 3 is the latest standard version (Fayers et al., 2001). It is a 30-item self-report questionnaire developed to assess the QOL of patients with cancer. It incorporates five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and QOL scale. Some single-item symptom measures are also included commonly reported by cancer patients (e.g., dyspnoea, loss of appetite, insomnia, constipation and diarrhoea). Twenty-eight of the items are rated on a 4-point Likert-type scale from 1 (Not at all) to 4 (Very much). Of these, thirteen ask the respondent to rate symptoms over the past week. The two global QOL questions are rated on a 7-point Likert scale from 1 (Very poor) to 7 (Excellent). The EORTC QLQ-C30 Version 3 was used in the study with permission from the EORTC Quality of Life Group.

Reliability

The official SPSS syntax file provided by the EORTC Quality of Life Group was used to score the data and generate function and symptom scale scores in accordance with the scoring manual, minimizing scoring errors (Fayers, et al., 2001). Internal consistency of
the original EORTC QLQ-C30 was established (>0.70) on all scales, apart from role functioning (work and household activities) (Aaronson, et al., 1993). Later versions were revised to improve reliability and the latest version (3) has demonstrated improved consistency (all scales alpha = >0.70) (Bjordal et al., 2000). Test-retest reliability was good on all functional scales, with reliability coefficients ranging from 0.82 for cognitive and role functioning to 0.91 for physical functioning, in a study of 190 cancer patients who had been off treatment for 3 months or more, tested four days apart at an outpatient clinic (Hjermstad, Fossa, Bjordal, & Kaasa, 1995).

Validity

A pre-post treatment study of 305 patients with lung cancer found that the functional and symptom measures on the original EORTC QLQ-C30 discriminated between patients differing in clinical status as measured by their recorded performance status, weight loss and treatment toxicity. There were also statistically significant changes in the expected direction, in global QOL, physical and role functioning, fatigue, and nausea and vomiting, for those whose performance status had improved or deteriorated during treatment (Aaronson, et al., 1993). The EORTC QLQ-C30 v3 has detected significant differences between disease status, site, performance status and physician rated toxicity scores in patients with head and neck cancer (Bjordal, et al., 2000).

Patient Health Questionnaire – Somatic Symptom Severity Scale (PHQ-15)

The PHQ-15 (Kroenke, Spitzer, & Williams, 2002) was derived from the original Patient Health Questionnaire studies and is used to assess somatic symptom severity and the presence of somatization and somatoform disorders. The subject is asked to rate how much they have been bothered by each symptom during the past month on a 3-point scale from (1) Not at all to (3) Bothered a lot. Cut-points of 5, 10 and 15 represent mild, moderate and severe levels of somatic symptoms.

Reliability

The PHQ-15 has been found to have good internal reliability (alpha = 0.80) and test-retest reliability (0.83) (Kroenke, Spitzer, Williams, & Lowe, 2010).

Validity

In a study of the PHQ-15 in 906 primary care patients, a cut-point of 3 or more severe ("bothered a lot") symptoms during the past four weeks had a sensitivity of 78% and a specificity of 71% for a DSM-IV somatoform diagnosis (van Ravesteijn et al., 2009).
Medical Outcomes Study (MOS) – Social Support 6-item short form

Perceived social support was measured by a 6-item abbreviated version of the Medical Outcomes Study social support survey, developed for the Australian longitudinal study of women’s health (ALSWH) of over 40,000 women in three age cohorts (W. J. Brown, Dobson, Bryson, & Byles, 1999). An initial study of the reliability of the full social support survey indicated that the internal consistency was extremely high (Cronbach’s alpha = 0.97) suggesting that there might be redundancy in some items (Russell & Smith, 2002). High correlations with item totals were maintained when individual items were deleted. A 6-item abbreviated survey was proposed, with items from each of the areas of social support: tangible support (a, d); emotional/informational support (o, p), positive social interactions (q); and affectionate support (s).

The mean total score was found to be the most reliable outcome measure for both forms. The mean of the 6-item abbreviated solution was compared to the mean of the full 19-item survey, as completed by a sample of 10,617 middle aged women. There was strong agreement (0.98) between the mean of the full survey and the abbreviated version (Russell & Smith, 2002). The abbreviated version was used by the ALSWH in the new recruitment studies of younger women (n = 9,316).

Reliability

The 6-item abbreviated social support measure has demonstrated good internal consistency (Cronbach’s alpha = 0.89) (Russell & Smith, 2002).

Validity

Factor analysis performed on 9,316 women completing all 6 items suggested a single factor solution, with high loadings for all items, explaining 64% of the variance (Russell & Smith, 2002).

World Health Organization 5-item Wellbeing index (WHO-5)

The WHO-5 (WHO Regional Office for Europe, 1998) was developed as part of a wider wellbeing instrument designed to assess QOL and detect depression in patients with diabetes. It does not include somatic symptoms as these can overlap with symptoms of diabetes or focus on reporting negative symptoms, which have a tendency to be under-reported (WHO Regional Office for Europe, 1998). It is a 5-item self-report instrument that assesses overall psychological wellbeing (e.g., positive mood, vitality, interest in things). The subject is asked to rate each statement as it applied over the past 2 weeks. Ratings are
on a 6-point Likert-type scale, from (0) At no time to (5) All of the time. The raw score is the sum of the five answers. High scores mean better wellbeing. To obtain a percentage score, the raw score is multiplied by four, with 0% reflecting worst possible and 100% reflecting best possible wellbeing. The WHO-5 cutoff point of <50% for identification of depression has been shown to have excellent sensitivity (94-100%) and specificity (78%).

Reliability

The internal consistency of the WHO-5 is good (alpha = 0.87) (Heun, Burkart, Maier, & Bech, 1999). The WHO-5 has been found to be responsive to change, with a 10% difference between time-points indicating clinical significance (WHO Regional Office for Europe, 1998).

Validity

Concurrent validity has been established with the CES-D ($r = -0.67$). In a study of 254 adults who had completed a 2-hour psychiatric diagnostic interview, the total score on the WHO-5 was able to highly discriminate those with and without a current psychiatric disorder (Heun, et al., 1999).

Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond & Snaith, 1983) is a 14-item self-report instrument that was designed to measure symptoms of depression and anxiety in non-psychiatric hospital patients. It excludes somatic or physiological symptoms of anxiety and depression (e.g., insomnia and weight loss) that can overlap with illness or treatment side effects in medically ill patients. Each item is presented as a statement with a four-point Likert-type scale. Respondents are instructed to rate each statement in relation to how it applied to them over the past week. Half of the items reflect symptoms of depression and half reflect symptoms of anxiety. Scores range from 0-21 for both anxiety and depression subscales and higher scores indicate greater depression or anxiety. Both scales are combined for a total distress score. The original standardization sample found a cut-off of ≤7 for non-cases, 8-10 for borderline or doubtful cases and ≥ 11 for definite cases produced the best sensitivity and specificity for both the anxiety and depression scales. In a sample of 568 cancer patients at time of initial diagnosis or first recurrence 27% were identified with clinical anxiety but less than 9% scored above the cut-off of 8 for depression (Moorey et al., 1991). Mean anxiety scores among this group were 5.44 ($SD = 4.07$) and mean depression scores were 3.02 ($SD = 2.98$). This has led to suggestions of lowered cut-offs on HADS sub-scales for cancer patients. A review of 747 papers using the HADS in patient populations, including 10 studies with cancer patients ($n = 1803$), found that in most studies an optimal balance
of sensitivity and specificity (approximately 0.80) was achieved when caseness was defined by a score of 8 or above for both the anxiety scale and the depression scale (Bjelland, Dahl, Haug, & Neckelmann, 2002). They recommended the HADS for assessing symptom severity and caseness of anxiety disorders and depression in patients and the general population.

Reliability

Internal consistency has been calculated for the HADS yielding a Cronbach's alpha of 0.93 for the anxiety scale and 0.90 for the depression scale (Moorey, et al., 1991). Based on a review of 747 studies using the HADS in various patient populations, the average internal consistency for the anxiety scale was 0.83 (Cronbach's alpha) and for the depression scale was 0.82 (Bjelland, et al., 2002). In a validation study of the HADS in a Dutch population, 86 adults completed the HADS twice over a mean 3-week period (Spinhoven et al., 1997). Good test-retest stability was found for subscale scores for anxiety ($r^2 = 0.89$), depression ($r^2 = 0.86$) and the total scale score ($r^2 = 0.91$).

Validity

Concurrent validity was established by comparing scores on the HADS with 5-point psychiatric ratings of 100 general medical patients (Zigmond & Snaith, 1983). The HADS depression subscale correlated well ($r = 0.79$) with the psychiatric ratings. Using the recommended cut-offs, the HADS yielded a 1% false negative rate and a 1% false positive rate. A factor analysis showed that the total HADS measures two factors among a population of cancer patients, giving support to the anxiety and depression subscales measuring different constructs (Moorey, et al., 1991).

3.4.4 Self-reported cognitive changes

The Cognitive Function scale of the EORTC QLQ-C30 was used as a self-report measure of overall cognitive function. The Mental Fatigue subscale of the Multidimensional Fatigue Inventory was taken as a self-report measure of attention and concentration. The Total Memory scale and the Retrospective Memory subscale of the Prospective and Retrospective Memory Questionnaire (PRMQ) were taken as self-report measures of memory function and the Prospective Memory subscale of the PRMQ was used as a self-report proxy measure of executive function. Five structured interview questions also examined self-reported cognitive changes at Time 2 and Time 3.
Multidimensional Fatigue Inventory – Mental Fatigue subscale

The 20-item Multidimensional Fatigue Inventory (Smets, Garssen, Bonke, & De Haes, 1995) was developed to measure perceived physical and mental fatigue in cancer patients and contains four somatic subscales and one mental fatigue (MF) subscale. Mental fatigue items relate to perceived loss of or ability to sustain attention and concentration. The mental fatigue subscale is a 4-item self-report survey, with two items formulated in a positive way, such as “I can concentrate well” and two items formulated in a negative direction, such as “My thoughts easily wander”. The subject is asked to rate statements as they applied over the past four weeks on a 5-point Likert scale from (1) None of the time to (5) All of the time. Two items are reverse scored so higher total scores reflect higher levels of mental fatigue.

Reliability

The internal consistency for the mental fatigue subscale is good in different samples (>0.70) (Smets, et al., 1995) as is the test-retest reliability (r = 0.74) (Unal et al., 2001).

Validity

Convergent validity has been established between the Visual Analogue fatigue scale scores in radiotherapy patients and the MFI Mental Fatigue subscale (Smets, et al., 1995). Mental fatigue scores have discriminated between chronic fatigue patients, psychology students, medical students and soldiers (Smets, et al., 1995).

The Prospective and Retrospective Memory Questionnaire (PRMQ)

The Prospective and Retrospective Memory Questionnaire (PRMQ) (Smith, Della Sala, Logie, & Maylor, 2000) is a 16-item self-report questionnaire developed to measure everyday prospective and retrospective memory problems. It is the only self-report instrument that assesses prospective (remembering to remember a planned event) and retrospective (recalling a past event) failures in equal depth. The authors pointed out that many people suffering from early dementia describe prospective memory problems and suggested that a higher frequency of reported failures might help to identify early signs of dementia. They designed the PRMQ to systematically measure prospective and retrospective memory in a range of contexts, including self-cued and environmentally cued; and short-term and long-term memory. Eight items ask about prospective memory problems, such as “Did you forget appointments if they were not prompted by someone else or by a reminder such as a calendar or diary?” The remainder ask about retrospective memory problems, such as “Did you fail to recall things that have happened to you in the
last few days?’ The subject is asked to rate the frequency each statement applied to them over the past two weeks on a 5-point Likert scale from (1) Never to (5) Very often. Subscales are summed to provide a Retrospective Memory total score, a Prospective Memory total score and a combined General Memory total score.

Reliability

The internal consistency of the Total scale and the Prospective and Retrospective scales are acceptable (Cronbach’s alpha = 0.89, 0.84 and 0.80, respectively) (J. R. Crawford, Smith, Maylor, Della Sala, & Logie, 2003). Age and gender did not influence PRMQ scores.

Validity

The PRMQ was administered to 551 members of the general adult population (females = 344) as part of a normative study (J. R. Crawford, et al., 2003). Results confirmed a three factor model, including a general memory factor on which all items loaded, plus orthogonal specific factors of prospective and retrospective memory. A number of studies have failed to find a significant relationship between Prospective Memory scores and objective cognitive measures (Uttl & Kibreab, 2011; Woods et al., 2007). However, these studies did not include tests of executive function. Prospective memory, such as forgetting a planned appointment, involves planning, managing competing demands and monitoring future intentions. These involve executive functions. When the PRMQ and a computerized neuropsychological battery was administered to HIV patients, the only significant association found between the PRMQ score and the neuropsychological measures was on a set shifting task, a measure of executive function (Garvey, Yerrakalva, & Winston, 2009). Imaging studies have implicated the frontal lobes and prefrontal cortex in prospective memory performance (Burgess, Quayle, & Frith, 2001; Burgess & Shallice, 1997). This supports the study’s use of the Retrospective memory score as a self-report measure of memory and the Prospective memory score as a self-report measure of executive function.

Structured interview questions

All participants were asked at Time 2 and Time 3 if they had noticed any changes to their memory or thinking since their last assessment. If so, they were asked what kind of changes they had noticed and whether they could give an example. They were also asked whether the changes had worsened, improved or stayed the same over time. Finally, they were asked if they had noticed anything that made these symptoms better or worse.
3.4.5 Cancer and treatment measures

A medical file review was conducted for each participant from hospital records following the Time 3 assessments. Data was collected regarding cancer detection, cancer pathology and staging, number and type of surgery, length of stay, adjuvant treatments, co-medications, adverse events, hospital readmissions and most recent follow-up status (e.g., disease free, recurrence, death). All data was deidentified. Coding of data was consistent with standard practices for coding data on breast cancer and treatment (BCTG, 2009; BCTG, 2004; NHMRC, 2001).

3.4.6 Clinical assessment measures

The Composite International Diagnostic Interview v2.1 (CIDI-Auto)

The CIDI (Robins et al., 1988) is a structured clinical interview, developed by the World Health Organization based on DSM-IV criteria, to assess the prevalence of mental health disorders across 30 countries. The CIDI-auto is the computerized version of the CIDI version 2.1.

The CIDI-Auto uses a diagnosis-oriented top down structure, starting from key criterion questions and moving down to further probes and symptoms. It provides customized wording based on responses and questions are skipped if they are not applicable based on previous responses. This reduces administration time and judgement errors. A computerized scoring algorithm provides diagnoses according to having met DSM-IV and ICD-10 criteria.

The modules selected for the study included the Mini-mental State Examination and the core anxiety disorders (i.e., specific phobia, social phobia, panic disorder, agoraphobia, generalized anxiety disorder) and mood disorders modules (i.e., depression, mania) (past 12-month prevalence). The questions were interviewer-administered.

Reliability

The inter-rater reliability ($r = 0.94$) and test-retest reliability (0.70-0.95) of the CIDI-auto were high when investigated in two sites (Sydney, Australia and San Juan, Puerto Rico) as part of the WHO reliability and validity study (World Health Organization, 1993).

Validity

It was the unreliability of clinician diagnoses in predicting recurrence or outcome that led to the development of structured diagnostic interviews (Grove, Zald, Lebow, Snitz, &
Nelson, 2000; Meehl, 1954). The CIDI is one of the most widely used structured clinical interviews in the world. It has been used in epidemiological studies, research, training and for clinical purposes. Using a clinician's diagnosis to validate any structured diagnostic interview is considered problematic, as a clinician's diagnosis is not perfectly reliable. A WHO study examined the agreement of DSM-IV diagnoses generated by two WHO/NIH structured diagnostic instruments: the CIDI-auto and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Concordance between the instruments was moderate for current (last 12 months) \( r = 0.69, p = 0.05 \) and lifetime \( r = 0.66, p = 0.05 \) diagnoses (Andrews, Peters, Guzman, & Bird, 1995).

### 3.4.7 Neuropsychological measures

The neuropsychological tests or subtest outcome measures are organized by the cognitive domain they most accurately measure based on Lezak et al. (2012) and relevant findings from the literature. The neuropsychological measures in the battery provide a coverage of different modalities (auditory, verbal, visual and spatial) and an assessment of the following cognitive functions/domains: a) general ability and IQ; b) language; c) motor; d) visuoconstruction; e) attention and speed of processing; f) learning and memory; and g) executive functions.

In the current study there were two main neuropsychological test batteries, specifically designed to measure executive functions in repeated assessments from which more tests were selected. One was computerized (CANTAB) and the other uses a traditional administration format (D-KEFS). These test batteries will be described below.

**Cambridge Neuropsychological Test Automated Battery (CANTAB)**

CANTAB (Cambridge Cognition, 2005) was originally developed by Sahakian, Robbins and colleagues to assess cognitive decline in the elderly. The CANTAB tests are computer administered to the subject via a touch screen, with some tests also requiring a press pad. This enables standardized control of stimulus presentation as well as precise recording of accuracy, latencies and errors with a level of sensitivity not possible in standard administrations. The tests were selected to include those that could relate to the extensive literature in animal and non-human primate research and those that could be broken down into discrete cognitive components. These include tests of visual attention and speed of processing, learning and memory, and executive functions. Many are similar to traditional neuropsychological tests, conducted in a game-like format that is user-friendly and adds a measure of fun to the experience. The tests have been designed to be language- and culture-free and have been graded in difficulty to minimize floor and ceiling effects.
### Table 3.1 Neuropsychological Test Battery by Cognitive Domain

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Test or subtest</th>
<th>Main abilities assessed</th>
<th>Verbal</th>
<th>Auditory</th>
<th>Visual</th>
<th>Spatial</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Premorbid ability/intelligence</td>
<td>The National Adult Reading test - 2</td>
<td>Estimate of premorbid general ability/IQ</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Language</td>
<td>Graded naming test (CANTAB)</td>
<td>Confrontation naming</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Category fluency: Verbal fluency (D-KEFS)</td>
<td>Semantic fluency</td>
<td></td>
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<tr>
<td></td>
<td>Colour naming speed: Color-Word Interference test</td>
<td>Naming speed</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>c. Motor</td>
<td>Motor screening test (CANTAB) latency and error</td>
<td>Motor accuracy, Motor speed</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reaction Time movement times (CANTAB)</td>
<td>Motor speed</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Big Little Circle (BLC) (CANTAB) correct latency</td>
<td>Motor speed and speed of processing</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>d. Visuoconstruction</td>
<td>The Complex Figure Test (CFT) - Copy accuracy</td>
<td>Visuoconstruction</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reaction Time (Simple and choice) (CANTAB)</td>
<td>Speed of processing, Selective attention, Divided attention</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Word Reading Speed: Color-Word Interference test</td>
<td>Speed of processing</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Pattern Recognition Memory (CANTAB) latency</td>
<td>Speed of processing</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Spatial Recognition Memory (CANTAB) latency</td>
<td>Speed of processing (SOP)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td></td>
<td>The Paced Auditory Serial Addition Test</td>
<td>SOP, Sustained attention, Divided attention, Working memory</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid Visual Information Processing test (CANTAB)</td>
<td>Sustained attention</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td></td>
<td>Digit Span (WAIS-III) (forwards &amp; backwards limit)</td>
<td>Attention span, Working memory</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Spatial Span (CANTAB) (forwards &amp; backwards)</td>
<td>Attention span, Working memory</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Learning and Memory</td>
<td>Pattern Recognition Memory (CANTAB)</td>
<td>Recognition memory (immediate and delayed)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Spatial Recognition Memory (CANTAB)</td>
<td>Recognition memory (immediate)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paired Associate Learning (CANTAB)</td>
<td>Associate learning, Recall (immediate), First trial memory</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td></td>
<td>Verbal paired associates (names)</td>
<td>Associate learning, Recall (immediate and delayed), Recognition</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td></td>
<td>Complex Figure Test – Recall and Recognition trials</td>
<td>Recall (immediate and delayed), Recognition</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>California Verbal Learning Test-2</td>
<td>Learning, Strategy, Recall (immediate and delayed), Recognition</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>g. Executive Functions</td>
<td>Similarities (WAIS-III) (Time 1 only)</td>
<td>Abstract reasoning, Concept formation</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>The Proverb test (D-KEFS) (Time 2 only)</td>
<td>Abstract reasoning, Concept formation</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>The Word Context test (D-KEFS) (Time 3 only)</td>
<td>Abstract reasoning, Concept formation</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td></td>
<td>Spatial Working Memory (CANTAB)</td>
<td>Strategy, Spatial working memory</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Condition 1 &amp; 3: Verbal Fluency (D-KEFS)</td>
<td>Verbal generativity, Attentional switching</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td></td>
<td>Stockings of Cambridge test (CANTAB)</td>
<td>Planning, Planning speed, Problem solving</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td></td>
<td>Condition 3 &amp; 4: Color-Word Interference test</td>
<td>SOP, Inhibition, Attentional switching, Selective attention</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td></td>
<td>Intra-Extra Dimensional Set Shift (IED) (CANTAB)</td>
<td>Cognitive flexibility, Rule formation, Reasoning, Problem solving</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complex Figure Test – Organization</td>
<td>Organization, Planning</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complex Figure Test – Copy speed</td>
<td>Planning speed</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Parallel versions are included for a number of tests for use in repeated testing. It has been used in over 1000 peer-reviewed papers, in more than 100 clinical drug trials, in over 50 brain imaging studies, and to test cognitive functioning for research in an estimated 300,000 people across the world. The authors used a rigorous theoretical framework to guide subtest selection and have undertaken a rigorous process to validate its neural correlates.

This process has included published studies of task performance in: the elderly and those with varying stages of dementia; adults with focal brain lesions; adults with specific neuropathologies; clinical populations; neuroimaging; healthy normals across the lifespan; paediatric populations; and pharmacological or drug manipulation. The normative data include more than 2000 subjects covering the age range from 4 to 90 years in seven different age bandwidths (for adults) and four different IQ bandwidths. In contrast to the validation studies, there has been no rigorous process for establishing reliability. There are no reliability data published in the technical manual for individual tests or for parallel forms. There have been a few studies that have examined the test-retest reliability of the CANTAB tests in healthy normal adults but none have compared the standard forms to the parallel forms.

**The Delis-Kaplan Executive Function System (D-KEFS)**

The D-KEFS (D.C. Delis, et al., 2001a) comprises nine tests that assess a wide spectrum of verbal and non-verbal executive functions. The tests are designed to use a process-oriented approach, where component functions of the executive task are measured so their relative contribution to any executive deficits can be assessed. Normative data are derived from a national standardization sample involving over 1800 children and adults, between the ages of 8 and 89. Each test is designed to be a stand-alone instrument that can be administered individually or with other tests. Some tests in the battery that are sensitive to practice effects are provided with parallel forms. Reliability and validity studies were conducted as part of the standardization study.

A detailed description of the test and the test administration procedure, as well as the reliability and validity of individual outcomes measures will be outlined in the following section according to the relevant domains: a) general ability and IQ; b) language; c) motor; d) visuoconstruction; e) attention and speed of processing; f) learning and memory; and g) executive functions.

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4 Information from CANTAB website and bibliography (www.camcog.com)
Estimates of premorbid ability are important in determining whether a given test performance represents impairment. Deterioration in performance for someone with a high premorbid ability is likely to remain within the normal range. Comparing individual performance below estimated premorbid ability helps to determine evidence of impairment. Furthermore, the level of premorbid intelligence or mental ability has been found to determine the amount of cognitive loss following brain injury or neurotoxic exposure, and also the risk of dementia and the rate at which it evolves (Lezak et al., 2012). The consistent finding of a significant relationship between estimated premorbid ability and level of cognitive impairment with brain injury or disease has spawned a broad literature on cognitive reserve, brain reserve capacity and threshold effects (Satz, 1993; Stern, 2003). People with lower premorbid cognitive reserve have poorer cognitive or functional outcomes following brain injury or disease. Estimated premorbid IQ has been found to be a sensitive measure of cognitive reserve.

The National Adult Reading Test (NART) – Second edition

The NART-2 (Nelson & Willison, 1991) is designed to estimate premorbid intellectual ability in adults aged from 16 to 70. It is a reading test for 50 irregularly spelled words. Each word is presented individually and subjects are required to read the word aloud. The reader has to know the word rather than rely on phonetics to read it aloud correctly (e.g., cellist, debt). This test is a widely used and accepted method of estimating premorbid intelligence in adults in neuropsychological research and clinical practice, because vocabulary correlates best with overall ability and is relatively unaffected by most neurological or psychiatric morbidity. This edition was re-standardized for adults aged 20 to 70 to address the restricted range found on the original NART. The NART-2 score is used to calculate a standardized estimate of full scale IQ in the manual and the upper limit now extends to a full scale IQ of 131.

The NART-2 estimated IQ score was used in both the group analyses and the individual analyses. It was included in the regression model analyses to assess possible explanatory variables associated with cognitive outcomes following treatment within the group analyses where evidence of chemotherapy-related impairment was found. It was also used to determine individual estimates of lower than expected performance in an individual analysis of cognitive change.
Reliability

The NART-2 is one of the most reliable tests in clinical use, with high levels of internal consistency ($r > 0.90$), test-retest reliability ($r^2 = 0.98$) and inter-rater reliability ($r > 0.88$) of NART-2 scores, as well as being resistant to the effects of normal ageing (J. R. Crawford et al., 1989; J. R. Crawford, Stewart, Garthwaite, Parker, & Besson, 1988). Some NART words have a disproportionate amount of inter-rater disagreement (e.g., puerperal) and Crawford (1989) has advised that particular care should be taken when scoring these words. Use of a pronunciation guide improves scorings accuracy for these items (Alcott, Swann, & Grafham, 1999). In this study each subject’s responses were recorded on audiotape and later reviewed for scoring purposes, using an Australian pronunciation audio guide5.

Validity

The NART has been found to demonstrate higher correlations to WAIS Full Scale IQ than those derived from demographic variables, for a number of cognitively impaired groups, including patients with Korsakoff’s syndrome, Alzheimer’s disease, frontal or temporal lobe lesions, as well as in healthy controls (Bright, Jaldow, & Kopelman, 2002). In a cross-validation sample of 151 healthy normal adults, NART scores predicted 66% of the variance in WAIS Full scale IQ (J. R. Crawford, et al., 1989). A retrospective study of a group of older adults without dementia ($M = 77$ years) found a high correlation ($r = 0.73$) between their NART scores and their scores on an intelligence test conducted at 11 years of age (J. R. Crawford, Deary, Starr, & Whalley, 2001). This supports the claim that NART estimates premorbid ability rather than current intelligence.

b. Language

Changes in language functions, such as naming abilities or semantic fluency, can be the first signs of: acute events, such as stroke or brain injury; language disorders, such as aphasia; learning disabilities or developmental disorders; or progressive disease, such as Alzheimer’s Disease (Groth-Marnat, 2000; Lezak, et al., 2012). Language has been understood as a lateralized function, with around 95% of right-handed people using the left hemisphere to process language. However, people with right hemisphere lesions have also been found to have communication problems, where they understand and can speak simple statements but have problems with more complex social interactions (Lezak, et al., 2012).

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5 For the NART-2 Australian pronunciation guide see: maccs.mq.edu.au/research/resources/nart/index.html.
Graded Naming Test (GNT) (CANTAB)

The Graded Naming Test (Cambridge Cognition, 2005; McKenna & Warrington, 1983) is designed to assess confrontation naming ability, but is also graded in difficulty to allow for individual differences, increasing sensitivity to mild deficits and reducing the risk of ceiling effects found in other naming tests. It is included in the CANTAB battery and is administered via computer.

The test consists of 30 black and white line drawings, ordered with increasing difficulty (see Figure 3.2). The examinee is asked to name the drawing and the examiner records, unobserved behind the computer screen, whether the response is correct or incorrect, via left and right keyboard arrows.

![Figure 3.2. The first test screen of the Graded Naming Test.](image)

In order to grade difficulty and reduce the risk of ceiling effects found in previous naming tests, it uses some relatively uncommon words, like cowl and bellows. This means that it has greater potential to detect word-finding difficulty or changes in those with an extensive vocabulary. In the standardization sample 100 people of average intelligence, aged from 18 to 77, had an average score of 20.4 ($SD = 4.1$). The outcome measure that was used for this study was the GNT total correct normative z-score, based on the most recent revised norms (Warrington, 1997).

Reliability

The test-retest reliability of the GNT is very good, both in healthy adults tested a month apart ($r = 0.92$), and patients with acute conditions tested again after 4.6 months, on average ($r = 0.92$) or neurological conditions ($r = 0.93$) tested again around 13 months on average (Bird & Cipolotti, 2007; Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004). The study of acute and neurological conditions were all patients assessed in the Neuropsychology Department of a National Hospital over seven years, and included
patients with stroke, head injury and dementia (Bird & Cipolotti, 2007). In the study of healthy adults, the average score at the first assessment improved by approximately one word on retesting one month later, consistent with a practice effect (Bird, et al., 2004). Initial GNT scores were not related to age but were significantly correlated with NART estimated IQ; however, there were no significant correlations between age or NART IQ and observed practice effects.

Validity

The GNT has been widely used in clinical practice and research (Garrard et al., 2001; Kapur, Ironside, Abbott, Warner, & Turner, 2001; Swainson et al., 2001). Reduced efficiency in naming an object can be the first indication of impaired or improved language functioning (Lezak, et al., 2012). The GNT, in combination the CANTAB Paired Associate Learning test, has been found to be highly sensitive and specific for predicting those at risk for developing Alzheimer’s disease (AD) in pre-clinical stages (Blackwell et al., 2004; Swainson, et al., 2001). In a group of 40 adults with questionable dementia, an algorithm using baseline performance on these two tests, predicted with 100% accuracy the probability of those in the sample ($n = 11$) who went on to receive a diagnosis of probable AD eight months later (Blackwell, et al., 2004).

Other measures used to assess language abilities were:

Category Fluency, the second condition from the D-KEFS Verbal Fluency test. This is a test of semantic fluency (for more details see 3.4.7g Executive functions: Verbal Fluency). Alternate forms are provided for this test, as it is susceptible to practice effects.

Colour naming, the first condition from the D-KEFS Color Word Interference test (Delis et al., 2001a), measures the speed of naming colours. (For more details see 3.4.7g Executive functions: Color-Word Interference test.)

c. Motor

Motor functions include the speed, strength and control of movement (Lezak, et al., 2012). There is considerable variation in motor abilities in the normal population. Motor functions are controlled by: the primary motor cortex; supplementary motor area; lateral premotor cortex; and the cingulate motor area. Damage to the primary motor cortex produces a weakness in the corresponding hemisphere of the body.
Motor Screening test (MOT) (CANTAB)

The Motor Screening test (MOT) (Cambridge Cognition, 2005) screens for visual, movement and comprehension problems. It also introduces the subject to the touchscreen. The subject is required to touch a flashing cross (X) in the centre as it appears in different locations on the screen. Ten crosses are presented and the subject must touch each of the crosses in turn.

The outcome measures used were mean latency and mean error, measures of motor speed and accuracy. Latency is measured in milliseconds and is defined as the time taken for the subject to touch each cross after it appeared, for each correct response. Mean error is a measure of the accuracy of the subject’s pointing. It measures the mean distance in ‘pixel units’ between the centre of the cross and the location the subject touched on the screen, for each correct response.

Reliability and Validity

There have been around 100 published studies using MOT, primarily as a screening test, but none reporting test-retest reliability or the effects of ageing on MOT performance. There have been significant age-related declines found in another CANTAB measure of movement speed (Boom-Saad et al., 2008). MOT raw scores were converted into age-standardized z-scores based on normative test data. MOT has been used with several tests of motor function and speed of processing to investigate the profile of cognitive deficits in children with a genetic disorder (22q11.2 Deletion Syndrome) (Howley, Prasad, Pender, & Murphy, 2012). The profile of performance provided evidence that the visual-motor profile in 22q11.2 was not entirely mediated by intellectual disability or attention but has specific visual motor integration deficits.

Other measures of motor ability and speed include:

Reaction Time (RTI: Simple and Five-Choice) movement times (CANTAB) (Cambridge Cognition, 2005) are designed to measure motor speed in a reaction time test. They measure the time it takes the subject to touch the stimulus on the touchscreen after the press pad button has been released. RTI Simple movement time is measured in trials where stimuli appear in one location only (predictable), whereas RTI Five-choice movement time is measured in trials where stimuli appear in one of five possible different locations (unpredictable). More details of the RTI test, including administration, can be found in 3.1.4 e Reaction time test. RTI movement time latency is normally distributed (Cambridge Cognition, 2005). Test-retest reliability has been found to be fair (r = 0.73) in healthy adults tested 1-8 weeks apart (Harrison et al, n.d.). There were significant age-
related declines found in movement times in a study of surgeons (age 45-75 years), medical students (age 24-35 years) and age-matched normative controls (Boom-Saad, et al., 2008). In this study, movement raw scores were converted into age-standardized z-scores based on normative test data.

Big Little Circle (BLC) (CANTAB) (Cambridge Cognition, 2005) is primarily a visual discrimination screening test and is used to prepare the subject for the Intra-extra dimensional set shifting (IED) test. The subject is asked to put their preferred hand on a tape marker on the table 15 cm from the touchscreen. They are presented with a series of pairs of circles, one large and one small. The subject is instructed first to touch the small circle and then, after 20 trials, to touch the larger circle for a further 20 trials, returning their hand to the marker after each trial. The outcome measure that was used was mean correct latency defined as the average time it takes the subject to touch the correct stimulus from the table marker after it was displayed on the screen. Latency is measured in milliseconds. Raw scores were converted into age-standardized z-scores based on normative test data. Performance deficits in BLC and MOT latencies have been found to be significantly associated with post-concussive symptom severity in adults with mild traumatic brain injury (Sterr, Herron, Hayward, & Montaldi, 2006).

d. Visuoconstruction

Visuospatial abilities range from basic perception to more complex visual processing abilities, such as visuoconstruction. Visuoconstruction abilities are an integrative visuospatial ability, that involve visuospatial perception, motor and planning abilities, in order to process visuospatial stimuli and construct or reproduce them (Lezak, et al., 2012). As a general rule, patients with right hemisphere lesions tend to take a piecemeal approach, losing the overall design, and produce a fragmented copy, with repetition of some elements and relationship errors. Patients with left hemisphere lesions tend to get the overall design but omit details and produce a poor copy. Visuoconstruction performance can also be affected by functioning in other domains, such as attention, motor or executive problems (Lezak, et al., 2012).

The Complex Figure Test (CFT) – Copy trial

The Complex Figure Test (CFT) was originally developed by Rey [(1941); translated by Corwin & Bylsma, (1993)] to investigate visuospatial constructional ability and visual memory in people with brain-injuries. It was first standardized by Osterrieth [(1944); translated by Corwin & Bylsma, (1993)] and more recently by Meyers and Meyers (1995).
It involves a copy trial of a complex geometric figure, followed by recall trials administered 3 minutes and 30 minutes after the copy trial, followed by a recognition trial. In the copy trial, the participant is asked to copy the figure (presented in portrait view) on a piece of blank paper with the instructions, "Copy it so that I would know that this is the figure you drew. Do a good job". When the copy is completed, the examiner removes the stimulus card and the copy. There is no time limit for the copy trial but the length of time to complete the copy is recorded, unobserved by the subject, in seconds using a stopwatch. Time to complete the copy and copy organization were recorded as measures of planning speed and organization (see 3.4.7g Executive functions: Complex Figure test—organization and copy speed).

![Figure 3.3. a. The Rey Complex Figure and b. the Modified Taylor Complex Figure.](image)

Reliability

Test-retest reliability on the copy trial of the Rey Complex Figure test was not reported due to the maximum or near maximum level of performance attained by most subjects, thus artificially reducing the magnitude of the test-retest reliability coefficients (Meyers & Meyers, 1995). The percentage of agreement, though, in the clinical interpretation between the first and second testing sessions was high (100%). Alternate form reliability
between the Rey and the Modified Taylor Complex Figure Copy correct was low \((r = 0.57)\) again likely due to the restricted range in scores, whereas the reliability estimates between forms were adequate on all other trials, where scores had sufficient range (Hubley & Jassal, 2006). The mean copy performances did not differ significantly, though, between the two forms. Rey CFT copy scores have been found to be fairly stable in adults to the age of 50 and then there is a gradual decline in copy proficiency as well as an increase in time required to copy the figure (Meyers & Meyers, 1995). There was no effect of education on copy. Raw scores were converted to age standardized z-scores based on normative data provided by Meyers and Meyers (1995). Rey argued that the task is not as affected by drawing skills as organizational strategy, because of the simple nature of the separate components of the figure (Corwin & Bylsma, 1993). This assertion has been supported by developmental studies. Children as young as six are able to draw most of the elements of the complex figure, but they use a piecemeal approach to copying the figure (Akshoomoff & Stiles, 1995). They improve in their ability to integrate the figure with age. By around nine years of age, drawing of the elements becomes more configurational and by around 13 years, a shift to the base rectangle strategy occurs.

Each copy drawing was scored by the examiner blind to group membership using the explicit standardized scoring criteria for accuracy and placement of the 18 elements, for the Rey (Meyers & Meyers, 1995) and the Modified Taylor CFT (Hubley & Tremblay, 2002). Inter-rater reliability was established by having 10% of the complex figure drawings in the study, including copy and recall figures, blind scored by another examiner, who was a clinical psychologist with extensive neuropsychological testing experience. Instructions were given to strictly adhere to the scoring criteria rules in the copy trial, as recommended (Lezak, et al., 2012; Meyers & Meyers, 1995). Inter-rater reliability coefficients (Pearson product-moment correlations) for total copy raw scores were high \((r = 0.94)\).

Validity

The Rey Complex Figure test is one of the most commonly used tests in neuropsychology (Rabin, Barr, & Burton, 2005). Concurrent validity of Rey CFT copy scores has been established with the Benton Visual Retention test and the Hooper Visual Organization test (Meyers & Meyers, 1995). Mean copy scores on the Rey CFT correlated strongly with cerebral perfusion ratios on functional SPECT imaging and dysfunction in right parietal brain regions and right hemisphere circuits, and differentiated the stage of cognitive decline in patients with Alzheimer's disease (Tippett & Black, 2008). Copy scores have discriminated patients with mild cognitive impairment from healthy controls (Kasai et al., 2006). Copy scores are sensitive to visuospatial constructional deficits in patients with

e. Attention and Speed of Processing

Attention is involved to some extent in all test performances (Lezak, et al., 2012). Definitions and theoretical models of attention vary widely, with many models coming and going, particularly under the influence of the information-processing approach, inspired by telecommunication or computer systems, that have had varying utility for clinical work. One influential metaphor used for attention is the spotlight (Posner, 1978, 1980). A spotlight is focused on a cued location and shifted as needed. The spotlight is selective (its beamwidth), has intensity and what is outside the spotlight is hardly noticed. This can apply to visual/spatial and verbal/auditory attention processing. Deficits in attention do not imply an absence of attention; rather they generally involve inconsistency in attention processes within a context.

Attention is carried out by a network of anatomical areas, and is not localized to a single brain region. Therefore, many brain injuries, diseases or neurotoxic exposure affect attention. Attention is not considered a unitary construct. Clinical assessment of attention functions have placed emphasis on: selective attention; sustained attention and divided attention (Lezak, et al., 2012). Attention overlaps with short-term storage and memory; and attention span and working memory are included within the assessment of attention by Lezak et al. (2012). Working memory is a limited capacity system that keeps active a limited amount of information for a limited time to allow it to be manipulated. The CANTAB Spatial Working Memory test overlaps with executive control, as it involves a strategy component. It was included in the measures of executive functions. Response inhibition, flexibility and switching, which involve top-down or supervisory attentional control, are either included in the assessment of attention or executive functions. As these measures involve executive control processes they have been included in the measures of executive function.

Underlying many attentional disorders is slowed processing (Lezak, et al., 2012). Speed of processing refers to the speed at which mental activities are performed and the speed of cognitive response. Slowed processing is a common characteristic of both ageing, brain damage, neurodegenerative diseases and neurotoxicity. It is often identified by delayed reaction times and in longer than expected total performance times in the absence of a specific motor disability. Measures that have visual, spatial and verbal/auditory analogues follow each other.
Reaction Time (RTI) (CANTAB)

The Reaction Time (RTI) test (Cambridge Cognition, 2005) is designed to measure the subject’s speed of reaction to a visual target where the stimulus is either predictable (Simple Reaction time) or unpredictable (5-Choice Reaction Time). It involves the subject using a touchscreen and a press-pad with response button, which is located 15 cm from the screen.

This test has five practice stages. The subject is trained to hold down a press pad button until a yellow dot appears, then release it and touch the screen where the dot appears with the index finger of their dominant hand.

![Figure 3.4. The test screen for simple reaction time (a) and 5-choice reaction time (b).](image)

In the simple reaction time test the yellow dot appears within a circle in the centre of the screen (Figure 3.4a). In the 5-choice reaction time test, the yellow dot can appear in any one of five circles located around the edge of the screen (Figure 3.4b). In all stages the subject is trained to a criterion of five out of six, within 18 trials for the simple RT task and 40 trials for the choice RT task. If the subject fails to reach criterion on any of these stages the test terminates. Parallel versions are provided for both tests. The simple reaction time task involves speed of processing, selective attention and motor ability; whereas the 5-choice reaction time task also involves divided attention.

The main speed of processing outcome measures that were used in this study were:

- simple reaction time, defined as the speed with which the subject releases the press pad button in response to the onset of a stimulus in a single location; and
- 5-choice reaction time, where the stimulus is in any one of five locations. Both reaction time latencies are measured in milliseconds. Movement times for simple and choice reaction time conditions are also recorded from the time it takes the subject to touch the screen after the press pad button has been released, and were used as a measure of motor speed.
Reliability

Very few published reliability studies have been done involving CANTAB RTI. The manual reports that Five-choice reaction time latencies are reliably observed to be longer than in simple reaction time (Cambridge Cognition, 2005). Test-retest reliability of RTI in healthy adults tested 1-8 weeks apart was reported to be poor for simple reaction time \((r = 0.54)\) and choice reaction time \((r = 0.57)\) (Harrison, et al., n.d.). Practice effects for reaction times were in the optimal range \(<0.2\) standard deviations improvement over two testing sessions). This study was conducted, though, using an earlier nine trial version of simple and choice reaction time with no practice trials (Harrison, et al., n.d.). Performances were found to be much more variable at first exposure than at retest, and there was a marked reduction in latency across the first trials of the task, an effect that was considerably less at retest. As the mean individual latency was based on only nine trials with no practice, the authors concluded that the poor test-retest reliability was due to a learning effect that was most evident at first exposure. Cambridge Cognition has since reformulated the Simple and Choice Reaction time tasks to include practice blocks of 10 trials and ‘test’ blocks of 18 trials for simple RT and 40 trials for 5-choice RT. This version of RTI, which was used in the study, has been reported to yield good test-retest reliability coefficients, greater than 0.80 (Harrison, et al., n.d.). RTI was studied in a group of surgeons (age 45-75 years), medical students (age 24-35 years) and age-matched normative controls (Boom-Saad, et al., 2008). There were significant age-related declines seen in reaction times. Reaction time raw scores were converted into age-standardized z-scores based on normative test data.

Validity

The neural basis of simple and 5-choice RT task has been examined extensively in animal lesion studies and drug studies, primarily in rats but also primates, in order to examine attentional processes (Robbins, 2002). Choice RT has activated neural systems centred on the prefrontal cortex, cingulate cortex and striatum.

Pharmacological studies have shown that methylphenidate, a psychomotor stimulant, shortened 5-choice reaction times in rats (Bizarro, Patel, Murtagh, & Stolerman, 2004) and in children with ADHD but did not affect performance on tasks with a prominent executive component (Rhodes, Coghill, & Matthews, 2006). Five-choice reaction time, taken together with five-choice movement time, has been used to distinguish speeding or slowing of motor function from that of cognitive function, associated with changes of dopaminergic medication in patients with Parkinson’s disease (Riekkinen, Kejonen, Jakala, Soininen, & Riekkinen, 1998). Only one study has used RTI to examine cognitive changes in cancer
patients (N = 47) associated with cytokine treatment, specifically interleukin-2 (IL-2) and interferon-a (IFN-a) (Capuron, Ravaud, & Dantzer, 2001). This study found that patients treated with IL-2 alone showed lower accuracy of planning abilities as soon as five days after treatment, whereas patients treated with IFN-a did not show any impairment in planning accuracy but showed slower speed of processing, especially when the task involved higher attentional resources (5-choice RT).

Other measures of speed of processing or latencies included in the battery are:

- Word Reading Speed, condition 2 from the D-KEFS Color-Word Interference test (see 3.4.7g Executive Functions: Color-Word Interference test).
- The CANTAB Pattern Recognition Memory mean correct latencies (immediate and delayed) and the Spatial Recognition Memory mean correct latency (see 3.4.7f Learning and Memory: Pattern Recognition Memory and Spatial Recognition Memory). These measure speed of processing in memory tasks. In a factor analytic study of CANTAB tests, the latency measures as well as the Reaction time test loaded on a factor related to speed of processing (Robbins et al., 1994).

The Paced Auditory Serial Addition Test (PASAT 3- and 2-seconds)

The PASAT (Gronwall, 1977) was developed to monitor the recovery of patients who had sustained mild head injuries and loss of consciousness or concussion. It was designed to measure changes to auditory information processing speed, but has been shown to use sustained attention, as well as divided attention and working memory (Lezak, et al., 2012; Lezak, Howieson, & Loring, 2004). Sixty-one randomized single digit numbers (from 1-9) are presented verbally at a specified regular interval. This task requires the subject to add each digit to the digit immediately preceding it and say the answer aloud. For example, if the first numbers presented were “9-1-3-5-2”, then the subject's correct responses, beginning as soon as the number “1” was presented, would be “10-4-8-7”. There is a brief repetition task included in the instructions, followed by a practice sequence of 11 digits, which can be administered a maximum of three times. The original version of the PASAT presented the digits at four rates of speed, each differing by 0.4 seconds (2.4 secs, 2.0 secs, 1.6 secs, 1.2 secs).

This is a challenging task. Normal middle age adults achieved 72% correct responses at the slowest rate but only 45% at the fastest (Fisk & Archibald, 2001). This test is also experienced as highly stressful, even by those who are cognitively intact (Lezak, et al., 2012). Healthy high-functioning women in the initial pilot study advised they felt under constant pressure and that they were failing, even when they were doing well. Practice
effects have been documented with the original PASAT, with gains only levelling off after the fourth and fifth administration (Cohen, Cutter et al 2001). There are no significant gender effects found for the PASAT but age, education and intellectual functioning have been found to affect scores (Mitrushina, Boone, Razani, & D’Elia, 2005).

There are several versions of the test and they differ on factors such as number of trials administered, the number of items within each trial and stimulus presentation rates (Mitrushina, et al., 2005). The original 61-digit PASAT was modified by Rao and colleagues to include only two trials, at 3-second and 2-second pacing rates, for studying the pattern of cognitive deficits in patients with MS (Rao, Leo, Bernadin, & Unversagt, 1991; Rao, Leo, et al., 1989). This version has been included as one of only three measures in the MS clinical trials core battery in order to examine cognitive slowing associated with MS (Benedict, et al., 2002; Cutter et al., 1999; Rao & Society., 1990). This version of the PASAT (3-second and 2-second), including practice trials for each trial and alternate forms, was used in the study. The outcome measures used for both the 3-second and 2-second trials were correct responses.

Reliability

The PASAT has demonstrated split-half reliabilities higher than 0.90, indicating high internal consistency (Egan, 1988). Like the original PASAT, performance on the 3-second and 2-second trial version have been found to be affected by level of education (12 years or more), but not age, unlike the original (Rao, et al., 1991). Raw scores were standardized into z-scores using normative test data, stratified by education level (12 years) collected from 100 normal healthy adults (75 females) with an average age of 46.0 (SD = 11.6) years, an average education of 13.3 (SD = 2.0) years and an average verbal IQ of 107.2 (SD = 11.2) (Rao, et al., 1991).

Significant practice effects have been widely observed in PASAT performance in normal and in neurologically impaired patients (Gronwall, 1977; Lezak, et al., 2012) Two alternate forms have been developed for use with the 3-second and 2-second trial version. Furthermore, precise control needs to be made over the rate of stimulus presentation. Tapes have been found to stretch after around 50-75 presentations (Rao & Society., 1990), lengthening the interval between stimulus presentations. A standardized presentation on CD, administered via computer, with practice trials and parallel forms was used6 to ensure consistency of stimulus presentation and reduce practice effects. Audio level was adjusted, as required, before the practice trial to appropriate levels for the respondent.

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6 CD, manual, scoring forms and normative data can be purchased from PASAT website http://www.pasat.us
Validity

This version of the PASAT (3-second and 2-second pacing) has been found to be sensitive to mild impairments and the amount of white matter disease associated with MS (Rao, Leo, et al., 1989; Rao, Mittenberg, Bernadin, Haughton, & Leo, 1989).

Rapid Visual Information Processing test (RVP) (CANTAB)

The Rapid Visual Information Processing test (RVP) (Cambridge Cognition, 2005) is a test of visual sustained attention or vigilance, with a small working memory component, similar to the traditional Continuous Performance Test (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). Digits from 2 to 9 appear one at a time in the centre of the screen in pseudo-random order at the rate of 100 digits per minute. Subjects are asked to detect any of three possible target sequences (i.e., 2-4-6, 4-6-8, or 3-5-7) and push the press pad when the third number in the target sequence appears.

In the training stage there are a number of cues (see Figure 3.5). The target numbers are on the screen and the target sequence appears in red and is underlined in yellow and there is a beeping sound if the button is pressed correctly. As the training stage (blocks 1-3) progresses these cues and the beeping sound are gradually phased off. The first block (block 4) in the test stage, where target sequences are introduced, is a ‘warm-up’ practice block.

![Figure 3.5. Task screen for RVP showing cues in the training stage.](image)

The test assessment follows (blocks 5-7), including 300 digit presentations and 27 target sequences, and lasts for 3 minutes. Target sequences occur at the rate of 16 every 2 minutes. The subject is reminded before the test commences that the sequences begin with a 2, 4 or 6 and go up in 2s and that the three target sequences will remain on the screen. This is to reduce the load on working memory. In RVP it is necessary for the subject to attend selectively to stimuli, which may form the beginning of a target sequence.
and disregard those which may not, and the subject must maintain attention to repetitive, monotonous stimuli in order to detect the occurrence of rare and unpredictable targets.

The RVP outcome measures used in the study can be divided into total hits, false alarms (defined as occasions upon which the subject incorrectly identified a target sequence) and correct rejections; sensitivity to the target ($A'$); and mean correct latency. The CANTAB program calculates the number of responses recorded as having occurred within 1800 milliseconds of the final digit presentation for each of the target sequences from the test blocks only. The signal detection measure $A'$ ($A$ prime) estimates how good the subject is at detecting target sequences (range 0.00 to 1.00, bad to good) and is evaluated using the calculated probability of hits and false alarms. The standardized measure of total false alarms transforms the z-score sign so that a positive z score means good performance (few false alarms).

Reliability

Total hits from the RVP has been found to have fair test-retest reliability ($r = 0.64$) in healthy middle-aged adults tested 1-8 weeks apart (Harrison, et al., n.d.). Practice effects were found to be optimal ($r = 0.15$). A significant age-related decline was found in RVP% correct performance in a study of surgeons (age 45-75 years), medical students (age 24-35 years) and age-matched normative controls (Boom-Saad, et al., 2008). RVP raw scores were converted into age-standardized z-scores based on normative test data.

Validity

Both RVP $A'$, the measure of target sensitivity, and RVP mean latency, have been found to be good indicators of sustained attention function. RVP $A'$ has been sensitive to sustained attention impairments associated with abnormal mental states, such as bipolar disorder (Clark, Iversen, & Goodwin, 2002), and neurological damage, especially those involving the cholinergic pathways. RVP $A'$ was one of six measures that, in combination, predicted outcomes 20 months later in 106 older adults with mild cognitive impairment based on baseline performance. The profile of baseline impairments predicted outcomes (recovered from mild cognitive impairment, remained stable, deteriorated) with 86.3% accuracy and 100% accuracy for those that progressed to Alzheimer’s Disease (Summers & Saunders, 2012).

Both RVP $A'$ and RVP mean latency have been sensitive to pharmacological manipulation, such as the administration of nicotine, a cholinergic agonist, which has been found to improve sustained attention in patients with Alzheimer’s Disease (Jones, Sahakian, Levy, Warburton, & Gray, 1992; Sahakian, Jones, Levy, Gray, & Warburton, 1989) and the
administration of scopolamine, a cholinergic antagonist, which has been found to impair sustained attention performance in normal, healthy subjects (Wesnes & Warburton, 1983). RVP has been used in imaging studies and found to be consistent with activation of a right fronto-parietal network (Coull, Frith, Frackowiak, & Grasby, 1996).

Digit Span (DSP) (WAIS-III) and extending the limits

Digit Span is one of the working memory subtests of the WAIS-III (Wechsler, 1997a) and WMS-III (Wechsler, 1997b). The examiner reads a string of random numbers aloud at the rate of one per second. In Digit Span Forward subjects repeat digits in the exact order they were presented. The sequences begin with two digits and end with nine digits. There are two trials given for each span length. If the subject repeats at least one sequence correctly, the examiner moves onto the next longer span sequence. In Digit Span Backward, the subject is required to recall the digits presented in the reverse order, beginning with two digits and ending with eight digits.

Digit Span Forward is considered primarily a measure of auditory attention span whereas Digit span Backward requires mental manipulation and is more demanding of auditory working memory. The correlation between the Digit Span Forward raw score and Digit Span Backward raw score in the standardization sample is only 0.60, suggesting that there are some differences between the two scores.

In order to reduce unnecessary test administration time, the first test sequence in Digit Forward to be administered was trial 3, which is four digits long. The first sequence in Digit Backward to be administered was trial 2, which is three digits long. All subjects were able to get these digit spans correct.

Some women in the study pilot tests reached the limit of this test (9 digits forward, 7 digits backward) indicating a ceiling effect. An examination of the frequency of item responses for Digit Forward and Digit Backward derived from the WAIS-III standardization sample (Tulsky et al., 2003) demonstrated that, in the relevant age range (30-64; n = 400), a proportion of the sample (7% for forwards and 5.25% for backwards) reached the limits of the test.

In order to minimise ceiling effects, which can reduce the ability to detect change in high functioning adults, it was necessary to extend the forwards and backwards trials to test the limits. The WAIS-III Digit Span Forward trial was extended from 9 to 13 digits (Digit Supraspan Forward) e.g., 3-10-8-1-9-5-7-2-4-6 (for details of sequences, see Appendix A.2). It followed the last of the WAIS-III Digit Span Forward trials, so it did not interfere
with the administration of the test or need further instructions. Administration and scoring was the same as for Digit Span (1/correct trial).

Two different sequences were developed from random numbers for each sequence length. No digit was repeated in a sequence. 'Eleven' was not used as a digit because three syllables could not be presented at the rate of one per second without rushing the presentation of the next digit.

The Digit Span Backward trial was extended from 7 to 11 digits (Digit Supraspan Backward) (for details of sequences, see Appendix A.2). It also continued on from the last of the WAIS-III Digit Span Backward trials and was administered and scored in the same way.

These sequences were pilot tested on eight postgraduate women. No one in the pilot testing or the study reached the limit of this test. The longest Digit Supraspan Forward was 11 digits and the longest Digit Supraspan Backward was 10 digits.

Digit Span in the Wechsler tests combines the forward and backward components into a single test and a total score (Wechsler, 1997a). The manual cites two reasons for this: the limited range of items that contributed to each of the scores (Forward and Backward) in the original standardization sample; and to prevent memory for spans from having too great an emphasis in the entire battery. It has continued to combine subtests in each revision as the total score has better psychometric properties. The combined total digit span score has been criticized as the two scores combine multidimensional constructs and limit clinical interpretation (Lezak, et al., 2012). However, this outcome measure is the most widely published and the psychometrically properties are good, so it was included along with individual measures for the longest Backward and Forward spans. The total score for Digit Span was based on the standard WAIS-III digit span trials and transformed into an age-standardized z-score based on WAIS-III normative data. The Digit Supraspan Forward Total score was used as the longest digit forward span achieved when the limits were tested. The Digit Supraspan Backward Total score was used as the longest digit backward span achieved when the limits were tested. The WAIS-III manual advises that larger individual differences between the Forward and Backward span length has been found to indicate problems in working memory (Wechsler, 1997a). This difference score was calculated for each individual at each timepoint and standardized based on WAIS-III normative data and included in the individual analyses.
Reliability

Test-retest reliability coefficients for Digit Span Total are good ($r^2 = 0.89$) in healthy adults (Lezak, et al., 2012). Age has not been found to affect digit span performance below the age of 65 and appears to affect forward span only minimally beyond 65 or 70 (Lezak, et al., 2012). Performance can be improved by chunking numbers (Bor & Owen, 2007) so it is important that the numbers are read at a steady pace. Digit sequences, including WAIS-III and Supraspan sequences, were pre-recorded on audio files and checked to ensure the digits were presented at the pace of one per second. Subjects were played the audio files to ensure reliable test administration and consistency between subjects.

Validity

Poor performance on Digit Span total has been negatively associated with the duration of exposure to occupational industrial solvents (Kishi, Harabuchi, Katakura, Ikeda, & Miyake, 1993). Digit span forwards has been sensitive to the number of concussions in soccer players ($p < 0.004$) indicative of mild chronic traumatic brain injury (Matser, A.G., Lezak, Jordan, & Troost, 1999). Digits Span Backwards has been sensitive to the impact and long term recovery from a traumatic brain injury (Ponsford, Draper, & Schonberger, 2008).

A functional imaging study of 14 healthy adults examined the pattern of neural activation with performance on Digit Forward and Backward (Gerton et al., 2004). Imaging data demonstrated that Digit Forward and Digit Backward rely upon a largely overlapping functional neural system associated with working memory, most notably in the right dorsolateral prefrontal cortex (DPC) and bilateral inferior parietal lobule (IPL), as well as the anterior cingulate, a region associated with attentional effort and error detection. The degree of activation increased linearly with increasing task difficulty in Digit Forward. Digit Backward produced greater activity in those areas serving working memory, including bilateral DPC and left IPL and Broca's area, beyond levels seen with Digit Forward. This was interpreted as consistent with Digit Backward requiring greater dependence on processing by the central executive component of Baddeley's model, including the phonological loop and subvocal rehearsal area. Surprisingly, medial occipital cortex was activated for both tasks suggesting a possible visual imagery strategy for these auditory tasks.

Spatial Span (SSP) (CANTAB)

The Spatial Span test (SSP) (Cambridge Cognition, 2005) is a test of spatial attention span and working memory. It is modelled on the Corsi blocks task (Milner, 1971) designed as a nonverbal analogue of the auditory Digit Span test. It has been used to test the
'visuospatial sketchpad' of Baddeley and Hitch's working memory model (Baddeley & Hitch, 1994). In SSP Forward nine white boxes are shown on the screen, some of which change colour, for three seconds, one at a time (see Figure 3.6). The subject is then signalled by a tone to recall the sequence by touching each of the boxes in the same order they were presented on the screen. There are two practice trials before the test begins. The number of boxes in the sequence is increased from two to nine as the test progresses. If the subject gets the sequence correct, they move to the next level of difficulty. If the subject does not get the sequence correct, two more attempts are allowed at each level. The test discontinues after three failed attempts at a given level. The sequence and colour is changed from sequence to sequence to minimize interference. The Forward test is considered a test of visuospatial attention span, defined by the maximum number of boxes correctly touched in sequence. In the Reverse test the subject must touch the boxes in the reverse order to how they were presented on the screen. The Reverse test is considered a test of spatial working memory.

![Image](image.png)

Figure 3.6. Test screen for Spatial Span.

The outcome measures for SSP Forward and Reverse used in this study were total span length. Span length is the longest sequence successfully recalled by the subject.

Reliability

Test-retest reliability of Spatial span length was fair ($r = 0.60$) in healthy middle aged adults tested 1-8 weeks apart (Harrison, et al., n.d.) and consistent with that found in healthy older adults ($M = 70, SD = 4.2$) ($r = 0.64$) (Lowe & Rabbitt, 1998). A study of cognitive performance across the lifespan in 194 Australian normal participants from 8-64 years, found an age effect on spatial span performance with 15-19 and 20-29 year olds displaying significantly longer spans than 8-10, 30-49 and 50-64 year age groups (De Luca et al., 2003). Outcome measures were transformed into age-standardized z-scores using normative test data.
Validity

No reported studies have compared the computerized CANTAB Spatial span directly with the traditional Corsi Blocks task format (Milner, 1971), although findings appear to be consistent across studies. Spatial span, in the Corsi blocks task format, generally runs one to two blocks lower than digit span (Lezak, et al., 2012). In the current study, spatial spans, on the computerized CANTAB test, also ran shorter than digit span ($M_{diff} = 1.09$).

Spatial Span forwards length has been found to be significantly impaired in adults with chronic fatigue syndrome (Joyce, Blumenthal, & Wessely, 1996) compared to healthy controls. It has also been sensitive to drug manipulation. Unmedicated children with attention deficit hyperactivity disorder (ADHD) performed significantly worse ($p < .001$) than healthy controls and medicated children with ADHD on Spatial Span Forward (R. Barnett et al., 2001). There was no significant difference, though, between medicated children with ADHD and matched healthy normal controls on this task. An unpublished study, reported in a chapter on the use of CANTAB in functional neuroimaging (A. Lee, Owen, Rogers, Sahakian, & Robbins, 2000), investigated forward and backward spatial span and digit span tasks using PET. They found backward spatial and digit span, relative to forward spatial and digit span, activated the dorsolateral prefrontal cortex. Patients with large lesions of the frontal lobe or with specific damage to the right dorsolateral prefrontal cortex have been significantly impaired on the spatial span task (D. Bor, Duncan, Lee, Parr, & Owen, 2006).

f. Learning and Memory

The ability to register, learn, retain and recall information is disrupted in a number of neurological and psychiatric disorders. Memory deficits are one of the first signs of progressive dementias, such as Alzheimer’s disease or Parkinson’s disease; and are prominent in a wide range of brain injuries, such a stroke, tumour, traumatic brain injury, substance abuse and neurotoxic exposure (Lezak, et al., 2012). Memory problems are also a frequent complaint of people with various psychiatric disorders, as well as normal ageing. In the past thirty years the conceptualization and understanding of memory and memory dysfunction has changed. Prior to that memory dysfunction was thought to represent a single construct, regardless of the aetiology or location of the brain pathology. Memory tests were, therefore, designed to test only the level of correct recall or recognition. However, findings from cognitive neuropsychology provided evidence of brain-behaviour relationships and distinct memory disorders associated with different neurological and psychiatric populations, refuting this unitary view. These disorders were
better explained by spared and impaired components of memory, including learning, encoding, storage, retrieval and retention.

Deficits in processes outside of the memory system can also affect memory performance, such as attention and speed of processing, organization, strategy and effort. Memory tests were designed to assess and normalize these aspects of memory in verbal and non-verbal domains, as well as assessing qualitative aspects, such as learning strategies, rate and pattern of acquisition of new information, error types and mechanisms of memory failure. These tests have been better able to aid differential diagnosis and discriminate neurological disorders and depression, as well as provide distinct memory profiles associated with different focal brain injuries or psychiatric disorders.

**Pattern Recognition Memory (PRM) (CANTAB)**

Pattern Recognition Memory (PRM) (Cambridge Cognition, 2005) tests visual recognition memory. Subjects are presented with a series of visual patterns in the centre of the screen. Each pattern is presented for 3 seconds, then the screen is cleared and the next pattern appears. In the recognition phase, subjects are required to choose between a pattern they have already seen and a novel pattern (see Figure 3.7).

![Figure 3.7. Test screen for recognition trial of PRM.](image)

The outcome measures used for both the immediate and delayed recognition trials were PRM % correct, defined as the number of correct responses expressed as a percentage. The other outcome measure was PRM Mean correct latency. This was the mean time, measured in milliseconds, to respond correctly. This was used in the attention and speed of processing analysis. The standard form and two parallel forms were used to minimize practice effects.
Reliability

Test-retest reliability of the PRM standard form was fair ($r = 0.72$) in healthy middle aged adults tested 1-8 weeks apart and good ($r = 0.84$) in healthy older volunteers ($M$ age=70, $SD = 4.2$) tested a month apart (Lowe & Rabbitt, 1998). The PRM parallel forms (1-4) were tested on healthy adults at least one week apart and the mean pattern recognition % correct scores were 92.8%, 92.4%, 91.7% and 86.7% respectively (Semple & Link, 1991). While significant differences were detected between the test versions, no post-hoc analyses were conducted to determine which form/s differed (such as only the fourth form). The first two parallel forms, which demonstrated similar results, were used in the current study. In a study of cognitive ageing in older adults, PRM performance was significantly predicted by age (Rabbitt & Lowe, 2000). In the current study PRM raw scores were converted into age-standardized z-scores based on normative test data.

Validity

Pattern Recognition Memory has been validated in patients with defined brain lesions and healthy normals, in pharmacological studies, and in clinical populations with memory problems. Neurosurgical patients with temporal lobe or other posterior excisions were significantly impaired on PRM % correct compared to healthy controls, but not on SRM% correct, while PRM performance was relatively preserved in patients with frontal lobe excisions (Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Owen, Sahakian, Semple, Polkey, & Robbins, 1995).

Pattern Recognition Memory has been sensitive to the cognitive effects of drugs and toxic substances. Chronic amphetamine users display more marked impairments on immediate PRM compared to opiate users, but no difference on delayed PRM, although both groups recognized significantly fewer patterns relative to healthy controls (Ersche, Clark, London, Robbins, & Sahakian, 2006). Chronic petrol sniffers, who did not have acute toxic encephalopathy, displayed deficits in PRM performance, as well as SRM and PAL, with no difference between current and former users (Maruff, Burns, Tyler, Currie, & Currie, 1998). Blood lead levels and duration of petrol sniffing significantly correlated with the magnitude of neurological and cognitive impairment (Maruff, et al., 1998). PRM % correct was one of a few tests found to be sensitive to cognitive impairments in early Alzheimer's disease and able to differentiate patients with diagnosed and questionable Alzheimer's from depressed and healthy controls (Swainson, et al., 2001). In a study of adults who had experienced childhood trauma, early physical neglect was significantly associated with impairment in PRM performance, suggesting the development of visual encoding and
recognition memory may be affected by childhood neglect (Majer, Nater, Lin, Capuron, & Reeves, 2010).

**Spatial Recognition Memory (SRM) (CANTAB)**

Spatial Recognition Memory (SRM) (Cambridge Cognition, 2005) is designed to test spatial recognition memory. The subject is instructed that five small boxes will appear, one by one, in different places on the screen and to remember "where they were, so it's their place on the screen you have to remember". In the presentation phase a white unfilled 2.5 cm square is presented for 3 seconds before the screen is cleared, and then the square appears in sequence in four different locations on the screen. In the recognition phase, the subject is shown pairs of squares, one of which is in the place previously seen in the presentation phase. The subject must touch the square that was in the same place as before. This is done with each of the five squares from the presentation phase. Visual feedback is provided in terms of a red cross or a green tick. The procedure is repeated three more times using new target and distractor locations.

The outcome measure used was SRM % correct. Mean correct latency was the mean time to respond correctly and was used as a measure of speed of processing. The standard form and two parallel forms were used.

**Reliability**

Test-retest reliability of the standard SRM Total correct was low ($r^2 = 0.57$) in a study of healthy older volunteers ($M$ age = 70, $SD = 4.2$) retested using the standard form a month apart (Lowe & Rabbitt, 1998). It was found to be even lower ($r = 0.48$) in healthy middle-aged adults tested over 1-8 weeks, even though the baseline mean ($M =16.5, SD = 0.21$) and retest mean ($M =16.5, SD = 0.22$) remained the same (Harrison, et al., n.d.). There are no published results of the test-retest reliability of the SRM using parallel forms. However, in a study where other CANTAB visuospatial memory tests with parallel forms were tested for reliability, practice effects vanished using the parallel forms and test-retest reliability improved (Semple & Link, 1991). Performance on SRM has been found to be sensitive to normal ageing, even when general fluid ability was taken into account (Rabbitt & Lowe, 2000). SRM raw scores were transformed to age-standardized z-scores based on normative test data.
Validity

Spatial Recognition Memory % correct has been shown to be impaired in patients with frontal lobe excisions, but not in patients with posterior excisions (temporal lobe or unilateral amygdalo-hippocampectomy) while Pattern Recognition Memory showed the reverse pattern (Owen, Morris, et al., 1996; Owen, et al., 1995). This is consistent with research in non-human primates, showing segregated pathways in the visual system that convey information relating to an object’s identity, such as colour and shape, along the ventral system, and to its location in space, along the occipital to parietal pathways (Funahashi, Bruce, & Goldman-Rakic, 1989, 1990; F. A. Wilson, Scalaidhe, & Goldman-Rakic, 1993). Increased medical complications at birth have significantly correlated with more incorrect responses on SRM in 11-year old children who had spent time in neonatal intensive care (Curtis, Lindeke, Georgieff, & Nelson, 2002). Spatial Recognition Memory has also been impaired in patients with Alzheimer’s disease and Parkinson’s disease (Sahakian et al., 1988), as well as individuals suffering from toxic substance abuse, such as chronic petrol sniffers (Maruff, et al., 1998).

Paired Associates Learning (PAL) (CANTAB)

The Paired Associates Learning test (PAL) (Cambridge Cognition, 2005) is designed to test the subject’s ability to form visuospatial (pattern and location) associations, as well as test visuospatial learning and memory. Six white boxes, increasing to eight in later trials, are displayed around the edge of the screen and the boxes are opened one at a time in a random order (see Figure 3.8).

![Figure 3.8. Test screen for Paired Associates Learning.](image)

Abstract coloured patterns are displayed in the boxes, starting with two patterns. The individual patterns are then displayed in the centre of the screen one at a time and the subject must recall the spatial location and touch the box in which the pattern occurred. If
the subject recalls a wrong location, the pairing is repeated with up to nine reminders, before the test is terminated. There are five stages, with increasing numbers of patterns (2, 2, 3, 6, 8).

The number of patterns identified correctly on the first trial is considered a measure of visuospatial span and working memory; the number of trials and trials needed to learn all the pattern location associations is considered a measure of associate learning. The outcome measures used in the study were: the first trial memory score; stages completed on first trial; mean trials to success; mean errors to success; total trials and errors (total and at the 6-pattern stage) adjusted for each stage not attempted due to failure. The standard form and two parallel forms were used.

Reliability

Test-retest reliability for PAL total errors was fair \(r = 0.68\) in a study on 100 healthy adults (J. Barnett et al., 2010). Test-retest coefficients for first trial correct memory score and average trials to success were 0.68 and 0.86 respectively in a group of 162 older volunteers (Lowe & Rabbitt, 1998). The parallel forms of the PAL were found to be equivalent in difficulty when tested in 49 healthy adults (33 women, mean NART-estimated IQ of 117, SD = 6) using a randomized balanced Latin-square design with four testing sessions at least one week apart (Semple & Link, 1991). Performance on PAL is sensitive to normal ageing, after accounting for general fluid ability (Rabbitt & Lowe, 2000). Paired Associates Learning raw scores were transformed to age-standardized z-scores based on normative test data.

Validity

Paired Associates Learning appears to involve contributions from frontal and temporal lobe regions, as patients with excisions in these areas demonstrated impairments in PAL performance but were indistinguishable on this task (Owen, et al., 1995). This test has been shown to be extremely sensitive to early, pre-clinical detection of Alzheimer's disease, up to 24 months ahead of other screening tools, such as the WMS, COWAT and RAVLT (Fowler, Saling, Conway, Semple, & Louis, 2002). The number of errors at the 6-pattern stage was able to differentiate with 98% accuracy patients with probable and diagnosed Alzheimer's disease from healthy and depressed controls (Swainson, et al., 2001). Paired Associates Learning has been used to study psychoactive drug administration in healthy volunteers, with significant impairments produced by diazepam, a benzodiazepine, but only marginal detriments produced by scopolamine, a cholinergic agent (Robbins et al., 1997).
Verbal paired associates (names) (VPAn)

The Verbal Paired Associates test from the WMS-III (Wechsler, 1997b) was designed to test verbal associate learning and memory. It requires the presentation of eight pairs of unrelated words over four trials. Recall of the pairs is assessed after each trial and after a 25-35 minute delay. This is done by stating the first word of the pair and asking the subject to recall the associated item. Recognition memory is then assessed. Most subjects in the pilot testing got a perfect or near perfect score on the first or second trial. The normative data in the WMS-III manual also shows clear evidence of ceiling effects, which limit the usefulness of this instrument. Many pilot test subjects advised they used visual strategies to associate the words. For example, for ‘insect – acorn’, they imagined an insect carrying an acorn. The WMS-III battery no longer characterizes performance on Verbal Paired Associates as ‘verbal’ instead using the label ‘auditory’, which refers only to the sensory modality of stimulus presentation.

The CANTAB Paired Associate Learning test had been selected as a visual paired associates test that was sensitive to mild cognitive impairment and change (Cambridge Cognition, 2005). It was considered worthwhile to have a paired associates test involving verbal functions in order to test a wide spectrum of verbal and nonverbal paired associate learning performance. The aim was to modify the stimuli used in the WMS-III Verbal Paired Associates to those that were not as easily visualizable, but use the same structure, administration format and scoring methods.

Remembering people’s names rank high among the subjective complaints of women reporting ‘chemobrain’. Name learning, though, has not been examined in studies of chemotherapy-related cognitive impairment. The words that are used in most verbal learning lists are nouns. People’s names are a type of noun (proper noun) but the literature has demonstrated that name learning is more difficult to learn than other nouns. Healthy normal adults who had to learn a name, an occupation or a possession for unfamiliar faces, later recalled significantly fewer names than occupations or possessions (Cohen, 1990). It was suggested by the authors that it is more difficult to put names to faces because proper names have a more arbitrary link to a reference than object names.

All name-pairs were matched for word length and for frequency in order to avoid confounding name frequency or familiarity. Names were selected from the top ten baby names in the ACT from annual data from 1930 onwards provided by the Office of Regulatory Services, ACT government. The popularity of baby names in the ACT was taken as a proxy measure of frequency. This was checked in the pilot study from ratings of eight age-matched women. These women were presented with a list of first names and asked to
identify the names of all the persons they knew with each name in the list, whether through the media or by personal acquaintance. The subjective frequency of the selected names over each of the final lists was matched. Two names in the pairs were names that can be used by men or women (e.g., Alex, Jo).

In the learning trial the examiner gave the following instructions: “You are organising a surprise birthday party for your best friend. You have overheard her talking about her friends from work, who you want to invite. I am going to say a list of their names. Listen carefully, because when I am finished I will say the first name and I want you to tell me the name that goes with it. For example, if the names were Mary – Kate, Mathew – John, then when I say the name Mary, you would answer (pause) Kate. When I say the name Mathew you would answer (pause) John. Do you understand? Now listen carefully to the list of names as I read them.”

The name pairs were presented verbally by the examiner at the rate of one pair every three seconds (following the WMS-III Verbal Paired Associates administration). The eight name pairs (e.g., Sophie – Anne and Daniel – Charles) used in the standard form, and those used in the alternate forms are provided in Appendix A.3. At the end of the list of eight name pairs, the examiner asked which name went with the first name of each pair in randomized order. Presentation and recall was repeated three times. At the end of the four trials, the examiner said, “Later on I will ask you to recall these names again, so try to remember them.” This was to ensure intentional paired associate recall was assessed at each time-point, rather than incidental recall. After a delay of 25 minutes, during which time no verbal tests were administered, a fourth recall trial took place. The examiner gave the following instructions:

“Remember the names that you learned earlier? I told you two names that went together. I want you to recall as many of those name pairs as you can remember one more time. I will say the first name of the pair and you say the name that goes with it. Ready?”

Finally, a recognition trial was conducted with the eight name pairs and 16 distractor pairs. The subject was asked to identify if the names were one of those asked to remember earlier. Six of the distractor pairs included a first name from the list incorrectly paired with a second name not from the list. The total correct recognition score was out of 24.

Parallel forms were administered at the follow-up assessments. In a pilot test, undergraduate student volunteers (N = 60) were administered the first trial of either the original or one of the two parallel forms. Results indicated no significant differences on a measure of first trial recall, suggesting that the parallel versions are equivalent in
difficulty. This test was included in the pilot testing of the final battery on age-matched women. Some people in the pilot testing of the full test reported that they used meaningful associations to aid recall, such as people they knew or famous people.

The scoring of the test was modelled on WMS-III Verbal Paired Associates. The outcome measures that were used in the study were: trials 1-4 total correct, learning slope, total immediate recall (sum trials 1-4); long delay recall, total correct; percent retention. As verbal learning and memory have shown to decline slightly after 50 and more markedly after 65 (Delis et al., 2000), z-scores were calculated on the basis of the control group results stratified by age (±50 years).

**Complex Figure Test – Recall and Recognition trials**

The Complex Figure test (CFT) is described in detail, including administration, previously in this chapter (see 1.4.7d). The original complex figure developed by Rey (Rey CFT) was used at Time 1 and Time 3, with the retest interval approximately 15 months apart, using the explicit scoring criteria, norms and recognition trial from Meyers and Meyers (1995). The modified Taylor Complex Figure and recognition trial (Hubley & Tremblay, 2002) was used at Time 2 as an alternate form, as it has been shown to produce comparable results to the Rey CFT (Hubley & Jassal, 2006; Lezak, et al., 2012). Each test had a 3-minute recall trial after the copy trial to test immediate memory, a 30-minute recall trial to test long-term memory, and a recognition trial to test encoding of the figural elements.

The outcome measures used in this study for each complex figure test were: immediate recall (3 minutes) total correct; long delay (30 minutes) total correct; and recognition total correct.

Reliability

Test-retest reliability of the Rey CFT tested in 12 healthy normal adults around six months apart was fair for immediate recall ($r = 0.76$), and good for delayed recall ($r = 0.89$) and recognition total correct ($r = 0.87$) (Meyers & Meyers, 1995). Alternate forms reliability between the Rey CFT with the Modified Taylor CFT (MTCF) in healthy adults tested one week apart was fair for immediate recall ($r = 0.78$), and delayed recall ($r = 0.74$) (Hubley & Jassal, 2006). Age correlated significantly and negatively on all recall and recognition measures for the Rey CFT and MTCF. There was no significant correlation found between education and performance. In this study raw scores were transformed into age-standardized z-scores based on normative data (Meyers & Meyers, 1995). Each drawing was scored blind to group membership according to explicit standardized criteria for accuracy and placement of the 18 elements. Ten percent of all drawings were blind scored
by a second examiner. Inter-rater reliability was high for immediate and delayed recall ($r > 0.90$).

Validity

Performance on the two recall conditions is sensitive to unilateral brain damage in the right hemisphere (Lezak, et al., 2012; Loring, Lee, & Meador, 1988). Impairment in recall scores have been demonstrated in patients with temporal lobe epilepsy or temporal lobe surgery (Hermann, Seidenberg, Schoenfeld, & Davies, 1997). Patients with frontal lobe lesions also do poorly on recall, due to difficulty planning their approach to the task (Lezak, et al., 2012). Slow processing of complex data or attention deficits can also affect recall. A profile analysis of performance on the complex figure outcomes measures in 98 brain injured patients identified distinct memory profile patterns (attention, encoding, storage, retrieval and normal) that significantly correlated with functional ability scores (Meyers & Meyers, 1995). Recall and recognition scores were effective in discriminating between age-matched brain-injured patients, psychiatric patients and healthy normal controls (Meyers & Lange, 1994). Complex Figure recall is sensitive to mild neuropsychological impairment in different clinical populations (Lezak, et al., 2012). Very little difference is observed in normal subjects between immediate recall and delayed recall trials using the Rey CFT or the MTCF, so a decline between immediate and delayed recall trials is of clinical significance (Meyers & Meyers, 1995; Spreen & Strauss, 1998).

One-third of a sample of neurology patients demonstrated higher delayed recall scores relative to immediate recall scores, and, of these, half the cases had a traumatic brain injury (unpublished data cited by Lezak et al., 2012, p. 501).

**California Verbal Learning Test (CVLT and CVLT-II)**

The California Verbal Learning Test (CVLT and CVLT-II) (D.C. Delis, et al., 1987; D.C Delis, et al., 2000) was designed to measure various aspects of verbal learning and memory, including learning strategies such as semantic associations. A list of 16 items (List A, including four words from each of four semantic categories) is presented orally at the rate of slightly slower than one per second with instructions to recall the words in any order. This list is repeated over five trials in total. Immediate recall of items from the list is recorded after each of the five learning trials. An interference list (List B) of 16 items is presented, including four words from each of four semantic categories, two categories of which are shared categories from List A. Immediate recall of the interference list is immediately followed by free and category-cued recall of the first list (List A). After a 20-minute delay, during which only nonverbal tests occur, free and cued-recall and recognition of the first list from 48 items (using a yes/no paradigm) are assessed.
Outcome measures used in the study were: total correct recall and recognition on all trials (List A 1-5, List B, free and cued, short and long delay); total errors (intrusions and repetitions); learning slope; learning strategies (chance adjusted) (e.g., semantic clustering); serial position effects (% recall from primacy/middle/recency region of word list); across trial recall consistency; and recall discriminability on all trials, assessing the ability to report target words relative to intrusion errors, a measure derived from signal detection theory. Raw scores were transformed into age and education-corrected standardized z-scores for the multivariate analysis using CVLT-II normative data via the CVLT-II scoring software.

Reliability

The internal consistency of the CVLT-II was estimated using three methods and found to be high ($r = 0.94$ split-half reliability of trials; $r = 0.83$ category word recall over trials 1-5; $r = 0.79$ across trial (1-5) recall consistency) (D.C. Delis et al., 2000). CVLT performance declines with age, most rapidly in the later years; while women score higher than men in free recall. In the normative sample, age explained 25.9% of the variance, sex explained an additional 5.1% and education explained an additional 4.5% of the variance.

Repeated testing with the CVLT and CVLT-II standard forms has shown significant learning effects with healthy adults recalling an average of 8 more words over the five learning trials on retesting (D.C. Delis et al., 2000). An alternate form was developed for the revised edition. A test-retest reliability study of the CVLT-II standard and alternate form in 34 patients with multiple sclerosis re-tested after one month, found that, although test-retest reliability coefficients were broadly comparable ($M r = 0.62$ standard form; $M r = 0.75$ alternate form), participants who received the alternate form at retest exhibited notably smaller practice effects across the CVLT-II summary measures (alternate form $M d = 0.0$, range $= -0.1$ to 0.1; standard form $M d = 0.76$, range $= 0.5$ to 1.0) (Benedict, 2005). Negligible practice effects were also found when the alternate form was used to retest 115 healthy adults one month after the CVLT-II standard form (Woods, Delis, Scott, Kramer, & Holdnack, 2006).

The CVLT-II correlates well with the CVLT. In the test reliability study, a group of 62 health adults were given the CVLT and CVLT-II in counterbalanced order, approximately a week apart (D.C. Delis et al., 2000). Most of the coefficients were adequate to high. The correlation for total immediate recall (trials 1-5) was 0.76. The normative data for the CVLT-II, though, is superior to the previous version, being larger ($N = 1087$, age range 16-89) and more representative, especially in terms of education levels, which were restricted in the previous normative sample. Normative data for the CVLT-II is stratified
by seven age groups and the data was stratified by gender and education for those variables that revealed significant gender and education differences, providing a more accurate classification of an individual's relative performance (D.C Delis, et al., 2000). Algorithms were also improved for deriving the clustering indices for the CVLT-II. The test authors caution against comparing standard scores derived from the CVLT normative sample or clustering algorithms with that of the CVLT-II if used for repeat testing as they have been modified. However, differences in CVLT and CVLT-II raw scores are negligible. This suggests the CVLT-II alternate form and CVLT can be used as appropriate alternate forms to diminish the confounding effect of practice without adversely affecting reliability. The CVLT-II standard form was used at Time 1. The CVLT-II alternate form was used at Time 2. The original CVLT standard form was used at Time 3 as a second alternate form, but was scored with the CVLT-II scoring algorithms and norms.

List A and B were recorded on audio files to ensure consistency of list item presentation. Instructions were followed as per the manual. The CVLT-II Administration and Scoring Software was used to facilitate administration and response recording and scoring as it automatically performs scoring and produces age and education-corrected standard outcome measures. Responses were entered directly by the examiner into the computer program during the administration for Time 1 and Time 2 but were recorded by hand at Time 3 and entered using a CVLT to CVLT-II list recoding sheet. Subject responses were also recorded on audio-tape to check data entry following the assessment.

Validity

The CVLT/CVLT-II is among the top three memory tests used by neuropsychologists (Rabin, et al., 2005). Six factors emerged in the standardization sample, similar to those found in the first edition, labelled general verbal learning, response discrimination, primacy-recency effects, organizational strategies, recall efficiency and acquisition rate (total learning slope) (D.C. Delis, Freeland, Kramer, & Kaplan, 1988; D.C Delis, et al., 2000). Patients with focal frontal lesions exhibit significant impairments compared to controls in overall poorer recall, increased intrusion errors, reduced semantic clustering and impaired recognition, due to endorsement of semantically related words and words from the interference list (Baldo, Delis, Kramer, & Shimamura, 2002). These findings support the CVLT’s method of assessing the use of semantic associations in order to identify the basis of verbal learning and memory deficits. The new scoring technique for semantic clustering and recall discriminability has been found to be more effective than previous CVLT measures in detecting differences between patients with Alzheimer’s disease, Huntington’s disease and healthy controls (D.C Delis et al., 2010; Fine, Delis, Wetter, Jacobson, Hamilton, et al., 2008). Recall and recognition discriminability scores
differentiated patients with a TBI from controls and varied according to severity of brain injury (M. L. Jacobs & Donders, 2007).

g. **Executive Functions**

'Executive functions' are a neuropsychological construct and umbrella term that refer to higher-order cognitive skills responsible for responding to novel or challenging situations, including reasoning, goal setting, planning, strategy, decision-making, multi-tasking, shifting attention, inhibiting distractions, self-regulation and review (Lezak et al., 2012). Traditionally, the concept of executive control were linked to the function of the frontal lobes (Luria, 1966). Early conceptualizations were unitary models such as the 'central executive' component of working memory (Baddeley, 1986) or the 'supervisory activating system' of attentional control (Norman & Shallice, 1986). Baddeley (1996) says the initial conceptualization of the 'central executive' was so vague it may have appeared to be "a little man who sits in the head and in some mysterious way makes the important decisions." Most early tests of executive function yielded a single achievement score where deficient performance was meant to directly implicate frontal lobe dysfunction. However, findings from cognitive neuropsychology demonstrated that the 'central executive' is composed of interrelated but distinct functions (Baddeley, 1998). This is evidenced by the fact that patients with frontal lobe lesions can have impairments in some tests of executive function and not others; executive dysfunction often arises following damage to the frontal lobe or prefrontal cortex but can also occur following damage to other brain regions; measures of executive functions correlate poorly with each other, factor analytic studies identify multiple factors and the developmental trajectories of specific executive functions vary (Lezak, et al., 2012). As a result, theoretical models have been modified to a more integrated supervisory or control system with several inter-related but distinct functions (Baddeley & Della Sala, 1996; Shallice & Burgess, 1996).

Traditionally executive function measures have been considered measures that are novel, complex and involve the integration of information as they require the subject to focus, formulate a plan or strategy, and self-regulate. Tasks that are simple and routine or familiar are thought to require minimal executive resources. This poses a challenge to the repeated assessment of executive functions. Not only do a number of executive functions need to be assessed, but the test may no longer measure an executive function on repeated assessment as the test is no longer novel. Even using parallel forms does not solve this problem. While parallel forms can minimize practice effects by changing content, they cannot account for procedural learning i.e., having learnt ways to approach the test.
through previous exposure. In the current study tests were mainly selected from two batteries designed to measure executive functions in repeated assessments. However, for one function (verbal abstract reasoning), where no available test had parallel forms, different tests were used that measure the same construct. The test batteries have been described previously [see 1.4.7: Cambridge Neuropsychological Test Automated Battery (CANTAB) and The Delis-Kaplan Executive Function System (D-KEFS)]. The description of the individual tests and outcome measures used to assess different executive functions is presented in the following section.

**Verbal abstract reasoning**

Impairments in verbal abstract reasoning and concept formation generally present in patients as overly concrete thinking. They are common in patients with brain injury and are linked to the prefrontal cortex and often incorporate impairments in other executive functions, such as planning or cognitive flexibility (Lezak, et al., 2012). The Similarities test from the WAIS-III (Wechsler, 1997a) was selected initially as it is a well-established test of verbal abstract reasoning and concept formation and has good test-retest reliability. In the pilot testing phase, however, a number of postgraduate students remarked that the test they had most remembered and discussed with friends or family after the assessment were questions from the Similarities test. There were no tests of verbal abstract reasoning that were found with parallel forms. In order to test verbal abstract reasoning changes involved in novel conceptual tasks, rather than known material, three different tests of verbal abstract reasoning were used over the course of the assessments. The Similarities test was administered at *Time 1*, the Proverb test at *Time 2* and the Word Context test at *Time 3*.

**Similarities (WAIS-III)**

The Similarities test (Wechsler, 1997a) is designed to assess verbal abstract reasoning and concept formation. The subject must state in what way two objects or concepts are alike. The concepts are graded in difficulty from simple (e.g., fork and spoon) to the most difficult (e.g., praise and punishment). The subject's response was recorded verbatim and scored later, using scoring guidelines from the WAIS-III manual. The raw score was transformed into an age-standardized score using normative data from the WAIS-III scoring manual.

**The Proverb test (D-KEFS)**

The Proverb test (D.C. Delis, et al., 2001a) is designed to assess abstract reasoning and concept formation. It requires the subject to translate a concrete statement into its
abstract, metaphorical meaning. Eight proverbs are read to the subject one at a time and the subject has to interpret the proverbs orally, without assistance or cues. These proverbs consist of varying degrees of familiarity (e.g., ‘Rome was not built in a day’ and ‘Too many cooks spoil the broth’.) The subject’s response was recorded verbatim and scored later, using scoring guidelines from the D-KEFS manual. Each response is scored 0 to 2 points for accuracy and 0 to 1 point for abstractness. The total achievement raw score for the free inquiry condition was transformed into an age-standardized score using normative data from the D-KEFS scoring manual.

The Word Context test (D-KEFS)

The Word Context test (D.C. Delis, et al., 2001a) was originally designed to examine the acquisition of word meanings in children. The authors adapted the original version for use with both children and adults. The subject has to discover the meaning of made up words based on its use in five clue sentences. For example, ‘What might sev mean? Many people eat sev?’ Clues are initially abstract or general but each clue sentence provides progressively more detailed information. Each clue sentence is displayed along with previously presented sentences. The aim is to decode the mystery word with as few clue sentences as possible and to then provide consecutively correct responses. It is designed to measure verbal abstract reasoning and concept formation. The outcome measure used for this test was total consecutive correct performance. The total consecutive correct raw score was converted into an age-standardized score using normative data from the D-KEFS scoring manual.

Reliability

Test-retest reliability is good for Similarities (0.83-0.89 for age 30+) (Wechsler, 1997a) and fair for the Word Context test (r = 0.70) and the Proverb test (r = 0.76) (D.C. Delis, E. Kaplan, & J.H. Kramer, 2001b). No studies were found that have reported correlations between the Similarities test and the D-KEFS tests, although a study using the Similarities test and a similar Proverbs test found a notable association between test scores (r = 0.49) and a similar ability between the two tests to differentiate between patients with schizophrenia and healthy controls (Hamdi, 1992). Median correlations among total correct scores for Word Context and the Proverb test are positively correlated (r = 0.54) (D.C. Delis, et al., 2001b).

Validity

Lower Similarities achievement scores are associated with bilateral frontal lesions (Lezak, et al., 2012). Performance decline on Similarities in middle-aged adults has been among
the early predictors of development of Alzheimer's disease (La Rue & Jarvik, 1987). Patients with frontal lobe epilepsy are significantly more impaired on Proverbs accuracy than healthy controls, whereas patients with temporal lobe epilepsy did not differ significantly from controls (C. R. McDonald, Delis, Kramer, Tecoma, & Iragui, 2008). Patients with prefrontal cortex lesions need significantly more sentence clues on the Word Context test to determine correct solutions and are less likely to arrive at correct responses than controls (D.C. Delis, et al., 2001b).

**Spatial Working Memory (SWM) (CANTAB)**

The Spatial Working Memory test (SWM) (Cambridge Cognition, 2005) is designed to assess spatial working memory and strategy performance. The aim of the test is for the subject to find a blue token in each of the boxes displayed and use them to fill up an empty column on the right hand side of the screen, while not returning to boxes where a blue token was found previously (see Figure 3.9). The subject is reminded to "remember not to return to a box where you have already found a blue token, as the computer will never hide it in that box again." After the three practice trials with three boxes, the test trials include four trials with four boxes, six boxes, and eight boxes. The colour and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies.

![Figure 3.9. Test screen for Spatial Working Memory.](image)

The SWM outcome measures used in the study are divided into errors and strategy score. Between Errors are defined as the times the subject revisited a box in which a token has previously been found. Within Errors are defined as the number of errors made within a search, i.e., the number of times a subject revisits a box already found to be empty during the same search. Double errors are occasions where the subject has committed an error that can be categorized as a between and within error. Between Errors, Within Errors and Double Errors were calculated for four or more tokens, as well as for the highest (8 box) level of difficulty. Total errors are defined as the number of times a box is selected that is
certain not to contain a blue token and therefore should not have been visited by the subject.

It is possible to reduce the memory load for a given trial by searching strategically for tokens. One strategy defined as efficient for completing this task is to follow a predetermined sequence by beginning with a specific box and then, once a blue token has been found to return to that box to start the new search sequence (Owen, Downes, Sahakian, Polkey, & Robbins, 1990). The Strategy score is calculated by counting the number of times the subject begins a new search with the same box for 6- and 8-box problems.

Reliability

Test-retest reliability of SWM Between errors \( r = 0.70 \) and Strategy Score \( r = 0.63 \) were fair in a study of healthy adults tested 1-8 weeks apart (J. Barnett, et al., 2010), consistent with a study using healthy volunteers tested 66 weeks apart \( r = 0.65 \) (Leeson et al., 2009). Test-retest reliability of SWM total errors was also fair \( r = 0.68 \) in healthy older volunteers tested one month apart (Lowe & Rabbitt, 1998). Spatial working memory performance is sensitive to ageing effects, with significant differences seen between younger adults \(<50\) and older adults, and steady declines displayed after the age of 65, although not for the strategy score (Robbins, et al., 1994). Spatial working memory raw scores were transformed to age-standardized z-scores based on normative test data.

Validity

A PET study demonstrated this task activates both the dorsal and ventral prefrontal regions (Owen, Evans, & Petrides, 1996). Patients with frontal lobe lesions have shown a distinct profile of performance, with a high number of errors, even at the least challenging level of task difficulty, and this impairment was found to relate to the low use of an efficient search strategy. In contrast, deficits were observed in patients with temporal lobe/posterior lesions only at the most difficult level of the test, and this was unrelated to use of strategy (Owen, Morris, et al., 1996). Furthermore, when these patients were tested with analogous visual (shapes for boxes) or verbal (surnames for boxes) working memory tests, the frontal lobe group did not display any deficits. The temporal lobe/posterior group were significantly impaired on the visual working memory test, at all levels of task difficulty, but there were no deficits on the verbal working memory test. This was interpreted in relation to the relative contributions of 'executive' and 'mnemonic' requirements of the tasks used. In tasks where no simple strategy exists to improve the
efficiency of working memory, subjects may rely on mnemonic processes, and, under these circumstances, frontal lobe patients are unimpaired.

Between errors is sensitive to the progressive staging of Parkinson’s disease (Owen, Iddon, Hodges, Summers, & Robbins, 1997) and to pharmacological manipulation, such as methylphenidate, showing it enhances executive performance on novel tasks but impairs previously established performance (Elliott et al., 1997). Cancer patients receiving cytokine immunotherapy displayed significantly more between errors at the most difficult level of the task five days after treatment (Capuron, et al., 2001).

**Verbal Fluency (D-KEFS)**

The Verbal Fluency test (D.C. Delis, et al., 2001a) is based on verbal fluency tests, such as the Word Fluency (F-A-S) test (Thurstone & Thurstone, 1962) and the Controlled Oral Word Association test (Benton, Hamsher, & Sivan, 1994). It includes a new switching condition to assess cognitive flexibility performance and a parallel form for repeat testing, as this test is susceptible to practice effects. It is designed to measure the ability to generate words quickly and verbally, according to phonemic or semantic categories.

This test is composed of three conditions: letter fluency, category fluency and category switching, the new condition. In the letter fluency condition, the subject is asked to generate as many words, not including names of people or places, as they can in 60 seconds beginning with a specified letter. There are three trials using the letters (F, A, S). Letter Fluency is considered a key measure of verbal executive function, involving verbal generativity. Efficient cueing of retrieval in phonemic word generation involves auditory attention and working memory, ability to initiate and maintain set, cognitive flexibility, response inhibition, and speed of processing (Mitrushina, et al., 2005). In the category fluency condition, the subject is asked to generate as many words, not including pronouns, as they can in 60 seconds belonging to a specified category. There are two trials using the categories animals and boys’ names. This is considered a measure of semantic fluency, involving retrieval from semantic stores, cognitive flexibility and self-regulation. It is easier than letter fluency in the normal population. It is argued to rely on the visuospatial sketchpad of Baddeley’s model (2000), rather than the phonological loop, as in letter fluency. In the new category switching condition, the subject is asked to generate as many words, not including pronouns, as they can in 60 seconds, switching between two categories one after the other (fruits/ furniture). This was designed to have a higher cognitive load, by combining semantic fluency and attentional switching. Alternate forms for Verbal Fluency included in the D-KEFS were used at Time 2.
The outcome measures used in the study were Letter Fluency Total Correct; Category Switching Total Correct; Category Switching Total Switching; Category Switching Percent Switching; and Verbal Fluency Total Set-Loss Errors and Total Repetition Errors.

Reliability

Internal consistency values from the standardization study ranged from good for the Letter Fluency condition (0.77-0.90) to low-moderate for Category Switching Total Correct (0.45-0.68) in adults aged 30-59. Test-retest reliability of the standard form in healthy normal adults tested on average 25 days apart was good for Letter Fluency ($r = 0.80$) and Category Fluency ($r = 0.79$). Category switching total correct and total switching accuracy had lower reliability coefficients ($r = 0.52$ and $r = 0.36$, respectively). This is consistent with other verbal executive measures where individuals can use improved strategies on retesting, improving performance, where others do not. Alternate form reliabilities between the standard and alternate form, administered in a counterbalanced design to 286 healthy normal adults, were good for Letter Fluency ($r = 0.83$) and moderate for Category Fluency ($r = 0.71$). Category switching total correct and total switching accuracy again had lower reliability coefficients ($r = 0.46$ and $r = 0.44$, respectively). Age effects were found on all verbal fluency measures, with marked improvements across the younger age groups (8-19 years), peaking in the 30's and remaining constant until 50, with a slow decline in the oldest age groups. Raw scores were transformed into age-standardized z scores based on normative test data from the D-KEFS.

Validity

Functional imaging of healthy young and old adults on a letter fluency task was strongly associated with a left lateralized frontal activity (Meinzer et al., 2009). Category fluency deficits in the older group were accompanied by additional right (inferior and middle) frontal activity, whereas the younger group recruited different portions of the left inferior frontal gyrus for both fluency tasks. This suggests that during language or semantic fluency tasks, right hemisphere activity may not be beneficial to performance.

Patients with focal frontal lesions have shown significant impairments on the D-KEFS Verbal Fluency test compared to age-matched normal controls (Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001). They produced significantly fewer items in the letter fluency and switching conditions compared to the category condition, and those with left frontal lesions showed more impairment than those with right frontal lesions. Patients with Alzheimer's Disease performed significantly better on the Letter Fluency condition than on the Category Fluency or Category Switching conditions, which appears to relate to a
breakdown in verbal-semantic knowledge in Alzheimer's Disease (D.C. Delis, et al., 2001b). A study of children with histories of heavy prenatal alcohol exposure found these children demonstrated significant impairments on the inhibition and inhibition/switching conditions compared to age-matched healthy normal controls, but they did not differ significantly on the baseline conditions (Mattson, Goodman, Caine, Delis, & Riley, 1999).

Stockings of Cambridge test (SOC) (CANTAB)

The Stockings of Cambridge test (SOC) (Cambridge Cognition, 2005) is based upon the traditional test of planning, the 'Tower of London' test (Shallice, 1982). The subject is shown two displays containing three coloured balls, one at the top of the screen and one at the bottom. They are described as "arrangements of coloured balls, like snooker or pool balls, hanging in stockings or socks". The subject is asked to make the bottom arrangement look like the top one using a specified number of moves (see Figure 3.10). The balls have to be moved one at a time. The subject is instructed, "don’t move until you think you know which move to make. Try to get it right first time. Think about it and when you are ready, make your move".

There is a demonstration and practice stage first. The subject moves the ball by touching it, whereupon the ball begins to flash, and then touching the position where it should go. There is a number on the right hand sign of the screen reminding the subject of how many moves to make. There are three rules that are demonstrated: it is not possible to move a ball that is beneath another ball; or move a ball into thin air; and if the subject changes their mind about moving a ball, they can touch it again to switch it off. At first it is only necessary to move one ball, increasing in steps to four moves. Feedback is given at this stage with a display of 'TOO MANY' if the number of moves is exceeded, or 'FINISHED' if the test is completed in the required number of moves and the screen will then display 'New pattern'.

*Figure 3.10. Task screen for Stockings of Cambridge at 2-move training stage.*
At this point a procedure controlling for motor performance is presented. The upper display moves one ball at a time, repeating the moves made by the subject in the corresponding previous planning phase. The subject follows the upper display by moving the balls in the lower display. Again, the number of moves increases from 2 to 4. The difference in time taken to complete (more especially, initiate) each problem is taken as an index of the additional time taken to plan the solution, as distinct from following.

The test block of planning problems of 2, 4 and 5 moves follows, without feedback, and the test is completed with a second round of motor control problems. Should the subject make more than double the number of moves necessary for the simplest solution, the problem is terminated. Should three problems be terminated in a row, the entire test ends. There is no time limit.

The outcome measures used for planning ability and accuracy were the number of problems solved in the minimum moves and the mean number of moves required to solve problems at the highest (5-moves) level of difficulty. The outcome measures used for planning speed include measures of initial and subsequent planning times. Initial planning time is the difference in time taken to select the first ball for the same problem under the copy and motor control conditions. Mean initial thinking time at the 3-, 4- and 5-moves levels were used as a measure of time taken to plan the solution at graded levels of difficulty. Subsequent thinking time is the difference in time taken between selecting the first ball and completing the problem under the two conditions (copy and motor control), and then dividing this result by the number of moves made at that level. Mean subsequent planning time at the 5-moves level was used, as it reflects the average speed of response after the initial move has been made at the highest level of difficulty. The raw score can be 0 if the subject is slower in the ‘follow’ condition.

Reliability

Test-retest reliability of SOC was fair for initial thinking time ($r = 0.69$), subsequent thinking time ($r = 0.64$) and problems solved in minimum moves ($r = 0.64$) in healthy adults tested 1-8 weeks apart (Harrison, et al., n.d.). Test-retest reliability of mean moves to success was also found to be fair in healthy older adults tested one month apart ($r = 0.60$) (Lowe & Rabbitt, 1998). In a study of cognitive performance over the lifespan, SOC performance was found to be sensitive to ageing more than most other CANTAB tests (Robbins et al., 1998), but in a study of 60-80 year old adults SOC performance was not associated with age (Rabbitt & Lowe, 2000). SOC raw scores were converted into age-standardized $z$-scores based on normative test data.
Validity

A functional imaging study using MRI with normal volunteers found that SOC activates different brain regions, consistent with PET studies (Baker et al., 1996), but also that different levels of performance exhibit different patterns of brain activation on SOC (Cazalis et al., 2003). All subjects showed significant bilateral activation in the dorsolateral prefrontal cortex, the anterior and posterior cingulate areas and the parietal cortex. However, good performers (>70% correct) showed a more spatially extended activation in the left dorsolateral prefrontal cortex than standard performers (<70% correct), who displayed more activation of the anterior cingulate region. Neurosurgical patients with different focal lesions have demonstrated different performance profiles on SOC. The performance of patients with temporal lobe/posterior lesions were unaffected but patients with frontal lobe lesions required significantly more moves to solve problems than normal controls (Owen, et al., 1990). Initial planning times, though, were not significantly different but subsequent planning times were significantly longer, suggesting that frontal lobe patients, unlike temporal lobe patients, initiate a response before fully thinking it through.

Deficits in SOC planning accuracy is sensitive to the progression of Huntington’s disease, and was found significantly impaired in adults with early Huntington’s disease, while a test of decision-making was unaffected (Watkins et al., 2000). SOC planning measures are sensitive to drug manipulation (Elliott, et al., 1997) and long-term effects of toxic substances. Korsokoff alcoholics, who had been abstinent for three years, displayed planning deficits and SWM deficits accompanied by poor use of strategy, not displayed by non-Korsokaff alcoholics, indicating a specific disturbance of executive function in Korsakoff’s syndrome (Joyce & Robbins, 1991). Cancer patients receiving cytokine immunotherapy with interleukin-2 had significantly lower planning accuracy (i.e., problems solved in minimum moves) five days after treatment (Capuron, et al., 2001). These problems were more pronounced at the more difficult stages of the test and persisted at the end of the first month of treatment.

The Color-Word Interference test (D-KEFS)

The Color-Word Interference test (D.C. Delis, et al., 2001a) is based on the widely used traditional test for studying verbal interference effects and response inhibition, the Stroop test (Stroop, 1935). This tests the ability to inhibit an overlearned verbal response (reading printed words) in order to generate a conflicting response of naming the dissonant ink colour in which the words are printed (see Figure 3.11).
The Color-Word Interference test is composed of four conditions: 1) colour naming; 2) word reading; 3) inhibition; and 4) inhibition/switching, the new condition. These conditions involve a “cognitive-process approach” so that the component functions (colour naming and word reading) are tested separately to the higher-level tasks of colour-word inhibition. This allows the examiner to assess whether poor inhibition performance is related to an underlying deficit in speed of reading or naming. In the colour naming condition, the subject is asked to name 50 colour patches as quickly as possible. This tests naming speed. In the word reading condition, the subject is asked to read out 50 words denoting colour names printed in black ink as quickly as possible. This tests speed of reading and speed of processing.

In the inhibition condition (see Figure 3.11), the subject is asked to name the ink colours as quickly as possible while inhibiting reading the word denoting dissonant colours. This tests inhibition, speed of processing and selective attention. In the new inhibition/switching condition, the subject is asked to switch between naming the dissonant ink colour and reading the conflicting words. This was designed to increase the processing demands on cognitive flexibility in order to increase the sensitivity of the test to mild brain damage.

The outcome measures that were used in the study were the speed (Total Correct Latency) and accuracy (Total Errors) on Inhibition (condition 3) and Inhibition/Switching (condition 4).
Reliability

Internal consistency for the combined colour naming and word reading composite score was good across 30-69 year olds (0.72-0.86) (D.C. Delis, et al., 2001a). Test-retest reliability was fair for colour naming ($r = 0.76$), word reading ($r = 0.62$), inhibition ($r = 0.75$), and inhibition/switching times ($r = 0.65$) in 101 healthy adults retested after an average of 25 days. Scores on the second testing were generally higher, suggesting a practice effect. In the standardization study, there was an age effect on the different outcome measures. Colour naming and word reading performance did not peak until early 20s and then remained relatively stable through the 40s with little decline until the 80s. Disproportionate slowing occurred for the youngest and oldest groups in both Inhibition and Inhibition/switching. Raw scores were transformed into age-standardized z-scores based on normative test data.

Validity

The Stroop test has demonstrated sensitivity in the detection of frontal lobe dysfunction in clinical and experimental settings (Lezak, et al., 2012). A switching procedure added to the interference condition of the Stroop test enhanced the sensitivity of the test to mild traumatic brain injury (Bohnen, Twijnstra, & Jolles, 1992). In a prospective study over one year of 24 normal elderly adults, significantly larger discrepancy scores (switching vs lower level conditions: 1 and 2) at the start of the study predicted decline on their dementia rating scale (DRS) in eight subjects a year ahead of cognitive changes (Fine, Delis, Wetter, Jacobson, Jak, et al., 2008). The cognitive discrepancy scores were superior to APOE type genotype in predicting DRS decline. Marked dissociations in performance have also been found between patients with Alzheimer’s disease and Huntington’s disease (D.C. Delis, et al., 2001b). Patients with Alzheimer’s disease were markedly worse on the Inhibition/switching condition compared to other conditions, particularly in terms of errors, whereas the patients with Huntington’s disease exhibited slow responding across all four conditions, but with significantly fewer errors on inhibition/switching.

**Intra-Extra Dimensional Set Shift (IED) (CANTAB)**

The Intra-Extra Dimensional Set Shift (IED) (Cambridge Cognition, 2005) is a visual test of cognitive flexibility and reasoning, involving rule acquisition and reversal based on feedback. It is similar to the traditional test of set-shifting and cognitive flexibility, the Wisconsin Card Sorting Test (Berg, 1948; Heaton, et al., 1993).

Two sets of stimuli are used: colour-filled shapes and white lines, as well as compound stimuli where white lines overlie colour filled shapes. The subject is initially presented
with two colour-filled shapes and is instructed to touch the one they think is correct. The first choice is a simple guess. However, the computer gives a message of 'Correct' or 'Incorrect' after each attempt. The subject is told there is a rule they can learn to find the correct stimulus each time, but that this rule will change once it is apparent they know the rule. The test consists of nine stages of increasing difficulty. After six consecutively correct choices at one stage, the test automatically proceeds to the next stage. If the criterion of six correct choices is not reached within 50 trials, the test is discontinued.

The IED begins with simple stimulus discrimination and reversals to allow subjects to establish an attentional set to a particular dimension (e.g., shape). Stimulus complexities are introduced in blocks, with distracting irrelevant stimuli (white lines) adjacent (compound discrimination) or superimposed to the stimuli of the relevant stimulus dimension (compound stimuli) (see Figure 3.12).

![Figure 3.12. Test screen for compound discrimination stage of Intra-Extra Dimensional Set Shift.](image)

Only after an attentional set has been established does an attentional shift take place, requiring the subject to first shift attention to a novel exemplar of the same perceptual dimension (e.g., line or shape) (i.e. an intra-dimensional [ID] shift). This is followed by a reversal and the compound stimuli are changed. Subjects are then required to shift attention to a novel exemplar of a different, previously irrelevant, perceptual dimension (i.e. an extra-dimensional [ED] shift). This is followed by another reversal, completing the test. Parallel forms were used at follow-up assessments, which use different shapes and lines for stimuli.

The IED outcome measures used in the study were: IED Stages completed; IED Extradimensional Shift errors (errors made in the extradimensional shift stage of the task); IED pre-extradimensional shift errors; IED Total errors (adjusted). Errors are defined as instances when the subject fails to select the stimulus that is compatible with
the current rule. The total number of errors is a measure of efficiency in attempting the test. While a subject may pass all nine stages, a substantial number of errors may be made in doing so. Subjects failing at any stage of the test by definition have had less opportunity to make errors. The adjusted score is calculated by adding 25 to each stage not attempted due to failure. The value of 25 is used since subjects must complete 50 trials to fail a stage and half of these could be correct by chance alone. The final measure was IED Total trials (adjusted). This is the number of trials completed on all attempted stages. The adjustment adds 50 for each stage not attempted due to failure at an earlier stage:

Reliability

Test-retest reliability of the IED standard form has been fair for both the measure of IED Stages Complete ($r = 0.75$) in healthy adults tested 1-8 weeks apart (Harrison, et al., n.d.) and pre-ED shift errors ($r = 0.70$) in healthy older adults tested one month apart (Lowe & Rabbitt, 1998). There are no published data comparing the standard to the parallel forms, although a study of the comparability of other CANTAB parallel forms found any differences were of small magnitude (Semple & Link, 1991). In a study of cognitive performance over the lifespan, IED performance was found to be sensitive to ageing, and age-related declines were shown in a discontinuous manner (Robbins, et al., 1998). IED raw scores were converted into age-standardized z-scores based on normative test data.

Validity

There were no published data found validating the IED with the Wisconsin Card Sorting test. As expected in healthy normal adults, when attending to a perceptual feature of a stimulus, learning to discriminate complex stimuli is more rapid when the discrimination rule is based on the same perceptual dimension (an intra-dimensional shift) than on a different perceptual dimension (an extra-dimensional shift) (Owen, Roberts, Polkey, Sahakian, & Robbins, 1991). The neural basis for attentional switching has been studied in primates (Dias, Robbins, & Roberts, 1996) and humans (Owen, et al., 1991), where lesions of the frontal lobes result in normal acquisition of attentional set and ability to ID shift to exemplars of a previously relevant dimension, but in significant impairment in the ability to ED shift to exemplars of a previously irrelevant dimension. In contrast, patients with temporal lobe/posterior lesions were unimpaired in the ability to perform either shift. In a study of patients with schizophrenia compared to healthy controls, performance at the earlier stages of the IED task, involving simple discrimination and reversal, were better explained by the Continuous Performance Test score, a test of vigilance, while the later switching stages of the task were better predicted by Wisconsin Card Sorting Performance, a traditional test of cognitive flexibility (Jazbec et al., 2007).
Poor performance on the extra-dimensional shift has been sensitive to signs of early Parkinson's disease (Downes et al., 1989) and sensitive to pharmacological manipulation, such as dopamine function by supiride that was found to mimic cognitive signs of Parkinson's disease in healthy volunteers (Mehta, Sahakian, McKenna, & Robbins, 1999).

Complex Figure Test – Organization, copy trial

The organizational approach used in the reproduction of the Complex Figure Test in the Copy trial has been found to affect subsequent recall (Lezak, et al., 2012). The examiner recorded qualitative information regarding the subject's organizational approach in the copy trial. The examiner duplicated the respondent's drawing simultaneously on a separate sheet of paper, recording the order in which the respondent reproduced the drawing by changing coloured pencils when the respondent completed a section of the drawing and noting the order of colour use. The coloured pencils were used by the examiner, not the respondent, as giving respondents different coloured pencils has been associated with better performance (Ruffolo, Javorsky, Tremont, Westervelt, & Stern, 2001). Noting the sequence of colours enabled the examiner to record the organizational approach. This process-oriented and qualitative information is not formally included in the Rey CFT administration, but is recommended by Meyers and Meyers (1995).

The quantitative total organization score, a measure of copy planning and organization, used a scoring system based on Savage et al. (1999) to evaluate the presence of the five figural elements in the copy, drawn as complete units. These figural elements were defined by Binder (1982) for the Rey CFT (base rectangle, diagonals, vertical midline, horizontal midline and vertex of triangle). The corresponding five figural units were used for the MTCF. These elements are assigned one point each, except for the base rectangle (or square for the MCTF), which was assigned two points reflecting its importance to the fundamental organization of the figure. Score ranges from 0 to 6 and high scores indicate a good organizational approach. The total organization score has demonstrated good inter-rater reliability ($r = 0.94$) and convergent validity, as it is highly correlated ($r = 0.80$) with a more complex measure of copy organization (Deckersbach et al., 2000). The total organization score was also a strong predictor of subsequent recall. This is consistent with other studies, such as in patients with obsessive compulsive disorder where nonverbal memory dysfunction has been found to be mediated by impaired organizational strategies during the copy trial (Savage, et al., 1999).

However, when the predictive value of each scoring element was analysed, weighting the base unit more heavily did not add to the ability to predict recall (Deckersbach, et al., 2000). The authors suggested that a possible modification to the system would be to
assign one point for the base unit or include another aspect of organization, such as drawing sequence. Drawing the base unit first has been found to aid subsequent recall (Lezak, et al., 2012). In this study, the base unit was assigned two points, for being drawn as a complete unit (1 point) and drawn first (1 point).

Another measure used to assess speed of planning was:

The CFT completion time for the Copy trial, which measures the speed of processing and planning on the copy trial. Copy completion times are measured in seconds with a stopwatch. In the absence of perceptual or motor difficulties, higher copy completion time scores indicate reduced speed of processing and planning. There were no significant differences between completion times on repeated administration of the Rey CFT from the first to second testing session (Meyers & Meyers, 1995). The Rey CFT took more time to complete than the MTCF when it was administered first (Hubley & Jassal, 2006). Copy times have been found to slow after the age of 50 (Meyers & Meyers, 1995). Furthermore, time to copy and copy accuracy measures loaded on different factors, suggesting these two variables measure different constructs.

3.5 Chapter summary

This chapter provided the rationale for the prospective cohort design, the methods used for sampling and pilot testing, and the measures selected for this study. These measures included: screening measures; demographic measures; self-report measures; cancer and treatment measures; and clinical and neuropsychological measures. The clinical assessment measure involved a structured clinical interview to assess for the presence of anxiety or mood disorders at each assessment. The neuropsychological measures were selected according to: their stability and sensitivity to mild cognitive impairment and change; their ability to discriminate different cognitive abilities and areas of impairment; and their practicality and user-friendliness. Standardized neuropsychological tests with normative data were included that have accrued a well-established body of knowledge on brain-behaviour relationships. A description was given of each neuropsychological test and its psychometric properties, organized by cognitive domain according to findings from the literature. One test was extended to test the limits and increase its sensitivity to change in high functioning adults. Another test was developed to be more sensitive to verbal processing, by changing the stimuli, but using the structure, administration and scoring methods of an existing test. The neuropsychological battery included tests of primary language, motor, and visuoconstruction functions, as well as a comprehensive assessment of attention, learning and memory, and executive functions.
The study was designed to provide the sensitivity to detect: differences between treatment groups; cognitive changes associated with adjuvant chemotherapy treatment; any profile of impairment associated with chemotherapy-related cognitive dysfunction; and possible mechanisms for impairment. The following chapter describes the procedures used in the study.
Procedure

This study used repeated clinical neuropsychological assessments to examine any cognitive changes associated with adjuvant chemotherapy treatment for early breast cancer. This chapter describes how the assessment was conducted, including the setting, materials and process for gaining informed consent, as well as the procedure for conducting the clinical and neuropsychological assessments.

4.1 Procedure

4.1.1 Information and initial screening

Study leaflets were distributed by breast cancer nurses in post-surgery patient information packs and were provided by the investigator to treating specialists (see Appendix B.1). Interested participants could refer themselves or be referred by one of their cancer care team, such as their breast care nurse, surgeon or oncologist. In the case of referral, the investigator would contact the patient directly by telephone. On first contact the interested participant was provided with information about the study and, if still interested, they were asked questions regarding exclusion criteria (see telephone interview in Appendix B.2). If they met the inclusion criteria and were still interested in participating, contact details were taken, a time was made for the first assessment and an information pack was mailed out. As people who experience memory impairments can forget having lapses, they were asked if there was someone they saw regularly (at least three times a week) who might be able to complete a brief survey on the participant’s recent everyday memory abilities. This was not an exclusion criterion, so they were still eligible to participate if they did not have someone suitable.

4.1.2 Inclusion and exclusion criteria

All clients meeting broad inclusion criteria (female, early stage breast cancer, fluent in English, 18-65, no previous chemotherapy, able to provide consent) were asked if they were interested in participating in the study. The decision about the potential participant’s eligibility for the study was undertaken by the investigator after assessing if the client met exclusion criteria involving a pre-existing condition that might affect their level of cognitive function (i.e., dementia/neurological disability, history of head injury, history or
current substance abuse). Women were excluded from the study if they met the following criteria:

- not able to meet for the first assessment prior to the commencement of chemotherapy;
- 65 years or over (at first contact);
- not fluent in English;
- a history of head injury with loss of consciousness (>5mins) or requiring hospitalisation (>24 hrs);
- currently seeing a doctor or other professional for memory problems or problems with thinking;
- currently taking medication that can affect thinking ability;
- regular history of alcohol consumption of over 3 standard drinks per day on 2+ days/week;
- a medical or psychiatric condition that could affect thinking ability, such as: stroke; recent electroconvulsive treatment (<2 wks); epilepsy; brain surgery; encephalitis or meningitis (<10 years); diagnosed Parkinson’s disease, Huntington’s chorea or Alzheimer’s dementia; or diagnosed Schizophrenia or Bipolar disorder;
- possible dementia, visuoperceptual deficits or colour blindness (screened at the first assessment. For further details see section 4.1.11).

All clients assessed as eligible for the study were invited to participate in the study.

4.1.3 Contact information

Contact details were collected on a separate sheet (see Appendix B.3) and included contact information and date of birth, the name of the referral source and the treating surgeon and oncologist. These details were kept in a separate locked cabinet.

4.1.4 Patient information and self report measures

A survey booklet was mailed to each participant before the assessment, along with a cover letter, and map/instructions to the ANU psychology visitor car park. Instructions for the assessment were provided in the cover letter, including: a reminder not to take any sleeping pills the night before; to drink no more than one standard alcoholic drink in the
24 hours before; to bring reading glasses or hearing aid (if needed); and, if possible, to fill the survey out; ask the informant to fill out their survey; both sign the informant consent form; and bring the surveys and informant consent form to the assessment.

The participant survey included the following QOL measures: the Patient Health Questionnaire 15-item somatic severity scale (Kroenke, et al., 2002); the Medical Outcome Study 6-item social support index (W. J. Brown, et al., 1999); the 16-item Prospective and Retrospective Memory Questionnaire (Smith, et al., 2000); the MFI 4-item Mental Fatigue scale (Smets, et al., 1995); the WHO 5-item Wellbeing index (WHO, 1988); the Hospital Anxiety and Depression 14-item scale (Zigmond & Snaith, 1983); and the EORTC QLQ-C v3 30-item QOL questionnaire (Fayers, et al., 2001) (see Appendix B.4). An open-ended question was included at the end asking if there was anything they wished to add that they thought might be relevant to the study.

The informant survey was included in a separate envelope, with an information sheet and consent form, for the participant and informant to sign (Appendix B.7 & B.8). The survey included an informant version of the 16-item Prospective and Retrospective Memory Questionnaire and the MFI 4-item Mental Fatigue scale. The informant was asked to rate each item on the basis of behaviour they had observed in the participant in the two or four weeks prior. This took around 5 minutes to complete. The informant was instructed to put the completed forms inside the envelope and seal it. This could then be given to the participant to return, or a reply-paid envelope was provided.

4.1.5 Setting

The testing room was a reasonably quiet, soundproofed, carpeted, lockable room, with no distracting views, situated on the second floor of the Research School of Psychology at the Australian National University. This room had no windows, which minimized distraction and glare, but was well ventilated and lit. The two interconnecting doors to other offices were locked, sealed, lined and filled with soundproofing material by workshop staff to limit noise transfer. The room had a sink and a nearby water cooler, which provided ready access to drinking water. A fan was used to provide white noise in order to minimise any noise from foot traffic from an outside corridor and to circulate warm/cool air. The layout of the testing room is presented in Figure 4.1.
A computer and touchscreen were located on a table, large enough to also conduct pencil and paper tests. Testing materials were located on a low coffee table beside the examiner to permit smooth transitions between tests, out of sight of the participant in order to limit distractions. The manual was set on a stand behind the touchscreen to ensure reliable administration but not interfere with eye contact, as well as observations. The examinee sat on one side of the table (1) and the examiner sat on the opposite side of the table for most of the assessment but moved to the end of the table for the training sections of the CANTAB tests (2). A piece of tape was stuck on the table to identify the correct location for the press pad. The press pad was placed there for the relevant tests and moved out of the way after the test was completed.

4.1.6 Instruments

The following instruments were used for the study:

- Windows PC computer;
- external audio speakers;
- touchscreen (15 inch Keytec Magic touch LCD integrated touchscreen monitor with antiglare hard coating);
• press pad (provided by Cambridge Cognition);
• Sanyo audiotape recorder and audiotapes;
• A4 paper (blank) and pencils (lead and coloured);
• a stopwatch;
• a table, coffee table, two ergonomic chairs and a fan.

The following test administration or scoring software was used:

• CIDI-auto v2.1 purchased by the Research School of Psychology from the Clinical Research Unit for Anxiety and Depression (Crufad) at St Vincent’s Hospital in Sydney;
• CANTABeclipse v2.0 (software licence for academic research) purchased by the Research School of Psychology from Cambridge Cognition;
• PASAT (3 second and 2 second presentation and parallel forms) purchased by the Research School of Psychology from www.pasat.us;
• CVLT-II comprehensive scoring system purchased by the Research School of Psychology from Harcourt Australia.

4.1.7 Preparation

The computer-administered neuropsychological CANTAB tests were selected and set up within the CANTAB program as batteries in the order of administration, for each assessment. The relevant assessment battery was loaded using a de-identified participant ID prior to the assessment. Other tests that were administered via computer, such as the PASAT, CVLT-II or audio files for verbal tests, were set up to reduce transition time between tests.

The selected modules for the computer-administered clinical interview (CIDI-Auto) were also loaded prior to the assessment using a de-identified participant ID. Initial demographic information, including gender and age, was entered in order to reduce administration time.

Audiotapes were checked to ensure they were not near the end of the tape and the audio levels of the speakers were checked. The touchscreen was cleaned and turned on prior to the assessment to allow time for the screen to warm-up.
4.1.8 Informed consent

In the testing room, the interested participant was taken through details regarding the purpose of the study, what was involved and how confidentiality would be maintained. They were reminded that, even if they consented, they could withdraw from the study at any time without it affecting their medical treatment in any way. Women were given time to read through the information sheet and consent form and ask questions (see Appendix B.5 & B.6). If they were willing to consent, an available departmental staff member or postgraduate student who was not involved in the study was asked to witness the participant’s signature on the consent form.

4.1.9 Establishing rapport

In the interests of establishing rapport, building trust and optimizing performance, the assessment began with acquiring some background details and doing a few screening tests. This was followed by the clinical interview and, finally, the neuropsychological assessment. It was explained that there would be regular breaks every hour, including morning tea and lunch.

4.1.10 Participant information

Demographic information was collected by the examiner, as well as information regarding current medications, menopausal status, perceived interference from menopausal symptoms, fatigue, sleep quality and performance status (see Appendix B.9 & B-10).

4.1.11 Screening tests

Participants needed to be cognitively able, and without visuoperceptual or colour vision impairments, to undertake the neuropsychological tests at baseline. Tests screening for visuoperceptual impairments (the VOSP), colour blindness (the Ishihara) and dementia (the MMSE) were conducted (for details see Chapter 3.4.1: Screening tests). The Mini-Mental State examination was administered as the first module of the clinical interview (CIDI). None of the participants failed the screening tests.
4.1.12 Clinical interview

Sections of the computerized Composite International Diagnostic Interview v2.1 (CIDI-auto; WHO, 1993)

The core anxiety and mood disorders modules were administered by the examiner, following the MMSE module. At Time 1 the questions were related to symptoms experienced 'over the past 12 months' to determine current DSM-IV diagnoses.

At follow-up assessments, the timeframe for symptoms was changed to 'Since your last assessment'. This was done in order to determine any changes to the participant's current clinical diagnoses. However, at Time 2 the timeframe between assessments was too narrow for some diagnostic criteria, such as generalized anxiety, where there needs to be a period of at least six months of persistent worrying. At Time 2 the timeframe for symptoms relating to generalized anxiety was changed to "since your diagnosis" as this covered a period of more than six months. This timeframe was changed to 'Since your last assessment' at the final assessment, as the period between these assessments was around nine months.

While the clinical interview was fully structured, these questions often gave participants an opportunity to review how they had been feeling and share their experiences. Taking the time to listen and understand these experiences was clinically important and it was essential for building rapport, putting participants at ease and ensuring reliable effort.

4.1.13 Neuropsychological assessment

a. Reliability

Two manualized test administration guides were created; one for the initial assessment and one for the follow-up assessments. These test administration guides included the test administration script and procedures to be followed by the examiner for each test in the battery in the order of administration. They also included all instructions for the introduction and breaks and when to use the press pad or audio recording. This was done to increase administration efficiency and reliability.

A number of verbal tests have specified interval pacing for the presentation of items, such as the PASAT, CVLT-2 and Digit span. A CD of the accurately paced PASAT (3 second and 2 second intervals) was loaded onto the computer used and played through external speakers. The other tests were recorded to control the rate of stimulus presentation and maintain between-subject consistency. This was recorded using a high quality microphone
onto computer audio files. These were played via external speakers. Volume was adjusted, as needed, to individual levels, on practice trials.

Most verbal test responses from participants were recorded on audiotape to allow for later scoring and checking. These included the NART-2, Verbal fluency, CVLT-II, PASAT, Digit supraspan and Color-word interference.

b. Introduction

The test introduction was modified from the WAIS-III introduction script. It was used to introduce all participants to the beginning of the neuropsychological test battery.

'I'll be asking you to do a number of things today like naming some pictures and solving a few number problems. Some will involve pencil and paper and some will use a computer touch screen. We will have a practice before each one. You will find some of these tasks easy, whereas others may be more difficult. Also, most people don't answer every question or finish every item; just give your best effort on all of the items. We will have a break every hour. Do you have any questions?'

c. Order of administration and duration

The order of administration of the neuropsychological tests in the battery at each assessment is presented in Table 4.1. The order was designed to maximize the participant’s interest, productivity and reduce test anxiety. The first test (MOT) was a simple test designed to introduce the participant to the touchscreen and screen for motor ability deficits. It was followed by a pattern recognition memory test (PRM) that was game-like and relatively easy in order to help the participant feel comfortable, rather than anxious, from the beginning of the test session.

An important consideration in sequencing the tests was the conditions required to reduce interference susceptibility. This involved tests administered during the interval preceding delayed trials on learning tests. Taking these limitations into account in regard to modalities (e.g., verbal or visual/pattern tests) as well as duration (e.g., 20-30 minutes between short delay and long delay recall), allowed a format to be designed making the most economical use of examination time. Within these constraints, the order of interval tests involved varying a computerized test with a traditional or pencil and paper test, and following a more difficult test, which tests the subject's limits, with an easier test. This was designed to maintain the participant's interest and not to discourage them. Otherwise, visual and verbal tests were ordered sequentially in order to increase variety and reduce test fatigue.
Average administration times for each test are identified as recorded in the pilot-testing phase of the complete neuropsychological battery. Most participants took similar times to complete tests. For those who took longer, clinical judgement was used to reschedule the test order to make sure the prescribed duration between specified trials was maintained and to make sure the time between refreshment breaks was similar. The names of tests used in the current study are provided in full in Appendix A.1.

Table 4.1
Order of Test Administration

<table>
<thead>
<tr>
<th>Order</th>
<th>Test (abbrev.)</th>
<th>Duration (mins)</th>
<th>Visual/verbal</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MOT</td>
<td>3</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PRM immediate</td>
<td>4</td>
<td>Visual</td>
<td>Parallel forms</td>
</tr>
<tr>
<td>3</td>
<td>RTI</td>
<td>5</td>
<td>Visual</td>
<td>Parallel forms</td>
</tr>
<tr>
<td>4</td>
<td>NART-2</td>
<td>3</td>
<td>Verbal</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Verbal fluency</td>
<td>8</td>
<td>Verbal</td>
<td>Parallel form</td>
</tr>
<tr>
<td>6</td>
<td>PRM delayed recall</td>
<td>2</td>
<td>Visual</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>SOC</td>
<td>10</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Break (Morning tea)</td>
<td>Subtotal: 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CVLT-II Trials 1-5, List B &amp; Short delay recall trials</td>
<td>20</td>
<td>Verbal</td>
<td>Parallel forms</td>
</tr>
<tr>
<td>9</td>
<td>RVP</td>
<td>7</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>SSP (fwd and bwd)</td>
<td>8</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CVLT-II LD recall and recognition trials</td>
<td>10</td>
<td>Verbal</td>
<td>Parallel form</td>
</tr>
<tr>
<td>12</td>
<td>SWM</td>
<td>9</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>DSP (fwd and bwd)</td>
<td>10</td>
<td>Verbal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Break (Lunch)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>CFT - Copy trial</td>
<td>4</td>
<td>Visual</td>
<td>Parallel form</td>
</tr>
<tr>
<td>15</td>
<td>C-W interference (1: CN)</td>
<td>2</td>
<td>Verbal</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>CFT-Immediate recall</td>
<td>4</td>
<td>Visual</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>C-W int (Conditions 2-4)</td>
<td>9</td>
<td>Verbal</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>PASAT (3 and 2 secs)</td>
<td>7</td>
<td>Verbal</td>
<td>Parallel form</td>
</tr>
<tr>
<td>19</td>
<td>GNT</td>
<td>2</td>
<td>Verbal</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>CFT LD recall and recog trials</td>
<td>5</td>
<td>Visual</td>
<td>Parallel form</td>
</tr>
<tr>
<td>21</td>
<td>PAL</td>
<td>7</td>
<td>Visual</td>
<td>Parallel forms</td>
</tr>
<tr>
<td>22</td>
<td>Similarities</td>
<td>4</td>
<td>Verbal</td>
<td>Alternate^a</td>
</tr>
<tr>
<td>23</td>
<td>Verbal PAL I</td>
<td>8</td>
<td>Verbal</td>
<td>Parallel forms</td>
</tr>
<tr>
<td>24</td>
<td>BLC</td>
<td>1</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>IED</td>
<td>9</td>
<td>Visual</td>
<td>Parallel forms</td>
</tr>
<tr>
<td>26</td>
<td>SRM</td>
<td>5</td>
<td>Visual</td>
<td>Parallel forms</td>
</tr>
<tr>
<td>27</td>
<td>Verbal PAL II recall &amp; recognition</td>
<td>4</td>
<td>Verbal</td>
<td>Parallel forms</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>Subtotal: 71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^aAlternate verbal abstract reasoning tests were used at Time 2 (The D-KEFS Word Context test) and at Time 3 (the D-KEFS Proverbs test).
4.1.14 Refreshment breaks

The first refreshment break (morning tea) fell about half an hour after the start of the neuropsychological assessment. This was about an hour from the beginning of the whole assessment, as the first sections, including introduction, screening, patient information and clinical assessment, lasted around 25 minutes.

Morning tea was provided and included tea or coffee (decaffeinated). Morning tea lasted approximately 10-15 minutes.

The lunch break was approximately an hour after morning tea, around midday, depending on start time. Lunch was provided and involved a vegetarian lunch designed to be palatable to women experiencing changes in taste perception associated with chemotherapy. All meals were prepared the night before the assessment and stored and heated in keeping with OH&S practices. Substitutes were provided for those with special dietary requirements. Lunch lasted approximately 20-30 minutes.

4.1.15 Follow-up assessments

The same procedure was followed for the follow-up assessments, except that screening tests were not conducted and only demographic information that had changed was recorded. At the beginning of the assessment the participant was asked whether they had noticed any changes to their memory or thinking since their last assessment and, if so, further questions probed the type and course of these changes (see Chapter 3.4.4). During the neuropsychological assessment, parallel forms were used for the memory tests and for some of the other tests to reduce the risk of practice effects and to maintain interest.

At the end of the Time 3 assessment, a feedback report was provided to each participant on their individual performance over the first two assessments. This was written in plain English and was prepared by the investigator and checked by the neuropsychological supervisor who was part of the study. The investigator took the participant through the report and answered any questions. A de-identified example is provided in Appendix B.11.

4.1.16 Medical data

At the end of the Time 3 assessments, a review was conducted on all participant medical files held at each hospital in the ACT in order to extract relevant information regarding hospital admissions and lengths of stays, cancer pathology, surgery, cancer treatment, toxicities and current status at the most recent follow-up. The medical information form is provided in Appendix B.12).
4.1.17 Retention

A key concern using a longitudinal design involving 4-hour assessments at a stressful period is that it might inevitably result in a significant loss to follow-up from high rates of drop-out. This had occurred in the few prospective studies in the field at the time using much briefer assessments. This study considered factors that may contribute to retention.

Responsiveness

This was a higher risk population. It was expected that there would be a need to reschedule for unforeseen events. Approximately one third of all assessments had to be rescheduled due to illness or injury. In some cases assessments needed to be shortened to allow participants to get to medical appointments. In the circumstance where a participant could not drive or have someone transfer them to the university, they were picked up and dropped home.

Rapport building and a nurturing environment

The introductory section and clinical interview allowed time to establish rapport. For some participants this was the first chance they had to express their feelings and share their experiences. The breaks were an important part of reducing fatigue in the neuropsychological assessment and they also helped participants to feel nurtured. This also allowed time that was not part of the "assessment" to catch up.

Token of appreciation

Participants were not paid for their time. A small financial compensation ($20) was provided for travel expenses incurred over the course of the assessments. At the end of the second assessment, participants were given a small token of appreciation (a lipstick pen). They were also advised that they would receive a feedback report on their individual performance over their first two assessments at their final assessment. Cards were sent out to all participants at the end of each year before Christmas/New Year to thank them for their contribution.

Individual feedback report at Time 3

An individual feedback report was prepared for each participant in the study who had completed the first two assessments (see Appendix B.11 for an example). This feedback report was welcomed by participants and responded to with interest and enthusiasm.
Referral and follow-up as needed

Where participants reported significant psychological distress or had a clinical diagnosis, they were referred to an appropriate mental health professional, such as a psychologist or psychiatrist with experience in psycho-oncology. Some women who gave feedback afterwards reported that they had found this helpful.

4.1.18 Use of alternate examiner

As this study involved a higher risk population, it was essential not to expose any participant about to undergo chemotherapy to illness, as this could delay treatment or increase the risk of adverse events. A psychologist, with clinical and research experience in neuropsychological test administration, was trained to conduct an assessment in the case of absence or illness on the part of the principal examiner. The training involved a step-by-step administration guide, a face-to-face workshop in which the trainee played the role of the examiner and a training video of a complete session conducted by the principal examiner. This trained examiner conducted only one assessment (<1%) over the study period. This was an initial assessment scheduled when the principal examiner was presenting at a conference. A consultation was conducted regarding the clinical observations and results of this assessment. The principal examiner conducted all the other assessments. This minimized the risk of inter-examiner variation.

4.2 Limitations and delimitations of the design

The study used strict eligibility criteria, common for neuropsychological studies, including age restrictions to reduce the risk of dementia in the study population. This study was also restricted to women and to breast cancer patients. This means the results may not generalize to men, older adults, other cancers or to other chemotherapy regimens.

The small window for baseline assessment following surgery and prior to chemotherapy made recruitment challenging for both groups, as the first assessment was matched to the target group from surgery. This, however, meant the groups were matched more closely.

The data collection involved three longitudinal assessment points over a fifteen month time period for each participant. Assessments were event and time based (before and after chemotherapy, or time matched from surgery/previous assessment). Follow-up assessments were due at different times and comparisons would have been compromised if assessments were brought forward to complete data collection.
Chemotherapy does not involve just one drug or the same combination of cytotoxic drugs. There are a number of different chemotherapy regimens used for the treatment of breast cancer and for other cancers. Women experiencing different chemotherapy regimens were grouped for the purposes of examining the effects of treatment on cognitive function between groups. Chemotherapy regimens can also change over the course of a study as new drugs are approved and introduced. There were some new chemotherapy regimens introduced but these were few and were introduced early in the course of the study.

4.3 Ethical considerations

4.3.1 Research permissions

Ethics protocols were approved for the study protocol, questionnaires and tests by the:

- Australian National University Human Research Ethics Committee;
- Australian Capital Territory (ACT) Survey Group;
- ACT Human Research Ethics Committee;
- Medico, Moral, Human Research and Ethics Committee for Calvary Hospital;
- John James Memorial Hospital Ethics Committee; and
- National Capital Private Hospital Ethics Committee.

Each hospital required an information letter and consent form with relevant ethics committee contact details for patients from their hospital, as well as an independent person, not associated with the research, to witness the participant signing the consent form. The information letters and consent forms for participants and informants that were approved by these committees are provided in Appendix B-5 to B-8. Regular reports were provided to each of these ethics committees while the study was being conducted and approval was sought for any variations or issues that may have ethical implications.

4.3.2 Ethical implications

No interference with usual treatment

This project involved research on patients waiting to commence adjuvant chemotherapy. The usual time between first referral to the medical oncology units at each hospital and commencement of chemotherapy is in the range of one to two weeks. Provided women were informed of the study as soon as possible after surgery, interested subjects had the
opportunity to participate in the study before the start of treatment. It was essential that treatment was not delayed by participation in the study. Where first contact was made the day of or the day before the commencement of chemotherapy, women were thanked for their interest but advised that it would not be possible to schedule an assessment before they needed to start chemotherapy. Appointments and the length of the assessment were arranged to accommodate scheduled medical appointments.

**Identification of neuropsychological disorder/ emotional distress**

There were no expected risks associated with participation in the study. Any person identified with possible dementia at the initial eligibility screening or over the course of the study was to be referred for follow-up to their oncologist. Women recognized in the course of testing to have significant emotional distress associated with diagnosis or treatment were referred to an appropriate mental health professional, or their Clinical Nurse Consultant and/or treating specialist, as needed.

**Voluntary participation**

All participants were adults. They had a breast cancer diagnosis, however, it was at an early stage with good prognosis. Information was provided in post-operative information packs to all women with early breast cancer so that interested women could self refer and contact the examiner directly.

Some participants suitable for participation in the study were identified by cancer care staff in routine clinical visits. This meant that willing participants could be identified early, allowing time for them to consider involvement. It was emphasized both by the Cancer care staff and the researcher, who was not involved in their medical care, that participation or non-participation in the project or withdrawal at any time, without explanation would not affect their medical care in any way. This was outlined in the information sheet and consent form for participants. No pressure was exerted by staff on potential subjects to participate. Informed consent was sought from potential participants for their involvement in the research and interview activities were conducted at the university, rather than their medical care setting.

**Access to information**

All women had the right to access their information collected during the study under the Freedom of Information Act for a period of 15 years. One participant died suddenly during the study, not long after having completed her second assessment shortly following completion of chemotherapy. Her husband requested access to her study records. It was
not clear whether this request breached the study's ethical responsibilities to maintain confidentiality. Advice sought from the ethics committees, as well as the university legal department, indicated that the limits of confidentiality cease in the event of death. Neuropsychological data, though, needs to be interpreted by a qualified person. The examiner suggested to the family that a neuropsychological feedback report, similar to the one that would have been provided to the participant at the final assessment, could be written and provided to the family. This was accepted readily. The treating oncologist and hospital ethics board were informed of this situation.

Privacy and Storage

All files are kept securely in the Research School of Psychology for a period of fifteen years. The privacy of participants was maintained by ensuring that all data were coded and safely and securely stored. A unique code number was assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator entered and reported research related data. Only members of the research group had access to the research data.

4.4 Role of the researcher

Following from a clinical psychology and clinical neuropsychology research framework, the researcher was the primary means of contact, assessment, data collection, data scoring, data entry, interpretation, analysis and feedback. The examiner was a trained psychologist, also working part-time in private practice. These roles were clearly known by participants. Identifying and reflecting on these roles in supervision helped to reduce role confusion or conflict. If a participant was distressed, it was important to shift from research priorities of collecting data to more clinical priorities of empathy and support. The focus in these circumstances was to provide supportive counselling, assess risk, take a break and, where needed, refer participants to a trained psychologist specialising in psych-oncology or relevant cancer care staff. After the study was completed, the examiner agreed to see past study participants if they requested and were referred directly to her, but not before, as there was a risk of role confusion.

4.5 Chapter summary

This chapter provided details of the procedures used to conduct this study. These included: recruitment and selection; the setting; the instruments; informed consent; the assessments and order of administration; medical data collection; and ethical implications.
The next chapter presents the first of the results chapters, involving the descriptive results regarding the study sample.
Chapter 5

Descriptive Results

The results of this study are presented in six chapters. This chapter (Chapter 5) presents results relating to the recruitment and retention of participants, as well as the descriptive results comparing participant, cancer and treatment characteristics for each treatment group.

5.1 Recruitment

The period of recruitment lasted just over two years (756 days), from 17 July 2006 to 11 August 2008. The chemotherapy group was recruited in 17 months (518 days) whereas the no-chemotherapy group took longer, and was recruited in 23 months (709 days). The primary sources of referral were: 43% (n = 32) by oncologist; 15% (n = 11) by surgeon; 13.5% (n = 10) by breast-care nurse; and 28% (n = 21) by patients themselves. Patients who contacted the investigator themselves had found out about the study from their breast-care nurse (n = 4) or from the study information leaflets included by breast-care nurses in post-surgery information packs (n = 11), or from their surgeon (n = 4), oncologist (n = 2) or friend (n = 1).

5.2 Recruitment and retention

Of 74 women with early breast cancer assessed for eligibility, 30% (n = 22) did not meet the inclusion criteria. A chart displaying the recruitment and retention of participants through the study is presented in Figure 5.1.

The reasons for ineligibility were that the patient: was unable to have an assessment scheduled prior to the commencement of the first chemotherapy treatment cycle (n = 10); had started chemotherapy or previously had chemotherapy (n = 7); met criteria for alcohol abuse (n = 2); was on medication affecting cognition (n = 1); was more than 65 years (n = 1); or lacked English fluency (n = 1). There was often a small window of time between the referral and the start of chemotherapy. In cases where women were due to start chemotherapy the following day/s but had other medical appointments scheduled in that time (e.g., surgical insertion of a port-a-cath), it would have been a breach of ethical responsibility to delay cancer treatment for study purposes. These women were deemed ineligible. Only six women declined to participate, with half of these due to levels of
distress and half due to other commitments. Of the 52 eligible women, 46 were enrolled in the study. This represents a recruitment rate of 88.5%.

### Figure 5.1. Recruitment and retention of participants over the study.

- **Assessed for eligibility**
  - (n = 74)

- **Enrolled**
  - (n = 46)

- **Chemotherapy**
  - (n = 30)
  - **Time 1**
    - Pre-chemotherapy
    - Post-surgery
      - (n = 30)
    - M = 6 months

- **Time 2**
  - Post-chemotherapy
    - (= 1 month)
    - Initial follow up
      - (n = 30)
    - M = 9 months

- **Time 3**
  - Post-chemotherapy
    - (= 10 months)
  - Longer-term follow up
    - (n = 29)\(^\text{b}\)

- **No-chemotherapy**
  - (n = 16)

- **Time 1**
  - Post-surgery
    - (n = 15)\(^a\)

- **Time 2**
  - Initial follow up
    - (n = 16)
  - M = 9 months

- **Time 3**
  - Longer-term follow up
    - (n = 16)

\(^a\) One participant was unable to attend assessment on this occasion.
\(^b\) One participant deceased.

Of the 46 women enrolled in the study, 30 women received adjuvant chemotherapy as part of their breast cancer treatment, and 16 women did not. Forty-five women were initially assessed approximately one month (\(M = 31.1\) days, \(SD = 19.3\)) following surgery for breast cancer (Time 1). One woman from the no-chemotherapy group could not undertake the assessment at this time but participated in the next two assessments at times matched to women in the chemotherapy group. As mentioned, there was often a short window of time for women following their initial meeting with an oncologist to discuss their pathology results, where recommendations were made regarding the benefit...
of adjuvant treatment. As women wanting to participate in the study had to be assessed prior to the commencement of chemotherapy, it is not surprising that women who received chemotherapy were assessed (at Time 1) significantly closer to their last surgery ($M = 25.2$ days, $SD = 7.4$) than women who did not receive chemotherapy ($M = 43.3$ days, $SD = 28.9$), $t(15) = -2.35, p = 0.033$.

![Figure 5.2. Mean time since last assessment by breast cancer treatment group.](image)

$T2-T1 = Time\ 2 - Time\ 1$ in days. $T3-T2 = Time\ 3 - Time\ 2$ in days.

Women receiving chemotherapy were assessed again following their final cycle of chemotherapy, before starting other treatment (Time 2). This was, on average, around six months from their initial assessment ($M = 157.7$ days, $SD = 26.97$). Women not receiving chemotherapy were assessed at a matched time to the chemotherapy group, that is, around six months ($M = 161.5$ days, $SD = 25.33$) from their initial assessment. As can be seen in Figure 5.2, there was no significant difference between the groups at Time 2 ($T2-T1$) in the time since their initial assessment, $t(43) = -0.46, p = 0.649$.

The longer-term follow-up (Time 3) assessment was conducted around nine months from the previous assessment, with the timing of the no-chemotherapy group ($M = 270.8$ days, $SD = 61.18$) similar to that of the chemotherapy group ($M = 268.5$ days, $SD = 51.71$), $t(43) = -0.13, p = 0.897$.

One participant from the chemotherapy group died after her initial follow-up assessment and this was the only participant lost to follow-up over the study. This represents a retention rate of 98%.
5.3 Participant characteristics

a. Demographic characteristics

The demographic characteristics of participants at their initial assessment are presented in Table 5.1 by treatment group. Women who received chemotherapy were generally younger ($M = 51.7, SD = 7.3$) than women who did not receive chemotherapy ($M = 56.3, SD = 7.9$), although this difference was not statistically significant, $t(44) = -1.07, p = 0.06$.

The age range of women at their initial assessment was from 38 to 65 years, with 4% in their thirties, 33% in their forties, 37% in their fifties and 26% aged from 60-65. Comparison with female breast cancer incidence in the ACT from 2002-2006 (ACT Cancer Registry, 2009) showed a similar pattern of breast cancer incidence increasing with age, with the majority diagnosed in their forties and fifties. There were only 6% of women in the ACT diagnosed before 40, 21% in their forties, 33% in their fifties and 10.4% aged 60-64.

Table 5.1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chemotherapy ($n = 30$)</th>
<th>No-chemotherapy ($n = 16$)</th>
<th>$p$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) $M$ ($SD$)</td>
<td>51.67 (7.33)</td>
<td>56.27 (7.90)</td>
<td>0.06</td>
</tr>
<tr>
<td>pIQ $M$ ($SD$)</td>
<td>108.1 (9.6)</td>
<td>113.1 (7.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Education (years) $M$ ($SD$)</td>
<td>13.90 (3.15)</td>
<td>17.38 (4.19)</td>
<td>0.003**</td>
</tr>
<tr>
<td>Education % ($n$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 years/ equivalent</td>
<td>20% (6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥12 years/ equivalent</td>
<td>80% (24)</td>
<td>100% (16)</td>
<td>0.078*</td>
</tr>
<tr>
<td>Dominant hand % ($n$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>80% (24)</td>
<td>100% (16)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>13% (4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ambidextrous</td>
<td>7% (2)</td>
<td>0</td>
<td>0.238*</td>
</tr>
</tbody>
</table>

* Predicted Full Scale IQ (pIQ) from the National Adult Reading Test-R.

Two cells (50%) had expected count less than 5, Fisher’s exact test was used.

Four cells (67%) had expected count less than 5, exact test was used for Pearson’s chi-square.

* significant at $p < 0.05$; ** significant at $p < 0.01$; *** significant at $p < .001$ (boldface).

The age distribution of women in the study treated with chemotherapy compared to women treated without chemotherapy is presented in Figure 5.3. All women under 40 years were treated with chemotherapy. This is consistent with clinical practice guidelines for the management of younger women with breast cancer (National Breast
Cancer Centre [NBCC], 2004). The guideline, based on Level 1 evidence, states "the benefit of chemotherapy is greater the younger the woman’s age. Chemotherapy reduces the risk of recurrence by about one-fifth in women aged 60 to 69 years, but by nearly two-fifths in women under the age of 40" (NBCC, 2004, p. 22).

![Figure 5.3. Age distribution of participants by breast cancer treatment group.](image)

Nearly half (47%) of women who received chemotherapy were under 50 years, whereas around one-fifth (19%) of women who did not receive chemotherapy were under 50. In a near reversal, almost half (44%) of women who did not receive chemotherapy were in the older age group (60-65 years), whereas only 17% of women who received chemotherapy were in this age group. This is consistent with published data in the ACT that indicates that chemotherapy is more likely to be received by younger women with breast cancer and less likely to be offered to older women (BCTG, 2009). As one expected cell count in the <40 year age group was less than one, the two younger age groups were pooled to form one group (<50 years) for the purpose of the analyses. There was no statistically significant association between age and treatment group, $\chi^2(2, N = 46) = 5.14, p = 0.083$.

The majority of participants were right handed (Table 5.1). There were four women who were left-handed and two who were ambidextrous, all of whom were in the chemotherapy group. There was no significant association between dominant hand and treatment group, $\chi^2(2, N = 46) = 3.680, p = 0.238$.

Women who did not receive chemotherapy had significantly more years of education ($M = 17$ years, $SD = 4.19$) than women who did receive chemotherapy ($M = 14$ years, $SD = 3.15$), $t(44) = -3.17, p = 0.003$. The number of years of education ranged from 9 to 29 years.
An education level of less than 12 years of education or matriculation equivalent has been shown to have more influence on cognitive performance than more years of education (Lezak, et al., 2012). Only 11% (n = 5) of participants in this study received less than 12 years of education, all of whom were in the chemotherapy group (see Table 5.2). There was a trend, which failed to reach significance, in the likelihood of having less than 12 years of education between treatment groups, p = 0.08. The estimated IQ of both groups was not significantly different, t(44) = -1.81, p = 0.08. While there was a trend, the difference was not clinically meaningful. The chemotherapy group was at the top of the Average range (M = 108.1, SD = 9.6) for estimated intelligence and the no-chemotherapy group was just over the border of the High Average range (M = 113.1, SD = 7.5).

Table 5.2

<table>
<thead>
<tr>
<th>Qualifications/ Employment</th>
<th>Chemotherapy % (n = 30)</th>
<th>No-chemotherapy % (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest qualification % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 10 or equivalent</td>
<td>16.67% (5)</td>
<td>0</td>
</tr>
<tr>
<td>Year 12 or equivalent</td>
<td>20% (6)</td>
<td>6.25% (1)</td>
</tr>
<tr>
<td>Trade certificate</td>
<td>23.33% (7)</td>
<td>37.5% (3)</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>20% (6)</td>
<td>18.75% (3)</td>
</tr>
<tr>
<td>Graduate diploma</td>
<td>10% (3)</td>
<td>18.75% (3)</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>10% (3)</td>
<td>18.75% (3)</td>
</tr>
<tr>
<td>Employment status % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not in paid employment</td>
<td>23.3% (7)</td>
<td>37.5% (6)</td>
</tr>
<tr>
<td>In paid employment</td>
<td>76.7% (23)</td>
<td>62.5% (10)</td>
</tr>
<tr>
<td>Occupation % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manager</td>
<td>13.6% (3)</td>
<td>37.5% (3)</td>
</tr>
<tr>
<td>Professional</td>
<td>50% (11)</td>
<td>37.5% (3)</td>
</tr>
<tr>
<td>Paraprofessional</td>
<td>18.2% (4)</td>
<td>12.5% (1)</td>
</tr>
<tr>
<td>Clerical/ Sales/ Service</td>
<td>18.2% (4)</td>
<td>12.5% (1)</td>
</tr>
</tbody>
</table>

Nearly half (46%) of participants had a Bachelor Degree or higher indicating a highly-educated cohort, even when compared to the Canberra rate of 30%, which is high compared to the national rate of 16% (Australian Bureau of Statistics [ABS], 2011). This suggests that more highly-educated women being treated for breast cancer may have been interested or willing to participate in a research study at this time. Over half (56%) of women from the no-chemotherapy group had a Bachelor Degree or higher, compared to...
40% from the chemotherapy group. There was no significant difference in the likelihood of holding or not holding a Bachelor Degree between treatment groups, \( \chi^2(1, N = 46) = 1.111, p = 0.292 \).

Approximately three-quarters (72%) of participants were in paid employment, equivalent to the ACT rates of 73% (ABS, 2011). More women (77%) in the chemotherapy group were in paid employment, with 60% \((n = 18)\) working full-time and 17% \((n = 5)\) working part-time. In comparison, 62.5% of women in the no-chemotherapy group were working in paid employment, with 50% \((n = 8)\) working full-time and 12.5% \((n = 2)\) working part-time. There was no significant difference in the likelihood of holding a Bachelor Degree between treatment groups, \( p = 0.292 \). The majority (84%) of participants in paid work were employed in more highly-skilled occupations, including 67% as managers or professionals, such as teachers, and 17% as paraprofessionals, such as nurses. This distribution was similar between treatment groups.

b. Ethnicity

None of the participants were from an Aboriginal or Torres Strait Islander background. As shown in Table 5.3 around one-fifth (19.5%) of participants were born overseas, mainly from English speaking countries. The 2006 census showed that only 1% of Canberra’s population was of indigenous origin and 22.9% were born overseas, mainly from English speaking countries (ABS, 2011).

Only 6.5% of participants \((n = 3)\) were born in a non-English speaking country, with the majority \((n = 2)\) starting to speak English before the age of 10 and all speaking English currently at home. More women in the no-chemotherapy group (12.5%) were born in a non-English speaking country compared to the chemotherapy group (3.3%). There was no significant difference in the likelihood of having a non-English speaking country of origin between treatment groups, \( p = 0.274 \).

Table 5.3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chemotherapy % ((n = 30))</th>
<th>No-chemotherapy % ((n = 16))</th>
<th>( p ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-English speaking country</td>
<td>3.33% (1)</td>
<td>12.5% (2)</td>
<td></td>
</tr>
<tr>
<td>English speaking country</td>
<td>96.66% (29)</td>
<td>87.5% (14)</td>
<td>0.274\a</td>
</tr>
<tr>
<td>Australia</td>
<td>83.33% (25)</td>
<td>75% (12)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13.33% (4)</td>
<td>12.5% (2)</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Two cells (50%) had expected count less than 5, Fisher’s Exact Test was used.
c. Relationship characteristics

The majority (65%) of participants reported they were married or in a defacto relationship, with similar proportions in the chemotherapy group (66.7%) and the no-chemotherapy group (62.5%). This is slightly higher than the 2006 census, where 59% of ACT residents reported they were in a registered marriage or in a defacto marriage (ABS, 2007). Only one woman in the study was widowed, from the chemotherapy group. Another 20% (n = 6) were divorced or separated, as were 12.5% of the no-chemotherapy group. One-tenth of women in the chemotherapy group (n = 3) had never married compared to one-quarter (n = 4) of women in the no-chemotherapy group (see Table 5.4). There was no significant relationship found between marital status and treatment group, \( \chi^2(2, N = 46) = 2.20, p = 0.354 \).

Around one-fifth (22%) of participants lived alone. More (37.5%) of the no-chemotherapy group lived alone than the chemotherapy group (13.3%). There was, however, no significant difference in the proportion of women living alone between treatment groups, \( p = 0.074 \).

Table 5.4

<table>
<thead>
<tr>
<th>Relationship Characteristics by Breast Cancer Treatment Group</th>
<th>Chemotherapy % (n = 30)</th>
<th>No-chemotherapy % (n = 16)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/defacto</td>
<td>66.67% (20)</td>
<td>62.5% (10)</td>
<td></td>
</tr>
<tr>
<td>Divorced/Separated/Widowed</td>
<td>23.33% (7)</td>
<td>12.5% (2)</td>
<td>0.354(^a)</td>
</tr>
<tr>
<td>Never married</td>
<td>10% (3)</td>
<td>25% (4)</td>
<td></td>
</tr>
<tr>
<td>Cohabitation status % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live alone</td>
<td>13.33% (4)</td>
<td>37.5% (6)</td>
<td></td>
</tr>
<tr>
<td>Live with someone</td>
<td>86.67% (26)</td>
<td>62.5% (10)</td>
<td>0.074(^b)</td>
</tr>
<tr>
<td>Partner</td>
<td>66.67% (20)</td>
<td>62.5% (10)</td>
<td></td>
</tr>
<tr>
<td>Family/friend</td>
<td>20.0% (6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Children % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20% (6)</td>
<td>31.25% (5)</td>
<td>0.478(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Three cells (50%) had expected count less than 5, exact test was used for Pearson’s chi-square.

\(^b\) One cell (25%) had expected count less than 5, Fisher’s Exact Test was used.
Around one-quarter (24%) of participants had not had any children, which was nearly one-third (31.2%) of the no-chemotherapy group and one-fifth (20%) of the chemotherapy group. There was no significant difference found in the proportion of women having had or not had children between treatment groups, \( p = 0.478 \).

Perceived social support was measured by items from the Medical Outcomes Study social support index. At their initial assessment, women in the chemotherapy group had similar perceived social support (\( M = 4.4, SD = 0.8 \)) as compared to women in the no-chemotherapy group (\( M = 4.3, SD = 0.8 \)), \( t(42) = 0.33, p = 0.740 \).

d. Menopausal status and cancer history status

As seen in Table 5.5 half of women in the study were postmenopausal, with more from the no-chemotherapy group (69%) than from the chemotherapy group (40%), due to it being an older cohort. There was a trend towards significance for the likelihood of women who were pre/peri menopausal receiving chemotherapy, \( \chi^2(1, N = 46) = 3.45, p = 0.063 \). This is in keeping with clinical guidelines for the treatment of early breast cancer (NHMRC, 2001).

Table 5.5

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chemotherapy % (n = 30)</th>
<th>No-chemotherapy % (n = 16)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal status % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>40% (12)</td>
<td>68.75% (11)</td>
<td></td>
</tr>
<tr>
<td>Pre/ Peri</td>
<td>60% (18)</td>
<td>31.25% (5)</td>
<td>0.063</td>
</tr>
<tr>
<td>Pre</td>
<td>46.67% (14)</td>
<td>18.75% (3)</td>
<td></td>
</tr>
<tr>
<td>Peri</td>
<td>13.33% (4)</td>
<td>12.50% (2)</td>
<td></td>
</tr>
<tr>
<td>Cancer history % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous cancer</td>
<td>86.67% (26)</td>
<td>81.25% (13)</td>
<td></td>
</tr>
<tr>
<td>Previous Cancer</td>
<td>13.33% (4)</td>
<td>18.75% (3)</td>
<td></td>
</tr>
<tr>
<td>Previous DCIS</td>
<td>3.33% (1)</td>
<td>12.50% (2)</td>
<td></td>
</tr>
<tr>
<td>Other cancer</td>
<td>10% (3)</td>
<td>6.25% (1)</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Two cells (50%) had expected count less than 5, Fisher’s Exact Test was used.

The majority of participants were without any history of previous cancer (see Table 5.5). Only 13% \( (n = 4) \) of the chemotherapy group had experienced a previous cancer, with one having had previous breast cancer (ductal carcinoma in situ). Almost one-fifth (19%, \( n = 3 \)) of the no-chemotherapy group had experienced a previous cancer, with two having...
had previous breast cancer (DCIS). The most common cancer experienced previously was melanoma, treated with surgery. There was no significant difference in the likelihood of having had a previous cancer between treatment groups, \( p = 0.681 \).

e. Clinical anxiety and depressive disorders

Around 15\% (\( n = 7 \)) of participants were assessed at the initial assessment following diagnosis as meeting the DSM-IV criteria for a current anxiety disorder, with nearly half having a specific phobia that interfered in their life and functioning (\( n = 3 \)). Over one-tenth (11\%, \( n = 5 \)) met the DSM-IV criteria for a current depressive disorder, with the majority (\( n = 4 \)) having depression (i.e., Major Depressive Disorder). The prevalence of anxiety disorders in the past 12 months in the study population (15\%) were higher than those of Australian women (12\%) in general, using the same clinical interview (Andrews, Hall, Teesson, & Henderson, 1999). The prevalence of depressive disorders (11\%) was substantially higher than found in Australian women in general (7.4\%). The rates of anxiety disorders found in participants were also higher than those found in a study of 303 Australian women with early breast cancer (11.6\%) but similar to the rates of depressive disorders (11.9\%) (Kissane et al., 1998).

As can be seen in Table 5.6, more of the no-chemotherapy group had an anxiety disorder (19\%) or a mood disorder (19\%) than the chemotherapy group (13\% and 7\%, respectively). There was no significant difference between the treatment groups in the likelihood of having either an anxiety disorder at the initial assessment, \( p = 0.681 \) or of having a mood disorder, \( p = 0.325 \).

Table 5.6

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chemotherapy % (( n = 30 ))</th>
<th>No-chemotherapy % (( n = 16 ))</th>
<th>( p ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorder % (( n ))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>86.7% (26)</td>
<td>81.2% (13)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13.3% (4)</td>
<td>18.8% (3)</td>
<td>0.681\textsuperscript{a}</td>
</tr>
<tr>
<td>Depressive disorder % (( n ))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>93.3% (28)</td>
<td>81.2% (13)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6.7% (2)</td>
<td>18.8% (3)</td>
<td>0.325\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Two cells (50\%) had expected count less than 5, Fisher's exact test was used.
5.4 Cancer detection

Screening mammography detected 35% \((n = 16)\) of cancers in all participants. As breast screening is targeted at women aged 50 to 70 years, cancers occurring in women aged less than 50 years are more likely to be detected by self (BCTG, 2004). Nearly three-quarters \((71%, n = 12)\) of participants aged less than 50 detected their cancers themselves.

As shown in Figure 5.4, the majority \((70%)\) of the chemotherapy group either detected their cancers themselves \((60%; n = 18)\) or had their cancer detected by a general practitioner \((10%; n = 3)\), suggesting more symptomatic cancers. Less than half \((44%)\) the no-chemotherapy group detected their cancer themselves \((n = 7)\), suggesting more asymptomatic cancers. Half of the no-chemotherapy group had their cancers detected by mammography screening \((n = 8)\).

5.5 Cancer characteristics

The pathological type of all detected breast cancers and the location of the primary breast cancer are presented by treatment group in Table 5.7. The laterality of primary breast cancers were divided fairly evenly between left and right breasts with 47% of the chemotherapy group having cancer in the right breast compared to 50% of the no-chemotherapy group. There was no significant difference in the probability of having right or left breast cancers between treatment groups, \(\chi^2(1, N = 46) = 0.05, p = 0.829\).

There was a significantly higher likelihood of the chemotherapy group having an invasive cancer \((100%)\) detected than the no-chemotherapy group \((75%)\), \(p = 0.011\). Most of the
invasive tumours (69%) detected in participants were invasive ductal carcinoma not otherwise specified (NOS) and 24% were infiltrating lobular carcinoma. The chemotherapy group had twice the proportion of lobular carcinomas (27%) compared to the no-chemotherapy group (12.5%). Only 7% were of special types such as mucinous carcinomas. This distribution was similar to the reported distribution of unilateral invasive breast tumours across the ACT (BCTG, 2004).

The likelihood of detecting a non-invasive cancer was nearly identical between groups, \( p = 1.000 \). Almost 87% of the chemotherapy group and 87.5% of the no-chemotherapy group had a non-invasive cancer. Of all non-invasive tumours detected in participants, 82.5% were ductal carcinoma in situ (DCIS), a cytologically malignant but non-invasive proliferation of breast duct epithelium.

Forty percent of the chemotherapy group were diagnosed with DCIS comedo (with necrosis) and 30% with DCIS non-comedo (without necrosis), whereas these rates were reversed in the no-chemotherapy group. Approximately 15% of the non-invasive tumours detected were lobular carcinoma in situ, with more detected in the chemotherapy group (17%) than in the no-chemotherapy group (6%).

Table 5.7

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chemotherapy % (n = 30)</th>
<th>No-chemotherapy % (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laterality of cancer % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>46.67% (14)</td>
<td>50% (8)</td>
</tr>
<tr>
<td>Left</td>
<td>53.33% (16)</td>
<td>50% (8)</td>
</tr>
<tr>
<td>Invasive % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>66.67% (20)</td>
<td>56.25% (9)</td>
</tr>
<tr>
<td>Lobular</td>
<td>26.67% (8)</td>
<td>12.50% (2)</td>
</tr>
<tr>
<td>Other</td>
<td>6.67% (2)</td>
<td>6.25% (1)</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>25% (4)</td>
</tr>
<tr>
<td>Non-invasive % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>70% (21)</td>
<td>75% (12)</td>
</tr>
<tr>
<td>LCIS</td>
<td>16.67% (5)</td>
<td>6.25% (1)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>6.25% (1)</td>
</tr>
<tr>
<td>None</td>
<td>13.33% (4)</td>
<td>12.5% (2)</td>
</tr>
</tbody>
</table>
5.5.1 Tumour size

Tumour size is associated with overall prognosis of primary breast cancer (Elston, 1999). Half of the tumours detected in participants were larger than 20mm. The average tumour size was larger in the chemotherapy group ($M = 25.68\text{mm}, SD = 15.02$) than the no-chemotherapy group ($M = 18.84\text{mm}, SD = 19.65$), although this size difference was not statistically significant, $t(44) = 1.32, p = 0.193$. The tumour size distribution of participants according to treatment group is presented in Figure 5.5.

![Tumour size distribution](image)

*Figure 5.5. Distribution of tumour size by breast cancer treatment group.*

There was a significant relationship between tumour size and treatment group, $\chi^2(3, N = 46) = 18.37, p < .001$. As seen in Figure 5.5, the no-chemotherapy group were more likely to have the smallest tumours (less than 10mm in size). Half of the no-chemotherapy group ($n = 8$) had the smallest tumours, whereas none of the chemotherapy group had tumours this size. More of the chemotherapy group (70%) had larger tumours (>20mm) than the no-chemotherapy group (31%). This is consistent with the reporting of treatment for early breast cancer over a ten year period in the ACT in which chemotherapy was more likely to be offered and received by women with larger tumours and more often not offered to women with smaller tumours (BCTG, 2009).

5.5.2 Histological grade

Histological grade is a useful predictor of prognosis, with grade three tumours having a poorer outcome compared to grade one and two tumours (Elston, 1999). Five women in the no-chemotherapy group did not have a histological grade recorded for their tumours,
either because they did not have an invasive cancer (n=4) or it was not on the pathology results (n=1). A significant association was detected between histological grade and treatment group, $\chi^2(3, N = 46) = 20.07, p < .001$. The distribution of tumour histological grade of all invasive cancers based on treatment group is presented in Figure 5.6. Grade 3 tumours were more likely to be treated with chemotherapy. All 15 of the tumours assessed as Grade 3 were treated with chemotherapy. This represented half of the women in the chemotherapy group.

![Figure 5.6. Distribution of tumour histological grade by breast cancer treatment group.](image)

### 5.5.3 Axillary surgery and nodal involvement

Removal of lymph nodes is a standard part of surgical management in invasive breast cancers, in order to minimize disease recurrence and to provide material for accurate pathological staging (NHMRC, 2001). However, axillary surgery can cause significant side effects, including stiffness, lymphoedema and altered sensation. A new technique, sentinel node biopsy, a node sampling procedure, allows women with a negative sentinel node biopsy to avoid axillary dissection for node clearance. Some form of axillary dissection or sentinel node biopsy was performed in 96% (n = 44) of all participants, including all chemotherapy patients. Of the two women in the no-chemotherapy group who did not undergo any form of axillary surgery, both had tumours that were less than 10mm in diameter and were DCIS non-comedo (without necrosis).

Of all the women who underwent axillary surgery, approximately half (49%) had nodal involvement (n = 21). As seen in Figure 5.7, the chemotherapy group was significantly more likely to have nodal involvement (67%) than the no-chemotherapy group (7%). $\chi^2(1, N = 46) = 15.35, p < .001$. Only one of the no-chemotherapy group had nodal involvement.
and this involved 1-4 nodes whereas 60% \((n = 18)\) of the chemotherapy group had 1-4 nodes involved and 7% \((n = 2)\) had more than four nodes involved.

Figure 5.7. Nodal involvement by breast cancer treatment group.

5.5.4 Vessel invasion

Tumour cells can break into small vessels when seen under a microscope.

Lymphovascular vessel invasion is associated with nodal involvement but also has independent prognostic significance (Querci della Rovere, Warren, & Benson, 2006). Vessel invasion within the breast tissue was detected in 37% \((n = 33)\) of tumours from the chemotherapy group, as opposed to none of the tumours in the no-chemotherapy group (see Figure 5.8). The chemotherapy group was significantly more likely to have vessel invasion present than the no-chemotherapy group, \(p = 0.008\).

Figure 5.8. Vessel invasion of invasive cancers by breast cancer treatment group.
5.5.5 Hormone receptor and HER2 status

The presence or absence of hormone receptors within breast cancer cells is important in predicting response to hormonal therapies (NHMRC, 2001). Hormone receptors, either oestrogen receptor (ER+) or progesterone receptors (PR+) were detected in 93% (n = 43) of all tumours, including 100% of tumours treated with chemotherapy and 85% of tumours treated without chemotherapy (see Table 5.8). Only two tumours were reported as both ER and PR negative by immunochemistry. Neither received adjuvant chemotherapy.

Around 20-25% of breast cancers over-express the HER2 protein. These cancers are more aggressive and are associated with a reduction in disease-free and overall survival. Around 13% (n = 6) of all participants had breast cancers that tested positive for amplification of HER2. More HER2 overexpressing breast cancers were found in the chemotherapy group (17%; n = 5) than the no-chemotherapy group (6%; n = 1).

Table 5.8

<table>
<thead>
<tr>
<th>Cancer Pathology in Participants by Treatment Group</th>
<th>Chemotherapy % (n = 30)</th>
<th>No-chemotherapy % (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone receptor status % (n)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+PR+</td>
<td>80% (24)</td>
<td>62.50% (10)</td>
</tr>
<tr>
<td>ER+PR-</td>
<td>16.67% (5)</td>
<td>12.50% (2)</td>
</tr>
<tr>
<td>ER-PR+</td>
<td>3.33% (1)</td>
<td>6.25% (1)</td>
</tr>
<tr>
<td>ER-PR-</td>
<td>0</td>
<td>12.50% (2)</td>
</tr>
<tr>
<td>NA</td>
<td>0</td>
<td>6.25% (1)</td>
</tr>
<tr>
<td><strong>HER2 status % (n)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>83.33% (25)</td>
<td>75% (12)</td>
</tr>
<tr>
<td>Positive</td>
<td>16.67% (5)</td>
<td>6.25% (1)</td>
</tr>
<tr>
<td>NA</td>
<td>0</td>
<td>6.25% (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>12.5% (2)</td>
</tr>
<tr>
<td><strong>Pathological stage % (n)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>25% (4)</td>
</tr>
<tr>
<td>I</td>
<td>30% (9)</td>
<td>62.5% (10)</td>
</tr>
<tr>
<td>II</td>
<td>56.67% (17)</td>
<td>12.5% (2)</td>
</tr>
<tr>
<td>II/IA</td>
<td>26.67% (8)</td>
<td>12.5% (2)</td>
</tr>
<tr>
<td>II/IB</td>
<td>30% (9)</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>13.33% (4)</td>
<td>0</td>
</tr>
</tbody>
</table>
5.5.6 Pathological stage

Overall pathological stage of the cancers, according to the American Joint Committee on Cancer (AJCC) system, is summarized in Table 5.8. The pathological TNM staging is a standardized way of summarizing how far a cancer has spread and takes account of whether the cancer is invasive or non-invasive, the tumour size, extent of nodal involvement and evidence of distant metastases. The pathological stage of a cancer is one of the most important factors in determining prognosis and treatment options (Querci della Rovere, et al., 2006).

Two-fifths (41%; n = 19) of women enrolled in the study had Stage I cancers (T1N0), with the majority of the no-chemotherapy group (63%; n = 10) having Stage I cancers. An examination of the distribution of the four staging groups (0-III) by treatment group found a significant relationship between pathological stage and treatment group, $\chi^2(3, N = 46) = 17.23, p < .001$. As seen in Figure 5.9, the chemotherapy group had more advanced pathological staging, with over half (57%) having Stage II cancers, compared to 12.5% of the no-chemotherapy group, and 13% having Stage III cancers, compared to none of the control group.

5.6 Primary surgical treatments

Surgery is the primary treatment for localized breast cancer (NHMRC, 2001). The decision between breast-conserving surgery and mastectomy is based on several factors including the tumour characteristics and location and the patient’s wishes. Of the 46 women who
underwent primary surgery. 33 (72%) required one operation, 11 (24%) had two operations and two (4%) had three operations before completing their surgical management. Nearly two-thirds (63%) of the chemotherapy group required only one operation compared to 87.5% of the no-chemotherapy group. There was no significant association found between number of operations and treatment group, $\chi^2(2, N = 46) = 3.52, p = 0.264$. The number of surgeries required to complete surgical treatment by final outcome is presented in Figure 5.10.

![Figure 5.10. The number of surgical treatments required and final outcome.](image)

C = Chemotherapy. NC = No-chemotherapy.

Nearly two-fifths (39%, $n = 17$) of women participating in the study received breast conservation from one operation. A higher proportion (63%) of the no-chemotherapy group had one surgery with breast conservation than the chemotherapy group (27%). Some 36% ($n = 11$) of the chemotherapy group and 6% ($n = 1$) of the no-chemotherapy group went through initial breast conserving surgery, but then required conversion to mastectomy because surgical margins were compromised by invasive disease or because of presence of extensive DCIS. One woman from the no-chemotherapy group underwent two procedures and achieved breast conservation. All other women who underwent two or three procedures had a unilateral mastectomy or bilateral mastectomy.

As breast cancer surgery can affect the range of movement and speed of response in the near arm, potentially affecting performance of the dominant hand, the laterality of the breast surgery and the dominant hand were compared. There were 37% ($n = 11$) of the chemotherapy group whose breast cancer surgery matched the side of their dominant hand, compared to 44% ($n = 7$) of the no-chemotherapy group. There was no significant difference in the likelihood of matching both laterality of surgery and dominant hand between treatment groups, $\chi^2(1) = 0.22, p = 0.639$. 156
5.7 Adjuvant therapies

After primary surgical treatment, adjuvant treatment such as localized radiotherapy, or systemic chemotherapy and hormonal therapy are frequently recommended, in order to reduce risk of recurrence. Most participants (91%, n = 42) received some form of adjuvant therapy after their primary surgical treatment. An overview of the adjuvant treatments is presented in Figure 5.11.

![Figure 5.11. An overview of adjuvant treatments received by treatment group. Radio = Radiotherapy or Radiation therapy. Hormonal = Hormonal therapy.](image)

Two-thirds (66.7%) of those who received adjuvant treatment received post-operative radiotherapy; 71% (n = 30) received chemotherapy and over four-fifths (83.3%) received hormonal therapy. Around one-fifth (n = 8) received a single adjuvant therapy. Just over 10% (n = 5) received radiotherapy therapy alone post-surgery, 5% (n = 2) received hormonal therapy alone and one person received chemotherapy alone. Of those who
received adjuvant treatment, 40% \((n = 17)\) were given a combination of all three forms of adjuvant therapy.

5.7.1 Radiation therapy

Post-operative adjuvant radiation therapy (radiotherapy) has been shown to reduce the rates of local or regional recurrence in the treatment of breast cancer (NHMRC, 2001). Adjuvant breast radiotherapy is recommended for all patients who undergo breast conserving surgery in order to reduce the risk of local recurrence, apart from those who have small, very early stage, receptor-positive breast cancer, who are unlikely to benefit from adjuvant radiotherapy. In this study 17 women who had breast conserving surgery were offered and received breast radiotherapy after surgery. Two women were offered radiotherapy and refused. Chest wall radiotherapy and regional node radiotherapy are recommended for women following mastectomy who have a high risk of chest wall recurrence and high risk lymph node involvement. Eleven women were offered and received post-mastectomy radiotherapy.

![Figure 5.12. Radiotherapy by breast cancer treatment group.](image)

Around three-fifths (61%, \(n = 28\)) of women in the study received radiotherapy as part of their treatment. This compares with 65.6% of breast cancer patients in the ACT who received early radiotherapy (BCTG, 2004). Figure 5.12 shows that the proportion of women treated with radiotherapy following chemotherapy or post-surgery (no-chemotherapy) were similar, with 60% \((n = 18)\) of the chemotherapy group compared to 63% \((n = 10)\) of the no-chemotherapy group having received radiotherapy. There was no significant difference in the probability of receiving radiotherapy between treatment groups, \(\chi^2(1) = 0.03, p = 0.869\). Furthermore, the average number of radiotherapy...
treatments was not significantly different between the chemotherapy group ($M = 27.39, SD = 3.26$) and the no-chemotherapy group ($M = 28, SD = 4.97$), $t(25) = -0.38, p = 0.704$.

The location of post-operative radiotherapy was distributed somewhat differently between the groups (see Figure 5.13). Over half of the radiotherapy received in the chemotherapy group was to the chest wall (56%) and two-fifths (39%) was to the breast, with one remaining person receiving radiotherapy directed to the supraclavicular region. In comparison, in the no-chemotherapy group most (90%) of the radiotherapy received was to the breast and only 10% was to the chest wall.

![Figure 5.13. Distribution of radiotherapy location by breast cancer treatment group.](image)

### 5.7.2 Chemotherapy and trastuzumab (Herceptin)

Multi-agent chemotherapy for the adjuvant treatment of early breast cancer has been shown to reduce the risk of cancer recurrence and improve overall survival, with the greatest benefit in node-positive cancers (NHMRC, 2001). The original chemotherapy regimen containing cyclophosphamide, methotrexate and 5-fluorouracil (CMF) has been followed by further clinical trials demonstrating that anthracycline regimens are more effective. These include Adriamycin (doxorubicin) and epirubicin. However, anthracycline regimens are associated with increasing toxicity, including increased risk of cardiotoxicity, particularly for patients receiving left-sided chest irradiation.

By the start of this study the use of CMF regimens had declined, replaced by newer anthracycline regimens. The use of taxane-containing chemotherapy regimens were being introduced, as clinical trials had shown further improvements in disease-free and overall survival. Taxanes, including paclitaxel (Taxol) and docetaxel (Taxotere), are given either sequentially or concurrently with an anthracycline, or a taxane regimen can be added to or used in place of part of a chemotherapy regimen. Taxanes are associated with an increased
risk of febrile neutropenia but may reduce cardiac toxicity by reducing the exposure to anthracyclines. The first patients in the study receiving docetaxel (Taxotere) based regimens concurrently with an anthracycline were among the first receiving these regimens in the ACT. All of these participants were hospitalised with febrile neutropenia with systemic infections/sepsis following their first cycle/s of treatment. These patients were then administered a new drug Neulasta (Pegfilgrastim) prior to each of their subsequent chemotherapy cycles to stimulate the level of white cells and neutrophils to fight infection. At its November 2006 meeting, the Pharmaceutical Benefits Advisory Committee recommended extending the pegfilgrastim listing to include the primary prophylaxis of chemotherapy induced neutropenia in patients with early breast cancer who were undergoing adjuvant chemotherapy with docetaxel (Taxotere) in combination with an anthracycline and cyclophosphamide. More than half (56.7%; n = 17) of participants who underwent chemotherapy received Neulasta as part of their treatment.

Figure 5.14. Distribution of chemotherapy using taxane-containing regimens.

Forty percent (n = 12) of women who received chemotherapy were administered an anthracycline based regimen (see Figure 5.14). This included ten women who received FEC (5-fluorouracil, epirubicin and cyclophosphamide) regimens and two women who received AC (Adriamycin and cyclophosphamide) regimens. Of the women who received FEC regimens, two had the F(5-fluorouracil) removed from the regimen partway through treatment due to an adverse reaction to this drug.

The other 60% (n = 18) were administered a taxane either sequentially or concurrently with an anthracycline. These included: eight women who received FEC-D (FEC for 3 cycles followed by docetaxel for 3 cycles); three women who received FEC-P (FEC for 4 cycles followed by paclitaxel for 4-5 cycles); one woman who received AC-Taxol (AC for 4 cycles...
followed by paclitaxel for 1 cycle) and six women who received TAC regimens (Taxotere, Adriamycin and cyclophosphamide). Of the women who received TAC regiments, four received TAC for six cycles, one had the docetaxel removed for the final cycle due to adverse events and one woman commenced a TAC regimen for one cycle and was changed to a FEC regimen for the following five cycles due to an anaphylactic reaction.

Nausea (70%), tiredness (67%), alopecia (73%) and changes in taste perception (80%) were the most frequently reported side effects experienced during chemotherapy by women in the study. Febrile neutropenia (53%), muscle or joint pain (53%), gastrointestinal disturbances (47%) involving diarrhoea or constipation, nail changes (50%), peripheral neuropathy (40%) and weight gain (40%) were also common. Rarer side effects were veins clotting (30%), mucositis (30%), infection (27%), oedema (10%), anaphylaxis (3%) and haemorrhage (3%).

The approval of trastuzamab (Herceptin), a monoclonal antibody, on the Pharmaceutical Benefits Scheme occurred after the commencement of the study and was the newest addition to the chemotherapy regimens. In breast cancers that have an overexpression of the HER2 protein, trastuzamab binds to the HER2 receptor and, in combination with chemotherapy, has been found to significantly improve disease-free and overall survival. Herceptin is associated with increased risk of congestive heart failure so is not used concurrently with anthracycline based regimens. Five women were treated with Herceptin following a FEC and taxane regimen.

5.7.3 Hormonal therapy

Adjuvant hormonal or endocrine therapy has been found to improve disease free and overall survival in patients with oestrogen receptor (ER) or progesterone receptor (PR) positive tumours (NHMRC, 2001). The main groups of endocrine treatments are the selective oestrogen receptor modulators (SERMs) that block the effects of oestrogen in the breast tissue, and the aromatase inhibitors, that stop the production of oestrogen in post-menopausal women. Tamoxifen is the main drug used of the selective oestrogen receptor modulators (SERMs). Aromatase inhibitors, including anastozole (Arimidex) and letrozole (Femara), are highly effective but contra-indicated in premenopausal women so premenopausal women with hormone receptor positive tumours are generally offered tamoxifen. Both classes of drugs are associated with significant side effects. An additional option for premenopausal women is ovarian oblation, which can be achieved by oophorectomy, the surgical removal of the ovaries, or radiotherapy or gonadotropin-releasing hormone to suppress ovarian function.
Three-quarters (76%, \( n = 35 \)) of participants received hormonal therapy as part of their adjuvant breast cancer treatment. There was a significant difference in the likelihood of receiving hormonal therapy between treatment groups, \( p < .001 \). As can be seen in Figure 5.15, more participants had hormonal therapy in combination with chemotherapy (93%) than had it without chemotherapy (44%). The distribution of hormonal therapy received in both groups is presented in Figure 5.16.

Over half (\( n = 15 \)) of the women who had hormonal therapy post-chemotherapy received aromatase inhibitors, including 39% arimidex and 14% femara. Two-fifths (\( n = 11 \)) received tamoxifen. An additional two premenopausal women (7%) received tamoxifen post-chemotherapy and then had an oophorectomy to suppress ovarian function, with one
then switching to arimidex. In comparison, one-quarter \((n = 2)\) of the women who had hormonal therapy in the no-chemotherapy group received aromatase inhibitors, all of which were arimidex. Half \((n = 4)\) received tamoxifen, including one woman who switched to arimidex once she was confirmed post-menopausal. An additional woman in the no-chemotherapy group received tamoxifen post-surgery but then had an oophorectomy, and switched to arimidex. One woman from the no-chemotherapy group had received an oophorectomy as part of her surgical treatment and had no further endocrine treatment.

5.8 Adverse events

Adverse events can result from breast cancer treatment. The investigator collected information from hospital records regarding treatment complications, hospital readmissions and presence of treatment-induced menopause.

a. Treatment complications

There were 55 treatment complications noted on patient hospital files over the course of the study, with the majority of these \((n = 46)\) recorded for the chemotherapy group. There was a significantly higher probability of the chemotherapy group \((100\%)\) having a treatment complication than the no-chemotherapy group \((31\%), p < .001\). The distribution of treatment complications recorded on file over the course of the assessments for each treatment group is shown in Figure 5.17.

![Figure 5.17. Distribution of treatment complications over time by treatment group.](image)

There were slightly more treatment complications \((30\%)\) noted in the chemotherapy group at Time 1 than in the no-chemotherapy group \((20\%)\). However, at Time 2 90% of the chemotherapy group had treatment complications noted on file, compared to only 13% of
the no-chemotherapy group. At Time 3, the proportions of complications were similar amongst each treatment group and similar to the initial assessment, with 34% in the chemotherapy group and 25% of the no-chemotherapy group having treatment complications recorded.

b. Hospital readmissions

Over half (54%) of participants \( n = 25 \) had at least one hospital readmission over the course of the study. The readmission distributions based on treatment group is presented in Figure 5.18.

There was a significantly higher likelihood of hospital readmission for women receiving chemotherapy (80%) compared to women not receiving chemotherapy (6%). \( \chi^2(1, N = 46) = 22.87, p < .001 \).

The hospital lengths of stay ranged from day-only to 11 days, with the average length of stay being four days. Three participants had two hospital readmissions over the course of the study, all from the chemotherapy group.

All the reasons for readmission for the chemotherapy group were due to adverse events relating to treatment, whereas the reason for readmission for the participant from the no-chemotherapy group was unrelated to breast cancer treatment. The profile of main reason for readmission noted on the hospital files for the chemotherapy group participants are presented in Figure 5.19.
The main reasons for hospital readmission for chemotherapy participants were due to acute adverse events, such as thrombosis \((n = 6)\), neutropenia \((n = 5)\) and septicemia \((n = 3)\). These reasons included the longest lengths of stay \(>9\) days. The average length of stay for chemotherapy participants readmitted for thrombosis, septicemia or neutropenia was 6 days. The main reasons for readmission for the longest lengths of stays \(>9\) days were thrombosis \((n = 2)\), septicemia \((n = 1)\) and kidney lesion \((n = 1)\).

c. Treatment-induced menopause

One of the common side effects reported from chemotherapy is treatment-induced menopause in pre- or peri-menopausal women. The sudden onset of menopause is also a consequence of endocrine treatments, such as oophorectomy. Treatment-induced menopause frequently results in hot flushes (otherwise called hot flashes) that occur at a greater frequency and/or intensity than hot flushes associated with natural menopause. Twenty participants \((43.5\%)\) experienced treatment-induced menopause. The distribution of treatment-induced menopause according to treatment group is presented in Figure 5.20.
There was a significant difference in the probability of treatment-induced menopause based on treatment group, $\chi^2(1, N = 46) = 9.58, p = 0.002$. More of the chemotherapy group (60%) experienced treatment-induced menopause than the no-chemotherapy group (12.5%).

5.9 Follow-up recurrence and survival

The study collected limited follow-up information from hospital records approximately five years from the date of the first assessment. Follow-up data collected were limited to the presence or absence of relapse and vital status. The current status of two women was unknown. Of all participants for whom information was available, 95.5% remained alive and disease free. Two participants (4.5%) were recorded as having died, both from the chemotherapy group. One had developed distant metastases secondary to breast cancer and the other had an extensive subarachnoid haemorrhage. This meant that only three women in total (6.5%) had died five years from diagnosis.

5.10 Chapter Summary

Women participating in the study were representative of women with early breast cancer in the Australian Capital Territory. Younger women tended to be more likely to receive chemotherapy and older women tended to be less likely to receive chemotherapy, although the association between age and treatment group did not reach significance. Women receiving chemotherapy were significantly more likely to have invasive cancers and larger tumours with higher tumour grade and pathological stage. They were also more likely to have nodal involvement and vessel invasion. These pathology results
confirm findings on breast cancer treatment in the ACT that women are less likely to receive chemotherapy if they are older and have small tumours with no lymph node or vessel invasion and more likely if they are younger and with increasing tumour grade, pathological stage and size (BCTG, 2009).

In terms of breast cancer localized treatments, the groups did not differ significantly in the number of operations received or their probability of receiving radiation therapy. However, in terms of systemic therapies women were more likely to receive hormonal therapy if they had received chemotherapy as part of their adjuvant treatment. Women receiving chemotherapy received several different types of chemotherapy regimens that could be categorized as anthracycline based regimens with or without taxanes. Women receiving chemotherapy were significantly more likely to experience an adverse event from treatment, including treatment complications, hospital readmissions and treatment-induced menopause.

Women participating in the study were also representative of women in the ACT in general, in terms of marital status, ethnicity and employment status, although they were over-represented by the more highly educated. In terms of demographic differences between treatment groups, women in the no-chemotherapy group had more years of education than the chemotherapy group. There was a trend towards significance in the likelihood of more women receiving chemotherapy having less than 12 years of education, which is the educational factor found to most critically influence cognitive performance (Lezak et al., 2012). There was also a trend for the no-chemotherapy group to have higher estimated intelligence, although both groups were estimated to be on the border of the Average to High Average range. The neuropsychological assessment is an assessment of cognitive functioning rather than intelligence, with tests designed to assess impairment in these functions. However, the influence of individual factors, like age, intelligence and education on performance were assessed in the analyses where chemotherapy-related impairment was found. The breast cancer treatment groups did not differ significantly in any other demographic characteristics, including age, menopausal status, cancer history, non-English speaking country of origin, employment status or relationship status. Not surprisingly, the prevalence of clinical anxiety and depressive disorders was higher than in Australian women in general. The rates of depressive disorders were similar to women with early breast cancer although the rates of anxiety disorders were higher. However, there was no significant difference in the likelihood of having an anxiety or depressive disorder between treatment groups.
The next chapter outlines the statistical methodology used in the data analyses. Chapters 7 to 10 present the results of the group analyses and Chapter 11 presents the results of the individual analyses.
Statistical Methodology

This chapter outlines the statistical methodology used in the group and individual analyses presented in Chapters 7 to 11. The statistical analyses involved three main stages of analysis, including: a) descriptive analyses; b) principal components analyses and group analyses; and c) individual analyses. SPSS 20 was used to perform analyses on descriptive data and Genstat 13.2 and 14 was used to perform multivariate analyses and analyses of variance. While a confidence level was set at 95% ($p < 0.05$) for statistical significance for all analyses, clinical significance was examined by considering whether there was a consistent profile of impaired scores and scores that trended towards significance. The analyses were conducted in the following stages.

6.1 Data screening and standardization

1. Data was examined for extreme values and checked for data entry errors.

2. Data was examined for floor or ceiling effects.

3. All raw scores for cognitive outcome measures were converted to standardized $z$-scores using appropriate age norms from published test data, including repeated testing age norms where available, prior to analysis. This allowed average performance to be interpreted by normative performance ranges (see Section 6.7), as well as to be compared between groups.

6.2 Descriptive analyses

The analysis for descriptive data in Chapter 5 included t-tests and chi-square analyses.

1. For descriptive analyses using continuous data, t-tests were conducted where test assumptions were met.

2. For descriptive analyses using categorical data, chi-squared analyses were conducted. In $2 \times 2$ tables where an expected cell count was less than five, Fisher's two-sided exact test was used. In $2 \times >2$ analyses where an expected cell count was less than five, the exact test (two-sided) for Pearson's chi-square was selected. In all other cases, the two-sided asymptomatic Pearson's chi-square was used.
6.3 Exclusions

Outcome measures that involved contrast scaled score differences (z-score differences between two scores for an individual) were not included in the principal components analyses and subsequent group analyses as they use a different (contrast) scale to other measures and also demonstrated low reliabilities. They were considered in the individual analyses.

CANTAB RVP B" (B double prime) was excluded from all analyses on the following basis. Two of the outcome measures for the CANTAB Rapid Visual Information Processing test, a continuance performance test of sustained attention, are calculated using the principles of Signal Detection Theory (SDT), namely RVP A' (A prime) and RVP B" (B double prime). The CANTAB test administration guide states that "standard methodology of SDT allows for the analysis of the two main components of the decision making process, the acquisition of information and the criterion required for a response. In the case of RVP, the optimal pattern of response is to maximise sensitivity so that no targets are missed and such that no false alarms are committed."

The RVP B" (B double prime) is the signal detection measure of the strength of trace required to elicit a response (range -1.00 to +1.00). It measures the tendency to respond regardless of whether the target sequence is present and uses the probability of a 'hit' (the subject responding correctly), calculated from hits/ (hits + misses) and the probability of a false alarm (the subject responding inappropriately), calculated from total false alarms/ (total false alarms + total correct rejections). The calculation used for RVP B" is:

$$B'' = \frac{P(h)(1 - P(h)) - P(fa)(1 - P(fa))}{P(h)(1 - P(h)) + P(fa)(1 - P(fa))}$$

where P(h) is RVP Probability of hit, and P(fa) is RVP Probability of false alarm.

RVP test runs where:

1. there was at least one hit on an applicable target sequence and at least one miss; or
2. there was at least one false alarm and one correct rejection of a stimulus presentation during an applicable block.

As a result, this measure is undefined for 'perfect' test runs, where there are no misses and no false alarms. In this study there were nearly 5% 'perfect' test runs in the results over the course of the assessments that were undefined for the B" measure. Furthermore, a B" score close to +1.00 indicates that the subject gave few false alarms. However, a subject
who scored 100% hits with only one false alarm, had a value of $B^*$ calculated as -1.00 (minus one) and received a z-score of -11.35, indicating an extremely high tendency to respond regardless of whether the target sequence is present. This obviously does not correspond with this subject's actual performance profile. This outcome measure was eliminated for the purposes of the analyses.

6.4 Adjustments

The learning slope calculation was adjusted for two verbal learning measures prior to analysis on the following basis.

6.4.1 Adjustment to original learning slope calculation.

The CVLT-II estimate of learning rate is calculated from the total correct recall of words from List A over each of the first five trials, calculated with the formula below.

\[
Slope = \frac{\sum xy - \left( \frac{\sum x \sum y}{n} \right)}{\sum x - \left( \frac{\left( \sum x \right)^2}{n} \right)}
\]

where $x =$ trial, $y =$ total correct (per trial), and $n =$ number of trials in slope. The learning slope computes a least-squares regression that fits the total correct response score across the five immediate recall trials of List A. The slope of the regression line reflects the amount of new learning per trial. For instance, a learning slope of 1 indicates that an examinee is able to learn an average of one new word per trial.

Unfortunately, this means that the regression slope is affected by initial achievement on trial one (where high achievement, especially in repeated testing, often reflects the use of good learning strategies) and a ceiling effect (maximum 16 words).

As can be seen in Figure 6.1a, an initial low recall on trial 1 of four words is accompanied by a marked learning slope of 3.1 to achieve the ceiling of 16 words. The age standardized score for this slope is 2.5, reflecting performance within the Extremely High range.

In another example (see Figure 6.1b), a participant again displayed an initial low recall of four words on trial 1, improving in word recall over the next four trials to reach a maximum score of 14/16, receiving an age standardized score of 2.5, reflecting learning performance within the Extremely High range.
Figure 6.1. Individual learning curves ($z = 2.5$) on CVLT-2 List A (trials 1-5) correct word recall.

In comparison, in Figure 6.2a, the participant demonstrated an initial recall of 11 words, in the Well Above Average range, leading to a much flatter learning slope (of 1) due to the ceiling effect. The age standardized score for this slope is -1 which indicates learning in the Low Average range, even though this respondent demonstrated excellent learning, reaching the 16 word maximum by Trial 2.

Figure 6.2. Individual learning curves with the same CVLT-2 learning slope calculated raw score (slope=1) across List A (trials 1-5) correct word recall.

This learning profile is not consistent with the fairly flat learning slopes demonstrated by others with an equivalent CVLT-2 learning slope score (of 1). In Figure 6.2b the participant demonstrated poor initial recall of five words, with a fairly consistent increase...
in learning over the five trials, even though the number of words recalled by the 5th trial (9) was in the Low Average range.

In Figure 6.2c, the recall demonstrated by this participant on trial 1 is in the Average range and the trial 1-2 slope is in the High Average range but the respondent then reached a learning plateau of 12 words.

Finally, the learning curve in the profile in Figure 6.2d does not increase consistently, but fluctuates over trials, with initial recall in the Average range and a gain in the High Average range from trial 1-2, but then a decline over trials 2-4, with some recovery on trial 5 but no additional learning from trial 2.

a. Reports of ceiling effects.

Other studies have reported evidence of ceiling effects for some respondents when using the CVLT-2 (e.g., Stepanov, Abramson, Wolf, & Convit, 2010), especially in repeated testing. However, there has been little examination in the literature of the impact of this ceiling effect on the learning slope calculation used by CVLT-2 or any proposed alternative learning calculation to adjust for the ceiling. Stepanov et al. (2010) suggested these individuals should be treated as outliers and excluded, arguing that including these outliers might substantially disfigure the mean.

b. Adjustment of learning slope for ceiling effect.

In this study, in cases where there was evidence of a ceiling effect on learning i.e., at least two consecutive scores of 16 on CVLT-2 including Trials 4-5, the following adjustment was made to the learning slope calculation.

\[
Slope = \frac{\Sigma xy - \left( \frac{\Sigma x \Sigma y}{n_i} \right)}{\Sigma x - \left( \frac{\Sigma x}{n_i} \right)}
\]

where \( x \) = trial, \( y \) = total correct (per trial in List A before consecutive ceiling ie 16, 16 for CVLT-2), and \( n_i \) = number of individual trials in slope before consecutive ceiling. This learning slope calculation was used for the CVLT-2 and the Verbal Paired Associate (names) test.

This modification enables an individual learning slope to be calculated based on the regression slope over the trials prior to the plateau caused by the ceiling effect.

There were twelve trial 1-5 performances that demonstrated a ceiling effect, including Trials 4-5, on the CVLT-2. With the standard learning slope calculation, the standard
scores ranged from -1 to 2.5, with a mean of 0.8. After the adjusted learning slope calculation, these standard scores ranged from 0 to 5, with a mean of 2.8.

As the learning slope is also affected by initial performance, the trial 1 age-standardized score was added as a covariate in further analysis using learning slope calculations for the CVLT-2 and Verbal Paired Associates (names) test.

6.4.2 Verbal paired associates (names) age-corrected scores

Standard age-corrected z-scores were derived for the Verbal Paired Associate (names) test developed for this study by using two age categories (under/over 50 years at entry to study). Many cognitive abilities, including verbal learning and memory, have been shown to decline with normal ageing, peaking with neurological maturation in the mid 20s and declining gradually until the mid 60s, when a more rapid decline takes place (Kaufman & Horn, 1996). Fifty years was chosen as an age categorization to account for age-related cognitive changes in verbal associate learning (Shimamura, Berry, Mangels, Rusting, & Jurica, 1995).

6.5 Group analyses

The group analysis involved two stages. First, a series of multivariate Principal Components Analyses (PCA) were conducted to examine relative associations and meaningful groupings within each cognitive domain among dependent cognitive outcome measures. The first principal component summary score was used to derive summary scores of the overall domain and nested groupings within domains that were independent and meaningful groupings for further analysis. Analyses of variance (ANOVA) were then conducted to compare changes in performance between groups over time within each cognitive domain. The rationale and details of this approach are provided in the next section.

6.5.1 Principal Components Analysis

A comprehensive neuropsychological assessment typically produces multiple, partially overlapping outcome measures, and a consistent pattern of deficits can be used to establish specific areas of cognitive impairment. For each individual in the current study there were three assessments over time, and each assessment produced 125 dependent cognitive outcome measures derived from 24 tests that assessed performance within six cognitive domains. Any given domain, such as learning and memory or executive...
functions, is composed of potentially correlated sub-functions examining different cognitive processes. Testing individual differences in multiple outcome measures independently, at a given \( \alpha \) (critical threshold), increases the risk of incorrectly rejecting the null hypothesis, a Type I error, as more hypotheses are tested (Ingraham & Aiken, 1996). Controlling Type I error is further complicated by the intercorrelated outcomes prevalent in neuropsychological data (Miller & Rowling, 2001). In statistical terms, highly correlated measures are generally undesirable, reflecting multicollinearity and statistical redundancy. Most neuropsychological models, though, view cognitive functions as represented by related patterns of brain activity and behaviour, and in large neuropsychological data sets, groups of outcome measures often are highly correlated.

Alternative data analytic approaches to control Type I error for neuropsychological data are often limited to: a restricted set of measures; taking the average of scores within a domain; global indices; or by making adjustments, such as standard \( p \) value adjustment methods like Bonferroni, that can increase the risk of genuine relationships going undetected (Type II error).

One way to address the statistical limitations outlined above in neuropsychological data is to use Principal Components Analysis (PCA) (Abdi & Williams, 2010). This is a quantitatively rigorous multivariate statistical method that capitalizes on the intrinsic multicollinearity within related measures in order to reduce the dimensionality of a complex data set and reveal the simplified structure that often underlies it. This method can be used to generate a new, smaller set of variables, called principal components, that retain much of the information and variation of the original data set. PCA is used extensively in data analysis, from breast cancer detection (Ertas, Doran, & Leach, 2011) to gravitational wave physics (Rover et al., 2009), and from neuroscience (Chapin & Nicolelis, 1999) to neuropsychology (Levin et al., 2013).

In PCA, the first principal component is the linear combination of the original variables that accounts for the maximum shared variance in the original data set. The second principal component accounts for as much of the remaining variation as possible and is uncorrelated with the first principal component and the other components are computed likewise. A plot of the latent vector loadings of each measure, represented as vectors, on the first two principal components (a biplot) provides a spatial and statistical representation of the associations between measures. The angles between vectors represent the correlations between measures so the narrower the angle, the more closely associated are the measures. Examination of the biplot, along with the latent vector loadings, highlights any nested natural groupings. Orthogonal groupings indicate measures that behave independently of each other. This process can be used to guide and
derive an optimum smaller number of principal component summary measures for further analysis. Principal components analysis thus provides an economic and efficient way to reduce dimensionality in complex neuropsychological data in a way that minimizes Type I error.

6.5.2 Different approaches using PCA

Both Ahles et al. (2010) and Collins et al. (2013) have used PCA to derive cognitive domain summary scores. However, the approach used in the current study differed from that used in both of these studies. For example, in the Ahles study a selected group of 35 outcome scores produced from the tests across all domains were entered into one PCA analysis. From this a corresponding number of principal components are produced (i.e., 35) and nine of these were selected and interpreted for use in further analysis. The first principal component score was interpreted as a summary score of overall cognitive performance and the eight following principal components scores were interpreted as domain summary scores. However, test measures often load on multiple principal components so interpreting principal components as separate cognitive domains can be difficult and later principal components can often represent noise in the data. For example, if all neuropsychological measures across different domains are entered into a principal components analysis then the first principal component can be argued to be a summary measure of the main underlying association between these measures. This may be interpreted as a summary measure of global intellectual functioning. However, it is harder to interpret the second principal component that by definition is independent of the first principal component. What is uncorrelated or independent of global intellectual functioning? The literature would suggest that no cognitive domain is entirely independent of this, calling into question the interpretation of any principal component beyond the first principal component summary score.

6.5.3 The PCA approach used in the current study

Another approach to PCA that is advocated is to group test measures a priori into domains based on the literature and to conduct a PCA on these scores and use the first principal component score to obtain a domain summary score (Scott, Eccles, Lloyd, & Carpenter, 2008). The first principal component summary score represents the underlying association between the measures within the domain. However, this does not provide any profile of functions that may behave differently on other dimensions within the domain. In order to determine whether measures within the domain are behaving consistently, the PCA biplot and latent vector loading of measures on the first two principal components are examined for any evidence of further distinct natural groupings. These groupings can
then be considered based on meaningful associations and consistency with the literature. Using the biplot and latent vector loadings for evidence of meaningful nested groupings, and using the first principal component score to derive a summary score for each distinct grouping for use in further analysis can help to build a neuropsychological profile across and within domains.

The approach used in this study was to categorize outcome measures according to domains based on the literature initially, confirmed by the PCA domain biplots. Individual scores at each timepoint were included on a wider variety of outcome measures within the PCA for each domain. Principal Components Analysis works best at finding underlying dimensions in larger datasets where there are meaningful associations, by maximizing multivariate similarities and differences within a set of variables. Where independent groupings were evident from the biplot of the measures on the first two principal components, these groupings were assessed separately via additional PCAs and the biplots were examined for evidence of further meaningful nested groupings. The first principal component score was used to capture and summarize the underlying association in each grouping of measures and only this first principal component summary score was used in further analysis. This method was considered an economic and efficient way to detect and describe the major relationships and patterns in rich, complex neuropsychological data in a way that maximizes power while minimizing Type I error.

Measures were initially grouped within cognitive domains based on their established performance in the literature (see Chapter 3.4.7 Neuropsychological Measures). Where outcome measures have been found to measure features of more than one domain, separate PCAs were conducted with the measure concerned included with measures from each of the respective domains. Examination of the biplots and latent vector loadings was used to determine whether the measure behaved more consistently with other measures in a given domain and guide in which domain to include the measure.

Once domain measures were determined, PCA was used to examine the entire set of relationships among neuropsychological outcome measures within a cognitive domain to identify:

1. the underlying dimensions that explain the correlations among the set of variables;
2. a smaller set of important summarized neuropsychological outcome variables from the larger set to use in subsequent analysis.
6.5.4 Group analysis procedure

The procedure used in the group analyses is outlined in Figure 6.3. Principal components analyses were used to derive summary scores for the domain and any nested groupings and subgroups within the domain. The first principal component summary scores were used in subsequent analyses of variance. Where there was a significant (or trend towards significant) Group × Time interaction effect or Time effect (reflecting a significant decline in performance) or Group effect (reflecting the chemotherapy group performing significantly worse than the no-chemotherapy group), regression analyses were conducted to identify any significant risk factors for cognitive impairment or decline.

![Flowchart for the procedure used in the group analyses.](image)

The analysis was conducted in the following steps:

1. All standardized outcome measures were categorized into cognitive domains based on Lezak et al. (2012). Where an outcome measure has been found to measure aspects of more than one domain in the relevant literature, that measure was entered into separate PCAs with the measures from each domain. The biplots from each PCA were examined to determine in which domain this measure more closely associated with other measures. Where it behaved more consistently with other measures, it was included with the measures in that domain analysis.

2. Principal components analysis was conducted on all age-standardized outcome scores for all individuals at each timepoint on all measures within a domain, adjusted for variance between measures using a correlation matrix. The use of a
correlation matrix is recommended, even when scores are standardized, if original variables do not share a common scale and have different distributions.

3. The first principal component score was then extracted as the summary score for this grouping for use in subsequent analysis using ANOVA (see Step 7).

4. The biplot and latent vector loadings of all measures on the first two principal components were examined for evidence of natural independent groupings. Where independent groupings were evident, additional PCAs were conducted on each of these groupings and the first principal component score was then extracted as the summary score for this grouping for use in subsequent analysis. Interpretative labels were proposed for these summary scores.

5. Step 4 was repeated for each major grouping to assess for evidence of nested independent groupings. Where independent groupings were evident with internal consistency that were meaningful based on the literature, additional PCAs were conducted on each of these groupings. A subgroup is a grouping that did not display evidence of further independent groupings. The first principal component score was then extracted as the summary score for this subgroup for use in subsequent analysis.

6. Missing values for each summary score were examined and assessed. These are reported in detail by cognitive domain in Section 6.5.6.

7. An Analysis of Variance (ANOVA), accounting for variation between and within subjects, was performed on each first principal component (summary) score. This was conducted in Genstat using General ANOVA by including ID as the Block Structure and ‘Group+Time+Group.Time’ as the Treatment Structure. This approach has advantages over repeated measures ANOVA. While still accounting for between and within subject variation, casewise deletion of missing observations is not necessary, allowing for the analysis of all available data. Furthermore, the mean values from the Genstat ANOVA included the imputed values predicted from the model.

8. Plots of the residuals against the fitted values were examined for violation of the homogeneity of variance assumptions to identify measures needing transformation.

9. Where there was a significant main or interaction effect, post-hoc comparisons using the Least Significance Difference (LSD) test were performed to isolate the pairwise means that were significantly different.
10. The performance profiles, meaning the slopes for each Group over Time, were compared between the overall summary score and each of the major groupings to examine which performance profile was most consistent with the domain summary score and whether the p value profiles were also the same. This exploratory examination of performance patterns was conducted because the domain summary score is not simply a summation or average of all the summary scores of the major groupings but represents an underlying dimension shared across domain measures. This indicates whether domain performance was dominated by one grouping i.e., where the performance profiles and p value profiles were the same. Where the performance profiles were the same but the p value profiles were different, this indicates key influences from other groupings to the overall domain p value profile. The p values for individual ANOVAs of the summary score for the domain (name italicized) and each major grouping were presented in summary tables. Finally, the performance profile of the group that was least consistent with the domain performance profile was identified and compared.

11. The performance profiles of each major grouping and their nested subgroups were compared as in Step 10 and the p values for individual ANOVAs on the summary score for each grouping and subgroups were compiled into summary tables. It is worth noting that as the subgroups are made up of only closely associated variables the first principal component scores accounts for more of the variance than at higher levels. Finally, each of the subgroups was compared to the individual measures that contributed to that grouping as in Step 10. The name of the summary grouping is displayed in italics in the figures and table. (Details of the ANOVAs for individual measures are outlined in Step 15).

12. Where there was a significant Group by Time interaction effect or a trend towards significance a regression analysis was conducted to determine which women were more vulnerable to decline. A regression model involving forwards stepwise selection was used to identify potential explanatory variables for change scores (Time 3 - Time 1), controlling for Time 1 baseline scores. A general linear regression was then conducted with up to six explanatory variables. Variables that significantly predicted or were significantly associated with cognitive decline at Time 3 are reported. This process was also conducted for significant Time effects where there was a significant decline in performance. If the decline was only between two time-points (e.g., Time 1 and Time 2) the regression was conducted on change scores calculated between those time-points, controlling for Time 1
scores. Where a Group effect was observed that involved the chemotherapy group performing significantly worse than the no-chemotherapy group a regression analysis was conducted on Time 1 scores with potential baseline explanatory variables in the regression model.

13. Within the regression model analyses the potential explanatory variables for cognitive change scores (Time 3 - Time 1) included: baseline characteristics, such as individual characteristics (age, premorbid IQ, years of education); cancer characteristics (cancer stage, tumour size); surgery characteristics (number of general anaesthetics, mastectomy); and expectation of cognitive decline. The association of change variables (Time 3 - Time 1) with decline at Time 3, controlling for Time 1 scores, was also assessed, including: psychological characteristics (clinical anxiety disorder, clinical depressive disorder, any clinical diagnosis, HADS anxiety scores, HADS depression scores, emotional wellbeing); QOL (physical wellbeing and role functioning, stress/somatic symptoms); treatment change (hormonal therapy, taxane-based regimen, more general anaesthetics); adverse events (readmission to hospital, neutropenia, treatment-induced menopause); and self-reported cognitive problems (overall, mental fatigue, retrospective and prospective memory, expectation of decline). The influence of the presence of a clinical anxiety or mood disorder at Time 3 on cognitive decline at Time 3 was also included in potential variables.

14. For significant Time effects where the decline was only between two time-points (e.g., Time 1 and Time 2) change scores were calculated for explanatory variables between those time-points, controlling for Time 1 scores. Where a Group effect was observed that involved the chemotherapy group performing significantly worse than the no-chemotherapy group baseline explanatory variables were included in the regression model.

15. Individual ANOVAs, adjusted for between and within subject variation, were conducted on all individual outcome measures.

16. Plots of the residuals against the fitted values were examined via ANOVA for violation of the homogeneity of variance assumptions to identify variables needing transformation. Variables were transformed and individual ANOVAs performed again where necessary. Four variables were transformed using a natural logarithmic transformation (with scores reflected before and after transformation) and individual ANOVAs performed again.
17. The p values for ANOVAs of individual measures and the first principal component score for each grouping within each cognitive domain were compiled into summary tables and figures are included in the Appendices (C-G).

6.5.5 Health-related quality of life summary measures

All 23 self-reported measures of HRQL were entered into a PCA. This was done to create a smaller set of key HRQL measures to use as potential explanatory variables in the regression analyses. Three distinct groupings were evident in the biplot with measures relating to a) physical wellbeing and role functioning b) emotional wellbeing and c) stress/somatic symptoms. Further PCAs were conducted on the measures in each group. The first principal component accounted for: 47% of the variance in the physical wellbeing and role functioning measures; 63% of the variance in the emotional wellbeing measures; and 40% of the variance in the stress/somatic symptom measures. The first principal component for each group of measures was used as a summary score in regression analyses of possible risk factors.

6.5.6 Missing values

a. Language, Motor and Visuoconstruction

The Language summary scores included 1% (n = 2) missing values, as did the Visuoconstruction (i.e., Complex Figure Copy accuracy) scores. This represented the missing data for the Time 1 and Time 3 assessment where individuals (n = 2) were unable to attend (one due to death).

The Motor summary scores included 4% (n = 5) missing values. This included the missing data (1.45%) where individuals (n = 2) were unable to attend, as well as 2.55% from other items, where individuals (n = 3) could not complete the whole assessment due to other appointments. Two of these could not complete Time 1 assessments due to a scheduled medical appointment, with one in the chemotherapy group and one in the no-chemotherapy group. All missing values in follow-up assessments (Time 2 (n = 1)) were in the chemotherapy group, also due to a medical appointment (i.e. radiation treatment). In cases where participants had to leave early, the investigator shortened the assessment with the Big Little Circle test (a screening measure) (n = 3) being the only test that was eliminated which contained a measure of motor accuracy speed.
b. Attention

Eighty-seven percent of participants \((n = 40)\) had complete data for attention and speed of processing. Of the 138 attention and speed of processing summary scores dataset, there were 5\% \((n = 7)\) missing values. This included the missing data (1.45\%) for the Time 1 and Time 3 assessment where individuals \((n = 2)\) were unable to attend, as well as 3.55\% from other items, where individuals could not complete the whole assessment due to other appointments. Seven of these could not complete Time 1 assessments due to a scheduled medical appointment, with the majority \((n = 5)\) in the chemotherapy group. All missing values in follow-up assessments \((Time 2 (n = 1); Time 3 (n = 2))\) were in the chemotherapy group, also due to a medical appointment (i.e. radiation treatment), with two of these having also not fully completed their Time 1 assessment. In cases where participants had to leave early, the investigator shortened the assessment, as needed, with the Spatial Recognition Memory Test (the final test in the assessment battery) \((n = 5)\) being the only test that was eliminated which contained a measure of speed of processing. Therefore, the attention and speed of processing summary scores included 5\% \((n = 7)\) missing values; the speed of processing summary scores included 5\% \((n = 7)\) missing values; and the attention summary scores included 1.45\% \((n = 2)\) missing values.

c. Learning and Memory.

Seventy-eight percent of participants \((n = 36)\) had complete data for learning and memory. Of the 138 learning and memory summary scores dataset, there were 8.7\% \((n = 12)\) missing values. This included the missing data (1.45\%) for the Time 1 and Time 3 assessment where individuals \((n = 2)\) were unable to attend, as well as 7.25\% from other items, where individuals could not complete the whole assessment due to other appointments. Of these, seven could not complete Time 1 assessments due to a scheduled medical appointment, with the majority \((n = 5)\) in the chemotherapy group. All missing values in follow-up assessments \((Time 2 (n = 1); Time 3 (n = 2))\) were in the chemotherapy group, also due to a medical appointment (i.e. radiation treatment), with two of these having also not fully completed their Time 1 assessment. In cases where participants had to leave early, the investigator shortened the assessment, as needed, by eliminating tests in the following order: 1) the Verbal Paired Associates (names) test (a new test) \((n = 10)\); 2) the Spatial Recognition Memory Test (the final test in the assessment battery) \((n = 5)\); 3) a randomly selected other test \((n = 3)\). Therefore, the verbal learning and memory summary scores included 1.45\% \((n = 2)\) missing values; the verbal primacy/recency recall and recall errors summary scores also included 1.45\% \((n = 2)\) missing values; and the
paired associates learning and visual recall summary scores included 8.70% (n = 12) missing values.

d. Executive Functions

Eight-five percent of participants (n = 39) had complete data for executive functions. Of the 138 executive function summary scores dataset, there were 5.8% (n = 8) missing values. This included the missing data (1.4%) for the Time 1 and Time 3 assessment where individuals (n = 2) were unable to attend, as well as 4.4% from other items, where individuals could not complete the whole assessment due to other appointments. Four of these could not complete Time 1 assessments, with the majority (n = 3) in the chemotherapy group. All missing values in follow-up assessments [Time 2 (n = 1); Time 3 (n = 1)] were in the chemotherapy group, due to a medical appointment (i.e. radiation treatment), with one also having not fully completed their Time 1 assessment. In cases where participants had to leave early, the investigator shortened the assessment as needed by eliminating longer executive function tests in the following order: 1) a test of verbal reasoning (n = 6); 2) the Intra-Extra Dimensional Set Shift test (n = 3). Therefore, the executive functions summary scores included 6% (n = 8) missing values; the verbal executive summary scores included 6% (n = 8) missing values; the visual executive summary scores included 3.6% (n = 5) missing values; and the visuospatial planning and copy summary scores included 1.4% (n = 2) missing values. The mean values from the analyses of variance include the imputed values predicted from the model.

The mean values from each of the analyses of variance include the imputed values predicted from the model.

6.6 Individual analyses

Individual analyses were conducted to explore signs of cognitive complications and lower than expected performance.

6.6.1 Cognitive complications

All individual cognitive outcome age-standardized z-scores were screened for very low scores ('cognitive complications') within each domain. Cognitive complications were defined as a score more than two standard deviations from the mean of published normative test data (z-score < -2). The analysis was conducted in the following steps:

1. The number of cognitive complications found across measures within each domain was collated for each individual at each timepoint. The percentage of individuals
displaying cognitive complications at *Time 1* was then compared between groups for each domain.

2. The proportion of individuals displaying more, less or the same amount of complications both at *Time 2* and *Time 3* relative to *Time 1* was compared between groups for each domain. Where there was a significant difference in the proportions of individuals displaying more complications between groups, the pattern of complications on individual measures within the relevant domain was examined for signs of a profile of impaired scores.

3. Individuals were identified who displayed more complications on domains that displayed proportional group differences. Selected demographic, psychological, cancer and treatment variables were dichotomized and entered into chi-square analyses and examined for associations that might increase individual risk of experiencing more cognitive complications. Potential explanatory variables included baseline characteristics: age (>50), education (<12 years), cancer stage (≥2) and tumour size; wellbeing characteristics (clinical anxiety, clinical depression, emotional wellbeing, physical wellbeing and role functioning; stress/somatic symptoms); treatment characteristics (number of anaesthetics, type of surgery, hormonal therapy, radiotherapy, taxane-based chemotherapy regimen); adverse events (neutropenia, readmission to hospital, treatment-induced menopause) and self reported cognitive problems.

### 6.6.2 Lower than expected performance

In line with widely accepted clinical practice, all individual cognitive outcome scores were compared to the individual’s estimated ability score to identify scores that fell below expected ability. This ability score was estimated from the National Adult Reading Test - 2nd edition (NART-2) (Nelson & Willison, 1991), a test that has been found to be resistant to the disrupting effects of brain injury and is widely used in clinical practice to estimate prior level of functioning and premorbid IQ. The NART-2 was conducted at the initial assessment as well as *Time 3*. There was a strong, positive Pearson pairwise correlation between these individual predicted IQ scores, \( r(43) = 0.957, p < .001 \). There was no significant difference found between the average first predicted IQ score \( (M = 109.8, SD = 9.18) \) and the second \( (M = 111.2, SD = 8.68) \), \( t(88) = -0.73, p = 0.466 \). A recent prospective study examined NART scores administered to 214 adults within one month of a traumatic brain injury and again at 6 and 12 months (Skilbeck, Dean, Thomas, & Slatyer, 2013). The NART scores from shortly after the traumatic brain injury were found to significantly underestimate premorbid IQ. As the initial assessment in the current study was conducted...
shortly after surgery, where some participants had received multiple general anaesthetics, the decision was made to select the highest of the two NART-estimated IQ scores for each individual as their estimate of premorbid IQ. The analysis was conducted in the following steps.

1. All individuals were identified who displayed performance that was lower than expected, defined as one and a half standard deviations or more below their own estimated premorbid IQ score. An overall 'lower than expected performance' score was then calculated for each individual at each timepoint from the mean of all scores that were ≤1.5 SD below their estimated premorbid IQ (converted to a z-score). This criterion was set in response to concerns outlined by Lezak et al. (2012, p. 171) that too many individuals who are intact will be judged impaired when using -1 SD as an impairment criterion from estimated premorbid functioning but that -2 SD can become overly strict so that truly impaired performance is judged normal.

2. An ANOVA was conducted to compare overall lower than expected performance between groups over time, accounting for variation between and within subjects.

3. A regression model analysis was conducted to examine the influence of possible risk factors. Model assumptions were assessed by means of residual analyses. An ANOVA was conducted to compare overall lower than expected performance between groups over time, accounting for variation between and within subjects. Model assumptions were assessed by means of residual analyses. A regression model involving forwards stepwise selection was used to identify potential explanatory variables for lower than expected performance change scores (Time 3 - Time 1), controlling for Time 1 baseline scores. A general linear regression on change scores was conducted to identify significant risk factors for decline.

4. Potential explanatory variables included baseline individual differences, including age, education, cancer stage and tumour size. Several interaction terms were entered as fixed factors to adjust for covariance, including; wellbeing (clinical anxiety, clinical depression, the summary score for emotional wellbeing, physical wellbeing and role functioning; stress/somatic symptoms); treatment (number of anaesthetics, type of surgery, hormonal therapy, radiotherapy, taxane-based chemotherapy regimen); adverse events (neutropenia, readmission to hospital, treatment-induced menopause) and self reported cognitive problems.
6.7 Classification of performance levels

The reporting of test performance by the use of standard scores in reference to the normal population and of descriptive terms that refer to a classification range is a standard practice in neuropsychology. Lezak (2012) advises that one way to avoid the many difficulties inherent in test score reporting is to describe test performances in terms of the commonly accepted classification of ability levels developed by Wechsler (1958). In the standard Wechsler classification system, each ability level represents a defined range of IQ scores, as shown in Table 6.1. The Wechsler standard IQ is expressed as deviation units from the norm, with a mean of 100 and a standard deviation of 15.

The Wechsler classification descriptive terms have attempted to become more value-neutral with revisions. The term 'Extremely Low' was substituted for 'Mentally Retarded' on the WAIS because this “avoids the implication that a very low IQ score is sufficient evidence for the classification of 'mental retardation'” (Wechsler, 1981). However, even terms like 'superior' can be seen as value-laden.

Table 6.1

<table>
<thead>
<tr>
<th>Early Classification</th>
<th>Current Classification</th>
<th>IQ</th>
<th>Lower Limit of Percentile Range</th>
<th>Z-score range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very superior</td>
<td></td>
<td>≥130</td>
<td>98</td>
<td>≥2</td>
</tr>
<tr>
<td>Superior</td>
<td></td>
<td>120 to 129</td>
<td>91</td>
<td>1.3 to 2.0</td>
</tr>
<tr>
<td>Bright normal</td>
<td>High Average</td>
<td>110 to 119</td>
<td>75</td>
<td>0.6 to 1.3</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>90 to 109</td>
<td>25</td>
<td>+/−0.6</td>
</tr>
<tr>
<td>Dull normal</td>
<td>Low Average</td>
<td>80 to 89</td>
<td>9</td>
<td>−0.6 to −1.3</td>
</tr>
<tr>
<td>Borderline</td>
<td></td>
<td>70 to 79</td>
<td>2</td>
<td>−1.3 to 2.0</td>
</tr>
<tr>
<td>Defective/Retarded</td>
<td>Extremely Low</td>
<td>≤69</td>
<td>-</td>
<td>≤−2.0</td>
</tr>
</tbody>
</table>

Descriptive labels and classification ranges have been used in the reporting of the study results that were considered more consistent with the normal distribution and more value-neutral. These labels and classifications are presented in Table 6.2.
Table 6.2

Study Classification of Performance Range

<table>
<thead>
<tr>
<th>Classification</th>
<th>Z-score range</th>
<th>Lower Limit of Normative Percentile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely high</td>
<td>+2 and above</td>
<td>98</td>
</tr>
<tr>
<td>Well above average</td>
<td>+1 to 2</td>
<td>84</td>
</tr>
<tr>
<td>High average</td>
<td>+0.5 to 1</td>
<td>69</td>
</tr>
<tr>
<td>Average</td>
<td>+/- 0.5</td>
<td>31</td>
</tr>
<tr>
<td>Low average</td>
<td>-0.5 to -1</td>
<td>16</td>
</tr>
<tr>
<td>Well below average</td>
<td>-1 to -2</td>
<td>2</td>
</tr>
<tr>
<td>Extremely low</td>
<td>-2 and below</td>
<td>-</td>
</tr>
</tbody>
</table>

6.8 Chapter Summary

This chapter presented the statistical methodology used in the current study for the analyses of cognitive changes between treatment groups and the assessment of possible mechanisms for impairment or decline. It also presented the statistical approach to the analyses of individual deficits and outlined the classification of performance levels that is used in the reporting of results. The following chapter presents the results of the analysis of cognitive changes associated with treatment in language, motor and visuoconstruction.
7.1 Introduction

The primary aim of this study concerned the possible negative effects of chemotherapy on cognitive changes in women with early breast cancer treated with chemotherapy compared to women not treated with chemotherapy. The neuropsychological assessment was designed to assess changes within six domains of cognitive functioning (see Figure 7.1). These were the primary verbal and nonverbal domains of language, motor and visuospatial construction (visuoconstruction), and the 'higher' order domains of attention and speed of processing, learning and memory, and executive functions.

Entry of information into the central processing system proceeds from sensory stimulation (verbal, visual, auditory, motor) to integration of sensory inputs, which are then accessed by higher order cognitive domains (Lezak, et al., 2012). Within these cognitive domains there are sub-functions that mediate verbal information and those that deal with information that is not communicated in words, such as visual input or sound patterns, as well as information mediated by motor skills. Therefore, it is important to assess these primary verbal and nonverbal domains independently. This helps to assess whether any impairment found in 'higher' order domains is due to an underlying impairment in fundamental language, motor or visuoconstruction skills. This chapter presents the results of a brief assessment of these abilities. Following chapters provide a
more comprehensive assessment of changes between groups over time within Attention and Speed of Processing (Chapter 8), Learning and Memory (Chapter 9) and Executive Functions (Chapter 10). This is followed by an analysis of individual deficits (Chapter 11).

7.2 Language

The primary outcome measure that was used to assess changes in language skills was the CANTAB Graded Naming Test (Cambridge Cognition, 2005; Warrington, 1997), a measure of confrontation naming and language abilities (Lezak, et al., 2012) (for more details see Chapter 3.4.7b). Another measure that also assesses naming was the speed of colour naming from the D-KEFS Color Word Interference test (D.C. Delis, et al., 2001a).

The ability to access words from one's lexicon is a key component of language processing and production. One means of studying and evaluating lexical access involves using measures of category or semantic fluency (e.g., Laws, 2004). Given this, the outcome measure of category fluency from trial 2 of the D-KEFS Verbal Fluency test was entered into a PCA with the Language domain measures. It was also entered into a separate PCA with measures from the Executive Functions domain in which it is often classed (Lezak, et al., 2012). The biplots from each PCA were examined to determine in which domain this measure was more closely associated with other measures. As it behaved more consistently with the language measures, assessed via the biplot and latent vector loadings, it was included in the language analysis.

The procedure used in the analysis is the same as described previously (in Chapter 6.5.4). Ninety-six percent of participants (n = 44) had complete data for language. Missing values were examined and assessed (for details see Chapter 6.5.6) and mean values from the analysis of variance included the imputed values predicted from the model.

A PCA was performed on data from the three outcome measures of language\(^7\). The first principal component accounted for 42\% of the variance in these measures. An ANOVA was performed on the first principal component score\(^8\).

As shown in Figure 7.2 the language performance profile (i.e., the slopes) of both treatment groups was similar over the course of the assessments, improving from Time 1 to Time 2 and then deteriorating at Time 3, although not below initial performance. There was no significant Group by Time interaction effect \([F(2,86) = 0.16, p = 0.849]\). This means

\(^7\) The latent vector loadings of language measures on the first two principal components are presented in Table C2 in Appendix C, p. C3.

\(^8\) The Language summary scores included 1\% (n = 2) missing values.
there was no significant change in language performance directly associated with chemotherapy.

![Graph showing mean summary score for language over time by treatment group.]

**Figure 7.2.** Means of summary score for language over time by treatment group.

*Time 1* = Post-surgery (pre-chemotherapy); *Time 2* = 6 months from *Time 1* (post-chemotherapy); *Time 3* = 15 months from *Time 1* (= 9 months post-chemotherapy).

There was a statistically significant main effect of *Time* \[F(2,86) = 7.54, p < .001\] reflecting a significant improvement in language performance across both groups from *Time 1* \((M = -0.240)\) to *Time 2* \((M = 0.223)\) followed by a significant deterioration from *Time 2* to *Time 3* \((M = -0.024)\) \((PD^9 > LSD = 0.237, \text{ at a 95\% confidence level})\). There was a trend approaching significance for a *Group* effect, indicating that the chemotherapy group displayed poorer language performance than the no-chemotherapy group over time \([F(1,44) = 3.33, p = 0.075]\).

As there was a significant unexpected decline in language performance between *Time 2* and *Time 3*, a regression model involving forwards stepwise selection was used to identify potential explanatory variables for language change scores \((Time 3 - Time 2)\), controlling for *Time 1* baseline scores. A general linear regression revealed that women (from both groups) who commenced hormonal therapy at *Time 2* were at greater risk of decline in language performance at *Time 3* \((p = 0.004)\).

---

9 Pairwise mean differences (PD) were compared to the least significant difference of means (LSD).
This performance profile was most consistent with the individual measure Category Fluency correct (see ‘VFctcz’ in Appendix C, p.C4) and the p value profiles were also the same. As shown in Table 7.1, both displayed a significant main effect of Time but not of Group, and there was no significant interaction effect. The language performance profile was least consistent with Colour naming speed where there was a cross-over of slopes at Time 2 but performance was the same at Time 3 (see ‘cwcnz’ in Appendix C, p.C4).

Table 7.1

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>Verbal</td>
<td>0.075</td>
<td>&lt;.001***</td>
<td>0.849</td>
</tr>
<tr>
<td>CWI Colour naming speed</td>
<td>Verbal</td>
<td>0.879</td>
<td>0.312</td>
<td>0.729</td>
</tr>
<tr>
<td>VF Graded Naming Test correct</td>
<td>Verbal</td>
<td>0.185</td>
<td>&lt;.001***</td>
<td>0.843</td>
</tr>
<tr>
<td>VF Category Fluency Correct</td>
<td>Verbal</td>
<td>0.083</td>
<td>0.004**</td>
<td>0.909</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).

7.3 Motor skills

The primary outcome measures employed to assess motor skills were the CANTAB Reaction Time (Simple and Five-Choice) movement times (Cambridge Cognition, 2005) that measure motor speed – defined as the time in milliseconds it takes to touch the stimulus on the touchscreen after the press pad button has been released (for more details see Chapter 3.4.7c). Other measures of motor speed and accuracy included the CANTAB Motor Screening Test Mean latency and Mean error outcome measures that are designed to screen for problems in vision and movement (Cambridge Cognition, 2005). Latency on this test is defined as the time in milliseconds it takes to touch the stimulus (a cross) on the touchscreen after it is presented, for the ten crosses presented to which the subject correctly responded. Error is defined as the accuracy of pointing measured by the mean distance in 'pixel units' between the centre of the cross and the location the subject touched on the screen.

The CANTAB Big Little Circle is a simple test of attention and visual discrimination designed to screen basic visual discrimination, attention, learning and reversal capacity before undertaking the Intra-Extra Dimensional Set Shift task (Cambridge Cognition, 2005). The CANTAB Big Little Circle mean correct latency outcome measure assesses the time in milliseconds it takes to touch the correct circle on the touchscreen after it is
presented. This measure was examined using separate principal components analyses with the Attention domain measures, due to the simple discrimination component, as well as with the Motor domain measures. As it behaved more consistently with the Motor measures, it was included in the Motor analysis.

A PCA was performed on data from these five outcome measures\(^\text{10}\). The first principal component accounted for 40% of the variance in these measures. An ANOVA was performed on the first principal component score\(^\text{11}\).

![Graph](image)

**Figure 7.3.** Means of summary score for motor skills over time by treatment group.

Both groups performed very similarly in motor performance across the assessments, improving at *Time 2* and then plateauing at *Time 3*, all within the *Average* range, as shown in Figure 7.3. There was no significant *Group* by *Time* interaction effect \(F(2,86) = 0.13, p = 0.883\) or main effect of *Group* \(F(1,44) = 0.00, p = 0.959\) on performance.

There was a statistically significant main effect for *Time* \(F(2,86) = 7.06, p = 0.001\) reflecting a significant improvement in motor performance from *Time 1* \((M = -0.404)\) to both the *Time 2* \((M = 0.195)\) and *Time 3* \((M = 0.231)\) follow up assessments \(\text{PD}>\text{LSD} = 0.3799\), at a 95% confidence level. This was consistent with a practice effect. However, there was no significant difference in this change over time between treatment groups.

\(^{10}\) The latent vector loadings of motor skill measures on the first two principal components are presented in Table C5 in Appendix C, p. C6.

\(^{11}\) The Motor summary scores included 4% \((n = 5)\) missing values.
This profile of summary score performance was most consistent with the individual measure 5-choice movement time (see ‘cRTI5mtz’ Appendix C, p.C7) and the p value profiles were also the same, as shown in Table 7.2. Both the summary score and 5-choice movement time displayed a significant Time effect but not a significant Group effect or a Group by Time interaction. The pattern of Motor summary performance was least consistent with the individual measure Motor Screening mean movement errors (see ‘bMOTMEza’ in Appendix C p.C7). On this individual measure the performance of the chemotherapy group was higher than the no-chemotherapy group across time but deteriorated below initial performance at Time 3, while the performance of the no-chemotherapy group remained the same.

Table 7.2

<table>
<thead>
<tr>
<th>Name</th>
<th>Verbal/ Motor</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor skills</td>
<td>Visual-motor</td>
<td>0.972</td>
<td>&lt;.001***</td>
<td>0.983</td>
</tr>
<tr>
<td>aBLC mean correct latency</td>
<td>Visual-motor</td>
<td>0.923</td>
<td>&lt;.001***</td>
<td>0.199</td>
</tr>
<tr>
<td>bMOT mean errors</td>
<td>Visual-motor</td>
<td>0.170</td>
<td>0.070</td>
<td>0.275</td>
</tr>
<tr>
<td>bMOT mean latency</td>
<td>Visual-motor</td>
<td>0.936</td>
<td>0.262</td>
<td>0.834</td>
</tr>
<tr>
<td>cRTI 5-choice mean movement time</td>
<td>Visual-motor</td>
<td>0.752</td>
<td>0.016*</td>
<td>0.959</td>
</tr>
<tr>
<td>cRTI Simple mean movement time</td>
<td>Visual-motor</td>
<td>0.824</td>
<td>0.005**</td>
<td>0.834</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; **p <0.01; *** p<.001 (boldface).

7.4 Visuoconstruction skills

The primary outcome measure employed to assess visuoconstruction skills was the total correct score from the Copy trial of the Complex Figure Test, a well established measure of visuoconstructional accuracy. The Complex Figure test consists of a complex geometric figure that the examinee is asked to copy as well as they can under no time limit. The complex figure developed by Rey (1941; reproduced in (Meyers & Meyers, 1995) was used at Time 1 and Time 3. The modified Taylor Complex Figure (Hubley & Tremblay, 2002) was used at Time 2 as an alternate form to minimize practice effects. It has been shown in several studies to produce comparable results to the Rey Complex Figure (Hubley & Jassal, 2006). Each copy drawing was scored according to explicit standardized criteria for accuracy and placement of the 18 elements.
The ranges of the Copy accuracy score in the normative data are restricted due to the maximum or near maximum level of performance attained by most normal subjects. For example, 70.7% of subjects in the normative sample used by Meyers and Meyers (1995) for scoring the Rey Complex Figure obtained Copy raw scores of 35.0 or greater (maximum score = 36.0). The manual uses percentile range categories to standardize the Copy raw score (i.e., >16, 11-16, 6-10, 2-5, ≤1) using age-corrected normative tables. For the study purposes, the Copy raw score was standardized as a z-score using age-adjusted normative data published in the manual. Examination of the residual plot displayed fanning of the residuals so the standardized scores were transformed using a natural log transformation, prior to further analysis. This improved the scatter in the residuals. An ANOVA was performed on this log transformed score\textsuperscript{12}.

![Figure 7.4](image)

**Figure 7.4.** Mean of copy accuracy score over time by breast cancer treatment group.  
*Note:* Natural log of total age adjusted z-score (reflected).

The visuoconstructional performance of both groups on the Complex Figure Copy accuracy score were initially lower than expected, in the Well Below Average range, with the chemotherapy group performing below the no-chemotherapy group over the course of the assessments, as seen in Figure 7.4. There was no Group by Time interaction effect found on visuoconstructional performance, $F(2,86) = 0.20$, $p = 0.820$. There was a statistically significant main effect of Group [$F(1,44) = 4.89$, $p = 0.032$] reflecting that the chemotherapy group displayed significantly worse copy accuracy than the no-

\textsuperscript{12} The Complex Figure Copy accuracy scores included 1\% ($n = 2$) missing values.
Chemotherapy group over time. There was no significant main effect of *Time* \[F(2,86) = 0.88, p = 0.418\].

The copy performance of women with breast cancer from both groups was in the *Well Below Average* range. Copy raw scores \((M = 31.08, SD = 3.7)\) were compared to relevant normative age group raw scores \((M = 34.56, SD = 0.8)\) published for the test and were found to be significantly worse than normative performance, \(t(44) = -10.63, p < .001\). The difference between the standardized copy performance of women at *Time 1* and their estimated IQ was also compared \((M \text{ diff} = -2.324, SD = 1.5)\) and copy accuracy was found to be significantly worse than estimated ability, \(t(44) = -10.63, p < .001\) (paired samples).

A regression model using forwards stepwise selection was used to identify potential explanatory variables for poor copy accuracy at *Time 1*. The variables that significantly estimated poorer copy accuracy were chemotherapy group \((p = 0.028)\), any clinical diagnosis (anxiety or mood disorder) \((p = 0.045)\), more general anaesthetics \((p = 0.003)\) and higher anxiety \((p = 0.002)\). Counterintuitively the variable associated with better copy accuracy performance was higher self-reported mental fatigue \((p < .001)\). This apparent subjective fatigue-motor copy accuracy paradox has been observed previously in patients with multiple sclerosis (Pardini, Bonzano, Roccatagliata, Mancardi, & Bove, 2013).

### 7.5 Chapter Discussion

a. **Language**

Both groups demonstrated significant improvement in language performance between *Time 1* and *Time 2* consistent with a practice or learning effect. This improvement was not maintained, instead declining significantly in both groups at *Time 3*. There was no significant difference in this change between groups so this change was not attributable to chemotherapy. This profile also did not indicate an acquired language deficit as performance at the final assessment was not below initial performance. Women who commenced hormonal therapy at *Time 2* showed an increased risk of decline in language performance between *Time 2* and *Time 3*.

b. **Motor**

There was significant and similar improvement in motor performance from the first to the second assessment in both groups, which was maintained at the final assessment, consistent with a practice or learning effect.
c. Visuoconstruction

The results found on the Complex Figure Test Copy task, a measure of visuoconstruction skills, indicated that the chemotherapy group displayed significantly worse copy accuracy than the no-chemotherapy group and that this persisted over time. Copy accuracy performance for both groups was in the Well Below Average range, significantly poorer than normative performance and expectations based on their estimated intellectual ability. This finding will be discussed in further detail in Chapter 12.2.3.

Women at highest risk for poorer copy accuracy at Time 1 were those who had received more general anaesthetics, were scheduled for chemotherapy, had higher anxiety or a diagnosis of clinical anxiety or depression. Surprisingly, higher self reported mental fatigue was associated with better copy accuracy performance but this is consistent with a ‘fatigue-motor performance paradox’ (Pardini, et al., 2013).

Accurately copying a complex geometric figure involves visuospatial perception/construction, efficient motor processing, attention and a strategic approach for planning and sequencing figure elements and reproducing their spatial localization (Lezak, et al., 2004; Meyers & Meyers, 1995). Any visuospatial deficits in these functions will be assessed with reference to the profile of visuoconstruction performance.

As there is no gold standard measure for organization on the complex figure test, it is recommended as best practice that the examiner record and examine the approach taken to copy, to identify organizational deficits (Lezak, et al., 2004; Meyers & Meyers, 1995). This was conducted and typical approaches to copying the complex figure found in the study, along with a comparison of the trends and relationships between the main measures from the Complex Figure Test, were examined further to aid differential diagnosis (see Appendix D). A total organization score was calculated and used in the analysis of measures of executive functions.

7.6 Chapter Summary

Language and motor skills were found to be within the expected range and not significantly negatively influenced by chemotherapy, as there were no significant interaction effects observed. There were also no significant differences between groups in these primary functions. Women who commenced hormonal therapy at Time 2 showed higher risk of decline in their language performance between Time 2 and Time 3. Visuoconstruction performance also did not vary significantly following chemotherapy between treatment groups. However, visuoconstruction performance was significantly
poorer in women from the chemotherapy group over time, including prior to chemotherapy. Moreover, visuoconstruction performance was significantly below normative and expected performance in women with early breast cancer from both groups. Women at increased risk for poorer copy accuracy at Time 1 were those who had received more general anaesthetics, were scheduled for chemotherapy, had higher anxiety or a diagnosis of clinical anxiety or depression.

The next chapter presents the results of the principal components and data analyses for the measures of attention and speed of processing.
Chapter 8

Attention and Speed of Processing

8.1 Introduction

The tests employed to assess changes to attention and speed of processing functions were the CANTAB Reaction Time test, including Simple and Choice Reaction Time, the Rapid Visual Information Processing test, the Spatial Span (forwards and reverse) test, the Paced Auditory Serial Addition Test (3 and 2 seconds), the WAIS-III Digit span test, as well as the extended Digit Supraspan test (forwards and backwards) designed to test the limits. These tests measure speed of processing and verbal and spatial attention span, working memory and sustained attention. Tests in other domains that measure latencies or speed of response were also included, namely the Word Reading Speed condition from the D-KEFS Color-Word Interference test and the CANTAB Pattern Recognition Memory mean correct latencies (immediate and delayed) and the Spatial Recognition Memory mean correct latency. Before proceeding to report results of the principal components and data analyses for attention and speed of processing, tests excluded from the analyses are discussed.

8.2 Exclusions and reporting procedure

Measures from tests of other cognitive domains that are reported to have attention or speed of processing components in the literature were examined in separate biplots of PCA derived domains. This indicated that the Trial 1 recall (Initial Word Span) measure from the California Verbal Learning test (v2) and the Trial 1 Recall (Visuospatial Span) measure from the CANTAB Paired Associate Learning test was more closely associated with Learning and Memory domain measures than Attention measures.

The Initial and Subsequent move planning speed measures from the CANTAB Stockings of Cambridge test shared characteristics with both Attention and Speed of Processing and the higher order Executive Functions domain measures. As they were grouped independently from other speed of processing measures, it was decided to enter these measures with the Executive Functions domain measures. The Complex Figure test copy speed measure was closely associated with the higher order planning speed measures, so it was entered into the Executive Functions domain analysis.
The measures from the CANTAB Spatial Working Memory test, which has a strong strategy and planning aspect, were more closely associated with the Executive Functions measures than the other working memory measures in Attention. Measures involving supervisory attentional control, such as attentional switching (Color-Word Interference Test, condition 4: inhibition/switching; Intra-Extra Dimensional Set Shift Test, Verbal fluency, condition 3: category switching) behaved more consistently with the Executive Functions measures, than the other Attention measures, so they were entered into the Executive Functions domain analysis.

Other measures that involve executive control processes include response inhibition. CANTAB Rapid Visual Information Processing (RVP) Total Correct Rejections involves a component of response inhibition. RVP Total False Alarms (responding incorrectly) and RVP B” which measures the tendency to respond regardless of the target sequence, can indicate impulsivity (responding too early) and problems with response inhibition. Rapid Visual Information Processing false alarms and correct rejections shared characteristics with other sustained attention measures as well as higher order Executive Function measures. As they differed from other inhibition measures and showed similarities with sustained attention measures, they were entered into the Attention analysis. Issues with the RVP B” measure is discussed in the following section. The D-KEFS Color-Word Interference Test, condition 3. inhibition was closely associated with verbal executive measures in the biplot, especially those involving inhibition, so it was entered into the Executive Functions analysis.

One of the outcome measures for the CANTAB Rapid Visual Information Processing test, RVP B” (B double prime), was eliminated for the purpose of the analysis due to a limitation identified in the calculation (for details see Chapter 6.3).

The procedure used in the analysis is the same as described previously (in Chapter 6.5.4). Eighty-seven percent of participants (n = 40) had complete data for attention and speed of processing. Missing values were examined and assessed (see Chapter 6.5.6). The results of the analyses are reported in the following chapters (8-10) in a topdown fashion where the the domain summary score profile is presented and compared with the major groupings; then each major grouping with its nested subgroups; and finally each subgroup with the individual outcome measures. This is presented in the following steps:

1. The variance accounted by the first principal component score derived from the PCA of all measures within the domain, as well as the main or interaction effects from the ANOVA conducted on this summary score is presented, as well as relevant post hoc comparisons for any significant main or interaction effect. Where
there was a significant Group × Time interaction effect or Time effect (reflecting a significant decline in performance) or Group effect (reflecting the chemotherapy group performed significantly worse than the no-chemotherapy group) results of regression analyses are presented that identify any significant risk factors for decline or impairment.

2. The PCA biplot is presented of all measures within the domain on the first two principal components for assessment of independent groupings.

3. All major groupings and nested subgroups found within the domain using the exploratory PCA procedure outlined in Chapter 6.5.4 are presented.

4. The domain summary performance profile (i.e., the slopes for each group) is compared with each of the major groupings to determine the most and least consistent. The p value profiles of the domain summary score and the most consistent grouping are compared. The name of the summary grouping is displayed in italics in the figures and table.

5. Each major grouping and their nested subgroups are compared according to Steps 1 and 4. As discussed previously, because the subgroups are made up of only closely associated variables the first principal component score for the subgroup measures accounts for more of the variance than at higher levels. Finally, each of the subgroups is compared to the individual measures that contributed to that subgroup as in Step 4.

8.3 PCA and data analyses

A PCA was performed on the 18 outcome measures from the eight tests of attention and speed of processing. The first principal component accounted for 26% of the variance in these measures. An ANOVA was performed on the first principal component summary score.\(^\text{13}\)

As seen in Figure 8.1, the Attention and Speed of Processing domain performance of both groups improved between Time 1 and Time 2, but while the chemotherapy group continued to improve at Time 3, the no-chemotherapy group did not.

\(^{13}\) Of the 138 attention and speed of processing summary scores dataset, there were 5% (n = 7) missing values.
Figure 8.1. Means (± SEM) of summary score for attention and speed of processing over time by breast cancer treatment group.

*Time 1* = Post-surgery (pre-chemotherapy); *Time 2* = 6 months from *Time 1* (post-chemotherapy); *Time 3* = 15 months from *Time 1* (~9 months post-chemotherapy).

There was no significant interaction effect \[ F(2,81) = 0.49, p = 0.616 \] and no main effect of *Group* on overall performance \[ F(1,44) = 1.00, p = 0.323 \]. There was a significant main effect of *Time* \[ F(1,44) = 15.74, p < 0.001 \] reflecting that *Time 2* \( M = 0.233 \) and *Time 3* \( M = 0.411 \) performances were significantly better than *Time 1* \( M = -0.653 \). Pairwise significance was determined by comparing each of the pairwise mean differences (PD) to the least significant difference of means (LSD) (PD > LSD = 0.404, at a 95% confidence level).

Examination of the biplot of the first two principal components indicated two groupings, shown in Figure 8.2.

Grouping 1 contains measures of attention. The only measure of response speed or latency, CANTAB Rapid visual information processing (RVP) mean correct latency, has been found to be a good indicator of sustained attention function (Sahakian, et al., 1989).

Grouping 2 contains only speed of processing measures. These groupings support models of attention that maintain that speed of processing underlies attention but involve independent processes (Lezak, et al., 2012).
Figure 8.2. Biplot of the attention and speed of processing data.

The first principal component axis (horizontal, PC-1 axis) represents the linear combination of the measures that maximize shared variance. The second principal component axis (vertical, PC-2 axis) represents component loadings* with the next most shared variance, independent of the first principal component. The vector represents the relative contribution from each variable on the first and second principal components. The smaller the angle between vectors, the larger the association between variables. Figure 8.2 suggests two groups of variables. Group 1 is located around the horizontal axis and includes variables predominated by the first principal component. These are measures of attention. Group 2 is located near the vertical axis indicating their relative contribution to the second principal component. These are measures of speed of processing.

**Grouping 1:** 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
All measure attention.

**Below Group 1:** 11RVP Total false alarms.

**Grouping 2:** 12, 13, 14, 15, 16, 17
All measure speed of processing.

**Between Groupings 1 and 2:** 18CANTAB Spatial span (forward).

* For details of latent vector loadings on the first two principal components, see Appendix E, p. E5
Below Grouping 1 is a standardized measure of total false alarms on Rapid Visual Information Processing. This measure is associated with executive control as well as sustained attention (Sahakian, et al., 1989). After further analysis, this measure was found to be consistent with the Attention grouping (Grouping 1). Between the groupings is a measure of span length on Spatial Span Forwards. This measure was more consistent with the Attention grouping (Grouping 1) than the Speed of Processing grouping (Grouping 2).

Additional principal component analyses were conducted on the two main groupings to explore further meaningful groupings before further analysis. Where orthogonal groupings were evident, a further principal components analysis was conducted and examined for meaningful groupings with internal consistency. The nested groupings within Attention and Speed of Processing are presented in Figure 8.3.

![Figure 8.3. Groupings within attention and speed of processing.](image)

Three subgroups were found within the Grouping 1: Attention measures, including those relating to spatial span and working memory, auditory span and working memory and sustained attention. The Grouping 2: Speed of Processing measures made a coherent and internally consistent grouping. The first principal component score was then extracted for use in subsequent analysis. An ANOVA was performed on the first principal score for each grouping to explore the impact of chemotherapy on attention and speed of processing.

A comparison of the mean summary score performance of Attention and Speed of Processing is presented in Figure 8.4 alongside the two major groupings.
The overall Attention and Speed of Processing performance profile (i.e., slopes of both groups) (Figure 8.4a) was most consistent with the Grouping 1: Attention performance (Figure 8.4b). Both showed the chemotherapy group performing slightly better than the no-chemotherapy group across each timepoint, with the chemotherapy group improving over time. In contrast, within the Grouping 2: Speed of Processing performance (Figure 8.4c), the performance of the chemotherapy group was lower than the no-chemotherapy group across each timepoint, and did not improve over the last two assessments.

The p values from these analyses are presented in Table 8.1. Both the performance profiles and the p values profiles were the same between the Attention and Speed of...
Processing domain summary, and attention. They both displayed a significant main effect of Time on cognitive performance but not a significant main effect of Group or a Group by Time interaction effect.

Table 8.1

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention and Speed of Processing</td>
<td>Visual-verbal</td>
<td>0.323</td>
<td>&lt;.001***</td>
<td>0.616</td>
</tr>
<tr>
<td>Attention</td>
<td>Visual-verbal</td>
<td>0.169</td>
<td>&lt;.001***</td>
<td>0.735</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>Visual-verbal</td>
<td>0.234</td>
<td>&lt;.001***</td>
<td>0.253</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).

Results from the analyses within each of the major groupings follow.

### 8.3.1 Attention

A PCA was conducted on all measures in Grouping 1 (Attention). The first principal component accounted for 38% of the variance. An ANOVA was performed on the first principal component summary score. The attention summary scores included 1.45% (n = 2) missing values.

![Graph](image-url)  
*Figure 8.5. Means (± SEM) of summary score for attention over time by breast cancer treatment group.*
While the attention performance of the no-chemotherapy group appears lower than the chemotherapy group in Figure 8.5, this difference was not significant as there was no main effect of Group on performance \[F(1, 44) = 1.96, p = 0.169\]. Both groups improved over the first two timepoints, with the no-chemotherapy group improving from the Below Average to the Average range, while the chemotherapy group improved within the Average range. The chemotherapy group continued to improve to the High Average range, while the performance of the no-chemotherapy group plateaued.

There was a main effect of Time on performance \[F(2, 86) = 11.16, p < .001\], reflecting that Time 3 performance (\(M = 0.398\)) was significantly better than Time 2 performance (\(M = 0.177\)), which was significantly better than Time 1 (\(M = -0.549\)) (PD>LSD = 0.210, at a 95% confidence level). However, there was no Group by Time interaction effect observed \[F(2, 86) = 0.31, p = 0.736\] indicating that these changes were not significantly different between treatment groups.

Inspection of the biplot and latent vector loadings suggested nested groupings. Three independent groupings were found within the Grouping 1: Attention measures, including those related to: a) spatial span and working memory; b) auditory span and working memory; and c) sustained attention. The mean summary score performance for attention is presented with the three nested groupings in Figure 8.6.

The Grouping 1: Attention summary profile (Figure 8.6a) is most consistent with the performance profile of both groups within sustained attention (Figure 8.6d). The p value profiles were somewhat different as shown in Table 8.2. Both p value profiles displayed a main effect of Time on performance and no interaction effect was observed but there was significant main effect of Group on sustained attention not found on overall attention.

### Table 8.2

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Visual-auditory</td>
<td>0.189</td>
<td>.001***</td>
<td>0.735</td>
</tr>
<tr>
<td>Spatial span and working memory</td>
<td>Visuospatial</td>
<td>0.268</td>
<td>0.022*</td>
<td>0.425</td>
</tr>
<tr>
<td>Auditory span and working memory</td>
<td>Auditory</td>
<td>0.927</td>
<td>0.042*</td>
<td>0.361</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>Visual</td>
<td>0.045*</td>
<td>&lt;.001***</td>
<td>0.648</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; **p < 0.01; ***p <.001 (boldface).
a. **Grouping 1: Attention**

![Graph showing Grouping 1: Attention](image)

b. **Subgroup 1: Spatial Span and Working Memory**

![Graph showing Subgroup 1: Spatial Span and Working Memory](image)

c. **Subgroup 2: Auditory Span and Working Memory**

![Graph showing Subgroup 2: Auditory Span and Working Memory](image)

d. **Subgroup 3: Sustained Attention**

![Graph showing Subgroup 3: Sustained Attention](image)

**Figure 8.6.** Means (± SEM) of summary scores for overall and major groupings in attention over time by breast cancer treatment group.

The Grouping 1: Attention performance profile was least consistent with the no-chemotherapy group performance profile in spatial span and working memory (Figure 8.6b) where the no-chemotherapy group demonstrated a decline in performance rather than an improvement over the first two assessments and then an improvement rather than no improvement between Time 2 and Time 3.

Results from each of the subgroups within attention will be explored in more detail.
a. **Spatial span and working memory**

The first principal component accounted for 69.5% of the variance in measures from the spatial span and working memory grouping. An ANOVA was performed on the first principal component score\(^{15}\).

![Figure 8.7](image)

**Figure 8.7.** Means (± SEM) of summary score for spatial span and working memory over time by breast cancer treatment group.

The spatial span and working memory performance profile of the chemotherapy group was higher than the no-chemotherapy group, as shown in Figure 8.7. This difference was not significant, as no main effect of Group on performance was observed \([F(1, 44) = 1.26, p = 0.268]\).

While the overall performance of the chemotherapy group improved within the *Average* range over the timepoints, the overall performance of the no-chemotherapy group dropped initially from the *Average* to the *Low Average* range and then returned to the *Average* range at the final assessment. There was a significant main effect of Time on performance \([F(2, 86) = 3.99, p = 0.022]\), reflecting that Time 3 performance \((M = 0.261)\) was significantly better than both the Time 1 \((M = -0.111)\) and the Time 2 performances \((M = -0.127)\) \((P>\text{LSD} = 0.156, \text{at a 95\% confidence level})\). However, there were no

\(^{15}\) The spatial span and working memory summary scores included 1.45% \((n = 2)\) missing values.
significant Group by Time interaction effects \( F(2, 86) = 0.86, p = 0.425 \) indicating that these changes were not significantly different between treatment groups.

This pattern of performance was most consistent for the no-chemotherapy group with the individual measure Spatial Span forward, a measure of spatial attention span (see ‘SSP\(_{pz}\)‘ Appendix E, p. E6). The chemotherapy group initially performed below the no-chemotherapy group and improved, while the performance of the no-chemotherapy group declined and then improved markedly at the final assessment. Although the performance profile was somewhat similar, the \( p \) values profiles obtained from the ANOVAs were different, as shown in Table 8.3. While the spatial span and working memory grouping displayed a significant main effect for Time, the spatial attention span measure did not, but demonstrated a trend towards a Group by Time interaction effect.

Table 8.3

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial span and working memory</td>
<td>Visuospatial</td>
<td>0.268</td>
<td>0.022*</td>
<td>0.425</td>
</tr>
<tr>
<td>Spatial span forward</td>
<td>Visuospatial</td>
<td>0.843</td>
<td>0.085</td>
<td>0.051</td>
</tr>
<tr>
<td>Spatial span reverse</td>
<td>Visuospatial</td>
<td>0.035*</td>
<td>0.118</td>
<td>0.723</td>
</tr>
</tbody>
</table>

\*CANTAB Spatial span. \*CANTAB Spatial span (reverse).

\*significant at \( p < 0.05 \) (boldface)

b. Auditory span and working memory

The first principal component accounted for 58% of the variance in measures from the auditory span and working memory grouping. An ANOVA was performed on the first principal component score\(^{16}\).

The auditory attention span and working memory performance profile of the no-chemotherapy group was initially slightly below the chemotherapy group, and these positions reversed at Time 2 but the performance of both groups were well within the Average range (see Figure 8.8).

There was a significant main effect found of Time \( F(2, 86) = 3.29, p = 0.042 \), reflecting that the Time 2 (\( M = 0.093 \)) and the Time 3 (\( M = 0.111 \)) auditory span and working memory performances were significantly better than those at Time 1 (\( M = -0.182 \))

\(^{16}\) The auditory attention span and working memory summary scores included 1.45% (\( n = 2 \)) missing values
(PD>LSD = 0.128, at a 95% confidence level). There was no main effect of Group on performance \([F(1, 44) = 0.01, p = 0.927]\), nor was there a significant Group by Time interaction effect observed \([F(2, 86) = 1.03, p = 0.361]\).

![Graph](image)

*Figure 8.8.* Means (± SEM) of summary score for auditory span and working memory over time by breast cancer treatment group.

This performance profile was most consistent with the individual measure, the Paced Auditory Serial Addition test (3 seconds), a measure of divided and sustained attention, as well as auditory working memory (see ‘pas3z’ Appendix E, p. E7). Both the performance profiles and the p value relationships were the same, with both displaying a significant main effect of Time on performance but not of Group or an interaction effect, as seen in Table 8.4.

The auditory span and working memory performance profile was least consistent with Digit Supraspan backward, a measure of auditory working memory, in which the average performance of the chemotherapy group deteriorated over the course of assessments, while remaining within the High Average range, whereas the performance of the no-chemotherapy group improved over the course of the assessments from the Average to the High Average range (see ‘DSSbz’ Appendix E, p. E7). Notably, both the individual measures with a larger auditory working memory component (Digit Supraspan backward and PASAT – 2 seconds) showed a trend towards a significant interaction effect but only Digit Supraspan backward displayed poorer performance by the chemotherapy group.
Table 8.4

*P* values for Group, Time and Interaction effects obtained from ANOVAs of Summary Score of the Auditory Span and Working Memory Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory span and working memory</td>
<td>Auditory</td>
<td>0.927</td>
<td>0.042*</td>
<td>0.361</td>
</tr>
<tr>
<td>Digit supraspan (backward)</td>
<td>Auditory</td>
<td>0.970</td>
<td>0.723</td>
<td>0.071</td>
</tr>
<tr>
<td>Digit supraspan (forward)</td>
<td>Auditory</td>
<td>0.567</td>
<td>0.156</td>
<td>0.678</td>
</tr>
<tr>
<td>1Digit span total</td>
<td>Auditory</td>
<td>0.953</td>
<td>0.501</td>
<td>0.572</td>
</tr>
<tr>
<td>2PASAT - 2 seconds</td>
<td>Auditory</td>
<td>0.378</td>
<td>0.145</td>
<td>0.091</td>
</tr>
<tr>
<td>3PASAT - 3 seconds</td>
<td>Auditory</td>
<td>0.859</td>
<td>0.006**</td>
<td>0.696</td>
</tr>
</tbody>
</table>

*a* WAIS-III Digit span total.  
bPaced auditory serial addition test (2 seconds).  
cPaced auditory serial addition test (3 seconds).  
*Significant at: *p < 0.05; **p < 0.01; ***p <.001 (boldface).

c. Sustained attention

The first principal component accounted for 68% of the variance in measures from the sustained attention grouping. An ANOVA was performed on the first principal component score.  

![Graph](image)

Figure 8.9. Means (± SEM) of summary score for sustained attention over time by breast cancer treatment group.

The sustained attention summary scores included 1.45% (n = 2) missing values.
Both groups improved over the first two assessments in overall sustained attention, but while the chemotherapy group continued to improve at the final assessment, the average performance of the no-chemotherapy group did not (see Figure 8.9). There was a significant main effect of Group on performance \([F(1, 44) = 4.27, p = 0.045]\) with the chemotherapy group \((M = 0.327)\) displaying better sustained attention than the no-chemotherapy group \((M = -0.605)\) across time. There was also a significant main effect found of Time on sustained attention \([F(2, 86) = 7.17, p = 0.001]\), reflecting that both the Time 2 \((M = 0.204)\) and Time 3 \((M = 0.318)\) performances were significantly better than those at Time 1 \((M = -0.514)\) (PD>LSR = 0.4739, at a 95% confidence level). This is consistent with a practice effect. No significant Group by Time interaction effect was observed \([F(2, 86) = 0.44, p = 0.648]\).

This performance profile was consistent with a number of CANTAB Rapid Visual Information Processing test measures, including Total hits, Total correct rejections and A’ (A prime), a measure of target sensitivity (see Appendix E, p. E9). The performance profiles and the p value profiles were similar, as shown in Table 8.5, with all displaying a significant main effect of Time and also trends towards significance for a main effect of Group. The sustained attention performance profile was least consistent with the individual measure RVP Mean latency for correct responses only for the chemotherapy group whose overall performance did not improve over the last two assessments (see ‘RVMCLz’ Appendix E, p. E9).

**Table 8.5**

\begin{tabular}{ |l|c|c|c|c| } 
\hline
Name & Visual/Verbal & Group & Time & Interaction \\
\hline
Sustained attention & Visual & 0.045* & 0.001** & 0.648 \\
‘RVP A’ (A prime) & Visual & 0.079 & 0.003** & 0.584 \\
RVP Mean correct latency & Visual & 0.023* & 0.256 & 0.671 \\
RVP Correct rejections & Visual & 0.062 & <.001*** & 0.587 \\
RVP Total false alarms & Visual & 0.575 & 0.186 & 0.971 \\
RVP Total hits & Visual & 0.081 & 0.004** & 0.568 \\
\hline
\end{tabular}

*CANTAB Rapid visual information processing (RVP)

*Significant at: *\(p < 0.05\); **\(p < 0.01\); ***\(p <.001\) (boldface).
8.3.2 Speed of processing.

A PCA was conducted on the six speed of processing measures in Grouping 2. The first principal component accounted for 43% of the variance. An ANOVA was performed on the first principal component score.\(^{18}\)

![Figure 8.10. Means (± SEM) of summary score for speed of processing over time by breast cancer treatment group.](image)

The speed of processing performance profiles of both groups showed improvement between Time 1 and Time 2, with the no-chemotherapy group improving from the Average to the High Average range (see Figure 8.10). There was a significant main effect of Time on speed of processing \([F(2, 81) = 8.10, p = .001]\) reflecting that both the Time 2 \((M = 0.325)\) and Time 3 \((M = 0.021)\) performances were significantly better (i.e., faster) than those at the Time 1 assessment \((M = -0.375)\) \((PD>LSD = 0.347, \text{ at a 95% confidence level})\). This is consistent with a practice effect. There was no main effect of Group on performance \([F(1, 44) = 1.46, p = 0.234]\). Furthermore, there was no significant Group by Time interaction effect indicating that overall speed of processing did not change significantly between groups over time \([F(2, 81) = 1.40, p = 0.253]\).

This profile of performance was most consistent with the individual outcome measure Choice Reaction Time (see 'RTI5rtrz' Appendix E, p. E12) and the p value patterns were also the same, as shown in Table 8.6. They both displayed a significant main effect of Time.

\(^{18}\) The speed of processing summary scores included 5\% \((n = 7)\) missing values.
on performance but no *Group* or interaction effect. The speed of processing performance profile was least consistent with Word reading speed where the performance of the chemotherapy group declined slightly over the first two assessments and then improved at the final assessment (see 'cw2wrz' Appendix E, p. E12).

Table 8.6

*P* values for *Group*, Time and Interaction effects obtained from ANOVAs of Speed of Processing Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of processing</td>
<td>Visual-verbal</td>
<td>0.234</td>
<td>&lt;.001***</td>
<td>0.253</td>
</tr>
<tr>
<td><em>a</em>Word reading speed</td>
<td>Visual-verbal</td>
<td>0.092</td>
<td>0.456</td>
<td>0.457</td>
</tr>
<tr>
<td><em>b</em>PRMi Mean correct latency</td>
<td>Visual</td>
<td>0.432</td>
<td><strong>0.003</strong></td>
<td>0.543</td>
</tr>
<tr>
<td><em>c</em>PRMd Mean correct latency</td>
<td>Visual</td>
<td>0.130</td>
<td>0.107</td>
<td>0.820</td>
</tr>
<tr>
<td><em>d</em>Simple reaction time</td>
<td>Visual</td>
<td>0.476</td>
<td>0.180</td>
<td>0.257</td>
</tr>
<tr>
<td><em>e</em>Choice reaction time</td>
<td>Visual</td>
<td>0.420</td>
<td><strong>0.010</strong></td>
<td>0.699</td>
</tr>
<tr>
<td><em>f</em>SRM Mean correct latency</td>
<td>Visuospatial</td>
<td>0.404</td>
<td>0.629</td>
<td>0.175</td>
</tr>
</tbody>
</table>

*a*D-KEFS Color Word Interference test, Word reading speed.  
bCANTAB Pattern recognition memory (immediate), mean correct latency.  
cCANTAB Pattern recognition memory (delayed), mean correct latency.  
dCANTAB RTI Simple reaction time.  
eRTI 5-choice reaction time.  
fCANTAB Spatial recognition memory, mean correct latency  
*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).

8.4 Chapter summary

This chapter presented the results of a multivariate method using PCA to facilitate data reduction of 18 outcome measures of attention and speed of processing based on the underlying associations between the measures. The two major groupings found were ‘attention’ and ‘speed of processing’. These are consistent with the literature on the basic dimensions of attention (Lezak et al., 2012). Attention displayed three further subgroups (spatial span and working memory, auditory span and working memory, and sustained attention). This will be discussed further in Chapter 12.2.4.

a. *Group by Time interaction effects*

There were no significant *Group by Time* interaction effects observed on Attention and Speed of Processing overall or in any of the nested grouping performances within the domain. This indicates that changes in Attention and Speed of Processing following treatment were not significantly different between those exposed to chemotherapy and those who were not.
b. *Group effects*

There was a significant main effect of *Group* on sustained attention, but this indicated that the chemotherapy group actually displayed better sustained attention than the no-chemotherapy group.

c. *Time effects*

The most consistent finding was the significant main effect of *Time* on attention and speed of processing performances. All summary measures within the Attention and Speed of Processing domain displayed a significant main effect of *Time*. Across this domain performances at the follow-up *Time 3* assessment were always significantly better than the baseline assessment at *Time 1*. With the exception of spatial span and working memory, all *Time 2* performances were also significantly better than *Time 1*. These improvements in performance within attention and speed of processing, from the initial assessment to follow-up assessments, are consistent with a practice effect. By using a control group differences in practice effects as an effect of treatment could be taken into account. Improvements in attention and speed of processing performance were not found to differ significantly between women with early breast cancer exposed to chemotherapy or not exposed to chemotherapy.

The following chapter presents the results of the analysis of the effect of chemotherapy on learning and memory over time.
Chapter 9

Learning and Memory

9.1 Introduction

The tests employed to assess changes to verbal learning and memory functions were the California Verbal Learning Test (CVLT-2) and the Verbal Paired Associates (names) test (VPA,) that was developed for this study. The visual learning and memory tests used were the Complex Figure Test (CFT), the CANTAB Paired Associates Learning test (PAL), the Pattern Recognition Memory test (PRM; immediate and delayed) and the Spatial Recognition Memory Test (SRM). Parallel forms were used for all tests at Time 2 and Time 3 with the exception of the Complex Figure Test where the Rey Complex Figure was used at Time 1 and readministered 15 months later at Time 3. An equivalent parallel form, the modified Taylor Complex Figure was used at Time 2. Fifty-eight outcome measures were derived from the six tests of learning and memory. These were converted to age-standardized z-scores based on relevant test norms. Data was examined for outliers and checked for data entry errors. Data was also checked for evidence of floor or ceiling effects. An adjustment was made to the learning slope for the CVLT-2 to account for the observed ceiling effect (see Chapter 6.4.1 for details).

The procedure used in the analysis is the same as described previously in Chapter 6.5.4 and the reporting of the results is as described in the previous chapter (Chapter 8.2). Seventy-eight percent of participants (n = 36) had complete data for learning and memory. Missing values were examined and assessed (see Chapter 6.7.2) and mean values from the analyses of variance included the imputed values predicted from the model.

9.2 PCA and data analyses

9.2.1 Learning and memory

A PCA was performed on data from the 58 outcome measures (z-scores) derived from the six tests of learning and memory. The first principal component accounted for 35% of the
variance in these measures. An ANOVA was performed on the first principal component score\(^{19}\).

\[ \text{Figure 9.1. Means (± SEM) of summary score for learning and memory over time by breast cancer treatment group.} \]

\( \text{Time 1 = Post-surgery (pre-chemotherapy); Time 2 = 6 months from Time 1 (post-chemotherapy); Time 3 = 15 months from Time 1 (=9 months post-chemotherapy).} \)

The Learning and Memory performance profile of the no-chemotherapy group improved markedly over time, as seen in Figure 9.1, from the Well Below Average range at Time 1 to the Well Above Average range at Time 3, whereas the performance of the chemotherapy group did not improve. There was a significant main effect of Time on performance \([F(2, 76) = 3.85, p = 0.025]\), reflecting that learning and memory at Time 3 \((M = 0.69)\) was significantly better than at Time 1 \((M = -0.58)\) \((\text{PD}>\text{LSD} = 0.917, \text{at a 95\% confidence level})\). There was no significant main effect of Group \([F(1, 44) = 0.09, p = 0.767]\). However, there was a trend towards significance observed in the Group by Time interaction effect on learning and memory \([F(2, 76) = 2.42, p = 0.096]\). This interaction reflected a significant difference in changes in learning and memory between groups, from the Time 1 to the Time 3 assessment (using pairwise comparisons: \(\text{T3}^{21}\text{GroupMD−T1GMD} = 2.11; \text{PD} > \text{LSD} = 1.36, \text{at a 95\% confidence level}\)). The performance of the no-chemotherapy group improved

\(^{19}\) Of the 138 learning and memory summary scores dataset, there were 8.7\% \((n = 12)\) missing values.

\(^{20}\) Pairwise significance was determined by comparing each of the pairwise mean differences \((\text{PD})\) to the least significant difference of means \((\text{LSD})\).

\(^{21}\) Group MD (GMD) is the group mean difference or difference between group means.
significantly between these timepoints (T3-1_MD = 2.64; LSD for Time = 0.917) while the performance of the chemotherapy group did not (T3-1_MD = 0.53).

These results suggest that the improvement, probably due to a practice effect, observed in Learning and Memory in women with early breast cancer not treated with chemotherapy, did not occur in women treated with chemotherapy still at nine months following the completion of treatment.

As the interaction effect showed a trend towards significance, a regression model involving forwards stepwise selection was used to identify potential explanatory variables for learning and memory change scores (Time 3 - Time 1), controlling for Time 1 baseline scores. A general linear regression revealed that higher anxiety at Time 1 and commencing hormonal therapy were significant determinants of decline in learning and memory performance at Time 3.

As women who received hormonal therapy were at greater risk of decline, the regression was repeated with a 2-way (hormone therapy × group) interaction. Women who received hormonal therapy following chemotherapy were more vulnerable to decline in learning and memory (p = 0.049) compared to women who received hormonal therapy only (p = 0.057). This is consistent with studies that have reported a negative cumulative impact of chemotherapy and hormonal therapy on cognitive functioning (e.g., Bender, et al., 2006; Collins, et al., 2009a).

Some studies have suggested that tamoxifen may be associated with poorer cognitive functioning (e.g., Schilder et al., 2010) but no significant interaction effect was found when the regression was repeated with either a 2-way tamoxifen × group or aromatase inhibitors × group interaction. However, when each of these regressions were conducted, neutropenia, a serious haematological toxicity and a potential explanatory variable in the model, displayed a significant unique contribution (p = 0.021 and p = 0.032 respectively). The regression was repeated to determine whether there was an interaction of hormone therapy and chemotherapy-induced neutropenia on changes in learning and memory by including a 2-way (hormone therapy × neutropenia) interaction. This general linear regression revealed that women who had higher anxiety at Time 1 (p = 0.040) or who received hormone therapy following chemotherapy-induced neutropenia (p = 0.016) were more vulnerable to decline in learning and memory performance at Time 3. The cumulative impact of chemotherapy + neutropenia + hormonal therapy was estimated to predict a 2.50 score decline in learning and memory from pre-treatment (Time 1) to 9 months post-treatment (Time 3).
Examination of the biplot of individual measures of learning and memory on the first two principal components indicated two major groupings and one minor grouping, as can be seen in Figure 9.2. The smaller the angle between vectors the larger the association between measures.

Grouping 1 consists of verbal learning and memory outcome measures from the CVLT-2.

Grouping 2 contains 3 measures from the CVLT-2. These include two verbal recall error measures and a measure of % recall from the recency end of the word list. As these measures were located opposite the verbal memory grouping, suggesting a possible negative relationship, it was explored whether to combine these two groupings. The biplot from a further principal components analysis demonstrated that these measures behaved independently.

Grouping 3 captures all paired associates learning and visual memory measures. The predominantly verbal and visual independent groupings within learning and memory are consistent with the literature. Baddeley's updated model of working memory (Baddeley, 2000) argues that verbal and nonverbal material are registered and stored short-term independently via the visuospatial sketchpad or the phonological loop. Research from focal brain injuries have also shown that visual memory deficits are associated with right hemisphere lesions and verbal memory deficits with left hemisphere lesions (Lezak, et al., 2012).

Measures on the borderline between groupings include a CVLT-2 measure of Percentage recall from the primacy region of the list, and a CVLT-2 measure of First trial total correct recall, otherwise known as word span. These measures were located opposite each other on the biplot. The Primacy region recall measure is located between Grouping 3 and Grouping 2, near a measure of First trial visuospatial span performance. The verbal First trial total correct recall measure is located between Grouping 1 and Grouping 2. After further analysis it was found that the Primacy region recall measure was more consistent with the Recency Recall and Recall Errors grouping (Grouping 2) than the Visual or Verbal Memory groupings, and that the CVLT-2 measure of First trial recall or word span was more consistent with the Verbal Learning and Memory grouping (Grouping 1).
Figure 9.2. Biplot of the learning and memory data.

The first principal component axis (horizontal, PC-1 axis) represents the linear combination of the measures that maximizes shared variance (35%)*. The second principal component axis (vertical, PC-2 axis) represents component loadings with the next most shared variance independent of the first principal component (9.6%). The smaller the angle between vectors, the larger the association between variables. Figure 9.2 suggests two main groupings and a minor grouping of variables. Grouping 1 contains measures of verbal learning and memory. Grouping 2 is located opposite Grouping 1 and includes mainly verbal recall error measures. Grouping 3 contains measures of paired associates learning and visual memory.

**Grouping 1:** All measures are CVLT-2 verbal and learning measures.

**Between Groupings 1 and 2:** CVLT-2 Total correct on Trial 1.

**Grouping 2:** All CVLT-2 measures, including errors and recall from recency region of list.

**Between Groupings 2 and 3:** CVLT-2 % Recall from primacy region.

**Grouping 3:** All measures are Paired associates learning [PAL] and visual memory measures.


*For latent vector loadings of measures on the first two principal components, see Appendix F, p. F5.*
Additional principal components analyses were conducted on the two main verbal and visual groupings to explore further meaningful groupings before further analysis. Where distinct groupings were evident, further principal components analysis was conducted and examined for meaningful groupings with internal consistency. The nested groupings within Learning and Memory are presented in Figure 9.3.

**Figure 9.3. Groupings within learning and memory.**

As can be seen in Figure 9.3 four independent subgroups were found within the Grouping 1: Verbal learning and memory measures, including those related to verbal memory encoding, verbal learning and immediate recall, verbal delayed recall and verbal recall discriminability. Five subgroups were found within the Grouping 3: Paired associates learning and visual memory measures, including visuospatial memory encoding, visuospatial span, verbal paired associates learning, visual paired associates learning and visual memory.

The first principal component score for each grouping was then extracted for use in subsequent analysis. An ANOVA was performed on the first principal component score for each grouping to examine the main and interaction effects of treatment group and time on learning and memory. The $p$ values from these analyses are presented in Table 9.1.

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Table 9.1

Summary of p values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Overall and Major Groupings in Learning and Memory

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning and Memory</td>
<td>Visual-verbal</td>
<td>0.767</td>
<td>0.025*</td>
<td>0.096</td>
</tr>
<tr>
<td>Verbal learning and memory</td>
<td>Verbal</td>
<td>0.803</td>
<td>0.074</td>
<td>0.115</td>
</tr>
<tr>
<td>Verbal primacy/ recency recall and recall errors</td>
<td>Verbal</td>
<td>0.800</td>
<td>0.967</td>
<td>0.996</td>
</tr>
<tr>
<td>Paired associates learning and visual memory</td>
<td>Visuospatial</td>
<td>0.443</td>
<td>0.189</td>
<td>0.590</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; **p < 0.01; *** p < .001 (boldface).

A comparison of the summary score performance profiles (i.e., the slopes) of both groups in Learning and Memory alongside the three major groupings is presented in Figure 9.4. The Learning and Memory summary performance pattern (Figure 9.4a) was most consistent with Grouping 1: verbal learning and memory performance pattern (see Figure 9.4b). The performance slope of the no-chemotherapy group improved markedly over time from the Well Below Average to the Well Above Average range, while the performance of the chemotherapy group remained fairly flat within the Average range, with a crossover of slopes between groups between Time 2 and Time 3 suggesting an interaction effect. Although the performance profiles were the same the p value profiles were slightly different (see Table 9.1), indicating contributions from other groupings to the overall Learning and Memory p value profile. While they both displayed a trend towards a significant interaction, there was a significant main effect of Time found in overall Learning and Memory, whereas Grouping 1: verbal learning and memory showed only a trend to significance.

In contrast, the performance slope of the no-chemotherapy group differed within Grouping 2: primacy/recency recall and recall errors (Figure 9.4c) displaying a flat profile instead of improvement. The Learning and Memory summary performance profile for both groups was most inconsistent with Grouping 3: paired associates learning and visual memory (Figure 9.4d). The performance slopes of both groups declined from Time 1 to Time 2 and while the performance of the no-chemotherapy group improved at Time 3, the chemotherapy group continued to decline from the Average to the Low Average range.
a. Summary: Learning and Memory

![Graph A]

b. Grouping 1: Verbal Learning and Memory

![Graph B]

c. Grouping 2: Verbal Primacy/Recency Recall and Recall Errors

![Graph C]

d. Grouping 3: Paired Associates Learning and Visual Memory

![Graph D]

Figure 9.4. Means (± SEM) of Summary Scores for Overall and Major Groupings in Learning and Memory over Time by Breast Cancer Treatment Group.
Results from the analyses within each of the major groupings follows.

### 9.2.2 Verbal learning and memory

A PCA was conducted on all 33 verbal learning and memory measures in Grouping 1. The first principal component accounted for 57% of the variance. An ANOVA was performed on the first principal component score\(^\text{22}\).

![Figure 9.5. Means (± SEM) of summary score for verbal learning and memory over time by breast cancer treatment group.](image)

As shown in Figure 9.5, the verbal learning and memory performance of the no-chemotherapy group improved over time, from the *Well Below Average* range to the *Well Above Average* range, while the chemotherapy group did not, remaining well within the *Average* range. While it failed to reach significance there was a trend towards significance observed for the Group by Time interaction effect \([F(2, 86) = 2.22, p = 0.115]\). There was also a trend for the main effect of Time \([F(2, 86) = 2.69, p = 0.074]\) but no main effect of Group \([F(1, 44) = 0.06, p = 0.803]\).

This interaction effect reflected a significant difference in changes in verbal learning and memory between groups, from both the Time 1 and Time 2 to the Time 3 assessment (using pairwise comparisons: \(T3_{\text{Group MD}} - T1_{\text{GMD}} = 2.18\); \(T3_{\text{Group MD}} - T2_{\text{GMD}} = 1.73\); PD > LSD =

\(^{22}\) The verbal learning and memory summary scores included 1.45% (\(n = 2\)) missing values.
1.54, at a 95% confidence level). The performance of the no-chemotherapy group improved significantly between these timepoints (T3-1_{MD} = 2.63 & T3-2_{MD} = 1.66 LSD for Time = 1.034) while the performance of the chemotherapy group did not (T3-1_{MD} = 0.45 & T3-2_{MD} = 0.02).

These results suggest that the improvement observed in verbal learning and memory in women with early breast cancer not treated with chemotherapy, probably due to a practice effect, did not occur in women treated with chemotherapy, following the completion of treatment.

As the interaction effect showed a trend towards significance, a regression model involving forwards stepwise selection was used to identify potential explanatory variables for verbal learning and memory change scores (Time 3 - Time 1), controlling for Time 1 baseline scores. A general linear regression revealed that baseline factors such as smaller tumour size, higher baseline scores and more mental fatigue, as well as starting hormonal therapy and a decline in emotional wellbeing over time were all significant determinants of decline in verbal learning and memory performance at Time 3.

As women who received hormonal therapy were at greater risk of decline the regression was repeated with a 2-way (hormone therapy T3-T1 × group) interaction term. Women who received hormonal therapy following chemotherapy were more vulnerable to decline in verbal learning and memory (p = 0.028) compared to women who received hormonal therapy only (p = 0.127). There was no significant interaction effect found when the regression was repeated with either a 2-way tamoxifen × group or aromotase inhibitors × group interaction.

This general linear regression revealed that women who had smaller tumours (p = 0.027), higher baseline scores (p = 0.039), more mental fatigue at Time 1 (p = 0.028), were receiving hormonal therapy following chemotherapy (p = 0.028) or who reported a decline in emotional wellbeing (p = 0.040) were more vulnerable to decline in verbal learning and memory performance at Time 3. The cumulative impact of chemotherapy + hormonal therapy was estimated to predict a 1.93 score decline in verbal learning and memory scores in women from pre-treatment (Time 1) to 9 months post-treatment (Time 3).

Inspection of the biplot and latent vector loadings of verbal learning and memory measures on the first two principal components suggested nested groupings. Four independent groupings were found within the Grouping 1: Verbal learning and memory measures, including those related to a) verbal memory encoding; b) verbal immediate
recall and learning; c) verbal delayed recall; and d) verbal recall discriminability. The mean summary score performance for verbal learning and memory is presented for comparison with the four nested groupings in Figure 9.6. The performance pattern in verbal learning and memory (Figure 9.6a) is consistent with most of the groupings but is most consistent for the no-chemotherapy group where performance improved over the timepoints in all groupings.

The Grouping 1: Verbal learning and memory performance pattern (Figure 9.6a) showed the slope of the no-chemotherapy group rising over the course of the assessments, unlike the chemotherapy group, with a cross-over of slopes between groups following chemotherapy suggesting an interaction. This performance profile was most consistent with two subgroups, verbal memory encoding (Figure 9.6b) and verbal recall discriminability (Figure 9.6e), especially verbal memory encoding.

Although the patterns of performance were similar, the p value profiles varied as can be seen in Table 9.2. There was a trend towards a significant interaction and Time effect on overall verbal learning and memory and this was more consistent with verbal memory encoding were there was a significant Time effect and a trend towards an interaction effect, whereas there was a significant interaction effect but no significant main effect of Time observed on verbal recall discriminability.

The performance pattern for verbal learning and memory was least consistent with verbal delayed recall (Figure 9.6d), where there was no cross-over of slopes between groups between the Time 2 and Time 3 assessments. The p values profiles were also different as the trend towards an interaction and Time effect found in overall verbal learning and memory was not found in verbal delayed recall.

Table 9.2

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal learning and memory</td>
<td>Verbal</td>
<td>0.803</td>
<td>0.074</td>
</tr>
<tr>
<td>Memory encoding</td>
<td>Verbal</td>
<td>0.870</td>
<td></td>
</tr>
<tr>
<td>Immediate recall and learning</td>
<td>Verbal</td>
<td>0.767</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>Verbal</td>
<td>0.742</td>
<td>0.547</td>
</tr>
<tr>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.807</td>
<td>0.623</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; ** p < 0.01; *** p <.001 (boldface).
Figure 9.6. Means (± SEM) of summary scores for overall and subgroups in verbal learning and memory over time by breast cancer treatment group.
Results from each of the groupings within verbal learning and memory will be explored in more detail.

a. **Verbal memory encoding**

The first principal component for the verbal memory encoding grouping accounted for 90% of the variance in these measures. An ANOVA was conducted on the first principal component score.  

![Figure 9.7](image)

*Figure 9.7. Means (± SEM) of summary score for verbal memory encoding over time by breast cancer treatment group.*

While both groups displayed an improvement in verbal memory encoding between Time 1 and Time 2, as seen in Figure 9.7, the no-chemotherapy group continued to improve between Time 2 and Time 3 to the High Average range, whereas the chemotherapy group did not. There was no significant main effect of Group \([F(1, 44) = 0.03, p = 0.870]\). There was a statistically significant main effect of Time \([F(2, 86) = 4.05, p = 0.021]\), reflecting that Time 3 encoding performance \((M = 0.33)\) was significantly better than at Time 1 \((M = -0.47)\) (PD>LSD = 0.572, at a 95% confidence level). However, the interaction effect showed a trend towards significance \([F(2, 86) = 2.45, p = 0.093]\). This interaction effect reflected a significant difference in changes in verbal memory encoding between groups from both the Time 1 and Time 2 to the Time 3 assessment (using pairwise comparisons: T3Group MD<sup>23</sup>.

<sup>23</sup> The verbal memory encoding summary scores included 1.45% \((n = 2)\) missing values.
The performance of the no-chemotherapy group improved significantly between these timepoints (T3-1Mo = 1.63 & T3-2Mo = 0.85; LSD for Time = 0.572) while the performance of the chemotherapy group did not (T3-1Mo = 0.35 & T3-2Mo = -0.11). These results suggest that the improvement observed in verbal memory encoding in women with early breast cancer not treated with chemotherapy, probably due to practice, did not occur in women treated with chemotherapy following the completion of treatment.

A general linear regression revealed that higher baseline scores (p = 0.005) and a clinical diagnosis of either an anxiety or mood disorder at Time 1 (p = 0.037) were significant determinants of decline in verbal memory encoding performance at Time 3. Surprisingly, an increase in self-reported retrospective memory problems over time was associated with improved performance at Time 3 (p = <.001).

The performance profile of the verbal memory encoding summary score was most consistent with the individual test measure, Total recognition discriminability (see Appendix F, p F6) and the p value profiles were also the same, with both measures displaying a main effect of Time but not a Group or an interaction effect, as seen in Table 9.3. The verbal memory encoding performance pattern was similar to all the individual measures but was least so for Source recognition discriminability (see Appendix F, p F6).

Table 9.3

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory encoding</td>
<td>Verbal</td>
<td>0.870</td>
<td>0.021*</td>
<td>0.093</td>
</tr>
<tr>
<td>Novel recognition discriminability</td>
<td>Verbal</td>
<td>0.771</td>
<td>0.011*</td>
<td>0.039*</td>
</tr>
<tr>
<td>Source recognition discriminability</td>
<td>Verbal</td>
<td>0.579</td>
<td>0.170</td>
<td>0.328</td>
</tr>
<tr>
<td>Recognition total hits</td>
<td>Verbal</td>
<td>0.782</td>
<td>0.395</td>
<td>0.164</td>
</tr>
<tr>
<td>Total recognition discriminability</td>
<td>Verbal</td>
<td>0.925</td>
<td>&lt;.001***</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Note: all are CVLT-2 measures.

*Significant at: *p < 0.05; **p < 0.01; ***p <.001 (boldface).
b. **Verbal Immediate Recall and Learning.**

The first principal component for the verbal immediate recall and learning grouping accounted for 56% of the variance in these measures. An ANOVA was performed on the first principal component score\(^{24}\).

![Figure 9.8](image-url)

*Figure 9.8. Means (± SEM) of summary score for verbal immediate recall and learning over time by breast cancer treatment group.*

As can be seen in Figure 9.8, both groups showed improvement in verbal immediate recall and learning over the course of assessments, with the no-chemotherapy group showing the most improvement from the Low Average to the Well Above Average range. There was no significant interaction effect \([F(2, 86) = 0.91, p = 0.406]\) or main effect of Group on performance \([F(1, 44) = 0.09, p = 0.767]\). There was a significant main effect of Time on verbal immediate recall and learning \([F(2, 86) = 8.41, p < .001]\), reflecting that the Time 3 \((M = 0.79)\) performance was significantly better than both the Time 1 \((M = -0.59)\) and Time 2 \((M = -0.33)\) performances \((PD > LSD = 0.710, at a 95\% confidence level)\). This significant improvement in both groups over time is consistent with a practice effect.

This pattern of performance was most consistent with the individual measures Average immediate recall (trials 1-5) and Semantic clustering learning strategy on trial 5 (see Appendix F, 'Ccorimz' p. F8 and 'Csemca5z' p. F10). While these performance profiles

\(^{24}\) The verbal immediate recall and learning summary scores included 1.45% \((n = 2)\) missing values.
were the same, the \( p \) value profiles varied, as seen in Table 9.4. Both the verbal immediate recall and learning summary score and *Average* immediate recall (trials 1-5) displayed a significant main effect of *Time*, whereas the Semantic clustering learning strategy on trial 5 did not. The verbal immediate recall and learning performance pattern was most inconsistent with List B total correct (interference trial), where there was no cross-over of slopes between groups between *Time 2* and *Time 3* (see '\textsuperscript{b}Cortzb' Appendix F, p F9).

Table 9.4

*P* values for Group, *Time* and Interaction effects obtained from ANOVAs of Immediate Recall and Learning Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th><em>Time</em></th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate recall and learning</td>
<td>Verbal</td>
<td>0.767</td>
<td>&lt;.001***</td>
<td>0.406</td>
</tr>
<tr>
<td>Across trial recall consistency, t1-5</td>
<td>Verbal</td>
<td>0.978</td>
<td>0.345</td>
<td>0.225</td>
</tr>
<tr>
<td><em>Average</em> immediate recall, t1-5</td>
<td>Verbal</td>
<td>0.580</td>
<td><strong>0.003</strong></td>
<td>0.169</td>
</tr>
<tr>
<td>List A First trial memory</td>
<td>Verbal</td>
<td>0.751</td>
<td><strong>0.001</strong></td>
<td>0.554</td>
</tr>
<tr>
<td>List A trial 2 total correct</td>
<td>Verbal</td>
<td>0.754</td>
<td>&lt;.001***</td>
<td>0.332</td>
</tr>
<tr>
<td>List A trial 3 total correct</td>
<td>Verbal</td>
<td>0.367</td>
<td><strong>0.007</strong></td>
<td>0.424</td>
</tr>
<tr>
<td>List A trial 4 total correct</td>
<td>Verbal</td>
<td>0.537</td>
<td>0.854</td>
<td>0.473</td>
</tr>
<tr>
<td>List A trial 5 total correct</td>
<td>Verbal</td>
<td>0.967</td>
<td>0.252</td>
<td>0.227</td>
</tr>
<tr>
<td>List B total correct (interference)</td>
<td>Verbal</td>
<td>0.429</td>
<td>0.161</td>
<td>0.819</td>
</tr>
<tr>
<td>% Recall from middle region of list</td>
<td>Verbal</td>
<td>0.789</td>
<td><strong>0.013</strong>*</td>
<td>0.470</td>
</tr>
<tr>
<td>Immediate Recall Discriminability</td>
<td>Verbal</td>
<td>0.790</td>
<td>0.068</td>
<td>0.134</td>
</tr>
<tr>
<td>Subjective Clustering, Bidirectional</td>
<td>Verbal</td>
<td>0.355</td>
<td><strong>0.013</strong>*</td>
<td>0.443</td>
</tr>
<tr>
<td>Semantic clustering, (t1-5)</td>
<td>Verbal</td>
<td>0.647</td>
<td>&lt;.001***</td>
<td>0.643</td>
</tr>
<tr>
<td>Semantic clustering, SDFR\textsuperscript{a}</td>
<td>Verbal</td>
<td>0.660</td>
<td><strong>0.045</strong>*</td>
<td>0.846</td>
</tr>
<tr>
<td>Semantic clustering, trial 5</td>
<td>Verbal</td>
<td>0.789</td>
<td>0.068</td>
<td>0.767</td>
</tr>
<tr>
<td>Semantic clustering, LDFR\textsuperscript{b}</td>
<td>Verbal</td>
<td>0.599</td>
<td><strong>0.028</strong>*</td>
<td>0.627</td>
</tr>
</tbody>
</table>

Note: all are CVLT-2 measures.

\textsuperscript{a} Short delay free recall. \textsuperscript{b} Long delay free recall.

*Significant at: *\( p < 0.05; ** p < 0.01; *** p <.001 \) (boldface).
c. **Verbal delayed recall.**

The first principal component for the verbal delayed recall grouping accounted for 84% of the variance in these measures. An ANOVA was performed on the first principal component score.  

\[ F(2, 86) = 0.6, p = 0.547 \]

The verbal delayed recall of the no-chemotherapy group improved between *Time 1* and *Time 2* while the chemotherapy group did not, although both groups remained well within the *Average* range, as shown in Figure 9.9. There was no significant interaction effect \[ F(2, 86) = 0.25, p = 0.777 \] or main effect of *Group* \[ F(1, 44) = 0.11, p = 0.742 \] or *Time* \[ F(2, 86) = 0.61, p = 0.547 \] found on performance.

This pattern of performance was not consistent for both groups with any of the individual measures. However, the pattern of no-chemotherapy performance was most consistent with the individual test measures, Short delay free recall and Long delay free recall, with the no-chemotherapy group initially performing below the chemotherapy group but then improving consistently over the course of the assessments, although the slopes crossed over between groups between *Time 2* and *Time 3* (see ‘Ccorsfz’, ‘Ccorlfz’ respectively in Appendix F, p F12). The profile of chemotherapy performance was variable, with Short delay free recall displaying the most similarity, even though there was improvement in

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25 The verbal delayed recall summary scores included 1.45% \( n = 2 \) missing values.
performance over the first two assessments, rather than a plateau, followed by a slight decline at the final assessment, rather than slight improvement. As can be seen in Table 9.5, even though the performance profiles were not the same between verbal delayed recall and Short delay free recall, the $p$ values profiles were consistent, with no significant main effect found for Group or Time or for an interaction effect. The pattern of verbal delayed recall performance was least consistent with Long delay cued recall overall (see 'Ccorlcz' Appendix F, p F12). The chemotherapy group improved consistently over the course of assessments, whereas the no-chemotherapy group initially improved then plateaued below the chemotherapy group.

Table 9.5

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal delayed recall</td>
<td>Verbal</td>
<td>0.742</td>
<td>0.547</td>
<td>0.777</td>
</tr>
<tr>
<td>Short delay cued recall</td>
<td>Verbal</td>
<td>0.779</td>
<td>0.799</td>
<td>0.951</td>
</tr>
<tr>
<td>Short delay free recall</td>
<td>Verbal</td>
<td>0.771</td>
<td>0.421</td>
<td>0.615</td>
</tr>
<tr>
<td>Long delay cued recall</td>
<td>Verbal</td>
<td>0.583</td>
<td>0.541</td>
<td>0.963</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>Verbal</td>
<td>0.897</td>
<td>0.340</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Note: all are CVLT-2 measures.

d. Verbal recall discriminability.

The first principal component for the verbal recall discriminability grouping accounted for 86% of the variance in these measures. An ANOVA was conducted on the first principal component score. The verbal recall discriminability performance of the chemotherapy group was initially in the Average range, as opposed to the no-chemotherapy group which was in the Low Average range, as shown in Figure 9.10. However, the performance of the no-chemotherapy group improved over the course of the assessments to the High Average range, while the performance of chemotherapy group declined between Time 2 and Time 3 to the bottom of the Average range.

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26 The verbal recall discriminability summary scores included 1.45% ($n = 2$) missing values.
There was no main effect of Group \(F(1, 44) = 0.06, p = 0.807\) or Time \(F(2, 86) = 0.48, p = 0.623\) but there was a significant Group × Time interaction effect on performance \(F(2, 86) = 3.40, p = 0.038\). This interaction effect reflected a significant difference in changes in verbal recall discriminability between groups, from both the Time 1 and Time 2 assessments to the Time 3 assessment (using pairwise comparisons: \(T3_{\text{Group}_{\text{MD}}}-T1_{\text{GMD}} = 1.77; T3_{\text{GMD}}-T2_{\text{GMD}} = 1.5\); PD >LSD = 1.033, at a 95% confidence level). The performance of the no-chemotherapy group improved significantly between these timepoints \(T3-1_{\text{MD}} = 1.25 \& T3-2_{\text{MD}} = 0.74; \text{LSD for Time} = 0.696\) while the performance of the chemotherapy group did not improve or declined significantly between these same periods \(T3-1_{\text{MD}} = -0.52 \& T3-2_{\text{MD}} = -0.76\). These results suggest that for women with early breast cancer, adjuvant chemotherapy is associated with a decline in verbal recall discriminability following the completion of treatment. This summary measure was derived from new measures of recall discriminability found to be more sensitive to recall accuracy and discrimination (D.C. Delis, et al., 2010; Fine, Delis, Wetter, Jacobson, Hamilton, et al., 2008; M. L. Jacobs & Donders, 2007).

A general linear regression revealed that lower premorbid intelligence, smaller tumour size, higher mental fatigue at Time 1 and commencing hormonal therapy or getting neutropenia were significant determinants of decline in verbal recall discriminability performance at Time 3. An additional analysis found there was a significant 2-way group ×
hormone therapy interaction, revealing that women who received hormone therapy following chemotherapy were at increased risk for decline ($p = 0.005$) in contrast to women who received hormone therapy alone ($p = 0.402$). Two-way group by type of hormone treatment (tamoxifen or aromatase inhibitors) interactions were not significant. However, when each of these regressions were conducted, neutropenia, an explanatory variable in the model, displayed unique significance.

The regression was repeated to determine whether there was an interaction of hormone therapy and chemotherapy-induced neutropenia on changes in verbal recall discriminability by including a 2-way (hormone therapy $\times$ neutropenia) interaction. This general linear regression revealed that women who had lower premorbid intelligence ($p = 0.007$), smaller tumour size ($p < .001$), higher mental fatigue at Time 1 ($p = 0.005$) and were receiving hormonal therapy after having had chemotherapy-induced neutropenia ($p = 0.002$) were more vulnerable to decline in verbal recall discriminability performance at Time 3. The cumulative impact of chemotherapy + neutropenia + hormonal therapy was estimated to predict a 2.06 score decline in verbal recall discriminability scores in women from pre-treatment (Time 1) to 9 months post-treatment (Time 3).

The performance pattern of verbal recall discriminability was consistent with a number of the individual recall discriminability measures, including Delayed recall discriminability, Free recall discriminability. Recall discriminability on trial 5 and Short delay free recall (SDFR) discriminability, where the slope of both groups rose over the first two assessments but there was a cross-over in slopes between groups between Time 2 and Time 3 with the chemotherapy group showing a drop in performance while the no-chemotherapy group continued to improve (see Appendix F respectively, ‘$Cdrdz’’, ‘$Cfrdz’’ and ‘$Crdit5z’’ p. F14 and ‘$Crdisfz’’ p. F15). While these performance profiles were the same, the $p$ value profiles varied for the interaction effects, as can be seen in Table 9.8. Both the verbal recall discriminability summary score and Recall discriminability on trial 5 displayed a significant interaction effect and Short delay free recall (SDFR) discriminability and Free recall discriminability approached significance, whereas the interaction effect for Delayed recall discriminability did not reach significance.

This performance pattern was also consistent with the other individual test measures, although it was least consistent with Total Recall Discriminability as it was the only measure where the performance of the no-chemotherapy group declined between Time 1 and 2, before making marked improvement (see ‘$Crdz$’ Appendix F, p. F15).

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Table 9.6 P values for Group, Time and Interaction effects obtained from ANOVAs of Verbal Recall Discriminability Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal recall discriminability</td>
<td>Verbal</td>
<td>0.807</td>
<td>0.623</td>
<td>0.038*</td>
</tr>
<tr>
<td>Cued recall discriminability</td>
<td>Verbal</td>
<td>0.935</td>
<td>0.509</td>
<td>0.208</td>
</tr>
<tr>
<td>Delayed recall discriminability</td>
<td>Verbal</td>
<td>0.858</td>
<td>0.663</td>
<td>0.122</td>
</tr>
<tr>
<td>Free recall discriminability</td>
<td>Verbal</td>
<td>0.838</td>
<td>0.074</td>
<td>0.065</td>
</tr>
<tr>
<td>Recall discriminability, Trial 5</td>
<td>Verbal</td>
<td>0.765</td>
<td>0.344</td>
<td>0.045*</td>
</tr>
<tr>
<td>Recall discriminability, LDCR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Verbal</td>
<td>0.696</td>
<td>0.685</td>
<td>0.056</td>
</tr>
<tr>
<td>Recall discriminability, LDFR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Verbal</td>
<td>0.661</td>
<td>0.341</td>
<td>0.006**</td>
</tr>
<tr>
<td>Recall discriminability, SDCR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Verbal</td>
<td>1.000</td>
<td>0.402</td>
<td>0.554</td>
</tr>
<tr>
<td>Recall discriminability, SOFR&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Verbal</td>
<td>0.781</td>
<td>0.446</td>
<td>0.066</td>
</tr>
<tr>
<td>Total recall discriminability</td>
<td>Verbal</td>
<td>0.795</td>
<td>0.864</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Note: all are CVLT-2 measures. Recall discriminability = List A vs. Intrusions, on specified trials.

<sup>a</sup> Long delay cued recall. 
<sup>b</sup> Long delay free recall. 
<sup>c</sup> Short delay cued recall. 
<sup>d</sup> Short delay free recall.

*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).

**e. Non-conforming variables.**

The only variable that behaved differently to all other variables in verbal learning and memory was Verbal Learning Slope (adjusted for ceiling effects). Trial 1 recall was included as a covariate in the ANOVA to adjust for any influence on learning slope.

The mean verbal learning slope performance adjusted for ceiling as well as trial 1 recall is shown in Figure 9.11. While the verbal learning performance of the chemotherapy group remained fairly consistent over the course of assessments, the no-chemotherapy group demonstrated improvement then deterioration, although remaining well within the Average range. There was no main effect of Group \(F(1, 43) = 0.47, p = 0.498\), Time \(F(2, 85) = 0.18, p = 0.831\) or an interaction effect \(F(2, 85) = 0.25, p = 0.782\) on performance. There was a significant main effect found for the covariate, trial 1 recall \(F(1, 85) = 12.43, p < .001\), demonstrating that learning slope performance was significantly influenced by initial word recall on trial 1, as discussed in Section 9.2.
Figure 9.11. Means (± SEM) of verbal learning slope (adjusted for ceiling and trial 1) over time by breast cancer treatment group.

9.2.3 Verbal primacy/recency recall and recall errors

A PCA was conducted on all verbal primacy/recency recall and recall errors measures in Grouping 2. The first principal component accounted for 34% of the variance. An ANOVA was performed on the first principal component score.

Both the chemotherapy and no-chemotherapy groups demonstrated similar consistent verbal primacy/recency recall and recall errors performances over the course of the assessments within the Average range, as shown by the parallel slopes in Figure 9.12. There was no significant main effect of Group [F(1, 44) = 0.06, p = 0.800], Time [F(2, 86) = 0.03, p = 0.967] or interaction effect [F(2, 86) = 0.00, p = 0.996].

This performance pattern, when compared to the performance patterns for each individual measure, was least dissimilar to Percentage recall from the recency region of the list, although the position of the groups was reversed, with the chemotherapy group performing worse than the no-chemotherapy group at each time (see '4Crepz' Appendix F, p. F17).

27 The verbal primacy/recency recall and recall errors summary score included 1.45% (n = 2) missing values.
Figure 9.12. Means (± SEM) of summary score for verbal primacy/recency recall and recall errors over time by breast cancer treatment group.

While the performance patterns showed some differences, the p value profiles were the same, as shown in Table 9.7, as both displayed no significant main effects for Time, Group or an interaction. The Verbal Primacy/Recency Recall and Recall Errors performance pattern was least consistent with Total intrusion errors where the performance of the chemotherapy group improved at the final assessment (see ‘Ctintz’ Appendix F, p. F17).

Table 9.7

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal primacy/recency recall and recall errors</td>
<td>Verbal</td>
<td>0.800</td>
<td>0.967</td>
<td>0.996</td>
</tr>
<tr>
<td>% Recall from Recency Region</td>
<td>Verbal</td>
<td>0.704</td>
<td>0.417</td>
<td>0.952</td>
</tr>
<tr>
<td>% Recall from Primacy Region</td>
<td>Verbal</td>
<td>0.901</td>
<td>0.242</td>
<td>0.895</td>
</tr>
<tr>
<td>Total intrusions</td>
<td>Verbal</td>
<td>0.908</td>
<td>0.005**</td>
<td>0.059</td>
</tr>
<tr>
<td>Total repetitions</td>
<td>Verbal</td>
<td>0.600</td>
<td>0.444</td>
<td>0.137</td>
</tr>
</tbody>
</table>

Note: all are CVLT-2 measures.
*Significant at: *p < 0.05; ** p < 0.01; *** p < .001 (boldface).
9.2.4 Paired associates learning and visual memory

A PCA was conducted on all paired associates learning and visual recall measures in Grouping 3. The first principal component accounted for 32% of the variance. An ANOVA was performed on the first principal component score28.

Figure 9.13. Means (± SEM) of summary score for paired associates learning and visual memory over time by breast cancer treatment group.

The paired associates learning and visual memory performance of both groups declined over the first two assessments, as shown in Figure 9.13, but while the chemotherapy group continued to decline from the Average to the Low Average range, the performance of the no-chemotherapy group improved. However, there was no significant interaction effect \( F(2, 86) = 0.56, p = 0.572 \) or main effect of Group \( F(1, 44) = 0.50, p = 0.485 \) or Time \( F(2, 76) = 1.77, p = 0.177 \) found on performance.

Inspection of the biplot and latent vector loadings suggested nested groupings. Five independent subgroups were found within the Grouping 3 Paired Associates Learning and Visual Memory measures, including those related to a) visuospatial memory encoding; b) visuospatial span; c) verbal paired associates learning; d) visual paired associates learning; and e) visual memory.

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28 The paired associates learning and visual memory summary scores included 8.70% \( (n = 12) \) missing values.
The summary score performance of paired associates learning and visual memory is presented for comparison with the five nested subgroups in Figure 9.14. The paired associates learning and visual memory performance pattern (Figure 9.14a) is not consistent overall with any of the subgroup measures. Between Time 1 and Time 2 the performance profile is most consistent with the performance within visuospatial span performance (Figure 9.14c) and visual paired associates learning (Figure 9.14e), as both groups declined and the no-chemotherapy group performed better than the chemotherapy group, but instead of the chemotherapy group performance declining further at Time 3, they improved parallel to the no-chemotherapy group.

While the performance patterns were partially similar, the p value profiles were not, as seen in Table 9.8. Both visual paired associates learning and visuospatial span performance demonstrated a significant main effect of Time on performance, unlike the paired associates learning and visual memory summary measure. Visuospatial span performance also demonstrated a significant main effect of Group on performance. The performance pattern in paired associates learning and visual memory most contrasts with visual memory (Figure 9.14f) in which the performance of groups improved markedly between Time 1 and both Time 2 and Time 3.

Table 9.8

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paired associates learning and visual memory</td>
<td>Visuospatial</td>
<td>0.443</td>
<td>0.189</td>
<td>0.590</td>
</tr>
<tr>
<td>Visuospatial memory encoding</td>
<td>Visuospatial</td>
<td>0.719</td>
<td>&lt;.001**</td>
<td>0.969</td>
</tr>
<tr>
<td>Visuospatial span</td>
<td>Visuospatial</td>
<td>0.034*</td>
<td>&lt;.001**</td>
<td>0.971</td>
</tr>
<tr>
<td>Verbal paired associates learning</td>
<td>Verbal</td>
<td>0.658</td>
<td>0.054</td>
<td>0.480</td>
</tr>
<tr>
<td>Visuospatial paired associates learning</td>
<td>Visuospatial</td>
<td>0.176</td>
<td>0.003**</td>
<td>0.976</td>
</tr>
<tr>
<td>Visual memory</td>
<td>Visuospatial</td>
<td>0.590</td>
<td>&lt;.001**</td>
<td>0.719</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; **p < 0.01; ***p <.001 (boldface).
Results from each of the subgroups within paired associates learning and visual memory will be explored in more detail.
a. Visuospatial memory encoding.

The first principal component accounted for 72% of the variance in the visuospatial memory encoding measures. An ANOVA was performed on the first principal component score\(^{29}\).

![Figure 9.15](image)

*Figure 9.15. Means (± SEM) of summary score for visuospatial memory encoding over time by breast cancer treatment group.*

The visuospatial memory encoding performance of both groups was similar, as shown by the parallel slopes in Figure 9.15, declining between *Time 1* and *Time 2* within the *Average* range and improving at *Time 3*, although not to baseline levels. There was a significant main effect of *Time* \([F(2, 81) = 7.54, p = <.001]\) on performance, reflecting a significant decline in visuospatial memory encoding from *Time 1* \((M = 0.304)\) to both the *Time 2* \((M = -0.320)\) and *Time 3* follow-up assessments \((M = -0.070)\) \((\text{PD}>\text{LSD} = 0.322, \text{at a } 95\% \text{ confidence level})\). However, there was no main effect of *Group* \([F(1, 44) = 0.13, p = 0.719]\) or an interaction effect \([F(2, 81) = 0.03, p = 0.969]\) found on performance. This means that while there was a decline in visuospatial memory encoding from *Time 1* to the follow up assessments, this change was not significantly different between women exposed to chemotherapy and women not exposed to chemotherapy.

\(^{29}\) The visuospatial encoding subgroup included 5.07% \((n = 7)\) missing values.
As there was a significant deterioration in performance in both groups over time, a regression model involving forwards stepwise selection was used to identify potential explanatory variables for visuospatial memory encoding change scores (Time 3 - Time 1), controlling for Time 1 baseline scores. A general linear regression revealed that higher baseline scores ($p = 0.007$) and an increase in mental fatigue ($p = 0.039$) were significant determinants of decline in visuospatial memory encoding performance at Time 3.

The visuospatial memory encoding performance pattern was most consistent with the individual measure Spatial Recognition Memory Percentage Correct (see 'SRM%cor' Appendix F, p. F19). This performance profile was also reflected in the $p$ value relationships, with both measures displaying a significant main effect of Time on performance, as seen in Table 9.9.

Table 9.9.

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visuospatial memory encoding</td>
<td>Visuospatial</td>
<td>0.719</td>
<td>&lt;.001***</td>
<td>0.969</td>
</tr>
<tr>
<td>Spatial recognition memory % correct</td>
<td>Visuospatial</td>
<td>0.423</td>
<td>&lt;.001***</td>
<td>0.730</td>
</tr>
<tr>
<td>Complex figure test recognition total correct</td>
<td>Visuospatial</td>
<td>0.944</td>
<td>0.578</td>
<td>0.946</td>
</tr>
</tbody>
</table>

*Significant at: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (boldface).

b. Visuospatial span performance.

The first principal component accounted for 87% of the variance in visuospatial span measures. An ANOVA was performed on the first principal component score\textsuperscript{30}.

As seen in Figure 9.16, both breast cancer treatment groups displayed a parallel decline in visuospatial span over the first two assessments from the Well Above Average range to the Low Average range, with no further decline evident at the Time 3 assessment.

\textsuperscript{30} The visuospatial span subgroup included 2.17% ($n = 3$) missing values.
There was a significant main effect of Time on performance \( F(2, 85) = 99.04, p < .001 \), reflecting a significant decline in visuospatial span performance from Time 1 \( (M = 1.446) \) to both the Time 2 \( (M = -0.789) \) and Time 3 assessments \( (M = -0.582) \) (PD>LSD = 0.349, at a 95% confidence level). There was also a significant main effect of Group on performance \( F(1, 44) = 4.77, p = 0.034 \) with the chemotherapy group demonstrating significantly poorer visuospatial span \( (M = -0.097) \) than the no-chemotherapy group \( (M = 0.252) \) over time. However, there was no significant Group by Time interaction effect found on performance \( F(2, 85) = 0.03, p = 0.971 \). This means that while there were significant differences in visuospatial span performance between the chemotherapy and no-chemotherapy groups, this difference in performance between groups did not vary over time. The lack of a significant interaction effect indicates that the marked decline in performance from Time 1 did not depend on exposure to chemotherapy.

A general linear regression revealed that higher baseline scores \( (p = < .001) \), increased cancer severity \( (p = 0.005) \) and having a mastectomy \( (p = 0.017) \) were significant determinants of decline in visuospatial span performance at Time 3.

This visuospatial span performance pattern was similar to both individual measures but was most consistent with Paired Associates Learning First trial mean recall, considered a measure of visuospatial span (see 'PAL1Mza' Appendix F, p. F20). While the performance
patterns were the same the \( p \) value relationships varied, as seen in Table 9.10. Both measures displayed a significant main effect of \textit{Time} on performance, but only Stages completed on the first trial of the Paired Associates Learning (PAL) test displayed a main effect of \textit{Group} on performance.

Table 9.10

\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Name} & \textbf{Visual/Verbal} & \textbf{Group} & \textbf{Time} \\
\hline
Visuospatial span & Visuospatial & 0.034* & <.001* \\
\hline
PAL \(^a\) Stages completed on first trial (adjusted) & Visuospatial & \textbf{0.035} & \textbf{<.001}* \\
\hline
PAL First trial mean recall & Visuospatial & 0.062 & \textbf{<.001}* \\
\hline
\end{tabular}

\(^a\)PAL refers to the CANTAB Paired Associates Learning test.

*Significant at: *\( p < 0.05 \); ** \( p < 0.01 \); *** \( p < 0.001 \) (boldface).

c. \textit{Verbal paired associates learning.}

The first principal component accounted for 64\% of the variance in the verbal paired associates learning measures. An ANOVA was performed on the first principal component score\(^{31}\).

The average performance of both groups was very similar at \textit{Time 1}, as shown in Figure 9.17. The no-chemotherapy group displayed some improvement over the first two assessments, within the \textit{Average} range, while the chemotherapy group performance did not. Both groups showed a drop in performance at \textit{Time 3} but while the no-chemotherapy group did not drop below baseline performance, the chemotherapy group did, into the \textit{Low Average} range. There was no significant interaction effect \([F(2, 76) = 0.74, p = 0.480]\) or main effect of \textit{Group} \([F(1, 44) = 0.20, p = 0.658]\) on performance. There was also no significant main effect of \textit{Time}, although there was a trend apparent \([F(2, 76) = 3.03, p = 0.054]\) indicating a decline in performance between the \textit{Time 2} \((M = 0.23)\) and \textit{Time 3} \((M = -0.41)\) assessments (PD>LSD = 0.526, at a 95\% confidence level).

\(^{31}\) The verbal paired associates learning grouping included 8.70\% \((n = 12)\) missing values.
As there was a trend towards a significant deterioration in performance in both groups between Time 2 and Time 3, a regression model involving forwards stepwise selection was used to identify potential explanatory variables for verbal paired associates learning change scores (Time 3 - Time 2), controlling for Time 1 baseline scores. A general linear regression revealed that lower estimated intelligence, higher anxiety at Time 1, getting neutropenia and having a clinical anxiety disorder at Time 3 were significant determinants of decline in verbal paired associates learning performance at Time 3. To explore the effect of cognitive reserve the regression was repeated to see if lower estimated premorbid intelligence interacted with neutropenia on decline. Women who had lower estimated premorbid intelligence and experienced chemotherapy-induced neutropenia \((p = 0.020)\) or higher anxiety at Time 1 \((p = 0.032)\) or clinical anxiety at Time 3 \(p = 0.027)\) were more vulnerable to decline in verbal paired associates learning at Time 3. A one standardized unit drop in cognitive reserve (IQ) + chemotherapy + neutropenia was estimated to predict a 2.12 score decline in verbal paired associates learning from pre-treatment to 9 months post-treatment.

The verbal paired associates learning summary performance pattern was most consistent with the individual measures, Trial 1 Total Correct Recall and Average Immediate Recall, trials 1-4 (see 'vPA1t1z' and 'vPA1z' Appendix F, p. F21). While the performance patterns were similar, the \(p\) value relationships differed (see Table 9.11). There was a trend to significance of Time on the verbal paired associates learning summary score that
was not indicated in these individual measures. The verbal paired associates learning performance pattern was least consistent with Percent Retention in which the positions of the groups were reversed, with the chemotherapy group performing slightly better on average than the no-chemotherapy group, and both groups declined consistently over the course of assessments (see ‘VPA_prtz’ Appendix F, p. F21).

Table 9.11

P values for Group, Time and Interaction effects obtained from ANOVAs of the Verbal Paired Associates Learning Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal paired associates learning</td>
<td>Verbal</td>
<td>0.658</td>
<td>0.054</td>
<td>0.480</td>
</tr>
<tr>
<td>VPA_6 Immediate recall (1 - 4)</td>
<td>Verbal</td>
<td>0.455</td>
<td>0.171</td>
<td>0.333</td>
</tr>
<tr>
<td>VPA_6 Long term recall</td>
<td>Verbal</td>
<td>0.876</td>
<td></td>
<td>0.004**</td>
</tr>
<tr>
<td>VPA_6 Percent Retention</td>
<td>Verbal</td>
<td>0.446</td>
<td>0.041*</td>
<td>0.999</td>
</tr>
<tr>
<td>VPA_6 Trial 1 recall</td>
<td>Verbal</td>
<td>0.665</td>
<td>0.702</td>
<td>0.310</td>
</tr>
<tr>
<td>VPA_6 Trial 2 recall</td>
<td>Verbal</td>
<td>0.223</td>
<td>0.175</td>
<td>0.811</td>
</tr>
<tr>
<td>VPA_6 Trial 3 recall</td>
<td>Verbal</td>
<td>0.777</td>
<td>0.416</td>
<td>0.298</td>
</tr>
<tr>
<td>VPA_6 Trial 4 recall</td>
<td>Verbal</td>
<td>0.557</td>
<td>0.378</td>
<td>0.474</td>
</tr>
<tr>
<td>VPA_6 Learning slope (adjusted)</td>
<td>Verbal</td>
<td>0.960</td>
<td>0.515</td>
<td>0.870</td>
</tr>
</tbody>
</table>

VPA_6 = Verbal Paired Associates (names)

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).

d. Visual paired associates learning.

The first principal component accounted for 77% of the variance in the visual paired associates learning measures. An ANOVA was performed on the first principal component score

The visual paired associates learning performance was similar in both groups over the course of the assessments as shown by the parallel slopes in Figure 9.18. Both groups deteriorated between the Time 1 and Time 2 assessments, from the Average to the Low Average range for the chemotherapy group and from the High Average to the Average range for the no-chemotherapy group. Both groups improved at Time 3 recovering to near baseline performance.

The visual paired associates learning summary score included 2.17% (n = 3) missing values.
Figure 9.18. Means (± SEM) of summary score for visual paired associates learning over time by breast cancer treatment group.

There was no significant interaction effect \([F(2, 85) = 0.02, p = 0.976]\) or main effect of Group \([F(1, 44) = 1.89, p = 0.176]\) found on performance. There was a significant main effect of Time \([F(2, 85) = 6.21, p = 0.003]\) reflecting that visual paired associates learning performance declined significantly between the Time 1 \((M = 0.40)\) and Time 2 \((M = -0.50)\) assessments and improved significantly between the Time 2 and Time 3 \((M = 0.16)\) assessments \((\text{PD}>\text{LSD} = 0.521\), at a 95% confidence level). 

As there was a significant deterioration in performance in both groups between Time 1 and Time 2, a regression model involving forwards stepwise selection was used to identify potential explanatory variables for visual paired associates learning change scores \((\text{Time} 2 - \text{Time} 1)\), controlling for Time 1 baseline scores. A general linear regression revealed that lower physical wellbeing and role functioning at Time 1 \((p = 0.024)\) and having a clinical anxiety or mood disorder at Time 2 \((p = 0.024)\) were significant determinants of decline in visual paired associates learning performance at Time 2.

The visual paired associates learning overall performance pattern was most consistent with the individual CANTAB Paired Associates Learning measures, Mean Errors to Success (log transformed) and Mean Trials to Success (adjusted) (see ‘\text{PALMESz}_{\text{AR}}\text{L}' and ‘\text{PALMTSz}_{\text{A}}\text{'}\text{Appendix F, p. F23}'). The \(p\) value profiles were also the same, as can be seen in Table 9.12, with all displaying a significant \text{Time} effect but not a \text{Group} or interaction.
effect. The visual paired associates learning summary score performance was least consistent with the individual measure of Total errors on the six shapes trial (log transformed) where the performance of both groups improved over the first two assessments, rather than declined, and deteriorated at the final assessment, instead of improving (see 'aPALTE6zaRL' Appendix F, p. F23).

Table 9.12

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual paired associate learning</td>
<td>Visuospatial</td>
<td>0.176</td>
<td>0.003**</td>
<td>0.976</td>
</tr>
<tr>
<td>PAL Mean errors to success (RLª)</td>
<td>Visuospatial</td>
<td>0.247</td>
<td>&lt;.001***</td>
<td>0.866</td>
</tr>
<tr>
<td>PAL Total errors, 6 shapes (RLª)</td>
<td>Visuospatial</td>
<td>0.240</td>
<td>0.891</td>
<td>0.928</td>
</tr>
<tr>
<td>PAL Total errors (adjusted) (RLª)</td>
<td>Visuospatial</td>
<td>0.256</td>
<td>0.011*</td>
<td>0.858</td>
</tr>
<tr>
<td>PAL Mean trials to success (adjusted)</td>
<td>Visuospatial</td>
<td>0.113</td>
<td>&lt;.001***</td>
<td>0.937</td>
</tr>
</tbody>
</table>

ª RL = natural log transformation and reflection was applied to data to correct non-random distribution of residuals prior to ANOVA.
*Significant at: *p < 0.05; ** p < 0.01; *** p <.001 (boldface).

e. Visual memory.

The first principal component accounted for 49% of the variance in the visual memory measures. An ANOVA was performed on the first principal component score\(^{33}\).

Both groups displayed an improvement in visual memory performance between Time 1 and Time 2, with the chemotherapy group improving from the Low Average to the Average range, as shown in Figure 9.19. Both groups plateaued at Time 3.

\(^{33}\) The visual memory summary score included 2.17% (n = 3) missing values.
There was no significant interaction effect \[ F(2, 85) = 0.33, p = 0.719 \] or main effect of Group \[ F(1, 44) = 0.29, p = 0.590 \] observed on performance. There was a significant main effect of Time \[ F(2, 85) = 21.58, p < .001 \] reflecting that visual memory performance at both the Time 2 \( (M = 0.377) \) and Time 3 \( (M = 0.272) \) follow-up assessments was significantly better than performance at Time 1 \( (M = -0.647) \) (PD>LSD = 0.341, at a 95% confidence level). This significant improvement over time was consistent with a practice effect.

The visual memory performance pattern was most consistent with the individual measure from the Complex Figure Test, Long Delay Recall (see ‘cCFTdrrz’ Appendix F, p. F25). This performance profile consistency was also maintained in the p value relationships between these measures, with both displaying a significant main effect of Time on performance but not a Group or interaction effect, as can be seen in Table 9.13. The visual memory performance pattern was least consistent with Pattern Recognition Memory Percentage correct on the immediate trial, where the performance of the no-chemotherapy group deteriorated over the first two assessments and then improved (see ‘cPRMi%cza’ Appendix F, p. F25).
Table 9.13

P values for Group, Time and Interaction effects obtained from ANOVAs of Visual Memory Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual memory</td>
<td>Visuospatial</td>
<td>0.590</td>
<td>&lt;.001***</td>
<td>0.719</td>
</tr>
<tr>
<td>9CFT immediate recall, total correct</td>
<td>Visuospatial</td>
<td>0.424</td>
<td>0.002**</td>
<td>0.878</td>
</tr>
<tr>
<td>9PRM immediate (% correct)</td>
<td>Visual</td>
<td>0.480</td>
<td>0.249</td>
<td>0.762</td>
</tr>
<tr>
<td>CFT delayed recall, total correct</td>
<td>Visuospatial</td>
<td>0.503</td>
<td>0.018*</td>
<td>0.528</td>
</tr>
<tr>
<td>PRM delayed (% correct)</td>
<td>Visual</td>
<td>0.919</td>
<td>0.001**</td>
<td>0.909</td>
</tr>
<tr>
<td>6PAL Total trials (adjusted)</td>
<td>Visuospatial</td>
<td>0.432</td>
<td>&lt;.001***</td>
<td>0.729</td>
</tr>
</tbody>
</table>

9CFT = Complex Figure test. 9PRM = CANTAB Pattern Recognition Memory. 9CANTAB PAL = Paired Associates Learning test.
*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).

9.3 Chapter summary

This chapter presented the results of principal components and data analyses on data from the 58 outcome measures produced from the six tests of learning and memory. From this analysis a subtle profile of impairment following chemotherapy emerged in verbal learning and memory. Women were identified who were more vulnerable to decline, including those with lower premorbid IQ and those who received hormonal therapy following chemotherapy and/or experienced neutropenia, a serious chemotherapy-induced adverse event. These findings are discussed in Chapter 12.2.7.

The groupings found within learning and memory are consistent with the literature (Baddeley, 2000; Lezak, et al., 2012) and are discussed in further detail in Chapter 12.2.5.

a. Group by Time interaction effects

A profile of chemotherapy-related cognitive impairment was found in verbal learning and memory that was reflected in the summary measure for the learning and memory domain. This impairment was most evident at the subgroup level in verbal memory encoding and verbal recall discriminability where the no-chemotherapy group showed significant improvement in performance over time, whereas the chemotherapy group demonstrated no improvement or decline following completion of chemotherapy. The verbal recall discriminability performance of the chemotherapy group declined significantly between Time 2 and Time 3. Recall discriminability was based on new measures developed for the CVLT-2 that uses a measure of target accuracy that corrects for intrusion rate, which has
been found to be more sensitive to recall accuracy and discrimination than traditional recall measures (D.C. Delis et al., 2005). Immediate memory and learning was found to be unaffected by chemotherapy as performance improved significantly in both groups over time and there was no significant difference in this change between groups. However, the performance profile of decline following chemotherapy found in verbal recall discriminability was similar to the profile of performance for the chemotherapy group in verbal paired associates learning, even though there was no significant interaction effect observed on this measure. Taken together these results adds support to a profile of verbal learning and memory functions being affected by chemotherapy.

Women with: lower premorbid IQ (verbal recall discriminability and verbal paired associates learning); smaller cancer size (verbal learning and memory and verbal recall discriminability); higher baseline scores; higher mental fatigue (verbal learning and memory, verbal recall discriminability); and higher anxiety (learning and memory, verbal paired associates learning) or a clinical anxiety or mood disorder at Time 1 (verbal memory encoding) were at greater risk of decline at Time 3. This demonstrates the multifaceted nature of the impact of both cancer, cognitive reserve, psychological disorders and chemotherapy on verbal learning and memory.

Women who received hormonal therapy in addition to chemotherapy were at greater risk for decline in overall learning and memory performance, verbal learning and memory and verbal recall discriminability at Time 3. This suggests a cumulative negative cognitive effect of hormonal therapy on verbal learning and recall accuracy following chemotherapy. Women who experienced chemotherapy-induced neutropenia were at increased risk of decline in verbal recall discriminability and verbal paired associates learning performance at Time 3. Neutropenia, a serious haematological toxicity, is characterized by a deficiency of neutrophils, a type of white blood cell, that protects the body against bacterial and fungal infections (J. Crawford, Dale, & Lyman, 2004). Severe neutropenia is a significant toxic side effect of chemotherapy, especially taxane-based chemotherapy regimens, and carries a risk of life-threatening infection. Women who experienced chemotherapy-induced neutropenia and then received hormone therapy were at greater risk of decline in overall learning and memory and verbal recall discriminability performance at Time 3. The cumulative impact of chemotherapy and neutropenia and hormonal therapy was estimated to predict a 2.50 score decline in learning and memory from pre-treatment (Time 1) to 9 months post-treatment (Time 3).

Women who were older were not found to be more vulnerable to decline. However, women with lower estimated premorbid IQ were more vulnerable to decline in verbal recall discriminability at Time 3. Risk of decline in verbal recall discriminability was also
higher in women who experienced chemotherapy-induced neutropenia and then received hormone therapy. Women who had lower premorbid IQ and experienced chemotherapy-induced neutropenia were more vulnerable to decline in verbal paired associates learning at Time 3. This would suggest that women who are exposed to chemotherapy toxicity, especially those with lower premorbid IQ, are more vulnerable to other toxicity, including neutropenia and hormonal therapy, especially when cumulative. This will discussed further in Chapter 12.2.7.

Women with higher baseline anxiety (learning and memory, verbal paired associates learning) or the presence of an anxiety or mood disorder at Time 1 (verbal memory encoding) or a decline in emotional wellbeing from Time 1 to Time 3 (verbal learning and memory) or clinical anxiety at Time 3 (verbal paired associates learning) were more vulnerable to decline in overall learning and memory, verbal memory encoding, verbal learning and memory and verbal paired associates learning at Time 3. This suggests there is a complex relationship between mental health and cognitive performance but the direction of the results cannot be determined. Acute anxiety could affect cognitive performance but awareness of cognitive decline could also increase anxiety.

Using more specific self-report measures for perceived cognitive problems helped to reveal different relationships of subjective reports with objective measures. Overall self-reported cognitive problems were not associated with decline in any aspect of learning and memory. Counter-intuitively, an increase in self-reported retrospective memory problems was associated with improved verbal memory encoding performance at Time 3. However, more self-reported mental fatigue at Time 1 was associated with a decline in verbal learning and memory and verbal recall discriminability at Time 3. This may help to identify women prior to treatment that are at greater risk of decline following treatment.

b. *Time effects*

A profile of significant improvement was found for both groups in verbal immediate memory and learning and visual memory. These two memory groupings also displayed Time 2 performance that was significantly better than at Time 1. These significant improvements in performance at follow-up are consistent with a practice effect.

A profile of decline emerged for visuospatial learning and memory that was not directly associated with chemotherapy. A profile of decline in visuospatial encoding, learning and memory span was found in women with breast cancer from both treatment groups. Women more vulnerable to decline in visuospatial memory encoding, visuospatial span or paired associate learning were women who had higher baseline scores.
visuospatial memory), increased cancer severity (visuospatial span), poorer physical wellbeing and role functioning at Time 1 (visual paired associate learning) or whose final surgery involved a mastectomy (visuospatial span). Women whose mental fatigue increased from Time 1 to Time 3 were at greater risk of decline in visuospatial memory encoding and women who presented with a clinical anxiety or mood disorder at Time 2 were more vulnerable to decline in visual paired associates learning performance at Time 2. While the causality of results cannot be determined, these results suggest avenues for intervention.

Notably, were the no-chemotherapy group not included in the current study it might have been concluded that there was no impact of chemotherapy on verbal learning and memory where performance improved over time and that the deterioration in visual learning and memory was associated with exposure to chemotherapy.

In summary, a subtle profile of impairment following chemotherapy on verbal learning and memory emerged. A profile of increased risk was found, including the cumulative impact of chemotherapy and/or neutropenia and/or hormonal therapy, as well as an interaction of premorbid IQ, a measure of cognitive reserve (Stern, 2003). This is discussed in detail in Chapter 12.2.7.
Executive Functions

10.1 Introduction

The tests employed to assess changes to executive functions were the WAIS-III Similarities Test, the D-KEFS Word Context Test, Proverbs Test, Verbal Fluency test and Color-Word Interference Test and the CANTAB Stockings of Cambridge Test, the Spatial Working Memory test and the Intra-Extra Dimensional Set Shift Test. These tests measure different executive functions, including abstract reasoning and concept formation, verbal fluency, attentional switching or cognitive flexibility, spatial working memory, strategy, planning and inhibition. They also include measures of higher order speed of planning.

The CANTAB Spatial Working Memory test assesses a participant’s ability to retain spatial information and manipulate remembered items in working memory. It is a self-ordered task, so it also assesses heuristic strategy. It has been found to be a sensitive measure of frontal lobe or executive dysfunction (Kaufmann et al., 2013; Owen et al., 1998; Robbins, et al., 1998). The outcome measures from this test were examined in separate principal component analyses with the Attention domain measures, due to the spatial working memory component, as well as with the Executive Functions domain measures. As they behaved more consistently with the Executive Functions measures, assessed via the biplot and latent vector loadings, they were included in the Executive Functions analysis.

The measures of response inhibition (Color-Word Interference Test, condition 3: inhibition) and attentional switching (Color-Word Interference Test, condition 4: inhibition/switching; Intra-Extra Dimensional Set Shift Test, Verbal fluency, condition 4: fluency/switching) also behaved more consistently with the Executive Functions measures, so they were entered into the Executive Functions domain analysis.

In addition, tests from other domains that have been shown to measure executive functions were included, namely the Complex Figure total organization score. The Complex Figure copy speed, a measure of visuospatial processing speed, was included as well as it behaved more consistently with planning speed measures than other reaction time or speed of processing measures in Attention and Speed of Processing. The procedure used in the analysis is the same as described previously (in Chapter 6.5.4) and this chapter is structured the same as the previous chapter (outlined in Chapter 8.2).
Eight-five percent of participants (n = 39) had complete data for executive functions. Missing values were examined and assessed (for details see Chapter 6.7.2).

10.2 Principal component and data analyses

A principal components analysis was performed on data from the 32 outcome measures produced from the nine tests of executive functions. The first principal component accounted for 21% of the variance in these measures. An ANOVA was performed on the first principal component score.

![Diagram showing means (± SEM) of summary score for executive functions over time by breast cancer treatment group.]

Figure 10.1. Means (± SEM) of summary score for executive functions over time by breast cancer treatment group.

Time 1 = Post-surgery (pre-chemotherapy); Time 2 = 6 months from Time 1 (post-chemotherapy); Time 3 = 15 months from Time 1 (≈ 9 months post-chemotherapy).

The Executive Functions summary performance profile of the no-chemotherapy group improved slightly from the Average to the High Average range over the course of the assessments, whereas the chemotherapy group did not improve, remaining within the Average range, as seen in Figure 10.1. However, there was no significant Group by Time interaction effect \([F(2,80) = 0.24, p = 0.788]\) or main effect of Group \([F(1,44) = 1.15, p = 0.290]\) or Time \([F(2,80) = 0.01, p = 0.995]\) on performance.

34 Of the 138 Executive Functions summary scores dataset, there were 6% (n = 8) missing values.
Examination of the biplot of the first two principal components indicated three groupings, as illustrated in Figure 10.2.

Grouping 1 contains mainly verbal measures of executive functioning.

Grouping 2 contains mainly visual executive functions measures. The first eight measures of Grouping 2 (11 to 18) are strategy and working memory measures from visual tests and they are positioned on the biplot between Grouping 1 and the rest of the measures in Grouping 2. These measures are directly located between measures of strategy and cognitive flexibility in the verbal executive grouping (Grouping 1) and the planning measures in the visual executive grouping (Grouping 2). Further biplots were conducted, from which it was clear that the strategy measures were closely associated with planning measures in Grouping 2. Grouping 3 is located opposite Grouping 1 in the bottom half of the plot, suggesting a possible negative relationship. This grouping contains visuospatial initial planning and processing speeds. It was explored whether to combine these two groupings. The biplot from a further PCA demonstrated that these measures behaved independently.

A measure that was located vertically opposite Grouping 2 on the border of Grouping 1 was Verbal Fluency Set Loss Errors. After further biplot analysis, this measure was more consistent with the Verbal Executive grouping (Grouping 1) than with the Visual Executive grouping (Grouping 2). A measure of Spatial Strategy was located on the border between verbal fluency switching measures in Grouping 1 and organization and spatial working memory measures in Grouping 2. After further analysis, this measure was considered more consistent with the Visual Executive grouping (Grouping 2).

A measure of initial planning speed for a 3 move problem was located on the border between Grouping 2 and Grouping 3. It was found to be more consistent with the measures in the Planning Speed grouping (Grouping 3) than in the Visual Executive grouping (Grouping 2). The only verbal measure located within Grouping 2 was Verbal Fluency Repetition Errors. It was more closely associated with measures in Grouping 2 and was retained within Grouping 2.
Figure 10.2. Biplot of the executive functions data.

The first principal component axis (horizontal, PC-1 axis) represents the linear combination of the measures that maximizes shared variance (25%). The second principal component axis (vertical, PC-2 axis) represents component loadings with the next most shared variance independent of the first principal component. The smaller the angle between vectors, the larger the association between variables. Figure 10.2 suggests two main groupings and one or two minor groupings of variables. Grouping 1 contains mainly measures of verbal executive functions. Grouping 2 contains mainly measures of visual executive functions. Group 3 is located opposite Grouping 1 and includes planning speed measures.

Grouping 1: 1, 2, 3, 4 D-KEFS Color-word Interference (CWI) test; 5, 6, 8, 9 D-KEFS Verbal Fluency (VF); 10 Verbal Reasoning, 11 CANTAB Spatial Working Memory (SWM).

Grouping 2: 12 Complex Figure Test (CFT), 13, 14, 15, 16, 17, 18 CANTAB Spatial Working Memory (SWM). 19, 20, 21, 22, 28 CANTAB Stockings of Cambridge (SOC). 23 D-KEFS Verbal Fluency (VF). 24, 25, 26, 27 CANTAB Intra-extra dimensional (IED) shift.

Grouping 3: 29, 30 CANTAB Stockings of Cambridge (SOC). 31 Complex Figure Test (CFT).

Between Groupings 1 and 3: 32 D-KEFS Verbal fluency (VF).

* For details of latent vector loadings on the first two principal components, see Appendix E, p. E5.
Additional principal component analyses were conducted on the main groupings to explore further nested groupings with internal consistency. Where distinct groupings were evident, further principal component analyses were conducted and examined for meaningful subgroups. The nested groupings within Executive Functions are presented in Figure 10.3.

Two subgroups were found within the Grouping 1: Verbal executive functioning measures (see Figure 10.3), including those relating to inhibition and to verbal fluency, flexibility and reasoning. Three subgroups were found within the Grouping 2: Visual executive function measures, including those relating to planning and problem solving, spatial working memory and cognitive flexibility. The visuospatial planning and copy speed measures made an internally consistent subgroup i.e., Grouping 3: Planning speed.

The first principal component score for each grouping was then extracted for use in subsequent analysis. An ANOVA was performed on the first principal component summary score for each grouping to explore the impact of chemotherapy on executive functions.

A comparison of the performance profiles (i.e., the slopes) of both treatment groups in Executive Functions over time alongside the three major groupings is presented in Figure 10.4. The overall Executive Functions performance profile (Figure 10.4a) was not entirely consistent with any of the major groupings but was most consistent with the Grouping 2: Visual executive performance profile (Figure 10.4c) as the slope of the no-chemotherapy group rose from Time 1 to Time 3, while the chemotherapy group did not.
The p values from these analyses are presented in Table 10.1. Not only were the overall Executive Functions and the Grouping 2: Visual executive performance profiles consistent, their p value profiles were the same. They both did not demonstrate any significant main effect of Group, Time or interaction on performance. In contrast, within the Grouping 1: Verbal executive and Grouping 3: Planning speed performance profiles (see Figure 10.4b and d), the chemotherapy group improved from Time 1 to Time 2, instead of remaining flat.
Table 10.1

Summary of p values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Overall and Major Groupings in Executive Functions

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Functions</td>
<td>Visual-verbal</td>
<td>0.290</td>
<td>0.995</td>
<td>0.788</td>
</tr>
<tr>
<td>Verbal Executive</td>
<td>Verbal</td>
<td>0.043*</td>
<td>0.155</td>
<td>0.476</td>
</tr>
<tr>
<td>Visual Executive</td>
<td>Visual</td>
<td>0.456</td>
<td>0.899</td>
<td>0.659</td>
</tr>
<tr>
<td>Planning Speed</td>
<td>Visuospatial</td>
<td>0.287</td>
<td>&lt;.001***</td>
<td>0.450</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).

Results from the analyses within each of the major groupings follows.

10.2.1 Verbal Executive Functions

A principal components analysis was conducted on all 10 executive functioning measures in Grouping 1. The first principal component accounted for 30% of the variance in these measures. An ANOVA was performed on the first principal component summary score35.

![Graph](image)

*Figure 10.5. Means (± SEM) of summary score for verbal executive over time by breast cancer treatment group.*

35 The verbal executive summary scores included 5% (n = 8) missing values.
The verbal executive performance profile of the chemotherapy group showed improvement from Time 1 to Time 2, within the Average range, and then deteriorated at Time 3 to the Low Average range, while the no-chemotherapy group showed a slight deterioration from the High Average to the Average range over the course of the assessments, as shown in Figure 10.5.

There was no significant Group by Time interaction effect \[ F(2,80) = 0.75, \ p = 0.476 \] on performance. There was a significant main effect of Group \[ F(1,44) = 4.36, \ p = 0.043 \] indicating that the chemotherapy group \( M = -0.319 \) displayed significantly poorer verbal executive skills than the no-chemotherapy group \( M = 0.626 \) across time. There was some trend observed for the main effect of Time \[ F(2,80) = 1.91, \ p = 0.155 \] reflecting that the average performance at Time 3 \( M = -0.177 \) was less than at Time 2 \( M = 0.246 \) across both groups, although the pairwise difference failed to reach significance when compared to the least significant difference of the means \( \text{PD}<\text{LSD} = 0.440, \ n.s. \) at a 95% confidence level).

As there was a significant main effect of Group, a regression model was conducted involving forwards stepwise selection to identify potential explanatory variables for verbal executive Time 1 baseline scores. A general linear regression on Time 1 scores revealed that women with lower estimated IQ were more likely to have lower scores at Time 1. When the regression was repeated with the 2-way interaction of IQ x number of general anaesthetics it was found that women with lower estimated IQ who had received more general anaesthetics were at greater risk of lower scores at Time 1 \( p = 0.015 \). Women with lower cognitive reserve who had more general anaesthetics were estimated to have a 0.68 score decrease in verbal executive performance at Time 1.

Inspection of the biplot of the verbal executive measures and latent vector loadings suggested nested groupings. Two independent subgroups were found within the Grouping 1 verbal executive measures, including those related to: a) verbal fluency, flexibility and reasoning and b) inhibition.

The mean summary score performance for verbal executive functions is presented with the three nested subgroups in Figure 10.6.
a. Grouping 1: Verbal Executive

b. Subgroup 1: Verbal Fluency, Flexibility and Reasoning

c. Subgroup 2: Inhibition

Figure 10.6. Means (± SEM) of summary score for overall and major groupings in verbal executive over time by breast cancer treatment group.

The verbal executive summary performance profile (Figure 10.6a) was most consistent with the performance profile of the verbal fluency, flexibility and reasoning subgroup (Figure 10.6b) although the p value profiles were slightly different, as can be seen in Table 10.2. Both profiles displayed a significant main effect for Group and a trend towards significance for a main effect for Time, although the trend was stronger for verbal fluency, flexibility and reasoning. However, there did appear to be a trend towards significance for an interaction effect in the verbal fluency, flexibility and reasoning profile that was not found in the verbal executive summary profile.
Table 10.2

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of the Verbal Executive Grouping and Subgroups

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Executive Function</td>
<td>Visual</td>
<td></td>
<td>0.043*</td>
<td>0.155</td>
</tr>
<tr>
<td>Verbal Fluency, Flexibility and Reasoning</td>
<td>Verbal</td>
<td></td>
<td>0.032*</td>
<td>0.054</td>
</tr>
<tr>
<td>Inhibition</td>
<td>Verbal-visual</td>
<td></td>
<td>0.388</td>
<td>0.286</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; **p < 0.01; ***p <.001 (boldface).

Results from each of the subgroups within verbal executive function will be explored in more detail.

a. Verbal Fluency, Flexibility and Reasoning

The first principal component accounted for 44% of the variance in measures from the verbal fluency, flexibility and reasoning grouping. An ANOVA was performed on the first principal component score. The first principal component score included 6% (n = 8) missing values.
The verbal fluency, flexibility and reasoning performance of the no-chemotherapy group was higher than the chemotherapy group over the course of the assessments, as seen in Figure 10.7. The chemotherapy group initially performed on the border of the Average to Low Average range while the no-chemotherapy group was in the High Average range. While the performance of the no-chemotherapy group declined slightly over the course of the assessments to the Average range, the chemotherapy group improved from Time 1 to Time 2 to well within the Average range, and then declined at Time 3 to the Low Average range.

There was a significant main effect of Group \( F(1,44) = 4.92, p = 0.032 \) indicating that the performance of the chemotherapy group \( (M = -0.324) \) was significantly poorer than the no-chemotherapy group \( (M = 0.553) \) across time. There was a trend for a Time effect \( F(2,80) = 3.02, p = 0.054 \) reflecting a deterioration in performance from Time 2 \( (M = -0.283) \) to Time 3 \( (M = -0.301) \) \( (P D > L S D = 0.474, at \ a \ 95\% \ confidence \ level) \). Moreover, the Group \( \times \) Time interaction effect displayed a trend towards significance \( F(2,80) = 1.92, p = 0.154 \).

This interaction effect reflected a significant difference in changes in verbal fluency, flexibility and reasoning between groups from the Time 1 and Time 2 assessment as well as a trend between the Time 2 and Time 3 assessment (using pairwise comparisons: \( T_{2\text{Group}} - T_{1\text{MD}} = -0.972; T_{3\text{Group}} - T_{2\text{MD}} = 0.581, \text{PD} < \text{LSD} = 0.703, \text{at a 95\% confidence level} \). Between Time 1 and Time 2 the performance of the chemotherapy group improved significantly \( (T_{2-1\text{MD}} = 0.66; \text{where LSD for Time} = 0.474) \) whereas the performance of the no-chemotherapy group did not significantly change \( (T_{2-1\text{MD}} = -0.312) \). Between Time 2 and Time 3 the performance of the chemotherapy group significantly declined \( (T_{3-2\text{MD}} = -0.79) \) whereas the performance of the no-chemotherapy group again did not significantly change \( (T_{3-2\text{MD}} = -0.21) \).

A regression model involving forwards stepwise selection was used to identify potential explanatory variables for verbal fluency, flexibility and reasoning change scores \( (\text{Time 3 - Time 2}) \), controlling for Time 1 baseline scores. The regression on change scores between Time 2 and Time 3 revealed that lower estimated premorbid IQ \( (p = 0.022) \), higher mental fatigue at Time 2 \( (p = 0.002) \) and receiving chemotherapy \( (p = 0.014) \) were all significant determinants of decline in verbal fluency, flexibility and reasoning performance at Time 3. Exposure to chemotherapy was estimated to lead to a 1.11 score decline in verbal fluency, flexibility and reasoning.

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37 Pairwise significance was determined by comparing each of the pairwise mean differences (PD) to the least significant difference of means (LSD).
The verbal fluency, flexibility and reasoning performance profile was most consistent with the Verbal Fluency Category Switching: Total Correct Switching and Total Switching measures of verbal fluency and flexibility (Appendix G, p. G6, \textit{VF}cstcz and \textit{VF}cstsz, respectively). While the performance profiles were the same, the \textit{p} value profiles were different, as shown in Table 10.3. Both category switching measures did not demonstrate the significant main effect for \textit{Group} or the trend towards significance for the interaction effect as found in the summary score. The Total Correct Switching measure displayed a significant main effect for \textit{Time} more consistent with the trend found in the summary score while Total Switching did not show any trend. This indicates the \textit{p} value profile for the summary measure was influenced by performance patterns from other measures.

The Verbal fluency, flexibility and reasoning performance profile for the chemotherapy group was least consistent with the individual measure of Verbal Reasoning, as performance deteriorated from \textit{Time 1} to \textit{Time 2}, instead of showing an improvement. For the no-chemotherapy group it was least consistent with the Verbal Fluency Set-loss Errors and Category Switching Percent Switching measures, as the performance of the no-chemotherapy group improved over the course of the assessments (Appendix G, p. G6-7, \textit{VR} and \textit{VF}selz, respectively).

### Table 10.3

* \textit{P} values for \textit{Group}, \textit{Time} and Interaction effects obtained from ANOVAs of the Verbal Fluency, Flexibility and Reasoning Grouping and Individual Measures*

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency, Flexibility and Reasoning</td>
<td>Verbal</td>
<td>0.032*</td>
<td>0.054</td>
<td>0.154</td>
</tr>
<tr>
<td>\textit{VF} letter fluency correct</td>
<td>Verbal</td>
<td>\textbf{0.025}*</td>
<td>0.394</td>
<td>0.466</td>
</tr>
<tr>
<td>\textit{VF} % Category switching</td>
<td>Verbal</td>
<td>0.217</td>
<td>\textit{&lt;.001}***</td>
<td>0.301</td>
</tr>
<tr>
<td>\textit{VF} CS total correct</td>
<td>Verbal</td>
<td>0.175</td>
<td>\textbf{0.006}**</td>
<td>0.363</td>
</tr>
<tr>
<td>\textit{VF} CS total switching</td>
<td>Verbal</td>
<td>0.129</td>
<td>0.433</td>
<td>0.363</td>
</tr>
<tr>
<td>\textit{VF} total set-loss errors</td>
<td>Verbal</td>
<td>0.905</td>
<td>0.113</td>
<td>0.138</td>
</tr>
<tr>
<td>Verbal reasoning</td>
<td>Verbal</td>
<td>\textbf{0.014}*</td>
<td>\textbf{0.001}**</td>
<td>0.777</td>
</tr>
</tbody>
</table>

\*\textit{D-KEFS Verbal Fluency (VF)}, \textit{b}Category Switching (condition 3).

\*Significant at: *\textit{p} < 0.05; ** \textit{p} < 0.01; *** \textit{p} < 0.001 (boldface).
b. Inhibition

The first principal component accounted for 54% of the variance in all measures from the inhibition grouping. An ANOVA was performed on the first principal component score\(^{38}\).

![Figure 10.8. Means (± SEM) of summary score for inhibition over time by breast cancer treatment group.](image)

The inhibition performance profile of the chemotherapy group was lower and flatter than the no-chemotherapy group over the course of the assessments, as shown in Figure 10.8. While the no-chemotherapy group improved from Time 1 to Time 2, the chemotherapy group did not, although both groups remained within the Average range. However, there was no significant Group by Time interaction effect \([F(2,86) = 0.83, p = 0.441]\) or main effect of Group \([F(1,44) = 0.76, p = 0.388]\) or Time \([F(2,86) = 1.27, p = 0.286]\) observed on performance.

The profile of inhibition performance was most consistent with the Color-Word Interference Trial 3 Inhibition Total Correct measure (Appendix G, p. G8, \(^{3}cw3iz\)). The p value profiles were also the same, as seen in Table 10.4, with neither displaying significant Group, Time or Group by Time interaction effects. The Inhibition performance profile for the chemotherapy group was least consistent with the Color-Word Interference Trial 3 Inhibition Total Errors measure, as performance improved at Time 2 and then

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\(^{38}\) The verbal inhibition summary scores included 1% \((n = 2)\) missing values
deteriorated at *Time 3*, instead of improving. The Inhibition performance profile for the no-chemotherapy group was least consistent with the Color-Word Interference Trial 4 Inhibition/Switching Total Errors measure, where higher z-scores indicates less errors, as performance deteriorated at *Time 2*, instead of improving, and then dramatically improved at *Time 3* (Appendix G, p. EG8, &witez and &cwitez).

Table 10.4

P values for Group, Time and Interaction effects obtained from ANOVAs of the Inhibition Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition</td>
<td>Verbal-visual</td>
<td>0.388</td>
<td>0.286</td>
<td>0.441</td>
</tr>
<tr>
<td>Inhibition correct</td>
<td>Verbal-visual</td>
<td>0.543</td>
<td>0.883</td>
<td>0.505</td>
</tr>
<tr>
<td>Inhibition/switching correct</td>
<td>Verbal-visual</td>
<td>0.534</td>
<td>0.211</td>
<td>0.327</td>
</tr>
<tr>
<td>Inhibition/switching errors</td>
<td>Verbal-visual</td>
<td>0.140</td>
<td>0.771</td>
<td>0.637</td>
</tr>
<tr>
<td>Inhibition errors</td>
<td>Verbal-visual</td>
<td>0.666</td>
<td>0.110</td>
<td>0.227</td>
</tr>
</tbody>
</table>

*DE-KEFS Color-word interference test, inhibition trial 3. bColor-word interference inhibition/switching trial 4.

*Significant at: *p < 0.05; **p < 0.01; ***p <.001 (boldface).

10.2.2 Visual Executive Functions

A PCA was conducted on all 18 executive function measures in Grouping 2. The first principal component accounted for 35% of the variance. An ANOVA was performed on the first principal component score.

The Visual executive summary performance of both groups was similar at *Time 1*, as seen in Figure 10.9, within the Average range. While the no-chemotherapy group improved over the course of the assessments to the High Average range, the performance of the chemotherapy group deteriorated slightly at *Time 2*, although remaining within the Average range. There was no significant interaction effect [F(2,83) = 0.42, p = 0.659] or main effect of *Group* [F(1,44) = 0.57, p = 0.456] or *Time* [F(2,83) = 0.11, p = 0.899] found on performance.

The visual executive summary scores included 4% (n = 5) missing values.
Figure 10.9. Means (± SEM) of summary score for visual executive over time by breast cancer treatment group.

Inspection of the biplot and latent vector loadings suggested nested groupings. Three independent groupings were found within the Grouping 2 Visual Executive measures, including those related to: a) Planning and Problem Solving; b) Spatial Working Memory; and c) Cognitive Flexibility.

The mean summary score performance for Grouping 2: Visual executive is presented with the three nested subgroups in Figure 10.10. The Visual executive summary performance profile (Figure 10.10a) was most consistent with the subgroup 2: Spatial working memory performance profile (Figure 10.10c), apart from that the slope of the no-chemotherapy group deteriorated slightly at Time 3 instead of continuing to improve. The p value profiles were also the same, as seen in Table 10.5. Both p value profiles did not demonstrate a significant main effect for Group, Time or a Group by Time interaction effect.

The Visual executive summary performance profile was least consistent with subgroup 1: planning and problem solving (Figure 10.10b) where the performance profile of the chemotherapy group was above the no-chemotherapy group over the first two assessments, as opposed to vice versa. The slope of the chemotherapy group also improved rather than declined between Time 1 and Time 2, while the no-chemotherapy group performance plateaued between Time 1 and Time 2, but then improved at Time 3 to match the chemotherapy group performance.
a. Grouping 2: Visual Executive

b. Subgroup 1: Planning and Problem Solving

c. Subgroup 2: Spatial Working Memory

d. Subgroup 3: Cognitive Flexibility

Figure 10.10. Means (± SEM) of summary score for overall and major groupings in visual executive over time by breast cancer treatment group.
Table 10.5

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of the Visual Executive Functions Grouping and Subgroups

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Executive Functions</td>
<td>Visual</td>
<td>0.456</td>
<td>0.899</td>
<td>0.659</td>
</tr>
<tr>
<td>Planning and Problem solving</td>
<td>Visual</td>
<td>0.469</td>
<td>0.003**</td>
<td>0.351</td>
</tr>
<tr>
<td>Spatial working memory</td>
<td>Visuospatial</td>
<td>0.390</td>
<td>0.940</td>
<td>0.819</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>Visual</td>
<td>0.496</td>
<td>0.031*</td>
<td>0.130</td>
</tr>
</tbody>
</table>

*Significant at: *p < 0.05; ** p < 0.01; *** p < .001 (boldface).

Results from each of the subgroups within visual executive function will be explored in more detail.

a. Planning and Problem Solving

The first principal component accounted for 29% of the variance in all measures from the planning and problem solving grouping. An ANOVA was performed on the first principal component score\textsuperscript{40}.

![Figure 10.11. Means (± SEM) of summary score for planning and problem solving over time by breast cancer treatment group.](image)

\textsuperscript{40} The visual planning summary scores included 4% (n = 5) missing values.
Both groups performed similarly in planning and problem solving initially, at the low end of the Average range (see Figure 10.11). While the performance of the chemotherapy group improved between Time 1 and Time 2, the no-chemotherapy group performance did not. Both groups improved at Time 3, within the Average range, but the no-chemotherapy group improved at a greater rate.

There was no significant Group by Time interaction effect \[F(2,83) = 1.06, p = 0.351\] or main effect of Group \[F(1,44) = 0.53, p = 0.469\] on performance. There was a significant main effect of Time \[F(2,83) = 6.29, p = 0.003\] reflecting that planning and problem solving performance was significantly better at Time 3 \((M = 0.394)\) than at either Time 1 \((M = -0.380)\) or Time 2 \((M = -0.048)\) \((PD > LSD = 0.436, at a 95\% confidence level)\). This significant improvement in performance over time in both groups is consistent with a practice effect.

This profile of performance was most consistent with the individual measure from the Stockings of Cambridge test, Problems Solved in Minimum Moves, a measure of overall planning ability (Appendix G, p. G10, eSOCpmiza). The \(p\) value profiles were also the same, as seen in Table 10.6. Both \(p\) value profiles displayed a significant main effect for Time but not for Group or for a Group by Time interaction effect.

**Table 10.6**

*P* values for Group, Time and Interaction effects obtained from ANOVAs of the Planning and Strategy Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning and Problem solving</td>
<td>Visual</td>
<td>0.469</td>
<td><strong>0.003</strong>**</td>
<td>0.351</td>
</tr>
<tr>
<td>4 CFT organization</td>
<td>Visuospatial</td>
<td>0.955</td>
<td>0.233</td>
<td>0.907</td>
</tr>
<tr>
<td>5 IED ED Shift errors</td>
<td>Visual</td>
<td>0.608</td>
<td>0.228</td>
<td>0.823</td>
</tr>
<tr>
<td>6 SOC mean moves</td>
<td>Visual</td>
<td><strong>0.038</strong>*</td>
<td>0.190</td>
<td>0.385</td>
</tr>
<tr>
<td>(5 move problems)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 SOC subsequent planning time</td>
<td>Visuospatial</td>
<td>0.199</td>
<td>0.057</td>
<td>0.953</td>
</tr>
<tr>
<td>8 SOC problems solved in</td>
<td>Visuospatial</td>
<td>0.720</td>
<td><strong>0.003</strong>**</td>
<td>0.074</td>
</tr>
<tr>
<td>minimum moves</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 SWM Strategy</td>
<td>Visuospatial</td>
<td>0.899</td>
<td>0.137</td>
<td>0.073</td>
</tr>
<tr>
<td>10 VF repetition errors</td>
<td>Verbal</td>
<td>0.543</td>
<td><strong>0.021</strong>*</td>
<td>0.277</td>
</tr>
</tbody>
</table>

*Complex Figure Test. 3 CANTAB IED Extra Dimensional Shift. 4 CANTAB Stockings of Cambridge mean moves (5 move problems). 5 SOC mean subsequent planning time after initial move (5 move problem). 6 CANTAB Spatial Working Memory. 7 D-KEFS Verbal Fluency

*Significant at: *\(p < 0.05\); **\(p < 0.01\); ***\(p < 0.001\) (boldface).
The planning and problem solving performance profile was least consistent with the Verbal Fluency Repetition Errors measure for the no-chemotherapy group, as performance declined from Time 1 to Time 2, below the chemotherapy group. For the chemotherapy group the summary score performance profile was least consistent with the IED Extra dimensional shift errors measure where performance deteriorated between Time 2 and Time 3 rather than improved (Appendix G, p. G10-11, sVFrez and bIEDEDSez).

b. Spatial Working Memory

The first principal component accounted for 76.5% of the variance in all measures from the spatial working memory grouping. An ANOVA was performed on the first principal component score.41

![Figure 10.12. Means (± SEM) of summary score for spatial working memory over time by breast cancer treatment group.](image)

The no-chemotherapy group demonstrated higher average spatial working memory than the chemotherapy group over the course of the assessments, as seen in Figure 10.12, although both groups remained within the Average range. While the spatial working memory performance of the no-chemotherapy group improved from Time 1 to Time 2, the no-chemotherapy group did not. However, there was no significant interaction effect.

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41 The spatial working memory summary scores included 1% (n = 2) missing values.
\[ F(2, 86) = 0.20, \ p = 0.819 \] or main effect of Group \[ F(1, 44) = 0.75, \ p = 0.390 \] or Time \[ F(2, 86) = 0.06, \ p = 0.940 \] found on performance.

This profile of performance was similar but not the same as any of the underlying measures. It was most consistent with the individual measure Spatial Working Memory double errors, apart from the fact that the no-chemotherapy group performance was initially slightly below the chemotherapy group (Appendix G, p. G12, \( \alpha_{SWMDEza} \)). The p value profiles were also the same, as there was no significant main effect for Group, Time or an interaction (see Table 10.7).

The Spatial Working Memory performance profile was least consistent with the Spatial Working Memory Within Errors at 8 boxes as there was a cross-over of slopes between groups between Time 1 and Time 2 where the no-chemotherapy group improved but the chemotherapy group declined (Appendix G, p. G13, \( \alpha_{SWMWE8za} \)).

### Table 10.7

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial working memory</td>
<td>Visuospatial</td>
<td>0.390</td>
<td>0.940</td>
<td>0.819</td>
</tr>
<tr>
<td>( ^{a}SWM ) Between errors (BE)</td>
<td>Visuospatial</td>
<td>0.330</td>
<td>0.428</td>
<td>0.490</td>
</tr>
<tr>
<td>SWM BE (8 boxes( ^{b} ))</td>
<td>Visuospatial</td>
<td>0.227</td>
<td>0.539</td>
<td>0.339</td>
</tr>
<tr>
<td>SWM Double errors (DE)</td>
<td>Visuospatial</td>
<td>0.449</td>
<td>0.883</td>
<td>0.438</td>
</tr>
<tr>
<td>( ^{d}SWM ) DE (8 boxes)</td>
<td>Visuospatial</td>
<td>0.637</td>
<td>0.712</td>
<td>0.366</td>
</tr>
<tr>
<td>( ^{c}SWM ) Total errors</td>
<td>Visuospatial</td>
<td>0.519</td>
<td>0.385</td>
<td>0.574</td>
</tr>
<tr>
<td>( ^{e}SWM ) Within errors (WE)</td>
<td>Visuospatial</td>
<td>0.398</td>
<td>0.890</td>
<td>0.459</td>
</tr>
<tr>
<td>( ^{f}SWM ) WE (8 boxes)</td>
<td>Visuospatial</td>
<td>0.617</td>
<td>0.726</td>
<td>0.293</td>
</tr>
</tbody>
</table>

\( ^{a} \)CANTAB Spatial Working Memory (SWM). \( ^{b} \)Box (highest) level.

### c. Cognitive Flexibility

The first principal component accounted for 89% of the variance in all measures from the cognitive flexibility grouping. An ANOVA was performed on the first principal component score\(^{42}\).

\(^{42}\) The cognitive flexibility summary scores included 4% \( n = 5 \) missing values.
Figure 10.13. Means (± SEM) of summary score for cognitive flexibility over time by breast cancer treatment group.

The chemotherapy group initially performed at the top of the Average range in cognitive flexibility, slightly higher than the no-chemotherapy group, as seen in Figure 10.13. While both groups demonstrated a decline in cognitive flexibility performance at Time 2, the chemotherapy group displayed a much steeper decline, to the bottom of the Average range. The no-chemotherapy group showed an improvement in cognitive flexibility at Time 3 to better than baseline performance, while the performance of the chemotherapy group did not improve.

There was no significant main effect of Group \([F(1,44) = 0.47, p = 0.496]\) on performance. There was a significant main effect found of Time \([F(2,83) = 3.64, p = 0.031]\), reflecting a significant deterioration in cognitive flexibility between Time 1 (\(M = 0.37\)) and Time 2 (\(M = -0.30\)) (PD>LSD = 0.518, at a 95% confidence level). While most of this deterioration appears to be due to the decline in the chemotherapy group performance, surprisingly the Group by Time interaction effect was not significant, although a trend was apparent \([F(2,83) = 2.09, p = 0.130]\).

This interaction effect reflected a significant difference in changes in cognitive flexibility between groups, between the Time 1 and Time 3 assessments and a trend between the Time 1 and Time 2 assessments (using pairwise comparisons: \(T2_{\text{Group MD}}-T1_{\text{GMD}} = 0.77; T3_{\text{Group MD}}-T1_{\text{GMD}} = 1.08, \text{PD} > \text{LSD} = 0.77\), at a 95% confidence level). The performance of the
no-chemotherapy group did not change significantly between these timepoints ($T2-1_{MD} = -0.17; T3-1_{MD} = 0.19$; LSD for $Time = 0.518$) whereas the performance of the chemotherapy group declined significantly between the same timepoints ($T2-1_{MD} = -0.94; T3-1_{MD} = -0.89$).

A general linear regression on change scores ($T3-T1$) revealed that some baseline factors predicted decline in cognitive flexibility performance at $Time 3$, including higher anxiety, depression or self-reported cognitive problems at $Time 1$. Women who had a readmission to hospital were also at a greater risk of decline at $Time 3$. All readmissions to hospital over the course of the study were due to an adverse event from chemotherapy, including mainly thrombosis, neutropenia and septicemia.

As women who were readmitted to hospital showed the greatest risk of decline the regression was repeated to investigate the influence of cognitive reserve with a 2-way (readmission $\times$ IQ) interaction term. Women with lower cognitive reserve who were readmitted to hospital due to a chemotherapy-induced adverse event were more vulnerable to decline at $Time 3$ ($p = 0.004$).

This general linear regression on change scores ($Time 3 - Time 1$) revealed that women who had higher anxiety ($p = 0.009$) or higher self-reported cognitive problems at $Time 1$ ($p = 0.038$), or who had lower cognitive reserve and were readmitted to hospital due to a chemotherapy-induced adverse event ($p = 0.004$) were more vulnerable to decline in cognitive flexibility performance at $Time 3$. Whereas a standardized one-unit increase in anxiety at $Time 1$ was estimated to predict a 0.22 score decline in cognitive flexibility at $Time 3$, a one unit decrease in estimated IQ (cognitive reserve) + chemotherapy-induced hospital readmission was estimated to predict a 1.23 score decline in cognitive flexibility performance at $Time 3$.

The cognitive flexibility performance profile was similar to all the individual measures but was most consistent with the IED Total errors and IED Stages completed (Appendix G, p. G14, $^a$IEDTEaz and $^b$IEDSCmz, respectively). While the performance profiles were the same, the p value profiles were somewhat different, as can be seen in Table 10.8. The Cognitive Flexibility grouping summary score displayed a significant main effect for Time, whereas the IED Total errors and Stages completed measures showed a trend. Both displayed a trend to significance for the interaction consistent with the summary score profile and no significant main effect for Group.
The Cognitive Flexibility performance profile was least consistent with the IED pre-Extra dimensional set shift errors measure, as there was no cross-over in slopes between groups between Time 1 and Time 2 (Appendix G, p. G14, 4IEDpEDSez).

Table 10.8

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive flexibility</td>
<td>Visual</td>
<td>0.496</td>
<td>0.031*</td>
<td>0.130</td>
</tr>
<tr>
<td>IED pre-ED shift errors</td>
<td>Visual</td>
<td>0.395</td>
<td>0.006**</td>
<td>0.734</td>
</tr>
<tr>
<td>IED Stages completed</td>
<td>Visual</td>
<td>0.563</td>
<td>0.134</td>
<td>0.084</td>
</tr>
<tr>
<td>IED Total errors</td>
<td>Visual</td>
<td>0.475</td>
<td>0.088</td>
<td>0.123</td>
</tr>
<tr>
<td>IED Total trials</td>
<td>Visual</td>
<td>0.611</td>
<td>0.074</td>
<td>0.092</td>
</tr>
</tbody>
</table>

*aCANTAB IED pre-Extra dimensional shift total errors. **Intra-Extra Dimensional Shift (IED).
| *(d)IED Total errors (adjusted). **IED Total trials (adjusted).

*Significant at: *p < 0.05; **p < 0.01; ***p <.001 (boldface).

10.2.3 Planning Speed.

A PCA was conducted on all four spatial planning speed measures in Grouping 3. The first principal component accounted for 58% of the variance. An ANOVA was performed on the first principal component score.

The planning speed performance profile of the chemotherapy group was initially in the Low Average range, below that of the no-chemotherapy group who were in the Average range (see Figure 10.14). The performance of both groups improved between the Time 1 and Time 2 assessments, with the chemotherapy group improving to the Average range and the no-chemotherapy group improving to the High Average range. While the performance of the chemotherapy group was the same at Time 3, the no-chemotherapy group returned to the Average range.

43 The planning speed summary scores included 1% (n = 2) missing values.
There was no significant interaction effect \( F(2,86) = 0.81, p = 0.450 \) or main effect of Group \( F(1,44) = 1.16, p = 0.287 \) found on performance. There was a significant main effect of Time \( F(2,86) = 8.52, p < .001 \) reflecting that planning speed at both the Time 2 \( (M = 0.262) \) and Time 3 \( (M = 0.187) \) follow-up assessments was significantly faster than at Time 1 \( (M = -0.399) \) (PD>LSD = 0.349, at a 95% confidence level). This significant improvement in performance over time is consistent with a practice effect.

The planning speed performance profile was most consistent with the Stockings of Cambridge mean initial planning speed at 5 moves, a measure of initial planning speed at the hardest level, and the CFT copy time (Appendix G, p. G16, ^SOCMi5za and ^CFTcytza). While the performance profiles were similar, the p value profiles varied, as can be seen in Table 10.9. While the Planning Speed summary profile and CFT copy time p value profiles were the same, displaying a main effect for Time but not for Group or an interaction, the individual measure of planning speed at the hardest 5-move level did not display a main effect for Time.

In contrast, the Planning Speed performance profile was least consistent with Stockings of Cambridge mean initial planning speed at 3 moves, a measure of initial planning speed at the easiest level (Appendix G, p. G16, ^SOCMi3za). There was a cross-over of slopes between groups at Time 2 when the chemotherapy group improved from below the no-chemotherapy group to higher than the no-chemotherapy group but then deteriorated to
below the no-chemotherapy group at Time 3. The performance of the no-chemotherapy remained fairly consistent across the course of the assessments.

Table 10.9

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial Planning Speed</td>
<td>Visuospatial</td>
<td>0.287</td>
<td>&lt;.001***</td>
<td>0.450</td>
</tr>
<tr>
<td>^aSOC initial planning speed (3 moves)</td>
<td>Visuospatial</td>
<td>0.541</td>
<td>0.071</td>
<td>0.251</td>
</tr>
<tr>
<td>SOC initial planning speed (4 moves)</td>
<td>Visuospatial</td>
<td>0.333</td>
<td>0.012*</td>
<td>0.277</td>
</tr>
<tr>
<td>SOC initial planning speed (5 moves)</td>
<td>Visuospatial</td>
<td>0.753</td>
<td>0.245</td>
<td>0.471</td>
</tr>
<tr>
<td>^bCFT copy speed</td>
<td>Visuospatial</td>
<td>0.186</td>
<td>&lt;.001***</td>
<td>0.888</td>
</tr>
</tbody>
</table>

^aCANTAB Stockings of Cambridge (SOC) mean initial planning speed (3 moves).
^bComplex figure test.
*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).

10.3 Chapter summary

This chapter presented the results of a principal components and data analysis on data from the 32 outcome measures produced from the nine tests of executive functions. The findings from this analysis indicated trends towards interaction effects at the subgroup level of executive functions, indicating subtle negative effects associated with chemotherapy on visual cognitive flexibility and verbal fluency, flexibility and reasoning. Women who were at greater risk for decline in these executive functions following chemotherapy had lower pre-treatment premorbid IQ or higher anxiety or a clinical anxiety or mood disorder at Time 1. Acute adverse events associated with chemotherapy requiring readmission to hospital also increased the risk of decline in cognitive flexibility, especially for women with lower premorbid IQ. These findings are discussed in reference to the literature on cognitive reserve in Chapter 12.2.7.

The first principal component score for all measures within the domain accounted for only 21% of the variance in these measures. This suggests that different executive functions are mostly independent of each other, and are not easily represented by a summary measure. This is consistent with the literature on executive functions (see Lezak et al., 2012). An examination of the biplot revealed two major groupings and one minor grouping within this domain (verbal executive, visual executive, and planning speeds).
Two nested subgroups were found within the verbal executive measures, including those related to verbal fluency, flexibility and reasoning, and inhibition. Three subgroups were evident within the visual executive measures, including planning and problem solving, spatial working memory, and cognitive flexibility. These groupings are consistent with the literature and will be discussed in more detail in Chapter 12.2.3.

a. Group by Time interaction effects

There were no significant Group by Time interaction effects found in the main groupings or subgroups within the executive functions domain at 95% confidence level. However, there were trends towards significant Group by Time interactions observed in two nested subgroups: Verbal fluency, flexibility and reasoning; and Cognitive flexibility. These subgroups both involved measures of cognitive flexibility. This provides support for a profile of chemotherapy-related impairment in cognitive flexibility in women with early breast cancer.

Women at higher risk of decline between Time 2 and Time 3 in verbal fluency, flexibility and reasoning were women with lower premorbid IQ, higher mental fatigue at Time 2 and exposure to chemotherapy. Exposure to chemotherapy was estimated to lead to a 1.11 score decline in verbal fluency, flexibility and reasoning.

Women identified at higher risk of decline in cognitive flexibility at Time 3 had lower premorbid IQ or higher anxiety or self-reported cognitive problems at Time 1, or were readmitted to hospital due to a chemotherapy-induced adverse event. There was a significant interaction of premorbid IQ and acute adverse events, with women with lower premorbid IQ showing a greater risk of decline after a chemotherapy-induced adverse event. A one standardized unit decrease in estimated IQ and a hospital readmission due to a chemotherapy-induced adverse event was estimated to predict a 1.23 score decline in cognitive flexibility performance at Time 3.

These findings are consistent with the literature on cognitive reserve (for review see Stern, 2003) and suggest that chemotherapy and cognitive reserve (measured by premorbid IQ) interact, so that women with lower cognitive reserve are more vulnerable to chemotherapy and associated acute or toxic adverse events. This will be discussed further in Chapter 12.2.7.
b. *Time effects*

There was a significant main effect of *Time* in the absence of any trend or significant interaction effect on performance in two groupings within the executive functions domain. These were visual planning and problem solving, and planning speed. Both planning and problem solving, and planning speed, showed a profile of improved performance over time. These significant improvements in performance at follow-up are consistent with practice effects. This is commonly found in repeated measurement using traditional tests of executive functions (Lezak, et al., 2012). Notably, only two groupings within the executive functions domain displayed such effects, suggesting that selecting measures with parallel or alternate forms may help to reduce practice effects on retesting.

c. *Group effects*

Only one executive functions grouping displayed a significant main effect of *Group* in the absence of a trend or significant interaction effect. This was found in the overall verbal executive summary performance. This reflected significantly poorer performance by the chemotherapy group compared to the no-chemotherapy group across time. Women with lower premorbid IQ who had received more general anaesthetics were at greater risk of lower scores at *Time 1*.

In summary, the overall Executive Functions domain summary measure did not display any evidence of chemotherapy-related impairment at the 95% confidence level, nor did the main groupings. However, a subtle profile of chemotherapy-related cognitive impairment emerged at the level of nested subgroups within Executive Functions. This is consistent with the literature that executive functions involve independent functions that are not easily represented by a single or composite measure (Lezak, et al., 2012). There were subtle interaction effects observed in the Verbal fluency, flexibility and reasoning subgroup within the Verbal Executive grouping, as well as the Cognitive flexibility subgroup within the Visual Executive grouping. These subgroups both involve measures of cognitive flexibility. Both displayed a performance profile of significant decline in women exposed to chemotherapy compared to no change in women not exposed to chemotherapy. These interaction effects suggest a subtle profile of chemotherapy-related impairment on cognitive flexibility that appears to be mediated by cognitive reserve (see Chapter 12.2.7). Furthermore, the cumulative toxicity of chemotherapy and chemotherapy-related adverse events increased vulnerability to decline in visual cognitive flexibility.
Individual Deficit Analysis

11.1 Introduction

This chapter presents the results of the analyses of individual neuropsychological test data at each of the three timepoints. For this individual analysis, two approaches were conducted in line with widely accepted clinical neuropsychological practice (Lezak, et al., 2012). For details of the statistical approach see Chapter 6.6. For the first, individual test scores were screened for very low scores at each timepoint. 'Cognitive complications' were defined as a score of more than 2 standard deviations below the mean of the published age-standardized normative data for each test (i.e., z-score < -2). The proportion of individuals displaying more, less or the same amount of complications at Time 2 and Time 3 relative to Time 1 was compared between groups for each domain using chi-square analyses. The pattern of deficits on individual measures within domains was examined for signs of a profile of impairment and factors were examined that may increase the risk of more complications.

The second approach involved identifying individuals who displayed performance that was lower than expected, defined as one and a half standard deviations or more below their own estimated premorbid IQ/ability score. An overall 'lower than expected performance' score was then calculated for each individual from the mean of all scores that were ≤1.5 SD below their predicted ability. An ANOVA and regression analysis was conducted to compare lower than expected performance between groups over time, while assessing the influence of possible risk factors.

11.2 Cognitive complications

A cognitive complication was defined as a score of more than 2 standard deviations below the mean of the published age-standardized normative data for each test (z-score < -2). The number of cognitive complications found across measures within each domain was collated for each individual at each timepoint. The percentage of individuals displaying cognitive complications at Time 1 was then compared between groups for each domain. The proportion of individuals displaying more, less or the same amount of complications at Time 2 or Time 3 relative to Time 1 was compared between groups for each domain.
pattern of deficits on individual measures within domains was then examined for signs of a profile of individual impairment. Individuals were identified who displayed more complications at Time 3 on domains where significant group differences were found. Factors were examined that may increase their risk of complications.

11.2.1 Cognitive complications at Time 1

The proportion of women in each group displaying at least one cognitive complication (z-score < -2) at Time 1 within each cognitive domain is presented in Table 11.1.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pre-chemotherapy</th>
<th>No-chemotherapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>7</td>
<td>0</td>
<td>0.545a</td>
</tr>
<tr>
<td>Motor</td>
<td>10</td>
<td>13</td>
<td>1.000a</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td>40</td>
<td>20</td>
<td>0.180b</td>
</tr>
<tr>
<td>Attention and Speed of Processing</td>
<td>10</td>
<td>20</td>
<td>0.384a</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>47</td>
<td>36</td>
<td>0.495b</td>
</tr>
<tr>
<td>Executive Functions</td>
<td>60</td>
<td>53</td>
<td>0.670a</td>
</tr>
</tbody>
</table>

a At least one cell with expected count < 5 so Fisher's Exact Test is reported. b Pearson chi-square

There were no significant differences at Time 1 in the proportion of women displaying a cognitive complication between groups within any cognitive domain. However, 33% of all women displayed a complication on the measure of visuoconstruction at Time 1 and 42% of all women displayed a complication within learning and memory at Time 1. More than half (58%) of women displayed a complication within executive functions. This included 60% of women prior to chemotherapy and 53% of women not undertaking chemotherapy. When the percentage of individuals who displayed complications on three or more tests in the executive functions domain were compared, 7% of women pre-chemotherapy and 13% of women not undertaking chemotherapy displayed three or more complications. This difference again was not statistically significant, $p = 0.651$. These results show that there was no difference within any cognitive domain in the likelihood of women showing complications between groups at Time 1, prior to chemotherapy.

Potential predictor and moderator variables were dichotomized and the proportion of individuals who displayed a cognitive complication at Time 1 was examined by each selected potential mechanism using chi-square analyses. Variables included those relating to: demographic characteristics (age, education), cancer severity (staging), psychological
distress (anxiety, depression); HRQL symptoms (fatigue, pain, sleep); and treatment (type of surgery, number of general anaesthetics).

Having a cognitive complications in any domain at Time 1 was not associated with age (<50, \( p = 0.399 \)), education (<12 years, \( p = 0.569 \)), cancer staging (>1, \( p = 0.243 \)), or having had more general anaesthetics (\( \geq 2, p = 0.199 \)) or a mastectomy (\( p = 1.000 \)). Having a cognitive complication was also not associated with reported fatigue (\( p = 0.315 \)), sleep problems (\( p = 0.597 \)) or pain (\( p = 1.000 \)).

More self-reported cognitive problems or total prospective and retrospective memory problems at Time 1 were not associated with objective cognitive complications (\( p = 1.000 \); and \( p = 0.597 \), respectively). There was also no significant association between having a cognitive complication at Time 1 and having clinical depression (\( p = 0.405 \)) or clinical anxiety (\( p = 0.569 \)) or HADS-defined depression (\( \geq 8, p = 1.000 \)) or anxiety (\( \geq 8, p = 0.656 \)).

These variables were also examined in individuals displaying three or more cognitive complications (\( z < -2 \)) in any domain at Time 1. There were no significant differences found in any of the relationships to these covariates, apart from HADS-defined anxiety. Over half (54.5%) of women with HADS-defined anxiety (\( \geq 8 \) for ‘caseness’) had more cognitive complications at Time 1, compared to 18% of women who did not have HADS-defined anxiety, \( p = 0.047 \).

11.2.2 Changes in the amount of cognitive complications

The number of complications (\( z \)-scores < -2) were collated for each individual at each timepoint within each domain. The proportion of individuals within each group displaying more, less or the same amount of complications within each domain at Time 2 and Time 3 compared to Time 1 is presented in Table 11.2.

The domains that showed the least complications initially in women from both groups (i.e., Language and Motor skills) displayed the most stability over time, as all women from both groups either had fewer complications or the same amount at Time 2 and Time 3. The domains that displayed the highest amounts of complications in both groups at Time 1 (i.e., Learning and Memory and Executive functions) displayed more complications at Time 2 and Time 3 but the profile varied between groups. The proportion of women in each group with more complications at Time 2 and Time 3 relative to Time 1 will be examined in more detail.
Table 11.2

Percentage of Each Group Showing More, Less or the Same Amount of Cognitive Complications (z-scores <-2) at Time 2 and Time 3 compared to Time 1

<table>
<thead>
<tr>
<th>Domains</th>
<th>Time 1 to Time 2</th>
<th></th>
<th>Time 1 to Time 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy group</td>
<td>No-chemotherapy group</td>
<td>Chemotherapy group</td>
<td>No-chemotherapy group</td>
</tr>
<tr>
<td></td>
<td>% (n = 30)</td>
<td>% (n = 15)</td>
<td>% (n = 29)</td>
<td>% (n = 15)</td>
</tr>
<tr>
<td></td>
<td>Less</td>
<td>More</td>
<td>Same</td>
<td>Less</td>
</tr>
<tr>
<td>Language</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Motor</td>
<td>10</td>
<td>0</td>
<td>90</td>
<td>13</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td>20</td>
<td>13</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>Attention and Speed of processing</td>
<td>7</td>
<td>7</td>
<td>87</td>
<td>20</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>10</td>
<td>63</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Executive Functions</td>
<td>23</td>
<td>30</td>
<td>47</td>
<td>0</td>
</tr>
</tbody>
</table>
a. **Women with more complications at Time 2**

The proportion of women in each group displaying more complications at Time 2 compared to Time 1 within each domain is presented in Table 11.3.

**Table 11.3**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Chemotherapy % (n = 30)</th>
<th>No-chemotherapy % (n = 15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Motor</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td>13</td>
<td>7</td>
<td>0.651*</td>
</tr>
<tr>
<td>Attention and Speed of Processing</td>
<td>7</td>
<td>7</td>
<td>1.000*</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>63</td>
<td>73</td>
<td>0.502b</td>
</tr>
<tr>
<td>Executive Functions</td>
<td>30</td>
<td>0</td>
<td>0.020**</td>
</tr>
</tbody>
</table>

*At least one cell with expected count <5 so Fisher’s Exact Test is reported. **Pearson chi-square.

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).

There were very few complications in language or motor skills initially and no more complications were found at Time 2 in both groups (see Table 11.3). About 7% of the no-chemotherapy group and 13% of the chemotherapy group displayed more complications in visuoconstruction at Time 2 but this difference was not significant, \( p = 0.651 \). The same proportion (7%) of each group displayed more complications within attention and speed of processing at Time 2. Most women displayed more complications within learning and memory at Time 2, including 73% of women from the no-chemotherapy group and 63% of women from the chemotherapy group. This difference was not statistically significant, \( \chi^2(1) = 0.450, p = 0.502 \). Finally, 30% of women in the chemotherapy group had more complications within executive functions at Time 2 compared to Time 1, whereas 0% of the women from the no-chemotherapy group displayed more complications. This difference was statistically significant, \( p = 0.020 \). As can be seen in Table 11.2 all of the women in the no-chemotherapy group displayed the same amount of complications in executive functions at Time 1.

b. **Women with more complications at Time 3**

The proportion of women in each group showing more complications at Time 3 compared to Time 1 within each domain is presented in Table 11.4.
Table 11.4

Percentage of Each Group Showing More Complications (z-scores < -2) at Time 3 compared to Time 1 by Cognitive Domain

<table>
<thead>
<tr>
<th>Domain</th>
<th>Chemotherapy % (n = 29)</th>
<th>No-chemotherapy % (n = 15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Motor</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td>17</td>
<td>20</td>
<td>1.000(^a)</td>
</tr>
<tr>
<td>Attention and Speed of Processing</td>
<td>10</td>
<td>0</td>
<td>0.540(^b)</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>62</td>
<td>13</td>
<td>0.002**(^h)</td>
</tr>
<tr>
<td>Executive Functions</td>
<td>34.5</td>
<td>0</td>
<td>0.009**(^a)</td>
</tr>
</tbody>
</table>

\(^1\) One participant from each group is not included, as they were not assessed at either Time 1 or Time 3. 
\(^a\) At least one cell with expected count <5 so Fisher's Exact Test is reported. 
\(^b\) Pearson chi-square.

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).

None of the women in either group displayed more complications in language or motor skills performances from Time 1 to Time 3. There was also no significant difference in the likelihood of women displaying more complications in visuoconstruction skills (p = 1.000) or attention and speed of processing (p = 0.540) at Time 3 between groups. Only 13% of women not treated with chemotherapy displayed more complications within learning and memory at Time 3, whereas 62% of women treated with chemotherapy displayed more complications. This difference was statistically significant, \(\chi^2(1) = 9.471, p = 0.002\).

Even though over half of all women with breast cancer displayed a complication in executive functions at Time 1, 34% of women exposed to chemotherapy displayed more complications at Time 3, whereas 0% of women who were not exposed to chemotherapy displayed more complications. This difference was statistically significant, \(p = 0.009\).

c. Profile of increased complications at Time 3 in Learning and Memory

At Time 1, the only measures in learning and memory that displayed at least three complications were the Complex Figure Test immediate recall and total recognition, all found in women from the chemotherapy group.

The distribution of more complications at Time 3 was examined for any profile of impairment. There were two measures that displayed far more complications. These were the CANTAB Paired Associates Learning (PAL) Stages Completed and PAL Stages Completed on Trial 1. All women who displayed more complications in learning and memory showed a complication on Stages Completed, a key indicator of success at paired
associate learning, and most (89%) women from the chemotherapy group displayed more complications on Stages Completed on Trial 1. This refers to the number of stages passed on the first trial. The distribution of other complications across learning and memory was scattered but three other visuospatial memory measures had three complications: the PAL first trial memory score and the Complex Figure Test total delayed recall and total recognition.

d. Profile of increased complications at Time 3 in Executive Functions

The measures at Time 1 in executive functions that displayed three or more complications for the chemotherapy group were initial planning speeds at the highest levels (4 move and 5 move problems) and a measure of the ability to shift attention between two dimensions [IED Extra-dimensional (ED) Errors]. The no-chemotherapy group displayed more complications on other planning measures (mean moves for 5 move problems, and mean subsequent thinking time for 5 move problems).

The distribution of more cognitive complications at Time 3 was examined for any profile of impairment. The measures with the most complications are presented in Table 11.5.

Table 11.5

<table>
<thead>
<tr>
<th>Measure</th>
<th>Chemotherapy % (n = 29)</th>
<th>No-chemotherapy % (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IED pre-ED errors</td>
<td>21 (6)</td>
<td>0</td>
</tr>
<tr>
<td>IED Total Trials</td>
<td>17 (5)</td>
<td>0</td>
</tr>
<tr>
<td>IED Total Errors</td>
<td>14 (4)</td>
<td>0</td>
</tr>
<tr>
<td>IED Stages Completed</td>
<td>14 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Initial planning speed at the highest level (5 move problems)</td>
<td>14 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Measures of cognitive flexibility from the Intra-Extra Dimensional Set Shift test showed more complications, including problems shifting attention within a dimension (pre-Extra Dimensional errors) and efficiency adjusting to new stimuli (Total Errors). Around 14-21% of women treated with chemotherapy displayed more complications on these measures compared to 0% of women not treated with chemotherapy. An increase in complications was not found at the extra dimensional shift stage so these findings suggest more specific problems with reversal learning.

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Initial planning speed at the highest level (5 move problems) also displayed more complications at Time 3, with 14% of women exposed to chemotherapy displaying very slow planning speed at this level compared to 0% of women not exposed to chemotherapy. More complications were not found on the problem solving measure for this task.

**e. More complications in Learning and Memory or Executive Functions**

Overall, 24 women with breast cancer (54.5%) displayed more complications at Time 3 compared to Time 1 in either Learning and Memory or Executive Functions.

![Figure 11.1. Percentage of treatment group with more complications in learning and memory or executive functions at time 3.](image)

A greater proportion (76%) of women treated with chemotherapy displayed more complications at Time 3 than women not treated with chemotherapy (13%), as seen in Figure 11.1. The likelihood of having more complications was significantly higher for women treated with chemotherapy, $\chi^2(1, \ N = 44) = 15.59, \ p = <.001$. Six women had more complications at Time 3 in both domains i.e., Learning and Memory, and Executive Functions. All these women had been treated with chemotherapy, representing 21% of the chemotherapy group (see Table 11.6).
Table 11.6

**Percentage of Each Group Showing More Complications (z-scores < -2) at Time 3 compared to Time 1 within Learning and Memory and Executive Functions**

<table>
<thead>
<tr>
<th>Learning and Memory and Executive Functions Domains</th>
<th>Chemotherapy % (n = 29)</th>
<th>No-chemotherapy % (n = 15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either Domain</td>
<td>76 (22)</td>
<td>13 (2)</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>Both Domains</td>
<td>21 (6)</td>
<td>0</td>
<td>0.080*</td>
</tr>
</tbody>
</table>

*Pearson chi-square. At least one cell with expected count <5 so Fisher’s Exact Test is reported.

*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).

11.2.3 Associations with other Possible Mechanisms

The proportion of individuals who displayed more or the same/less complications in either learning and memory or executive functions at Time 3, was examined for possible mechanisms by examining the relationship to potential explanatory variables using chi-square analyses. Variables were dichotomized and included: demographic, cancer and treatment characteristics; adverse events; fatigue, pain, sleep problems and psychological distress. The results are presented in Table 11.7.

There was no significant difference found in the likelihood of women with less education to have more cognitive complications at Time 3. Women displaying more complications were also not more likely to report worse physical fatigue, sleep, or pain.
### Table 11.7

**Percentage of Individuals Showing More Complications (z-scores < -2) in Either Learning and Memory or Executive Functions at Time 3 by Covariate**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>More complications % (n = 24)</th>
<th>Same or less % (n = 20)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (at Time 3 &lt;50)</td>
<td>54% (13)</td>
<td>15% (3)</td>
<td>0.007**</td>
</tr>
<tr>
<td>Education (&lt;12 years)</td>
<td>17% (4)</td>
<td>5% (1)</td>
<td>0.356a</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer severity (≥Stage 2)</td>
<td>71% (17)</td>
<td>25% (5)</td>
<td>0.002**</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anaesthetics (≥2)</td>
<td>71% (17)</td>
<td>40% (8)</td>
<td>0.040*</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>62.5% (15)</td>
<td>45% (9)</td>
<td>0.246a</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>92% (22)</td>
<td>65% (13)</td>
<td>0.057a</td>
</tr>
<tr>
<td>Taxane regimen (Chemotherapy)</td>
<td>64% (14)</td>
<td>43% (3)</td>
<td>0.403a</td>
</tr>
<tr>
<td><strong>Adverse events (After Time 1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-induced menopause</td>
<td>71% (17)</td>
<td>15% (3)</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>Hospital readmissions</td>
<td>79% (19)</td>
<td>21% (5)</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>50% (12)</td>
<td>15% (3)</td>
<td>0.015**</td>
</tr>
<tr>
<td><strong>QOL (Time 3)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigueb (T-score ≥50)</td>
<td>25% (6)</td>
<td>21% (4)</td>
<td>1.000a</td>
</tr>
<tr>
<td>Painb (T-score ≥50)</td>
<td>17% (4)</td>
<td>26% (5)</td>
<td>0.477a</td>
</tr>
<tr>
<td>Sleepb (T-score ≥50)</td>
<td>33% (8)</td>
<td>26% (5)</td>
<td>0.619</td>
</tr>
<tr>
<td><strong>Psychological (Time 3)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>46% (11)</td>
<td>30% (6)</td>
<td>0.283</td>
</tr>
<tr>
<td>Clinical anxiety</td>
<td>21% (5)</td>
<td>25% (5)</td>
<td>1.000a</td>
</tr>
<tr>
<td>Clinical depression</td>
<td>29% (7)</td>
<td>10% (2)</td>
<td>0.150a</td>
</tr>
<tr>
<td>HADS anxiety (≥8)</td>
<td>37.5% (9)</td>
<td>21% (4)</td>
<td>0.244</td>
</tr>
<tr>
<td>HADS depression (≥8)</td>
<td>8% (2)</td>
<td>10.5% (2)</td>
<td>1.000a</td>
</tr>
</tbody>
</table>

*At least one cell with expected count <5 so Fisher's Exact Test is reported. In all other cases Pearson's chi-square was used. bEORTC-30 function subscales (higher scores mean more reported problems).

### Age and cognitive complications

Age was associated with an increased likelihood of cognitive complications, \( \chi^2 (1, N = 44) = 7.23, p = 0.007 \). Unexpectedly, women who were younger (<50) were more likely to display more cognitive complications at Time 3 (n = 13), as seen in Figure 11.2. The majority of younger women (81%; n = 13) displayed more cognitive complications at
*Time 3* compared to 40% of women aged 50 or older. Most (85%) younger women who experienced more cognitive complications had been treated with chemotherapy.

![Bar chart showing the proportion of women with more complications at time 3 by age group (<50: n = 16; ≥50: n = 28).](image)

**Figure 11.2.** Proportion of women with more complications at *time 3* by age group (<50: n = 16; ≥50: n = 28).

**Cancer and cognitive complications**

More advanced cancer staging (≥Stage 2) was significantly associated with more cognitive complications, $\chi^2(1, N = 44) = 9.17, p = 0.002$. The majority (77%) of women with more advanced cancers (≥Stage 2) displayed more complications compared to 32% of women with less advanced cancers (see Figure 11.3). Cancer staging is a predictor of overall prognosis. Most women (94%; n = 16) who had more advanced staging and displayed more cognitive complications at *Time 3* were treated with chemotherapy.

![Bar chart showing the percentage of women with more cognitive complications at time 3 by cancer stage (≤ Stage 1: n = 22; ≥ Stage 2: n = 22).](image)

**Figure 11.3.** Percentage of women with more cognitive complications at *time 3* by cancer stage (≤ Stage 1: n = 22; ≥ Stage 2: n = 22).
Treatment and cognitive complications

Women who had received two or more general anaesthetics were more likely to display more cognitive complications at Time 3, $\chi^2(1, N = 44) = 4.23, p = 0.040$. As seen in Figure 11.4, 68% of women who received more than one general anaesthetic displayed more complications at Time 3 compared to 37% of women who received only one general anaesthetic. Most (94%; $n = 16$) women who had more than one general anaesthetic and experienced more cognitive complications received adjuvant chemotherapy. Having had a mastectomy was not significantly associated with more cognitive complications, $p = 0.246$.

![Figure 11.4. Percentage of women with more cognitive complications at time 3 by number of general anaesthetics (1: n = 19; >1: n = 25).](image)

A chemotherapy regimen including a taxane was not significantly associated with more cognitive complications, $p = 0.403$. There was a trend for women who were receiving hormone therapy to display more complications at Time 3, $p = 0.057$.

Adverse events and cognitive complications

Women who experienced treatment-induced menopause were significantly more likely to experience more cognitive complications at Time 3, $\chi^2(1, N = 44) = 13.72, p = <.001$. The majority (85%) of women who experienced treatment-induced menopause had more cognitive complications at Time 3, compared to 29% of women who did not experience treatment-induced menopause (see Figure 11.5). Most of these women (94%; $n = 16$) experienced treatment-induced menopause as a result of chemotherapy.
Women who were readmitted to hospital at any time following Time 1 were more likely to experience more cognitive complications, $\chi^2(1, N = 44) = 12.91$, $p < .001$. The majority (79%) of women who were readmitted to hospital over the course of the study had more cognitive complications at Time 3, compared to 21% of women who were not readmitted to hospital. All but one of these women who were readmitted to hospital were from the chemotherapy group. The most common reasons for hospital readmissions were neutropenia and thrombosis, followed by septicaemia, anaphylaxis and acute myalgia/neuropathy. Women who experienced chemotherapy-induced neutropenia were also more likely to experience more cognitive complications, $\chi^2(1, N = 44) = 5.95$, $p = 0.015$. 

Figure 11.5. Proportion of women with treatment-induced menopause displaying more cognitive complications at time 3 (yes: $n = 20$; no: $n = 44$).

Figure 11.6. Percentage of women experiencing neutropenia by cognitive complications (yes: $n = 15$; no: $n = 29$).
Most women (80%; n = 12) who suffered neutropenia as a side-effect of chemotherapy experienced more cognitive complications at Time 3 compared to 41% (n = 12) of women who did not experience neutropenia (Figure 11.6).

**Anxiety and depression**

There were 23% (n = 10) of women at Time 3 who met the criteria for a clinical anxiety disorder and 20.5% (n = 9) who met the criteria for clinical depression. Almost 40% (n = 17) of women met the criteria for either a clinical anxiety or mood disorder. About 12% of Australian women meet the criteria for an anxiety disorder and 7% meet the criteria for clinical depression, assessed during the National Survey of Mental Health and Wellbeing using the same structured interview (CIDI) (Andrews, et al., 1999). This means there is an increased prevalence of anxiety or depression in women with early breast cancer compared to the population in general more than 15 months after diagnosis at a level that warrants clinical attention. Around ten months after the completion of chemotherapy, 28% (n = 8) of women had an anxiety disorder compared to 13% (n = 2) of women who had not received chemotherapy. However, this difference was not statistically significant, \( p = 0.452 \). About 24% (n = 7) of women who had received chemotherapy had clinical depression compared to 13% (n = 2) of women who had not received chemotherapy. This difference was also not statistically significant, \( p = 0.400 \).

![Figure 11.7. Proportion of women with clinical a) anxiety (n = 15) or b) depression (n = 9) displaying more cognitive complications at time 3.](image-url)
As seen in Figure 11.7, half of the women who had an anxiety disorder at Time 3 experienced more cognitive complications at Time 3. In contrast, the majority of women (78%) who had clinical depression displayed more cognitive complications. There was a trend towards significance for women with clinical depression to have more cognitive complications at Time 3; $\chi^2(1, N = 44) = 2.46, p = 0.150$.

When anxiety and depression was assessed by self-report as defined by the Hospital Anxiety and Depression Scale (HADS) scores, there were 30% ($n = 13$) of women who had anxiety (HADS-A $\geq 8$) and 9% ($n = 4$) of women who had depression (HADS-D $\geq 8$) at levels defined for 'caseness'. Neither HADS-defined anxiety nor HADS-defined depression was associated with having more cognitive complications at Time 3 [$\chi^2(1, N = 44) = 1.36, p = 0.244$; and $p = 1.000$, respectively]. The HADS cut-off for 'caseness' of $\geq 8$ is set to indicate the probable presence of a clinical disorder. This level was found to overdiagnose anxiety disorders by 7% but underdiagnose depression by 11.5% in women with breast cancer.

11.2.4 Association with self-reported cognitive problems

Women who had more objective cognitive complications in either learning and memory or executive functions at Time 3 were not significantly more likely to report more retrospective memory problems ($p = 0.952$), prospective memory problems ($p = 0.952$), total prospective and retrospective memory problems ($p = 0.633$) or overall cognitive problems ($p = 1.000$).

The structured interviews that were conducted at Time 3 with women who had experienced more objective cognitive complications in both learning and memory and executive functions were examined for themes. All women who displayed more objective complications in both learning and memory and executive functions gave examples of cognitive changes that they had noticed including problems with: retrieving names or word finding; and planning, flexibility and remembering to remember to do things. Some women gave examples involving finding it harder to concentrate, learn a new task or concept, or having difficulties with problems solving or spatial accuracy. Examples of each of these are provided below.

Name retrieval and word finding difficulties

"The main thing I have noticed is that I have a bit of trouble sometimes recalling words. When I am speaking I can't remember the word. The other day I was trying to think of Kurosawa's Rushomon movie and I knew what I wanted to say but I couldn't remember
what it was called. Being an ex-journalist that is what I have noticed the most because words are always my forte."

"I am dreadful with people's names and I know I know them. One of the girls who ... I meet regularly for lunch and I bumped into her at the supermarket and do you think I could think of her name? ... With the family I say, 'Mrs so-and-so' and someone will fill it in and give me the name. It will come to me but not instantly."

**Planning, cognitive flexibility and prospective memory**

"Other things I have noticed, I am more forgetful. I have to have a diary to remember my appointments or I'll forget to go or forget someone is coming around. My mother is 75 and she and I both feel we are at the same level now of dementia because we wander around the house saying 'I forgot this' and 'I forgot it as well' or 'We have to get this at the shops' and then we get to the shops and both forget."

"They say women can multitask and you would do it but now, even in the kitchen, I'll be doing a couple of things, putting something in the oven and doing the vegetables for dinner and think, 'I've got to turn that down' and forget. ... where I would never have done that before."

**Concentration**

"If you call in and ask me a question on your account and, somewhere along the line I've looked at it and said, 'I'm sorry, I didn't quite hear. Was that an inquiry on your account, a dollar value or do you just want an update?' and that's when I break out in perspiration. It is work that I have done for years."

**New learning**

"With work it is hard because I changed jobs so it also a learning curve with this new job. I haven't done this kind of thing before that I am doing but sometimes I feel I am not grasping it as quick as maybe I used to grasp a new concept or a new skill. I tend to forget."

**Problem solving**

"There was a period when I was on chemo when I couldn't even do level one Sudoku. ... That was something I did daily before, have breakfast in bed and do the crosswords and the Sudoku."
Spatial accuracy

“I’m worried about driving... I have lost a lot of confidence. I’m in the wrong place a lot of the time. I am a little too far here or there. I seem to have lost... spatial awareness. Yes, that would be the word. And how to put the car in and park it. I’m often, when I get out and look, I think, ‘Oh, I thought I was much closer than that.’”

11.2.5 Association between self-reported cognitive problems and distress

Women who reported more retrospective memory problems at Time 3 were more likely to have clinical anxiety ($p = 0.043$) as were women who reported more total prospective and retrospective memory problems ($p = 0.017$). There was no relationship found between HADS-defined anxiety and reported prospective and retrospective memory problems ($p = 0.460$).

There was no significant association between self-reported overall cognitive problems or prospective and retrospective memory problems and clinical depression at Time 3 ($p = 0.619$ and $p = 1.000$, respectively). There was also no significant difference between prospective and retrospective memory problems and HADS-defined depression ($p = 0.308$). However, there was a trend towards significance in the association between overall self-reported cognitive problems and HADS-defined depression ($p = 0.087$).

11.2.6 Summary

A significantly greater proportion (76%) of women treated with chemotherapy displayed more cognitive complications at Time 3 than women not treated with chemotherapy (13%). Younger women and women with more advanced cancers, as well as women who had more general anaesthetics, were more likely to experience complications. Those women who experienced significant side effects from chemotherapy such as treatment-induced menopause or an adverse event requiring readmission to hospital, such as neutropenia, appear to be at more risk of experiencing longer term cognitive complications. These complications were more evident on a visual paired associates learning measure, cognitive flexibility measures and initial planning speed at the hardest level. These complications were unrelated to education, anxiety, depression, fatigue, sleep, pain, a mastectomy, or chemotherapy regimens including taxanes. There was a trend for women who were receiving hormone therapy to display more complications at Time 3.
Problems in word finding, planning and prospective memory were most often reported by women who suffered more objective complications across domains. However, overall, self-reported cognitive problems were not significantly associated with objective cognitive complications on neuropsychological testing. Reporting more prospective and retrospective memory problems was significantly more likely to be reported at Time 3 by women with a clinical anxiety disorder.

11.3 Lower than expected performance

All individuals were identified who displayed performance that was lower than expected, defined as one and a half standard deviations or more below their own estimated premorbid IQ/ability score. An overall 'lower than expected performance' score was then calculated for each individual from the mean of all scores that were $\leq 1.5 \text{ SD}$ below their predicted ability.

An ANOVA was conducted to compare overall lower than expected performance between groups over time, adjusted for variation between and within subjects. The performance profile of both groups deteriorated somewhat between Time 1 and Time 2, as shown in Figure 11.8, but whereas the chemotherapy group continued to decline at Time 3 the no-chemotherapy group did not.

![Figure 11.8. Lower than expected performance by treatment group over time.](image-url)
There was no significant Group by Time interaction observed on performance \[ F(2,86) = 0.63, p = 0.534 \]. There was a trend towards significance for the main effect of Group \[ F(1,44) = 3.10, p = 0.085 \] reflecting that lower than expected performance was worse in women from the chemotherapy group (\( M = -1.77 \)) than women from the no-chemotherapy group (\( M = -1.39 \)) across time. There was also a significant main effect of Time \[ F(1,44) = 6.47, p = 0.002 \]. This indicated that lower than expected performance was significantly worse at Time 2 (\( M = -1.70 \)) and Time 3 (\( M = -1.70 \)) compared to Time 1 (\( M = -1.51 \)) across groups (PD>LSD = 0.120, at a 95% confidence level).

A regression model involving forwards stepwise selection was used to identify potential explanatory variables for lower than expected performance change scores (Time 3 - Time 1), controlling for Time 1 baseline scores. A general linear regression on change scores revealed that women with higher baseline scores (\( p = 0.016 \)), lower estimated IQ (\( p = 0.004 \)), more self-reported cognitive problems over time (\( p = 0.002 \)) and women who experienced chemotherapy-induced neutropenia (\( p = 0.038 \)) were more vulnerable to decline in lower than expected performance at Time 3. A one standardized unit decrease in IQ was estimated to predict a 0.573 decline in lower than expected performance and chemotherapy-induced neutropenia was estimated to predict a 0.221 score decline in lower than expected performance.

### 11.4 Chapter discussion

**Individual cognitive complications**

There was no difference within any cognitive domain in the likelihood of women showing a cognitive complication between groups at Time 1, prior to chemotherapy. However, 33% of all women displayed a complication on the measure of visuoconstruction at Time 1 (Complex Figure Test copy accuracy), 42% displayed a complication within learning and memory and 58% displayed a complication within executive functions. Having three or more cognitive complications at Time 1 was significantly associated with HADS-defined anxiety. Anxiety associated with the impact of diagnosis and uncertainty regarding fear of recurrence and treatment may be interfering with cognitive performance at this time or problems with performance may be causing anxiety. This anxiety appears to be related more with diagnosis and treatment rather than worry about perceived cognitive problems as self-reported cognitive problems were not associated with objective cognitive complications. The measures displaying more complications at Time 1 were the Complex Figure Test copy, immediate recall and total recognition and initial planning speeds at the
highest levels (4 move and 5 move problems) as well as a measure of the ability to shift attention between two dimensions [IED Extra-dimensional (ED) Errors].

A significantly greater proportion (76%) of women treated with chemotherapy displayed more cognitive complications in either learning and memory or executive functions at Time 3 than women not treated with chemotherapy (13%). This is consistent with the original proportion of 75% found by Wiencke and Dienst (1995). However, only 21% of women treated with chemotherapy displayed more complications in both domains as compared to 0% of the women who were not treated with chemotherapy.

There were two measures in learning and memory that displayed far more complications at Time 3. These were the CANTAB Paired Associates Learning (PAL) Stages Completed and PAL Stages Completed on Trial 1. All women who displayed more complications in learning and memory showed a complication on Stages Completed and most (89%) women from the chemotherapy group displayed more complications on Stages Completed on Trial 1. Stages completed is a key indicator of the individual's success at paired associate learning, recording how many stages were completed overall. Stages Completed on Trial 1 refers to the number of stages passed on the first trial. This relates to the PAL first trial memory score, which showed 3 complications. The paired associate learning test has been found to be a sensitive test for detecting mild cognitive impairment and hippocampal dysfunction (de Rover, et al., 2011; Fowler, et al., 2002).

More complications in executive functions at Time 3 within the chemotherapy group were found on measures of cognitive flexibility and initial planning speed at the highest level. Around 14 - 21% of women treated with chemotherapy displayed more complications on the IED measures compared to none of the no-chemotherapy group. More complications were not found at the extra dimensional shift stage so these findings suggest more specific problems with reversal learning (Elliott, McKenna, Robbins, & Sahakian, 1995; Hampshire & Owen, 2006). Difficulties at the earlier stages of the task, prior to the extra dimensional shift, have been attributed to ‘recurrent perseveration’ or inappropriate repetition of a previous behaviour although task demands have altered.

Initial planning speed at the highest level (5 move problems) was the only other measure that displayed more complications at Time 3, with 14% of women treated with chemotherapy displaying slower planning speed on the most challenging level compared to none in the no-chemotherapy group. However, there were no more complications found on problem solving on this task as measured by the minimum number of moves needed to complete this task.
Different mechanisms appear to play different roles in cognitive complications at different timepoints following diagnosis. At Time 1 anxiety was associated with having more complications. At Time 3 clinical anxiety was associated with more self-reported memory problems but was not related to objective cognitive complications. Instead, younger women (<50) and women with more advanced cancers were more likely to experience more complications at Time 3. Younger women are also more likely to have more advanced cancers and be recommended adjuvant chemotherapy. Those women who had more general anaesthetics or experienced significant side effects from chemotherapy, such as treatment-induced menopause or neutropenia or an adverse event requiring a readmission to hospital, were significantly more likely to experience longer term cognitive complications. These complications were more evident on a visual paired associates learning measure, cognitive flexibility measures and initial planning speed at the hardest level. These complications were unrelated to education, anxiety, fatigue, sleep, pain, type of surgery or taxane-based regimens. There was a trend for women who were receiving hormone therapy or were clinically depressed to display more complications at Time 3.

Problems in word finding, planning and prospective memory were most often reported by women who suffered more objective complications across domains. However, overall, self-reported cognitive problems were not significantly associated with objective cognitive complications on neuropsychological testing. Reporting more prospective and retrospective memory problems was significantly more likely to be reported at Time 3 by women with a clinical anxiety disorder.

*Lower than expected performance*

There was no significant interaction effect found for lower than expected performance. There was a trend towards significance for the main effect of Group reflecting that lower than expected performance was worse in women from the chemotherapy group than women from the no-chemotherapy group across time. There was also a significant main effect of Time reflecting that lower than expected performance was significantly worse at Time 2 and Time 3 compared to Time 1. Women with higher baseline scores, lower estimated IQ, more self-reported cognitive problems over time and women who experienced chemotherapy-induced neutropenia were more vulnerable to decline in lower than expected performance at Time 3. A one standardized unit decrease in IQ was estimated to predict a 0.573 decline in lower than expected performance and chemotherapy-induced neutropenia was estimated to predict a 0.221 score decline in lower than expected performance.
11.5 Chapter summary

This chapter presented the results of individual analyses of performance before and after treatment. Two approaches were conducted in line with widely accepted clinical neuropsychological practice (Lezak, et al., 2012). One involved an assessment of the proportion of women who achieved very low scores and the other involving an assessment of individual performance relative to estimated premorbid IQ.

An analysis of individual cognitive complications ($z$-scores $< -2$) over time revealed that there was no difference within any cognitive domain in the likelihood of women showing a cognitive complication between groups at Time 1, prior to chemotherapy. However, a significantly greater proportion (76%) of women treated with chemotherapy displayed more cognitive complications at Time 3 than women not treated with chemotherapy (13%). Younger women and women with more advanced cancers, as well as women who had more general anaesthetics, were more likely to experience complications. Those women who experienced significant side effects from chemotherapy such as treatment-induced menopause or an adverse event requiring readmission to hospital, including neutropenia, were significantly more likely to experience longer term cognitive complications. There was also a trend for women who were receiving hormone therapy or were clinically depressed to display more complications at Time 3. Complications were more evident on a visual paired associates learning measure, cognitive flexibility measures and initial planning speed at the hardest level.

Overall, self-reported cognitive problems were not significantly associated with objective cognitive complications on neuropsychological testing. Reporting more prospective and retrospective memory problems was significantly more likely to be reported at Time 3 by women with a clinical anxiety disorder.

Lower than expected performance, calculated for each individual from the mean of all scores that were $\leq 1.5$ SD below their estimated premorbid IQ, was significantly worse at Time 2 and Time 3 compared to Time 1 across both groups. There was a trend for women exposed to chemotherapy to display worse lower than expected performance over time than women not exposed to chemotherapy. Women with higher baseline scores, lower estimated IQ, more self-reported cognitive problems over time and women who experienced chemotherapy-induced neutropenia were more vulnerable to decline in lower than expected performance at Time 3. These findings provide evidence for the role of lower cognitive reserve and the cumulative effects of chemotherapy and chemotherapy-induced neutropenic toxicity in increasing vulnerability to individual cognitive decline.
Chapter 12

Discussion

12.1 Introduction

Findings from the group analyses presented in the previous chapters provide limited support at the 95% confidence level for the hypothesis that women treated with chemotherapy for early breast cancer would demonstrate significantly worse cognitive functioning over a 9-month post treatment follow-up period relative to women not treated with chemotherapy. Only verbal recall discriminability displayed a significant interaction effect. In neuropsychological practice one statistically significant finding is rarely clinically meaningful unless it is supported by a body of evidence of poorer performance on related measures. When groupings trending towards a significant interaction effect were examined, a profile of impairment in cognitive performance following chemotherapy was found within verbal learning and memory, and executive functions. This was supported by the results from the individual deficits analyses. This provides evidence for a subtle profile of chemotherapy-related impairment. The following section (12.2) discusses the results of the group analyses by cognitive domain, ending with a detailed discussion of the risk factors that were identified within these analyses and the potential mechanisms for chemotherapy-related impairment (sections 12.2.7-12.2.9). A discussion of supporting findings from the individual deficits analyses is presented in section 12.3.

12.2 Group analyses by cognitive domain

The results of the analyses of cognitive changes over time between treatment groups are presented in Table 12.1 by cognitive domain. There were six significant or trending to significant interactions effects within Learning and Memory, as well as Executive Functions, where the no-chemotherapy group generally demonstrated improvement, consistent with a practice effect, while the chemotherapy group either did not improve or declined. There were 18 significant or trending to significant Time effects, in the absence of an interaction effect, observed on cognitive performance, 13 of which reflected improvement and five of which reflected decline over time. There were four significant Group effects, in the absence of an interaction effect, three of which indicated that the chemotherapy group performed worse than the no-chemotherapy group across time.
### Table 12.1

**Group, Time and Interaction Effects obtained from ANOVAs of Summary Scores for Groupings Within Each Domain**

<table>
<thead>
<tr>
<th>Name</th>
<th>Group</th>
<th>Time</th>
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</tr>
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<td>Language</td>
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<tr>
<td>Motor</td>
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</tr>
<tr>
<td>Visuconstruction</td>
<td>✓C&lt;NC</td>
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<tr>
<td>Attention and Speed of Processing</td>
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<td>Auditory attention span</td>
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<td>Fluency, flexibility &amp; reasoning</td>
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<td>Inhibition</td>
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</tr>
<tr>
<td>Planning speed</td>
<td>X</td>
<td>✓</td>
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✓ Significant interaction effect at $p < 0.05$. $X_A$ Trend at $p = 0.10$ (90% CI); $X_B p = 0.12$ (88% CI); $X_C p = 0.10$ (90% CI); $X_D p = 0.15$ (85% CI); $X_E p = 0.13$ (87% CI).

✓ Significant difference at $p < 0.05$. ✓ Trend towards significant difference.


C<NC Chemotherapy group significantly worse than no-chemotherapy.

C>NC Chemotherapy group significantly better than no-chemotherapy group.
12.2.1 Language

Both groups (chemotherapy/ no-chemotherapy) demonstrated a significant improvement in language performance from Time 1 to Time 2 followed by a significant deterioration from Time 2 to Time 3. There was a trend towards the chemotherapy group having significantly poorer language performance than the no-chemotherapy group over time. However, there was no significant difference in changes in language performance between groups, so this difference cannot be attributed to exposure to chemotherapy. Women commencing hormonal therapy at Time 2 were greater at risk of decline in language performance at Time 3.

Other prospective cohort studies that included a measure of language or verbal ability did not find any significant decline over time following chemotherapy (Ahles, et al., 2010; Collins, et al., 2009a; Tager, et al., 2010). However, attrition rates were quite high and people experiencing problems may not have been reassessed. One study reported significant improvement at each timepoint (Tager, et al., 2010) and another an interaction effect (Ahles, et al., 2010) where the no-chemotherapy group improved significantly between the baseline and the first post-treatment follow-up, whereas the chemotherapy group did not improve at this timepoint but then significantly improved over the next two assessments. All of these studies used a composite or summary measure as a verbal ability domain summary score but they were computed differently. They derived the domain score from either: the average of the z-scores for tests in the domain (Tager, et al., 2010); the sum of the standard regression based scores (Collins, et al., 2009a); or a principal component score on which verbal measures loaded higher (Ahles, et al., 2010).

Furthermore, the measures used to derive these scores were not the same as in the current study. They all included a measure of phonemic or letter fluency, rather than semantic fluency, and one study (Ahles, et al., 2010) did not include a measure of confrontation naming, the traditional measure of language or verbal ability. Letter fluency is not a specific measure of language or verbal ability as it has been found to be a sensitive measure of executive function and frontal lobe injury or executive dysfunction (Lezak, et al., 2012). In the study which found the interaction effect, the Verbal Ability domain score was derived from a principal component on which measures of reading ability, vocabulary and verbal fluency loaded highest (Ahles, et al., 2010). Two of the measures used are often used to estimate intelligence (WRAT-3 and Vocabulary) as they are less susceptible to change after brain damage. It is possible that this score reflects more generalized cognitive functioning, or verbal fluency, which is susceptible to practice effects, may have dominated the measure. More specific measures of verbal ability or language, such as confrontation
naming, may need to be included in the PCA for a more specific verbal ability dimension to be derived and interpreted. While the measure of semantic fluency from the D-KEFS Verbal Fluency test was used in the current study in the Language domain analysis, both letter fluency and category switching measures were included in the Executive functions analysis. These were included in the summary score for Verbal fluency, flexibility and reasoning, which demonstrated a trend for an interaction effect.

12.2.2 Motor

There was a significant improvement in motor performance from Time 1 to both the Time 2 and Time 3 follow up assessments. This was consistent with a practice effect. However, there was no significant difference in this change over time between treatment groups.

This is in keeping with previous studies which have not found a detrimental effect of chemotherapy on motor skills compared to women not treated with chemotherapy (Ahles, et al., 2002; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009b; de Ruiter, et al., 2011; Donovan, et al., 2005; Stewart, et al., 2008; van Dam, et al., 1998). However, one prospective study found a significant interaction effect between group and time on the motor domain summary score, where the no-chemotherapy group demonstrated a significant improvement over time whereas the chemotherapy group demonstrated a lack of a practice effect (Tager, et al., 2010). This was attributed to chemotherapy-induced peripheral neuropathy. The summary score consisted of the mean of z-scores on the Grooved Pegboard test and the Finger Tapping test. These tests were not used in the current study and it is possible that they might be more sensitive to chemotherapy-related impairment. However, another prospective study using the Grooved Pegboard test did not find such an effect (Stewart, et al., 2008). Other studies using the Finger Tapping test did not find any significant difference in performance between women treated with standard-dose chemotherapy and women not treated with chemotherapy (Ahles, et al., 2002; Donovan, et al., 2005; van Dam, et al., 1998).

The Grooved Pegboard test score is based on the number of seconds to place metal pegs in all the grooved slots on the pegboard and the Finger Tapping test score is based on the number of taps made in 10 seconds. The test instructions referred to (i.e., 1963-4 instructions) involve the examiner using manual recording with a hand held timer. This can be prone to measurement error (Lezak, et al., 2012). In contrast, the motor skills domain score in the current study was derived from measures of motor response speeds and pointing accuracy that were calculated electronically using a presspad and/or touchscreen at the level of millisecond and pixel accuracy. This enables a more accurate measurement of motor response and might account for the difference in findings.
12.2.3 Visuoconstruction

Complex Figure Copy accuracy performance was significantly poorer in women from the chemotherapy group over time, including prior to chemotherapy. Moreover, visuoconstruction performance was significantly below normative and expected performance in women with early breast cancer from both treatment groups, in the *Well Below Average* range. There was no significant *Group x Time* interaction effect found on visuoconstructional performance.

This performance was based on one outcome measure, the total correct score from the Copy trial of the Complex Figure Test. This measure was calculated from each copy drawing blind scored by the examiner for accuracy and placement of 18 figure elements according to defined scoring criteria and standardized using normative test data. It is possible that consistently low scores might be due to overly strict adherence to scoring criteria. However, 10% of all complex figures copy drawings were blind scored by an independent examiner with extensive neuropsychological testing experience. Inter-rater reliability coefficients (Pearson product-moment correlations) for total copy raw scores were high ($r = 0.94$).

Even if the overall low copy scores could be accounted for by a scoring effect, copy accuracy performance was significantly worse in the chemotherapy group than the no-chemotherapy group. This was at all times, including prior to chemotherapy. These findings are consistent with results from the original study by Wienke and Dienst (1995) where Complex Figure Copy accuracy scores of women who had been treated with chemotherapy were significantly below normative performance and also in the *Well Below Average* range ($M = -1.30$, $SD = 1.12$). Tager et al. (2010) also reported that women who were scheduled to receive chemotherapy demonstrated Copy scores at Time 1 that were in the *Well Below Average* range ($M = -1.52$, $SD = 2.84$). Castellon et al. (2004) found that Copy scores were one of the measures that best discriminated between breast cancer survivors who received adjuvant therapy and those that did not.

Complex figure copy accuracy involves visuospatial perception/construction, efficient motor processing, attention and a strategic approach for planning and sequencing figure elements and reproducing their spatial localization (Lezak, et al., 2004; Meyers & Meyers, 1995). Problems in visuoconstruction can also affect later recall and reproduction of the figure. The performance profile for Copy accuracy scores were unrelated to any motor, attention, planning speed or planning and problem solving performance profiles or $p$ value profiles, none of which showed a main effect for *Group*. This suggests a specific problem with visuoconstruction. Notably, the Copy performance and $p$ value profiles were not
consistent with performance on the individual measures of complex figure recognition, copy times, immediate recall or delayed recall. The p value profile showed some consistency with the visuospatial span summary score p value profile, as the chemotherapy group also demonstrated worse visuospatial span performance over time compared to the no-chemotherapy group and there was a trend towards worse visuospatial paired associate learning in the chemotherapy group as well.

As encoding, planning speed and planning and organization were not impaired at Time 1 this may mean that compensatory strategies were used to process and reorganize the figure following the copy trial so reproduction was improved at recall. Visuospatial memory encoding, and visuospatial span performance declined significantly following chemotherapy, and visuospatial paired associated learning performance showed significant decline at Time 2, as did visual cognitive flexibility, with a trend for more decline in the chemotherapy group. If compensatory strategies were affected, this would explain why visuoconstruction problems would affect performance on more visuospatial functions.

Women at highest risk for poorer copy accuracy at Time 1 were those who had received more general anaesthetics, were scheduled for chemotherapy, had higher anxiety or a diagnosis of clinical anxiety or depression. This will be discussed further in Section 12.2.9.

Counter-intuitively the variable associated with better copy accuracy performance was higher self reported mental fatigue. This apparent subjective fatigue-motor copy accuracy paradox has been observed previously in patients with multiple sclerosis (Pardini, et al., 2013). Functional MRI analysis indicated that this association is potentially mediated by cerebellar and orbital frontal activity, suggesting subjective fatigue is a correlate of increased resource demand for motor copy activities.

12.2.4 Attention and Speed of Processing

The principal components analyses for each of the three higher-order cognitive domains, namely Attention and Speed of Processing, Learning and Memory, and Executive Functions, revealed nested groupings within each domain. These findings will be discussed at the beginning of each relevant section followed by a discussion of the results of the group analyses.

Principal components analysis

The two major groupings found were 'attention' and 'speed of processing'. These are consistent with the literature on the basic dimensions of attention (Lezak, et al., 2012).
Attention displayed three further subgroups (spatial span and working memory, auditory span and working memory, and sustained attention). The attention tests put demands on either attention capacity or sustained, focused attention so these groupings were consistent with this. The spatial versus auditory groupings are consistent with Baddeley’s updated model of working memory (2000) where short-term storage is dedicated to content domains: a visuospatial sketchpad, which holds information for what is seen; and a phonological loop, which stores information for what is heard. While attention span and working memory are distinct constructs, they are similar in that they have limited capacity. These measures have been found to be highly correlated within cognitively intact individuals, and to rely on largely overlapping functional neural systems (Gerton, et al., 2004). These groupings are, therefore, consistent with the literature on these attention measures in normal populations.

Group analyses

a. Group by Time interaction effects

There were no significant Group by Time interaction effects observed on the Attention and Speed of Processing domain summary measure or in any of the nested groupings within this domain. This indicates that changes in Attention or Speed of Processing following treatment were not significantly different between women exposed to chemotherapy and those who were not. This is consistent with findings from previous prospective cohort studies (Ahles, et al., 2010; Mehlsen, et al., 2009; Quesnel, et al., 2009; Tager, et al., 2010). One prospective study found that women demonstrated more decline in the Working Memory summary score shortly following the completion of chemotherapy when compared to women who had not been treated with chemotherapy, but there were no significant differences in changes 1 year later (Collins, et al., 2009a). The Processing Speed summary score was significantly lower 1 year after the completion of chemotherapy in women who received hormonal therapy following chemotherapy. This study was conducted on post-menopausal women which may account for differences in findings. Also, analyses were conducted on raw scores rather than age-standardized scores based on normative test data.

b. Time effects

The most consistent finding was the significant main effect of Time on attention and speed of processing performances. All summary measures of major groupings (Attention, Speed of Processing) and subgroups (Spatial attention span and working memory, Auditory
attention span and working memory, Sustained attention) within the Attention and Speed of Processing domain displayed a significant main effect of Time. Across this domain performances at the follow-up Time 3 assessment were always significantly better than the baseline assessment at Time 1. With the exception of spatial span and working memory, all Time 2 performances were also significantly better than Time 1. These significant improvements in both attention and speed of processing performances, from the initial assessment to follow-up assessments, are consistent with a practice effect. Improvements in attention and speed of processing performances were not found to differ significantly between women with early breast cancer exposed to or not exposed to chemotherapy. This is consistent with other prospective studies that found significant improvements in attention and speed of processing performance across both groups or in the chemotherapy group over time (Quesnel, et al., 2009; Vearncombe, et al., 2009).

c. Group effects

There was a significant main effect of Group on sustained attention, but this showed that the chemotherapy group actually displayed better sustained attention than the no-chemotherapy group. This indicates that sustained attention was not adversely affected by chemotherapy. The PASAT was the only individual measure within the sustained attention grouping that was included in any previous prospective studies. It was included within a summary score of Executive Functions and they also found that women in the chemotherapy group demonstrated significantly higher PASAT and Executive Function summary performance across time (Collins, et al., 2009a).

12.2.5 Learning and Memory

Principal components analysis

One overall summary measure was derived for Learning and Memory from the 58 outcome measures produced from the six tests of learning and memory with two major groupings and one minor grouping evident within this domain (verbal learning and memory, paired associates learning and visual memory, and verbal recall errors). The primarily verbal and visual independent groupings found within learning and memory support contemporary models of memory (Baddeley, 2000) and research into unilateral brain lesions that indicate that verbal and visual memory are processed independently in different brain regions (Lezak, et al., 2012).
Verbal learning and memory had four subgroups and Paired Associates Learning and Visual Memory had five subgroups. Four independent groupings were found within the verbal learning and memory measures, including those related to verbal memory encoding, immediate recall and learning, delayed recall and recall discriminability. Five groupings were found within the paired associates learning and visual memory measures, including visuospatial memory encoding, visuospatial span, verbal paired associates learning, visual paired associates learning, and visual memory. These groupings are commensurate with information processing models of memory that involve stages of encoding, storage and retrieval in the formation and retrieval of memory (Baddeley, 2000). Encoding involves receiving and registering different sensory information and laying down a memory trace. Storage creates a record temporarily as immediate memory and maintains the memory trace over time as long-term memory, using learning processes to consolidate new information. Retrieval is the process of locating and recalling that stored information for current use.

The association of verbal and visual paired associates learning within the grouping of visual memory measures may indicate that visual strategies were being used to aid verbal paired associates learning and recall. Some participants who performed well at this task advised they pictured familiar or famous people together as the name pair was being read aloud to help link the pair and aid recall. This combination of visual strategy and meaningful associations may mean the type of learning strategies adopted underlie associations between both verbal and visual associative recall. However, within the biplot of the paired associates learning and visual memory measures, verbal paired associates learning measures and visual paired associates learning measures displayed distinct, independent groupings. This validates that this new paired associate learning test assessed verbal associate learning as distinct from visual associate learning, as it was designed to do.

**Group analyses**

A subtle profile of chemotherapy-related cognitive impairment was found in verbal learning and memory that was reflected in the summary measure for the learning and memory domain. This was most evident in verbal memory encoding and verbal recall discriminability where the no-chemotherapy group showed improved performance over time, whereas the chemotherapy group demonstrated no improvement or decline following completion of chemotherapy. A profile of decline for both groups was found in visuospatial encoding, memory span and visual associate learning.
a. Group by Time interaction effects

There was one significant interaction effect and three groupings with an interaction effect that displayed a trend towards significance within the learning and memory domain. These included the overall learning and memory domain and the verbal learning and memory grouping, as well as two nested groupings within verbal learning and memory, namely verbal memory encoding and verbal recall discriminability. The performance profiles in these groupings reflected that the performance of women not exposed to chemotherapy demonstrated improved performance over time, whereas women exposed to chemotherapy demonstrated no improvement or decline. This is consistent with previous studies that have found reduced verbal memory function in women following the completion of chemotherapy treatment (Rolfe, et al., 2011; Ruzich, et al., 2007; Vearncombe, et al., 2009). These studies found that average verbal learning and memory performance improved at longer term follow-up. Ruzich et al. 2007 used the Rey Auditory Visual Learning Test (RAVLT) a measure of verbal learning and memory which has been documented to have practice effects and the study did not include a control group. At the follow-up assessment where an alternate form was used (immediately post-chemotherapy) impairment was detected. At the longer term follow-up assessment the original form of the RAVLT that had been used at baseline was re-administered and a significant improvement was found in performance. Practice effects were likely the cause of the improvement in scores but, without a control group, any differences in the amount of change cannot be established.

Learning and memory tests are commonly influenced by practice effects (Lezak, et al., 2012; McCaffrey, Duff, & Westervelt, 2000). The lack of a practice effect or an attenuated practice effect on repeat testing can be an indicator of mild cognitive impairment (Howieson et al., 2008; Zehnder, Blasi, Berres, Spiegel, & Monsch, 2007). Other prospective studies have not detected differences between groups in verbal learning or memory changes following treatment (Ahles, et al., 2010; Debess, et al., 2010; Jenkins, et al., 2006; Mehlsen, et al., 2009; Quesnel, et al., 2009; Stewart, et al., 2008; Tager, et al., 2010). In general this appears to reflect the methodology used, including: not using alternate forms; selecting tests or measures that are not sensitive to change; or correcting for factors that may influence outcomes (as discussed in section 12.2.7 in relation to Premorbid IQ).

Logical Memory I and II has often been used to assess verbal memory, a test which has been demonstrated to be highly sensitive to practice effects (Schnabel, 2012), and the WMS-III does not include an alternate form. Ahles et al. 2010 included Logical Memory
and the CVLT-2, with an alternate form at Time 2. The two outcome measures from the CVLT-2 included in the overall principal components analysis were the Total Score trials 1-5, a measure of immediate memory, and Long delay raw score, a measure of verbal delay recall. Neither of these displayed significant interaction effects in the current study and nor did the respective groupings summary scores.

The significant Group by Time interaction effect was found on verbal recall discriminability, a summary measure of the nine individual CVLT-2 measures of recall discriminability from different trials. Recall discriminability measures recall accuracy and discrimination by comparing hits to false positives. Memory tests usually measure memory accuracy in terms of total recall of target items. However, this measure can artificially inflate memory accuracy scores where there is a high intrusion rate. Recognition tests often correct for this problem by using discriminability measures that provide a measure of hit rate relative to false positive rate. Recall discriminability is a new measure developed for the CVLT-2 that uses a measure of target accuracy that corrects for intrusion rate. This measure has been found to be more sensitive than traditional recall measures in distinguishing memory performance in patients with Alzheimer’s disease and Huntington’s disease (D.C. Delis, et al., 2005) and differentiating the severity of traumatic brain injury (M. L. Jacobs & Donders, 2007). As the current study is the first to include verbal recall discriminability outcome measures, it is possible that previous studies using global measures of total recall may have overlooked these subtle effects. This suggests that using more sensitive measures of verbal recall accuracy may help identify changes in the accuracy of verbal recall associated with exposure to chemotherapy.

The significant interaction effect reflected that changes in verbal recall discriminability performance varied significantly between groups following chemotherapy. The performance of the no-chemotherapy group significantly improved from both the Time 1 and Time 2 assessments to the Time 3 assessment, while the chemotherapy group significantly declined following chemotherapy (Time 2 to Time 3).

Having seen a significant interaction effect in verbal recall discriminability, one would expect to have seen a similar interaction effect in other verbal memory groupings. Two verbal memory groupings showed an interaction effect approaching significance, including the summary measure for verbal learning and memory, and verbal memory encoding, as well as the domain summary measure for learning and memory. In all these measures there was a trend towards performance improving over time in the no-chemotherapy group but not in the chemotherapy group, following treatment. In addition, verbal paired associates learning displayed a similar performance pattern of decline in the chemotherapy group between Time 2 and Time 3 as was found in verbal recall.
discriminability. While there was no significant interaction effect observed on verbal paired associates learning performance it adds support to chemotherapy being associated with decline in verbal learning and memory measures. Women at higher risk of decline at Time 3 were those with lower premorbid IQ and those receiving hormonal therapy following chemotherapy or who had experienced chemotherapy-induced neutropenia. These results will be discussed further in Section 12.2.7.

b. Time effects

A consistent finding across the domain was the significant main effect of Time on learning and memory performances. A profile of significantly improved performance over time across both groups, where there was no trend towards an interaction effect, was found within verbal immediate memory and learning, as well as in visual recall. These two memory groupings also displayed Time 2 performance that was significantly better than at Time 1. These significant improvements in performance at follow-up are consistent with a practice effect. Vearncombe et al. (2009) also found significant improvement in visual memory performance over time across both groups. Collins et al. (2009a) found that the chemotherapy group performed significantly worse on a summary measure of visual learning and memory than the hormonal therapy group shortly after chemotherapy but no significant difference was evident one year later. In contrast Bender et al. (2006) found that it was women who received tamoxifen following chemotherapy who displayed significant deterioration on visual memory following chemotherapy but there were no significant changes in women who received chemotherapy alone or local therapy alone. Within visual learning and memory in the current study there were subgroups that performed very differently, either improving or declining, so the difference in findings may be explained by the difference in methodological approaches i.e., summing scores versus deriving a principal component summary score for each nested grouping based on the associations between measures.

There were groupings within visual learning and memory where the significant main effect of Time represented a decline in performance in both groups. This was true of the visual memory encoding, visuospatial span grouping and visual paired associate learning groupings. Within both the visual memory encoding and visuospatial span grouping there was a significant decline from Time 1 to both the Time 2 and the Time 3 follow-up assessments. Visual paired associate learning displayed a significant decline from Time 1 to Time 2 but then a corresponding improvement in performance from Time 2 to Time 3. The visual paired associate learning test has been found to be one of the most sensitive
tests for detecting mild cognitive impairment and hippocampal dysfunction (de Rover, et al., 2011; Fowler, et al., 2002).

These changes over time did not vary significantly by treatment group, so they do not indicate an adverse effect of chemotherapy on performance in these learning and memory groupings. Factors that were significant determinants of decline will be discussed in Section 12.2.8.

c. Group effects

There was only one significant main Group effect found within the domain of learning and memory. This was in visuospatial span where the chemotherapy group performed significantly worse than the no-chemotherapy group over time, as well as there being a significant decline over time. This may relate to problems with visuoconstruction performance which was discussed previously.

Notably, were the no-chemotherapy group not included in the current study it might have been concluded that: there was no impact of chemotherapy on verbal learning and memory where performance improved over time; and that the deterioration in visual learning and memory was associated with exposure to chemotherapy. This highlights the importance of including a no-chemotherapy control group tested over the same timepoints in determining whether cognitive changes can be attributed to chemotherapy.

12.2.6 Executive functions

Principal components analysis

A PCA was conducted on the 32 outcome measures produced from the nine tests of executive functions. An examination of the biplot revealed two major groupings and one minor grouping within this domain (verbal executive, visual executive, and planning speeds). Two nested subgroups were found within the verbal executive measures, including those related to verbal fluency, flexibility and reasoning, and inhibition. Three subgroups were evident within the visual executive measures, including planning and problem solving, spatial working memory, and cognitive flexibility. These groupings are consistent with the literature on: theoretical models of the central executive (Baddeley, 2000); the functions that these measures are designed to measure (see Chapter 3.4.7g Executive Functions); and the literature on deficits found in patients with frontal lobe injuries (for overview see Lezak et al., 2012).
The predominantly verbal and visual independent groupings within the measures of executive functions is again commensurate with Baddeley’s updated model of working memory, which includes a central executive that is responsible for monitoring and coordinating the subsystems (i.e., the phonological loop, the visuospatial sketchpad) (Baddeley, 2000). The phonological loop is responsible for the manipulation of language based information, whereas the visuospatial sketchpad is responsible for the manipulation of non-verbal information. The model proposes that the components are relatively independent of each other. The episodic buffer stores and integrates information fed from the two subsystems temporarily and is linked to the central executive. The central executive manages and controls attention to this information, including focusing and selectively attending to some stimuli while ignoring others, switching between stimuli, and generating and reviewing strategies to resolve problems. This suggests that it is important to include both verbal and non-verbal tests of executive functions. Planning speed was an independent grouping but it was also located opposite verbal inhibition and self-regulatory functions in the biplot which might suggest that cognitive efficiency and control are interdependent. Increased speed can affect attentional control.

The only verbal measure located and retained within the visual executive grouping was Verbal Fluency Repetition Errors. In further exploration of the biplot of measures within this grouping it behaved consistently with the visual strategy and planning measures. While the Verbal Fluency test is administered and responded to verbally, some participants reported using visual strategies to help generate new words and keep track of switching between categories. This strategy may be helpful at reducing perseverative or repetition errors.

The inhibition measures were grouped with verbal executive measures. In the inhibition trial on the Color-Word Interference test, subjects are asked to name the colour that words are printed in when the ink colour and word conflict (e.g., ‘RED’ printed in green ink). Executive functions are needed to successfully perform this task, as the relatively overlearned and automatic behaviour (word reading) has to be inhibited in favour of a less practised task, naming the ink colour. Both stimuli are presented visually but are language based (words and names) and naming itself is a verbal function. It is interesting that the measures of response inhibition of visually presented stimuli needed to perform a naming task were clearly grouped with other verbal measures of executive functions (e.g., verbal fluency, verbal reasoning). This suggests that it is not the mode of administration of stimuli (visual or verbal) but whether the stimuli need verbal or non-verbal skills to resolve that determines how these measures were associated.
It is worth noting that switching conditions of Verbal Fluency and Color-Word Interference newly added to the D-KEFS were more associated with their respective test measures (i.e., Letter Fluency and Inhibition) than with measures of cognitive flexibility, i.e., the Intra-Extra Dimensional Set Shift, a test similar to the Wisconsin Card Sorting Test. This is in keeping with recent findings that suggest that the new switching conditions are less challenging than the traditional conditions for many participants and are highly correlated with those conditions (Lezak, et al., 2012; Lippa & Davis, 2010).

Two independent groupings were apparent within the verbal executive measures, including those related to verbal fluency, flexibility and reasoning, and inhibition. Three groupings were evident within the visual executive measures, including planning and problem solving, spatial working memory, and cognitive flexibility. These groupings are consistent with the functions of the central executive and the functions that these measures are designed to measure (for more details see Chapter 3.4.7g Executive Functions). They are also consistent with the kinds of deficits found in patients with frontal lobe injuries (for overview see Lezak et al., 2012). These patients are found to be highly distractible, impulsive and concrete in their thinking. They have trouble with problem solving and managing competing demands. These behaviours have shown up on neuropsychological assessment as impairments in several executive functions, including response inhibition, cognitive flexibility, abstract reasoning, fluency or generativity, perseveration or repetition errors, strategy, planning and problem solving.

**Group analyses**

*a. Group by Time interaction effects*

The overall Executive Functions domain summary measure and the main groupings within Executive Functions did not display any evidence of chemotherapy-related impairment – there was no significant interaction effect. However, a profile emerged at the level of nested subgroups within Executive Functions. This is consistent with the literature that executive functions involve independent functions that are not easily represented by a single or composite measure (Lezak, et al., 2012). There were subtle interaction effects observed in the verbal fluency, flexibility and reasoning subgroup within the Verbal Executive grouping, as well as the cognitive flexibility subgroup within the Visual Executive grouping. These subgroups both involve measures of cognitive flexibility. They both displayed a performance profile of significant decline in women exposed to chemotherapy compared to women not exposed to chemotherapy following treatment. These interaction effects suggest a subtle profile of chemotherapy-related impairment on fluency and cognitive flexibility. This is consistent with findings from a previous
prospective study where verbal fluency was found to decline immediately following chemotherapy (Quesnel, et al., 2009). Improvement was found at the longer term assessment where a parallel form was not used. Other prospective studies did not find such an effect but they either: did not include measures of these executive functions; included tests without parallel forms; or selected tests that are not sensitive to change in these executive functions (Ahles, et al., 2010; Collins, et al., 2009a; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Jenkins, et al., 2006; Ruzich, et al., 2007; Vearncombe, et al., 2009).

Executive functions are particularly difficult to measure on repeated assessment as they generally involve assessing the ability to respond to novel tasks or situations (Lezak, et al., 2012). One of the most commonly used test of executive functioning and cognitive flexibility is the Wisconsin Card Sorting Test (WCST). However, it is both highly sensitive to practice effects and also has been found to only measure executive functioning on the first exposure to the test. Lezak et al. (2012) describes it as a “one-shot” test as it is not a reliable measure of problem solving abilities for subjects who have solved it once and whose memory is reasonably intact. The WCST does not have an equivalent alternate form so studies that used this test have used the same form at each assessment (although the D-KEFS version ‘Sorting’ has one parallel form). These studies have found improvements in cognitive flexibility performance using the WCST with no significant differences found between women exposed or not exposed to chemotherapy (Collins, et al., 2009a; Stewart, et al., 2008) nor to norms using the WCST (Ruzich, et al., 2007) or the D-KEFS Sorting test (Ahles, et al., 2010; Vearncombe, et al., 2009).

Recent structural MRI studies have found reductions in frontal grey matter density associated with exposure to chemotherapy that were accompanied by increases in self-reported executive functioning problems (B. C. McDonald, et al., 2010; B. C. McDonald, et al., 2013). However, no objective executive functioning test was included. A retrospective fMRI study of breast cancer survivors using the WCST found that women who had been treated with chemotherapy displayed significantly reduced prefrontal cortex activation and poorer cognitive flexibility (i.e., more perseverative errors) compared to women not treated with chemotherapy and healthy controls (Kesler, et al., 2011). Furthermore, a retrospective study of older breast cancer survivors who had completed chemotherapy at least 10 years previously found significantly poorer cognitive flexibility on the WCST (i.e., more perseverative errors) and the CANTAB Intra-Extra Dimensional Set Shift test (i.e., more reversal errors) compared to age-matched healthy controls (Yamada, et al., 2010). The current study used the Intra-Extra Dimensional Set Shift test to assess changes in cognitive flexibility. It was designed with a number of parallel forms to assess changes in
executive functions in cognitive ageing and neurodegenerative disorders to determine the early indicators of impairment (Sahakian & Owen, 1992). It is a test that is established as being sensitive to changes in cognitive flexibility. This is likely to explain the difference in findings from previous prospective studies.

Pre-treatment lower premorbid IQ and chemotherapy and the cumulative toxicity of chemotherapy-related adverse events increased vulnerability to decline in verbal fluency, flexibility and reasoning and visual cognitive flexibility. This is consistent with the literature on cognitive reserve (for review see Stern, 2003) and will be discussed further in Section 12.2.7, Premorbid IQ (Cognitive reserve).

b. *Time effects*

There was a significant main effect of *Time* in the absence of any trend or significant interaction effect on performance in two groupings within the executive functions domain. These were visual planning and problem solving, and planning speed. Both planning and problem solving, and planning speed showed a profile of improved performance over time. In the planning and problem solving grouping, performance at the *Time 3* assessment was significantly better than at *Time 1* or *Time 2*. This indicates that planning and problem solving skills were not negatively affected by chemotherapy. In the planning speed grouping, performance at both the *Time 2* and *Time 3* follow-up assessments were significantly better than at *Time 1*. These significant improvements in performance at follow-up are consistent with practice effects.

Notably, the four subgroups within Executive Functions to display no significant or approaching significant interaction effect (planning and problem solving, planning speed, spatial working memory and inhibition) were derived from tests that provided only one mode and alternate forms were not available. These were: the CANTAB Stockings of Cambridge test, based on the Tower of London test; the CANTAB Spatial Working Memory test; and the D-KEFS Color-Word Interference test. Therefore, it cannot be concluded with any certainty that there is no chemotherapy-related impact on these executive functions. The marked improvements on planning may relate to the fact that an appropriate strategy has been found, so problem solving was faster and more efficient on retesting (Strauss, Sherman, & Spreen, 2006). Other prospective studies using the Tower of London test at each assessment also failed to detect any differences in performance following treatment (Ruzich, et al., 2007). While including a control group helps to assess differences in practice effects, it is possible that the lack of alternate forms mean these tests were less sensitive to subtle disturbances to functions, such as planning and problem solving, that involve responses to novel situations. A further study might use different tests of planning.
and problem solving ability, such as the Tower of London, Tower of Hanoi and Stockings of Cambridge as alternate forms, after assessing for equivalence.

The only subgroup that did not display a Group, Time or interaction effect was Inhibition, derived from measures from the D-KEFS Color-word interference test. This is a version of the classic Stroop test included as part of the D-KEFS battery as a stand alone test. It does not include a parallel form as the test has been found to have adequate test-retest reliability (D.C. Delis, et al., 2001b). However, the performance profile of the summary score and the individual inhibition total correct measure, the traditional measure of inhibition, showed practice-related improvement over time (i.e. reduced interference) in the no-chemotherapy group, whereas the chemotherapy group did not benefit from practice, suggestive of an interaction effect. The Inhibition summary score failed to detect a significant interaction effect. Previous exposure to colour naming has been found to aid young adults to develop a reading suppression or ‘priority learning’ strategy leading to improved performance in the inhibition trial (for overview see Davidson, Zacks, & Williams, 2003). Other prospective studies using the same form of the Stroop test at each session also failed to detect any significant difference between groups in changes following treatment (Jansen, et al., 2008; Jenkins, et al., 2006; Mehlsen, et al., 2009; Vearncombe, et al., 2009). It cannot be ruled out that if an alternate form or equivalent alternate test of inhibition were used at follow-up assessments, differences between groups in changes in inhibition skills following treatment may have become more evident.

As the two groupings within the executive functions domain which displayed interaction effects were derived from measures that included alternate forms, but the four groupings that did not display interaction effects were not, one explanation may be that single mode tests of executive functions have limited use for indexing changes over time that are associated with exposure to chemotherapy, even using a control group. Some tests of executive ability, especially planning and problem solving, may depend for their sensitivity on their novelty, restricting their use to a single occasion. Selecting measures with parallel forms or pilot testing alternate tests that assess the same function for equivalence may be needed to assess subtle changes to executive functions associated with chemotherapy in prospective studies.

c. Group effects

Only one Executive Functions grouping displayed a significant main effect of Group in the absence of a trend or significant interaction effect. This was found in the overall verbal executive summary performance. This reflected significantly poorer performance by the chemotherapy group compared to the no-chemotherapy group across time. Women with
lower cognitive reserve who had received more general anaesthetics were at greater risk of lower scores at Time 1 (see Section 12.2.9).

12.2.7 Mechanisms for interaction effects

The baseline or change variables that were significant determinants of decline at Time 3 will be discussed first in relation to the functions which displayed a significant (or approaching significant) interaction effect. Where relevant to this discussion, other functions are included which displayed similar risk factors where the chemotherapy group showed significant decline (Time effect) or worse performance (Group effect) and this is specified.

Tumour size

Unexpectedly, smaller tumour size was a risk factor for decline in both verbal learning and memory performance and verbal recall discriminability. When it comes to tumour size it has generally been established that the larger the tumour size, the worse the outcome (Carter, Allen, & Henson, 1989; Narod, 2012). However, small core basal tumours have a worse than expected outcome at 10-year follow-up, as do the more aggressive ‘triple negative’ breast cancers (Foulkes, 2012). There are suggestions that core basal breast cancer have a proportion of cells that have cancer stem-like properties such that small tumours have a greater propensity to metastasize early (Foulkes, Reis-Filho, & Narod, 2010). It is possible that cancer properties associated with small tumour size, like stem-like tumour cells, may have a direct or indirect effect on the central nervous system or neural stem cells, and increase vulnerability to cognitive decline but this would be an area for further study.

Premorbid IQ (cognitive reserve)

In this study women with higher premorbid intelligence were more likely to demonstrate improved cognitive performance following the completion of chemotherapy, consistent with a practice effect, while women with lower premorbid intelligence were at greater risk for decline over the same timeperiod. Lower premorbid intelligence was found to be a risk factor for decline post treatment in four areas of cognitive functioning: verbal recall discriminability; verbal paired associates learning (Time effect); verbal fluency, flexibility and reasoning; and visual cognitive flexibility.

This is consistent with the concept of ‘cognitive reserve,’ where premorbid intelligence is considered a measure of cognitive reserve (for review see Stern, 2003). Cognitive reserve is the ability of the brain to sustain damage without a decline in cognitive function.
Underlying this is the concept that there is a critical threshold of brain reserve capacity and once brain reserve capacity is depleted past this threshold, clinical or functional deficits emerge. Higher cognitive reserve is a protective factor, while lower cognitive reserve is a vulnerability factor in the ability of the brain to sustain damage without symptoms of impairment. An explanation for this effect is that cognitive reserve may assist the brain to develop compensatory mechanisms to cope with the buildup of neuropathological damage (Bigler, 2007). Cognitive reserve is based on brain reserve capacity and enriched experience, involving factors such as intelligence, education, occupation and leisure or social engagement.

There is a body of evidence to support this theory and it is now a major factor in explaining individual threshold differences in the onset of clinical symptoms in progressive disease or impaired test performance after acquired brain injury (Satz, 1993; Satz et al., 1993; Stern, 2003). People with lower levels of premorbid intelligence are more vulnerable to cognitive decline following traumatic brain injury (Bigler, 2007), HIV disease (Satz, et al., 1993), neurotoxic exposure (Bleecker, Ford, Celio, Vaughan, & Lindgren, 2007) and risk of dementia (Daffner, 2010) or Alzheimer’s disease (Katzman, 1993).

In the current study, women with lower pre-treatment lower premorbid IQ (cognitive reserve) who received more general anaesthetics were at higher risk of lower verbal executive performance at Time 1 prior to treatment (Group effect, see Section 12.2.6). They were also more vulnerable to decline following chemotherapy in verbal fluency, flexibility and reasoning. Those who were readmitted to hospital due to a chemotherapy-induced adverse event were at higher risk of decline in visual cognitive flexibility. Those who experienced chemotherapy-induced neutropenia alone or followed by hormone therapy were at greater risk of decline in verbal paired associates learning and verbal recall discriminability respectively nine months post-treatment.

Not many studies in the field have examined the role of cognitive reserve or estimated premorbid intelligence on cognitive changes associated with breast cancer treatment. One study found that chemotherapy subjects who demonstrated decline were less educated (Jenkins, et al., 2006; Stewart, et al., 2008). To date, only one other study in the field has examined the influence of IQ on chemotherapy outcome (Ahles, et al., 2010). While Ahles et al. (2010) found a significant Group × Time interaction effect on the Verbal Ability domain alone initially, when the interaction of cognitive reserve and each domain performance was examined, both verbal ability and speed of processing showed a significant interaction effect. Women with lower cognitive reserve were more likely to show lower performance shortly following treatment while women not exposed to chemotherapy and healthy controls improved over time. They also found that older
patients with lower cognitive reserve who were exposed to chemotherapy displayed slower processing speed shortly following the completion of chemotherapy than women not exposed to chemotherapy and healthy controls, which improved at longer term follow-up (Ahles, et al., 2010). Age was not found to be a significant explanatory variable in the current study probably because all raw scores were age-standardized before analysis. However, this study confirms that lower cognitive reserve increases the risk of poorer chemotherapy-related cognitive outcomes.

Note that in previous prospective studies that adjusted for education or premorbid intelligence, no evidence of chemotherapy-related neuropsychological impairment was found (Jenkins, et al., 2006; Stewart, et al., 2008) or was found on only one measure (Ahles, et al., 2010; Quesnel, et al., 2009) when performance was compared between women with breast cancer treated with or not treated with chemotherapy. Based on the literature on cognitive reserve, the effects of IQ and education on disease, brain injury or neurotoxic outcome are more clearly seen when these variables are treated as risk factors rather than confounds.

In this study higher cognitive reserve was a protective factor and lower cognitive reserve was a vulnerability factor for decline following treatment, particularly following the cumulative toxic effects of acute adverse events induced by chemotherapy, like neutropenia, and followed by other systemic treatment (hormonal therapy) that appear to aggregate to lower the symptom threshold and trigger the onset of clinical symptoms. These findings are consistent with the threshold theory (for review see Satz, 1993) that underlies contemporary cognitive reserve models. Women with lower cognitive reserve are then more likely to show functional impairments and cognitive decline earlier, as less efficient or flexible use of brain networks are more susceptible to disruption, so the threshold is reached more easily when the brain sustains damage.

Threshold differences in the ability of the brain to sustain damage from the cumulative effects of cancer, general anaesthesia, chemotherapy and chemotherapy-induced adverse events and hormonal therapy without a decline in cognitive function appear to be influenced by cognitive reserve, consistent with the literature. The cumulative effects of chemotherapy and associated acute adverse events and hormonal therapy on verbal recall discriminability, verbal paired associates learning, verbal fluency, flexibility and reasoning and visual cognitive flexibility were mediated by cognitive reserve, as women with lower cognitive reserve were more vulnerable to decline at Time 3.
Anxiety and depression (cognitive resilience)

Women with higher baseline anxiety or the presence of an anxiety or mood disorder at Time 1 or a decline in emotional wellbeing from Time 1 to Time 3 or clinical anxiety at Time 3 were more vulnerable to decline in overall learning and memory, verbal memory encoding, verbal learning and memory, verbal paired associates learning (Time effect) and visual cognitive flexibility at Time 3. This suggests there is a relationship between mental health or cognitive resilience and cognitive performance or outcomes.

Two recent studies have found women with higher baseline depression scores (Stewart, et al., 2008; Vearncombe, et al., 2009) or poorer emotional functioning (Vearncombe, et al., 2009) were at greater risk of cognitive decline post-treatment. Vearncombe et al. (2009) found increases in anxiety over the course of chemotherapy (Time 1 to Time 2) predicted ‘multiple test impairment’ (decline of >1.96 SD on two or more cognitive outcome measures). More participants showed impairment (decline of >1.96 SD) on the two verbal and learning measures. However, most of the retrospective and prospective studies have not found a relationship between psychological variables and objective cognitive performance or decline in breast cancer patients. Retrospective studies by their nature cannot examine the relationship of baseline anxiety and depression or changes in emotional wellbeing to post-treatment outcomes. Prospective studies have not included a clinical interview to determine whether anxiety and depressive symptoms at a level to meet diagnostic criteria for an anxiety and mood disorders have a relationship to cognitive outcomes. It is also possible that studies using surveys of anxiety or depression that include somatic symptoms, such as the CESD and BDI or STAI, or global cognitive outcome measures may have masked these psychological effects. The World Health Organization defines mental health as a state of wellbeing and the WHO-5 wellbeing index has been found to be the best screening tool for identifying depression in primary care (Henkel et al., 2003). In the current study, the emotional wellbeing summary score was derived from several measures of psychological and emotional wellbeing, including the WHO-5 wellbeing index, as well as psychological distress and may have been more sensitive to changes in overall mental health and emotional wellbeing.

Depression can interfere with the normal expression of cognitive abilities (Christensen, Griffiths, Mackinnon, & Jacomb, 1997). It has been widely assumed that adults with depression display more problems on effortful tasks due to diminished effort and motivation (Roy-Byrne, Weingartner, Bierer, Thompson, & Post, 1986). Christensen et al. (1997) conducted a meta-analysis of neuropsychological studies of patients with depression and dementia and found a flat profile of deficits across nearly every test for patients with depression. However, the current study did not support the hypothesis that
impaired memory performance was due to diminished effort or poor motivation, but instead was related to speed of processing or attention deficits. A flat profile of chemotherapy-related cognitive impairment was not observed in this study as would be expected if changes were solely due to depression.

Higher test-taking anxiety at baseline assessments and lower anxiety at subsequent assessments commonly lead to improved test performance over time in longitudinal studies (Lezak, et al., 2012). Subtle memory impairment has been found in a meta-analysis of studies of adults with posttraumatic stress disorder (Brewin, Kleiner, Vasterling, & Field, 2007). Visual memory impairments were found to be less pronounced than verbal memory impairments and impacted most on the initial acquisition and learning phases of verbal memory. One previous study in women with breast cancer following chemotherapy treatment found a significant relationship between higher posttraumatic instrusions and global cognitive impairment (Schirmer, et al., 2009). In the current study clinical anxiety at Time 3 was a determinant of decline in verbal paired associates learning at Time 3. This is consistent with the cognitive profile that would be expected from clinical anxiety, although the cause and effect of results cannot be determined. Anxiety, associated with diagnosis, treatment and fears for the future, could affect cognitive performance. Alternatively, awareness of increased cognitive problems may lead to persistent worry and higher anxiety. However, this anxiety appears not to be associated simply with worry about perceived cognitive problems, as self-reported cognitive problems were not associated with objective cognitive complications in verbal learning and memory at Time 3.

The most interesting finding is that the presence of higher anxiety or any clinical anxiety or mood disorder at Time 1 increased the risk of decline in overall learning and memory, verbal memory encoding, verbal paired associate learning and verbal learning and memory post-treatment at Time 3. Higher self-reported problems at Time 1 were not a determinant of any cognitive decline at Time 3. Furthermore, an expectation of cognitive decline at Time 1 was not a determinant of any cognitive decline at Time 3.

The presence of a clinical anxiety or mood disorder can be an indicator of lower cognitive resilience to further challenge. Cognitive resilience describes the capacity to overcome challenges and associated stress on cognitive function and outcomes (Lukey & Tepe, 2008). A prospective study of mild traumatic brain injury found that premorbid psychiatric history predicted postconcussional symptoms and outcomes three months post-injury (Ponsford et al., 2012). The findings in the current study suggest that anxiety and mood disorders at baseline may lower cognitive resilience against exposure to chemotherapy and related challenges. Lower cognitive resilience may reduce cognitive reserve capacity, increasing vulnerability to impairment in verbal encoding, learning and
memory following chemotherapy. This might mean that those with less psychological and cognitive resilience use less adaptive, compensatory cognitive coping strategies in response to cognitive toxicity and challenge. This suggests that individuals showing clinical anxiety or mood disorders or high anxiety following surgery and prior to adjuvant treatment might be targeted for early preventative intervention.

Previous prospective studies have not conducted a clinical assessment of anxiety or mood disorders and these results may be useful in identifying women at greater risk of cognitive impairment after treatment and suggest avenues for intervention to increase psychological and cognitive resilience.

Chemotherapy + hormonal therapy

Hormonal therapy in addition to chemotherapy was a significant risk factor for decline in overall learning and memory performance, verbal learning and memory and verbal recall discriminability at Time 3. This provides additional support for a cumulative negative cognitive effect of hormonal therapy on verbal learning and recall accuracy following chemotherapy. This is consistent with findings from other studies (Ahles, et al., 2010; Bender, et al., 2006; Castellon, et al., 2004; Collins, et al., 2009a; Schilder, et al., 2009). These studies examined the effects only in women who received chemotherapy (Bender, et al., 2006; Collins, et al., 2009b; Schilder, et al., 2009) or, alternatively, women who did not receive chemotherapy and then extrapolated these findings (Ahles, et al., 2010). A few studies did not find that hormonal therapy contributed to cognitive compromise in women with breast cancer (Hermelink, et al., 2008; Phillips et al., 2012) while one study found that hormonal therapy alone contributes to cognitive decline (Brezden, et al., 2000). Some have found tamoxifen in particular was associated with the greatest compromise (Castellon, et al., 2004; Schilder, et al., 2010; Silverman, et al., 2007) although this was not the case in the current study.

These findings are again consistent with the concept of a threshold effect on cognitive reserve capacity (Satz, 1993). Exposure to chemotherapy alone may remain subthreshold but then aggregate with the cumulative effect of subsequent exposure to hormonal therapy to produce functional impairment in verbal learning and memory.

Chemotherapy-induced neutropenia and threshold effects

Women who experienced chemotherapy-induced neutropenia were at increased risk of decline in verbal recall discriminability and verbal paired associates learning (Time effect) performance at Time 3. Women who experienced chemotherapy-induced neutropenia and
then received hormone therapy were at greater risk of decline in overall learning and memory and verbal recall discriminability performance at Time 3.

Neutropenia, the most serious haematological toxicity, is a granulocyte disorder in the blood characterized by a deficiency of neutrophils, a type of white blood cell, that protect the body against bacterial and fungal infections (J. Crawford, et al., 2004). Acute neutropenia generally involves the sudden onset of flu-like symptoms, fever and infection. Severe neutropenia carries a risk of life-threatening infection as the patient is unable to fight off invading germs so patients with severe neutropenia are hospitalized in isolation and administered strong antibiotics. Neutropenia is a significant toxic side effect of chemotherapy, especially taxane-based chemotherapy regimens.

In this study women who experienced chemotherapy-induced neutropenia were found to be at increased risk of decline in overall learning and memory, verbal paired associate learning and verbal recall discriminability. While to the best of the author's knowledge this is a new finding, neutropenia has not been examined as a risk factor in previous prospective studies, nor where these outcome measures were assessed. Although the mechanism is uncertain, there may be direct or indirect neurotoxic effects, secondary inflammatory or autoimmune responses, including increased levels of proinflammatory cytokines, or a neurotoxic threshold effect which is reached by the cumulative negative impact of chemotherapy and haematological toxicity. There is evidence that cytokines, non-antibody proteins released by activated immune cells after exposure to an antigen, can disrupt neural activity and verbal memory performance (Maier & Watkins, 2003). Serum cytokines levels have been found to be elevated in patients with neutropenia, with the highest levels encountered in the febrile neutropenic period (Buyukberber, Buyukberber, Sevinc, & Camci, 2009).

In addition, women who were readmitted to hospital due to a chemotherapy-induced adverse event were at increased risk for decline in cognitive flexibility at Time 3. The main reasons for readmission were thrombosis, neutropenia and septicaemia. 1 in 5 women were readmitted because of chemotherapy-induced neutropenia.

These findings also support a threshold effect on cognitive reserve capacity and suggest that women who are exposed to chemotherapy are more vulnerable to other systemic adverse or toxic events, like neutropenia or hormonal therapy, especially when cumulative. These cumulative effects support previous neuropsychological and neuroimaging findings from prospective and retrospective studies of cumulative dose-response effects associated with chemotherapy, including standard-dose and/or high-dose chemotherapy, or cumulative cycles or duration of treatment (Ahles, et al., 2002; M.

**Self-reported cognitive function**

The relationship between subjective and objective impairment in learning and memory varied depending on the measure. More self-reported mental fatigue at Time 1 or Time 2 was associated with a decline in verbal learning and memory, verbal recall discriminability and verbal fluency, flexibility and reasoning at Time 3. Interestingly, changes in mental fatigue over time did not predict decline. Women who reported more cognitive problems at Time 1 were more vulnerable to decline in cognitive flexibility at Time 3.

Counter-intuitively, an increase in self-reported total retrospective memory problems was associated with improved verbal memory encoding performance at Time 3. This finding was partially consistent with a previous study where self-reported complaints of cognitive problems were related to better performance on measures of visual memory (Bender et al., 2008). Perceived memory problems did not indicate objective memory impairments.

Most studies have not found an association between self-reported complaints and objective impairment. However, many previous studies have used a global measure of cognitive failures rather than domain specific self-report measures. This may have masked significant associations. The global self-reported cognitive function measure used in the current study also did not find any relationship to learning and memory performance. Importantly, perceived memory problems did not indicate objective memory impairments but the finding that women reporting higher self-reported mental fatigue following surgery are at greater risk of learning and memory impairment following treatment is worth further study.

**12.2.8 Mechanisms for time effects**

There were 13 groupings that displayed a significant main effect of Time on performance, in the absence of any trend or significant interaction effect. Four time effects represented a significant decline and 12 represented a significant improvement between timepoints across groups.
Practice effects

There were significant improvements in performance at follow-up assessments, in the absence of a trend or significant interaction effect, found in: motor skills; all six groupings within attention and speed of processing; two groupings within learning and memory (verbal immediate recall and learning, visual recall), and two groupings within executive functions (planning and problem solving, and planning speed). These significant improvements on repeated administration did not vary significantly between groups and are consistent with practice effects.

Baseline factors

Women with greater cancer severity, as measured by cancer stage, and women who received a mastectomy were at greater risk of decline in visuospatial span at Time 3. Cancer staging is a predictor of prognosis and risk of recurrence. Women with poorer physical wellbeing and role functioning at Time 1 were at greater risk of decline in visual paired associate learning at Time 3. Poorer social role functioning has also been associated with poorer executive functioning in women one month post-chemotherapy (Reid-Arndt, et al., 2009).

Psychological changes

Women who presented with a clinical anxiety or mood disorder at Time 2 were more vulnerable to decline in visual paired associates learning performance at Time 2. This suggests that anxiety or depression at a level warranting clinical attention is a predictor of decline in visuospatial learning across both treatment groups. While the direction of results cannot be determined it does suggest avenues for intervention.

Previous prospective studies have not included a clinical diagnostic assessment. However, a small study of breast cancer survivors found that women who used emotion-focused coping strategies displayed poorer visuospatial learning and immediate memory, whereas those who used problem-focused coping strategies displayed better delayed memory retention (Ayala-Feliciano, et al., 2011).

Self-reported changes

An increase in self-reported mental fatigue from Time 1 to Time 3 was accompanied by a decline in visuospatial memory encoding. Self-reported mental fatigue was related to objective changes in visuospatial memory while self-reported memory measures were not. The MFI Mental fatigue scale has not been used in previous prospective studies.
Hormonal therapy

Women commencing hormonal (anti-estrogen) therapy at Time 2 were at greater risk of decline in language performance at Time 3. This is partially consistent with a previous study which found that current tamoxifen users had significantly lower semantic memory scores than women with breast cancer taking estrogen or not taking hormonal therapy (Eberling, Wu, Tong-Turnbeaugh, & Jagust, 2004) Another study found that current tamoxifen users displayed significantly lower performance on a narrative task compared to past users or never users (Paganini-Hill & Clark, 2000).

In the etiology of breast cancer, hormones play a major role. A high percentage of the breast tumours depend on oestrogens for their growth. In order to stop or slow down the growth of the tumour or prevent further tumours, hormonal therapy for breast cancer interferes with estrogen biosynthesis (aromatase inhibitors) or with the growth promoting activity of estrogen (SERMs). As oestrogens have been found to have a beneficial effect on brain functioning (Norbury et al., 2003; Sherwin, 2006) it is possible that hormonal therapy for breast cancer may have an effect on cognitive function.

Research into the effects of hormonal therapy on cognitive functioning has shown mixed results (Bender et al., 2007; Ernst et al., 2002; Mar Fan, et al., 2005; Phillips, et al., 2012; Schagen, et al., 1999; Tchen, et al., 2003). A double-blind randomized prospective study found women randomized to receive anastrazole did not show any significant difference in cognitive function 2 years later compared to women allocated a placebo (Jenkins et al., 2008). However, in a study where women were randomized to tamoxifen, anastrozole or the combination of both agents, women receiving hormone therapy demonstrated significantly impaired verbal memory and information processing speed compared to healthy controls (Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004). Another study comparing women taking anastrozole to tamoxifen found that women receiving either hormonal therapy showed more reliable cognitive decline after 6 months compared to a healthy control group (Collins, et al., 2009b).

The current finding provides limited support for an effect of hormonal therapy on cognitive decline, specifically on language or verbal skills. The cumulative effects of hormonal therapy and chemotherapy appear to affect other verbal functions, namely verbal learning and memory in women with early breast cancer.

Possible treatment-related ocular changes

In light of the fact that three of the significant performance declines across both treatment groups involved the visual system and involved decline in initial visual acquisition and
learning, the visual system might be affected with systemic treatment. The majority of women with breast cancer were being treated with either chemotherapy or hormonal therapy so it is possible these declines could be explained by ocular degeneration induced by chemotherapy or hormonal therapy (al-Twegeri, Nabholtz, & Mackey, 1996). This is not uncommon, although it is often underestimated and under-reported. Some women in the study reported having to have their glasses changed to correct for changes in their vision since starting adjuvant treatment. The development of more aggressive regimens has resulted in a significant increase of reported cases of chemotherapy-induced ocular side effects (Raffa & Tallarida, 2010; Singh & Singh, 2012). Adverse ocular events associated with cyclophosphamide, methotrexate and 5-Fu, used in CMF and FEC chemotherapy, include blurred vision, kerato-conjunctivities sicca, blepharo-conjunctivitis and pin point haemorrhages (Singh & Singh, 2012). Optic disturbance has also been reported as a side-effect of taxanes, such as paclitaxel (Capri et al., 1994) and docetaxel, as well as anthracyclines, such as doxorubicin (Singh & Singh, 2012).

Retinopathy, cataracts and corneal lesions have also been reported in patients receiving adjuvant hormonal treatments for early breast cancer (Singh & Singh, 2012). Cataracts were described in about seven percent of patients receiving tamoxifen and six percent of patients receiving anastrozole (Howell et al., 2005). This might be a possible explanation for the lack of improvement in visuoconstructional copy accuracy performance on repeat testing across both groups.

12.2.9 Mechanisms for group effects

Only two groupings displayed a significant main effect of Group in the absence of a trend or significant interaction effect. This was found in the Complex Figure copy accuracy score (visuoconstruction) and overall verbal executive summary performance. This reflected significantly poorer performance by the chemotherapy group compared to the no-chemotherapy group across time, including prior to adjuvant treatment.

More general anaesthetics

Women who had received more general anaesthetics were at higher risk for poorer copy accuracy performance at Time 1, prior to chemotherapy, and women with lower premorbid IQ who had received more general anaesthetics were at greater risk of lower verbal executive summary performance at Time 1.

Nearly one third of women in the study received two general anaesthetics before Time 1 either for a local re-excision to achieve wider clearance margins, or a conversion to
mastectomy. General anaesthesia is a drug-induced reversible coma. Very little is known about what happens in the brain during general anaesthesia although recent advances in EEG monitoring during anaesthesia have indicated that there is a disruption in internal communication between the anterior and posterior area of the brain, leading to a disconnect between frontal-parietal networks (U. Lee et al., 2013). The frontal-parietal network has been found to be engaged in visuospatial planning tasks (Spreng, 2012). Most studies of post-operative cognitive decline have been conducted in children, or after cardiac surgery or in the elderly (van Harten, Scheeren, & Absalom, 2012), where persistent post-operative dysfunction has been observed in visuospatial ability, including copy accuracy (Ancelin et al., 2001). Furthermore, elderly patients with higher pre-operative depressive symptoms were found to be at higher risk of cognitive alteration after anaesthesia. No published research was found on the cognitive effects of short-term repeated exposure to general anaesthetics in adults. Women with breast cancer can receive repeated general anaesthetics as well as procedural sedation involving anaesthesia over an interval of a few weeks with additional exposure over the course of treatment.

**Anxiety or depression (cognitive resilience)**

Women with higher self reported anxiety or a diagnosis of clinical anxiety or depression at *Time 1* were at higher risk of poorer copy accuracy performance at *Time 1*. Women at higher risk of poorer copy accuracy were also those who received more general anaesthetics and were scheduled for chemotherapy. Combined with the findings regarding decline on functions involving the visual system (p. 334-5), this suggests there may a multifaceted interaction of the impact of more general anaesthesia, lower cognitive resilience, and systemic treatment on visuoconstruction and the visual system.

**Self reported mental fatigue**

Higher self reported mental fatigue was associated with better copy accuracy performance at *Time 1*. Subjective fatigue and task-related copy accuracy has been found to be positively associated on a temporal copy task (keeping up the metronome rhythm) in multiple sclerosis, revealing a ‘fatigue–motor performance paradox’ (Pardini, et al., 2013). Functional MRI analysis indicated that this association is potentially mediated by cerebellar and orbital frontal activity, suggesting subjective fatigue is a correlate of increased resource demand for motor copy activities.
12.3 Individual deficit analysis

An analysis of individual complications (z-scores < -2) revealed that there was no difference between groups within any cognitive domain in the likelihood of women showing a cognitive complication at Time 1, prior to chemotherapy. However, a significantly greater proportion (76%) of women treated with chemotherapy displayed more cognitive complications in learning and memory or executive functions at Time 3 than women not treated with chemotherapy (13%). This proportion is similar to the 75% found by Wiencke and Dienst (1995) in the original study. However, only 21% of women treated with chemotherapy displayed more complications in both domains, compared to 0% of the no-chemotherapy group.

Increased complications were more evident on two visual paired associates learning measures, a number of cognitive flexibility measures and a measure of initial planning speed at the hardest level. Different mechanisms appeared to play different roles in cognitive complications at different timepoints following diagnosis. At Time 1 anxiety was associated with having 3 or more complications. At Time 3 clinical anxiety was associated with more self reported memory problems but was not related to objective cognitive complications. Instead, younger women (<50) and women with more advanced cancer, as well as women who had more general anaesthetics, were more likely to experience complications at Time 3. Those women who experienced significant side effects from chemotherapy such as treatment-induced menopause or an adverse event requiring readmission to hospital, including neutropenia, were significantly more likely to experience longer term cognitive complications. There was also a trend for women who were receiving hormone therapy to display more complications at Time 3. Most of these risk factors were the same as for the group analyses. Women who experienced treatment-induced menopause were not found to be at greater risk of decline in the group analyses but were found to be at higher risk of more individual complications consistent with some previous findings (Jenkins, et al., 2006; Vearncombe et al., 2011) but not others (Hermelink, et al., 2008).

Lower than expected performance was significantly worse at Time 2 and Time 3 compared to Time 1 across both groups. There was a trend for women exposed to chemotherapy to display worse lower than expected performance over time than women not exposed to chemotherapy. Women with lower premorbid IQ and women who experienced chemotherapy-induced neutropenia were more vulnerable to decline at Time 3. An increase in self-reported cognitive problems over time was associated with further cognitive decline.
Unlike previous prospective studies, the findings from the individual analyses were generally consistent with the group analyses and provide further support for the role of cognitive reserve and the cumulative effects of chemotherapy and adverse events from treatment, including chemotherapy-induced neutropenia, on decline in individual performance.

12.4 Summary

Consistent with the aim, the findings from the current study provide evidence of a subtle chemotherapy-related profile of impairment nine months following the completion of treatment. This profile was subtle and domain-specific, rather than global, and was found within verbal learning and memory, and executive functions. This profile of impairment was associated with a cumulative chemotherapy-related toxic threshold involving adverse events, especially neutropenia, and hormonal therapy. Women who were at greater risk of impairment were those with lower pre-treatment cognitive reserve and cognitive resilience.
Conclusions and Future Work

13.1 Conclusions

Findings from these analyses provided limited support at the 95% confidence level for the hypothesis that women treated with chemotherapy would demonstrate significantly worse cognitive functioning over a nine-month post treatment follow-up period relative to women not treated with chemotherapy for breast cancer. However, at the 85% confidence level or greater a profile emerged of chemotherapy-related impairment within verbal learning and memory and executive functions, including verbal fluency, flexibility and reasoning, and visual cognitive flexibility. These performance profiles often demonstrated a trend for the no-chemotherapy group to improve over time, consistent with a practice effect, while the chemotherapy group either did not improve or declined over time. This effect was not transient and differences were evident nine months following the completion of treatment. This supports previous research that has found subtle chemotherapy-related impairment in verbal learning and memory, and executive functioning.

It appears that chemotherapy-related impairment is a complex condition. Contributing factors related to pre-treatment factors, including lower cognitive reserve (premorbid IQ) and cognitive resilience (clinical anxiety and depression) and the cancer itself. Treatment-related factors included acute adverse events, such as neutropenia, and the cumulative effects of hormonal therapy following chemotherapy, as well post-treatment existence of clinical anxiety. These findings converge with other recent studies to indicate that systemic chemotherapy in combination with hormonal therapy has adverse effects on cognitive functioning and supports findings of cumulative dose-response effects. It also confirms previous findings that education or IQ (cognitive reserve) influences outcome.

This study extends previous findings unveiling a complex interaction of pre-treatment cognitive reserve and cognitive resilience with chemotherapy-related cumulative threshold effects on cognitive outcome following chemotherapy. The cognitive reserve threshold appears to be lowered by the cumulative effects of chemotherapy and acute adverse events, like neutropenia, and hormonal therapy, but individual threshold differences are moderated by cognitive reserve and cognitive resilience. Unlike previous
prospective studies, the results of the group analyses were supported by the findings from the individual analyses. These results are consistent with the extensive body of research on cognitive reserve that has demonstrated that individual threshold differences in the brain’s ability to sustain damage without functional impairment are moderated by cognitive reserve and that the threshold is lowered by cumulative toxicity.

13.1.1 Significance/Implications of findings

Few studies to date have prospectively examined women with breast cancer scheduled to receive chemotherapy compared to women not receiving chemotherapy with medium to longer-term follow-up, and prospectively examined the relative influence of explanatory factors on outcome. None of these have included a comprehensive clinical neuropsychological assessment. The findings from the current study provide a subtle profile of chemotherapy-related impairment as distinct from a profile of pre-treatment impairment or a profile of decline common to women with early breast cancer. The findings demonstrate a cumulative chemotherapy-related threshold effect. This is the first study to examine the effect of acute adverse events, particularly neutropenia, on cognitive outcomes. This has helped to distinguish between a profile associated with chemotherapy alone or in combination with hormonal therapy and a profile that is better explained by chemotherapy-related cumulative toxicity.

Unlike previous prospective studies, the results of the group analyses were supported by the findings from the individual analyses. Also, some self-reported problems were related to objective changes. Self-reported mental fatigue was related to objective changes in learning and memory, while self-reported memory measures were not. Finally, mental health and cognitive resilience showed a significant but complex relationship with objective impairment, as has begun to emerge in recent prospective cohort studies. These relationships were mainly revealed by clinical levels of anxiety and depression or by measures that did not include somatic symptoms.

The detection of these changes in this study may have been due to methodological differences from some previous studies, including the use of: a no-chemotherapy control group; a standardized testing environment; standardized and specific measures; parallel forms; and tests robust against ceiling effects. Some of these interaction effects were not revealed at a domain level, but only in subgroup functions within a domain, so global or domain summary measures would fail to detect these effects. All of the interaction effects were found on summary scores derived from tests where parallel or alternate forms were used at each follow-up assessment. Lack of the use of parallel forms at each follow-up assessment may reduce sensitivity to detect such effects. In addition, some of the
relationships were revealed by examining the association of variables like premorbid IQ to outcome, rather than correcting for IQ or education.

Taking into account these factors, this study demonstrated the presence of a subtle profile of chemotherapy-related impairment in verbal learning and memory and executive functions nine months after the completion of treatment. This profile of impairment was associated with cumulative chemotherapy-related threshold effects, involving acute adverse events and hormonal therapy, mediated by pre-treatment cognitive resilience and cognitive reserve. The effects of cancer, cognitive reserve, cognitive resilience and chemotherapy-related cumulative toxicity are complex and multifactorial and provide a framework for further study.

13.1.2 Limitations of the current study

Despite careful attention to the design of the study, there were certain limitations. Unless one has access to a large population or a multi-centred study it is not possible to avoid a mixed sample. Different chemotherapy regimens were included and the number of cycles varied as a function of treatment regimen. The no-chemotherapy group included those who were receiving other treatments, including different hormonal therapies and/or radiotherapy. A large multi-centred prospective study could explore profiles within treatment-specific and cumulative treatment groups.

By including a pre-treatment baseline and measuring change from baseline in both the chemotherapy group and no-chemotherapy group it was possible to measure and examine effects that might influence cognitive outcomes. A prospective study that includes a comprehensive neuropsychological assessment is not suitable for large scale studies. However, in a smaller group study, using a prospective cohort design and a multivariate analytical method helped to increase sensitivity to change because summary measures were derived from underlying associations between multiple measures. This approach produced results consistent with the neuropsychological literature and unmasked a subtle profile of chemotherapy-related changes.

Despite the limitations, the study contributes to the small but growing number of prospective cohort studies examining cognitive effects of chemotherapy.

13.1.3 Recommendations for future research

It would be recommended that all future studies include an estimate of premorbid IQ and clinical interview in order to examine the influence of lower cognitive reserve and lower cognitive resilience on cognitive outcomes, especially as they interact with chemotherapy-.
related adverse events or hormonal therapy following chemotherapy. Future studies should also consider the use of the first principal component score from a principal components analysis to derive domain summary measures rather than using an average of individual measures.

In a large scale prospective study, it is recommended that a core battery should at least include an estimate of premorbid IQ and: the CVLT-II (using the included parallel form and original test as a second parallel form but using the CVLT-II scoring methods and norms); the D-KEFS verbal fluency test (with equivalent alternate letters and categories used at any follow-up); alternate/parallel forms of abstract reasoning at each assessment; and the CANTAB Intra-extra dimensional set shift test (using parallel forms at follow-up assessments). A clinical assessment of anxiety and mood disorders, the MFI Mental Fatigue self-report survey, and an eye test are also recommended at each assessment. Tests should be administered by trained psychologists in a quiet, standardized testing environment without distractions or interruptions.

It would be valuable to recruit a no-cancer control group that has received a similar number and duration of general anaesthesia in a comparable interval to women with early breast cancer before the first assessment, to assess the effects of general anaesthesia. This group would need to be selected carefully, so they are not confounded by the effects of possible hypoxia (cardiac patients).

The findings suggest that cancer properties associated with small tumour size, like stem-like tumour cells, may have a direct or indirect effect on the central nervous system or neural stem cells, and increase vulnerability to cognitive decline and warrant further study.

Changes to initial visual processing and learning that may implicate ocular changes associated with systemic treatments warrants further investigation. The role of cumulative general anaesthesia in visuoconstruction impairments also warrants further study.

Importantly, perceived memory problems did not indicate objective memory impairments but the finding that women reporting higher self-reported mental fatigue following surgery are at greater risk of learning and memory impairment following treatment is worth further study.

Wherever possible parallel or alternate forms should be used, especially within learning and memory and executive functions. Some tests of executive ability, especially planning and problem solving, may depend for their sensitivity on their novelty, restricting their
use to a single occasion. Further work needs to be done in comparing the sensitivity of executive measures with single forms to parallel forms and to equivalent alternate tests that assess the same function in detecting changes in executive skills like planning and problem solving. One might use different tests of planning and problem solving ability, such as the Tower of London, Tower of Hanoi and Stockings of Cambridge as alternate forms, after assessing for equivalence.

Women with a clinical diagnosis of anxiety or depression and those showing high levels of anxiety after surgery could be targeted for interventions such as Cognitive Behaviour Therapy (CBT) or Interpersonal Therapy (IPT) to facilitate adjustment to stressful life events and assess the impact on longer term cognitive outcomes.

In regard to clinical practice, if the models of cognitive resilience and cognitive reserve in relation to individual threshold effects have predictive clinical value, then a simple, quick test of premorbid intelligence (e.g., NART-2) and a clinical interview prior to adjuvant treatment may identify individuals at greatest risk of decline following chemotherapy. The clinician might then be able to design an early preventative intervention to increase resilience and cognitive coping strategies for individuals at highest risk. This may also help oncologists and patients to decide as part of the overall assessment of cost-benefit of adjuvant treatments, whether the reduction of risk in additional treatments is worth any potential cognitive cost.

With the introduction of new systemic adjuvant treatments for early breast cancer there has been an increasingly high survival rate. Women have concerns about the implications of treatment on longer term QOL. When educating clients about the longer-term implications of chemotherapy on cognitive functioning, cancer care providers will be able to communicate that such outcomes are more likely to arise from the cumulative effects of chemotherapy with hormonal therapy or acute adverse events. These changes tend to be subtle and domain specific rather than global. Not every woman experiences these effects and women can be identified who are at higher risk.
References


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Kasai, M., Meguro, K., Hashimoto, R., Ishizaki, J., Yamadori, A., & Mori, E. (2006). Non-verbal learning is impaired in very mild Alzheimer’s disease (CDR 0.5): normative data from the learning version of the Rey-Osterrieth Complex Figure Test. *Psychiatry and Clinical Neurosciences, 60*(2), 139-146. doi: 10.1111/j.1440-1819.2006.01478.x


Attention.

Everyday of Test (1994).


365


Appendix A

A.1. Test names

<table>
<thead>
<tr>
<th>Test</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANTAB</td>
<td>Cambridge Neuropsychological Test Automated Battery</td>
</tr>
<tr>
<td>BLC</td>
<td>Big Little Circle</td>
</tr>
<tr>
<td>GNT</td>
<td>Graded Naming Test</td>
</tr>
<tr>
<td>IED</td>
<td>Intra-Extra Dimensional Set Shift</td>
</tr>
<tr>
<td>MOT</td>
<td>Motor Function</td>
</tr>
<tr>
<td>PAL</td>
<td>Paired Associates Learning</td>
</tr>
<tr>
<td>PRM</td>
<td>Pattern Recognition Memory</td>
</tr>
<tr>
<td>RTI</td>
<td>Reaction Time</td>
</tr>
<tr>
<td>RVP</td>
<td>Rapid Visual Information Processing</td>
</tr>
<tr>
<td>SOC</td>
<td>Stockings of Cambridge</td>
</tr>
<tr>
<td>SRM</td>
<td>Spatial Recognition Memory</td>
</tr>
<tr>
<td>SSP</td>
<td>Spatial Span</td>
</tr>
<tr>
<td>SWM</td>
<td>Spatial Working Memory</td>
</tr>
<tr>
<td>CFT</td>
<td>Complex Figure Test</td>
</tr>
<tr>
<td>D-KEFS</td>
<td>Delis-Kaplan Executive Function System</td>
</tr>
<tr>
<td>CWI</td>
<td>Color-Word Interference Test</td>
</tr>
<tr>
<td>PRV</td>
<td>Proverb Test</td>
</tr>
<tr>
<td>VF</td>
<td>Verbal Fluency Test</td>
</tr>
<tr>
<td>WC</td>
<td>Word Context Test</td>
</tr>
<tr>
<td>DSSP</td>
<td>Digit Supraspan</td>
</tr>
<tr>
<td>NART-2</td>
<td>National Adult Reading Test – Second Edition</td>
</tr>
<tr>
<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
</tr>
<tr>
<td>VPA&lt;sub&gt;n&lt;/sub&gt;</td>
<td>Verbal Paired Associates (names)</td>
</tr>
<tr>
<td>WAIS-III</td>
<td>Wechsler Adult Intelligence Scale – Third Edition</td>
</tr>
<tr>
<td>DSP</td>
<td>Digit Span</td>
</tr>
<tr>
<td>SIM</td>
<td>Similarities</td>
</tr>
</tbody>
</table>
A.2 Digit span – extending the limits

The WAIS-III Digit Span Forward trial was extended from 9 to 13 digits (Digit Supraspan Forward) (see Table A1)

Table A1
Digit Supraspan Forward Sequences

<table>
<thead>
<tr>
<th>Item</th>
<th>Trial</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>1</td>
<td>3-10-8-1-9-5-7-2-4-6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8-3-7-1-4-2-9-6-5-10</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>10-9-4-3-7-6-2-5-8-12-1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7-8-5-6-4-1-3-10-12-2-9</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>12-8-5-7-3-4-10-13-9-1-2-6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4-1-9-5-10-3-13-12-8-2-6-7</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>3-5-12-14-7-9-4-13-10-8-2-6-1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>9-1-13-4-14-2-5-10-3-6-12-7-8</td>
</tr>
</tbody>
</table>

Item numbers follow on from WAIS-III Digit Span Forward item numbers.

The Digit Span Backward trial was extended from 7 to 11 digits (Digit Supraspan backward) (see Table A2).

Table A2
Digit Supraspan Backward Sequences

<table>
<thead>
<tr>
<th>Item</th>
<th>Trial</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>1</td>
<td>6-9-7-4-3-8-5-2-1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7-4-1-6-2-5-9-8-3</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>10-6-7-3-1-8-2-4-9-5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5-2-4-7-9-3-1-8-10-6</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>3-6-5-4-2-7-10-9-12-8-1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>9-2-8-12-10-3-7-1-5-4-6</td>
</tr>
</tbody>
</table>

1. Item numbers follow on from WAIS-III Digit Span Backward item numbers
A.3. Verbal paired associates (names)

The eight name pairs used at each of the assessments are listed in Table A3.

Table A3

*Name Pair Lists in Verbal Paired Associates (Names) for Each Assessment*

<table>
<thead>
<tr>
<th>List 1</th>
<th>Parallel form 1</th>
<th>Parallel form 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sophie – Anne</td>
<td>Richard – Neil</td>
<td>Ashley – May</td>
</tr>
<tr>
<td>Megan – Grace</td>
<td>Michael – John</td>
<td>Hannah – Meg</td>
</tr>
<tr>
<td>Riley – Max</td>
<td>Chloe – Ruth</td>
<td>Joseph – Ross</td>
</tr>
<tr>
<td>Emma – Jo</td>
<td>Erin – Lyn</td>
<td>Ethan – Rick</td>
</tr>
<tr>
<td>Daniel – Charles</td>
<td>Caitlin – Sam</td>
<td>Andrew – Luke</td>
</tr>
<tr>
<td>Alex – George</td>
<td>Thomas – Nick</td>
<td>Holly – Beth</td>
</tr>
<tr>
<td>David – Mark</td>
<td>Robert – Scott</td>
<td>Sarah – Kate</td>
</tr>
<tr>
<td>Laura – Jane</td>
<td>Michelle – Rose</td>
<td>Jacob – Ben</td>
</tr>
</tbody>
</table>
## Appendix B

### B.1. Study leaflets

<table>
<thead>
<tr>
<th>A. IS FOGGY THINKING CAUSED BY BREAST CANCER TREATMENT?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your participation in this research may help provide the answers that can help other women in a similar situation to yourself in future.</td>
</tr>
<tr>
<td>To complete this study we need:</td>
</tr>
<tr>
<td>b. 30 women post-surgery with early breast cancer who WILL receive chemotherapy;</td>
</tr>
<tr>
<td>c. 30 women post-surgery with early breast cancer who WILL NOT receive chemotherapy (can receive other treatment e.g., hormone or radiation therapy).</td>
</tr>
<tr>
<td><strong>Participant Inclusion Criteria:</strong></td>
</tr>
<tr>
<td>a. Female;</td>
</tr>
<tr>
<td>b. Early breast cancer;</td>
</tr>
<tr>
<td>c. 18 – 65 years of age;</td>
</tr>
<tr>
<td>d. No previous chemotherapy treatment;</td>
</tr>
<tr>
<td>e. Fluent in English.</td>
</tr>
<tr>
<td><strong>Participation</strong> in this study involves around 3 hours of clinical neuropsychological assessment at the ANU, 3 times over a year, including:</td>
</tr>
<tr>
<td>a. pre chemotherapy (post-surgery);</td>
</tr>
<tr>
<td>b. after chemotherapy (or at 6 mths);</td>
</tr>
<tr>
<td>c. 6-9 mths later.</td>
</tr>
<tr>
<td>The tests are set up to be challenging but interesting, in a game-like format.</td>
</tr>
<tr>
<td>If you are interested in helping or learning more, please contact:</td>
</tr>
<tr>
<td>Ms Rachel Lacey</td>
</tr>
<tr>
<td>School of Psychology</td>
</tr>
<tr>
<td>The Australian National University</td>
</tr>
<tr>
<td>Ph: 6125 xxxx Mob: 0418 xxxx</td>
</tr>
<tr>
<td>Thank you for your consideration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. IS FOGGY THINKING CAUSED BY BREAST CANCER TREATMENT?</th>
</tr>
</thead>
<tbody>
<tr>
<td>This is what this study is trying to establish.</td>
</tr>
<tr>
<td>To complete this study we need:</td>
</tr>
<tr>
<td>a. 30 women post-surgery with early breast cancer who WILL receive chemotherapy;</td>
</tr>
<tr>
<td>b. 30 women post-surgery with early breast cancer who WILL NOT receive chemotherapy (can receive other treatment e.g., hormone or radiation therapy).</td>
</tr>
<tr>
<td><strong>Participant Inclusion Criteria:</strong></td>
</tr>
<tr>
<td>• Female;</td>
</tr>
<tr>
<td>• Early breast cancer;</td>
</tr>
<tr>
<td>• 18 – 65 years of age;</td>
</tr>
<tr>
<td>• No previous chemotherapy treatment;</td>
</tr>
<tr>
<td>• Fluent in English.</td>
</tr>
<tr>
<td><strong>Participation</strong> in this study involves around 3 hours of clinical neuropsychological assessment at the ANU, 3 times over a year, including:</td>
</tr>
<tr>
<td>c. pre chemotherapy (post-surgery);</td>
</tr>
<tr>
<td>b. after chemotherapy (or at 6 mths);</td>
</tr>
<tr>
<td>c. 6-9 mths later.</td>
</tr>
<tr>
<td>The tests are set up to be challenging but interesting, in a game-like format.</td>
</tr>
<tr>
<td>To refer a patient interested in learning more about the study, please contact:</td>
</tr>
<tr>
<td>Ms Rachel Lacey</td>
</tr>
<tr>
<td>School of Psychology</td>
</tr>
<tr>
<td>The Australian National University</td>
</tr>
<tr>
<td>Ph: 6125 xxxx Mob: 0418 xxxx</td>
</tr>
<tr>
<td>Email: xxxx</td>
</tr>
<tr>
<td>Thank you for your help</td>
</tr>
</tbody>
</table>

Figure B-1. Study leaflet for breast cancer patients (A) and for cancer care staff (B).
B.2. Telephone screening protocol

Hi, my name is Rachel Lacey and I'm a doctoral candidate at the Australian National University School of Psychology. You recently indicated that you might be interested in participating in a study we are conducting with women with early breast cancer. Would this be a convenient time to talk? (If no, make another time.)

First, I will tell you a little about the study. Some women receiving chemotherapy for breast cancer have complained of a change in memory and concentration while on treatment. Some women call this "chemo fog" or "chemo brain". Women report this can be distressing for them. There is very little research in this area or with other breast cancer treatment. We are investigating any changes or problems women may experience using standard neuropsychological tests.

We are doing this by asking you to complete some paper and pencil, question and answer or computerized game-like tests to examine any changes over time to your memory and thinking. These are not IQ tests but tests of brain behaviour. Women participating in the study have described them as interesting and fun.

The whole process takes about 4 hours, including breaks. Lunch and morning tea are provided. We would meet three times at the ANU over the next 12-15 months, once before chemotherapy (or at a similar time from diagnosis/surgery), once on completion of chemotherapy (around 6 months later), and once around 6-9 months after that.

Do you think you might be interested? Good. Before I take your details though, I need to check whether there is anything that might exclude you from the study (you can tell me in general without being specific). OK?

I'm looking for people who have:

- no history of head injury with loss of consciousness (>5mins) or requiring hospitalisation (>24 hrs);
- not currently seeing a doctor or other professional for memory problems or problems with thinking;
- not currently taking medication that might affect your thinking ability;
- no regular history of alcohol consumption of over 3 standard drinks per day on 2+ days/week;
- no medical or psychiatric condition that could affect thinking ability such as
  - stroke (specify)
  - recent electroconvulsive treatment (<2 wks)
  - epilepsy
  - brain surgery
  - encephalitis or meningitis (<10 years)
  - diagnosed Parkinson's disease, Huntington's chorea or Alzheimer's dementia
  - diagnosed Schizophrenia or Bipolar disorder.

That is a long list of things not to have - do you have questions about anything I've said, and is there anything you think might exclude you from this study? Good - well now I will take down some details from you and then we will arrange a time for you to come in for the assessment. [Fill out Client Contact form].

OK. Then let's set up an appointment time at the university [Book date and time - preferably 10am].

I will send out a letter to you with the date and time of your first appointment and a map of the ANU with the way to the visitor parking. When you arrive in the visitor parking give me a call and I will come down and put a parking voucher in your car.
I will also include a questionnaire in the information I send on your health and wellbeing for you to fill in and bring with you. As someone with memory problems often forget such instances, we ask you to nominate someone close to you (who you see at least 3 times per week for at least 1 hour/day) who can complete some questions about your recent everyday memory abilities. This would take them around 5 minutes. Is that OK? (If they don’t have anyone that knows them well enough to comment, say that is fine. It does not exclude them from the study).

Good, the last thing I need to let you know is if you do drink alcohol, for the testing it is important you not drink more than 1 standard drink for 24 hours before we meet. Or take any sleeping pills. Is that all right with you? If you use a hearing aid or glasses/contacts to correct visual or hearing impairment, you will need to wear these for testing.

Thank you for your generosity in helping with this breast cancer research and I’m looking forward to meeting you.
<table>
<thead>
<tr>
<th><strong>Client Contact Form</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLIENT ID:</strong></td>
</tr>
<tr>
<td><strong>DOB:</strong></td>
</tr>
<tr>
<td><strong>Family name:</strong></td>
</tr>
<tr>
<td><strong>Given name(s):</strong></td>
</tr>
<tr>
<td><strong>Address:</strong></td>
</tr>
<tr>
<td><strong>Phone (home):</strong></td>
</tr>
<tr>
<td><strong>Phone (work):</strong></td>
</tr>
<tr>
<td><strong>Mobile</strong></td>
</tr>
<tr>
<td><strong>Email:</strong></td>
</tr>
<tr>
<td><strong>Alternate contact (who does not live with you, in case you move):</strong></td>
</tr>
<tr>
<td><strong>Name:</strong></td>
</tr>
<tr>
<td><strong>Phone:</strong></td>
</tr>
<tr>
<td><strong>Referred by (e.g., self, BCN, treating doctor):</strong></td>
</tr>
<tr>
<td><strong>Doctor (e.g., Surgeon, oncologist):</strong></td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
</tr>
<tr>
<td><strong>Date of last surgery:</strong></td>
</tr>
<tr>
<td><strong>Chemotherapy (yes/no):</strong></td>
</tr>
<tr>
<td><strong>Chemotherapy (expected start date):</strong></td>
</tr>
</tbody>
</table>
Cognitive function, mood and quality of life in women with early breast cancer receiving adjuvant chemotherapy: a multi-centre prospective controlled study

Questionnaires

Session no. ___
YOUR HEALTH AND WELLBEING

This survey asks for your views about your health, how you feel and how well you are able to do your usual activities.

Answer every question by circling the response that best describes your answer. If you are unsure about how to answer a question, please give the best answer you can.

PHQ-15

During the past 4 weeks, how much have you been bothered by the following problems? (Circle one number on each line)

<table>
<thead>
<tr>
<th>ACTIVITIES</th>
<th>Not Bothered At All</th>
<th>Bothered A Little</th>
<th>Bothered a Lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Stomach pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>b. Back pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>c. Pain in your arms, legs or joints (knees, hips etc)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>d. Menstrual cramps or other problems with your periods</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>e. Headaches</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>f. Chest pains</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>g. Dizziness</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>h. Fainting spells</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>i. Feeling your heart pound or race</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>j. Shortness of breath</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>k. Pain or problems during sexual intercourse</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>l. Constipation, loose bowels or diarrhoea</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>m. Nausea, gas or indigestion</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>n. Feeling tired or having low energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>o. Trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
The following questions ask about minor memory mistakes that everyone makes from time to time, but some of them happen more often than others. We would like to know how often these things have happened to you over the past 2 weeks. For each question please circle the one answer that comes closest. Please answer all of the questions even if they don't seem entirely applicable to your situation.

**Over the past 2 weeks**

<table>
<thead>
<tr>
<th>Question</th>
<th>Very Often</th>
<th>Quite Often</th>
<th>Sometimes</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Did you decide to do something in a few minutes time and then forget to do it?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Did you fail to recognise a place you have visited before?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Did you fail to do something you were supposed to do a few minutes later even though it was there in front of you, like take a pill or turn off the kettle?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Did you forget something you were told a few minutes before?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Did you forget appointments if they were not prompted by someone else or by a reminder such as a calendar or diary?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Did you fail to recognise a character in a radio or television show from scene to scene?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Did you forget to buy something you planned to buy, like a birthday card, even when you saw the shop?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h. Did you fail to recall things that have happened to you in the last few days?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i. Did you repeat the same story to the same person on different occasions?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>j. Did you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it's there in front of you?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>k. Did you mislay something that you had just put down, like a magazine or glasses?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>l. Did you fail to mention or give something to a visitor that you were asked to pass on?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>m. Did you look at something without realising you had seen it moments before?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>n. If you tried to contact a friend or relative who was out, would you forget or try again later?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Over the past 2 weeks

<table>
<thead>
<tr>
<th>Question</th>
<th>Very Often</th>
<th>Quite Often</th>
<th>Sometimes</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>o. Did you forget what you watched on television the previous day?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>p. Did you forget to tell someone something you had meant to mention a few minutes ago?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Have you noticed any other problems with your memory or thinking since diagnosis or treatment? Please specify. (Use end page if you need more space)

MOSOC

Some people look to others for companionship, assistance or other types of support. How often is each of the following kind of support available to you if you need it?

<table>
<thead>
<tr>
<th>Support</th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Someone to help you if you are confined to bed.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>b. Someone to take you to the doctor if you need it.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>c. Someone to share your most private worries and fears with</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>d. Someone to turn to for suggestions about how to deal with a personal problem.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>e. Someone to do something enjoyable with</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>f. Someone to love and make you feel wanted</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

WHO-5 WELLBEING INDEX (1998)

The following questions ask about your overall wellbeing over the last 2 weeks. For each question please circle the one answer that comes closest to how you have been feeling. Notice that higher numbers mean better wellbeing.

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>More than half of the time</th>
<th>Less than half of the time</th>
<th>Some of the time</th>
<th>At no time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. I have felt cheerful and in good health.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>b. I have felt calm and relaxed.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>c. I have felt active and vigorous.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>d. I woke up feeling fresh and rested.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>e. My daily life has been filled with things that interest me</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
FEELINGS SCALE (HADS)

Below are some statements about how you have been feeling over the past week. Please underline the answer which comes closest to how you have felt in the past 7 days - not just how you feel today. Try not to think too long about your answers and just give your immediate response.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>I feel tense or &quot;wound up&quot;.</td>
</tr>
<tr>
<td></td>
<td>Most of the time</td>
</tr>
<tr>
<td></td>
<td>A lot of the time</td>
</tr>
<tr>
<td></td>
<td>From time to time, occasionally</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
</tr>
</tbody>
</table>

| 2. | I still enjoy the things I used to enjoy. |
|   | Definitely as much |
|   | Not quite as much |
|   | Only a little |
|   | Hardly at all |

| 3. | I get a sort of frightened feeling as if something awful is about to happen. |
|   | Very definitely and quite badly |
|   | Yes, but not too badly |
|   | A little, but it doesn't worry me |
|   | Not at all |

| 4. | I can laugh and see the funny side of things. |
|   | As much as I always could |
|   | Not quite so much now |
|   | Definitely not so much now |
|   | Not at all |

| 5. | Worrying thoughts go through my mind. |
|   | A great deal of the time |
|   | A lot of the time |
|   | From time to time but not too often |
|   | Only occasionally |

| 6. | I feel cheerful. |
|   | Not at all |
|   | Not often |
|   | Sometimes |
|   | Most of the time |

| 7. | I can sit at ease and feel relaxed. |
|   | Definitely |
|   | Usually |
|   | Not often |
|   | Not at all |

Please go on to the next page.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8.</td>
<td>I feel as if I am slowed down.</td>
</tr>
<tr>
<td></td>
<td>Nearly all of the time</td>
</tr>
<tr>
<td></td>
<td>Very often</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
</tr>
<tr>
<td>9.</td>
<td>I feel a sort of frightened feeling like &quot;butterflies&quot; in the stomach.</td>
</tr>
<tr>
<td></td>
<td>Nearly all of the time</td>
</tr>
<tr>
<td></td>
<td>Very often</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
</tr>
<tr>
<td>10.</td>
<td>I have lost interest in my appearance.</td>
</tr>
<tr>
<td></td>
<td>Definitely</td>
</tr>
<tr>
<td></td>
<td>I don't take as much care as I should</td>
</tr>
<tr>
<td></td>
<td>I may not take quite as much care</td>
</tr>
<tr>
<td></td>
<td>I take as much care as ever</td>
</tr>
<tr>
<td>11.</td>
<td>I feel restless as if I have to be on the move.</td>
</tr>
<tr>
<td></td>
<td>Very much indeed</td>
</tr>
<tr>
<td></td>
<td>Quite a lot</td>
</tr>
<tr>
<td></td>
<td>Not very much</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
</tr>
<tr>
<td>12.</td>
<td>I look forward with enjoyment to things.</td>
</tr>
<tr>
<td></td>
<td>As much as I ever did</td>
</tr>
<tr>
<td></td>
<td>Rather less than I used to</td>
</tr>
<tr>
<td></td>
<td>Definitely less than I used to</td>
</tr>
<tr>
<td></td>
<td>Hardly at all</td>
</tr>
<tr>
<td>13.</td>
<td>I get sudden feelings of panic.</td>
</tr>
<tr>
<td></td>
<td>Very often indeed</td>
</tr>
<tr>
<td></td>
<td>Quite often</td>
</tr>
<tr>
<td></td>
<td>Not very often</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
</tr>
<tr>
<td>14.</td>
<td>I can enjoy a good book or radio or TV program</td>
</tr>
<tr>
<td></td>
<td>Often</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>Not often</td>
</tr>
<tr>
<td></td>
<td>Very seldom</td>
</tr>
</tbody>
</table>
EORTC QLQ-C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**During the past week:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

   | 1  | 2  | 3  | 4  | 5  | 6  | 7  |
   | Very Poor |       |       |       |       |   | Excellent |

30. How would you rate your overall quality of life during the past week?

   | 1  | 2  | 3  | 4  | 5  | 6  | 7  |
   | Very Poor |       |       |       |       |   | Excellent |

Is there anything that you would like to add that you feel may be relevant to the study?

Thank you for your participation in this research
You have been invited to participate in a study looking at possible changes to cognitive function including memory, attention and problem solving associated with chemotherapy. Over recent years, some women receiving chemotherapy for breast cancer have complained of a decrease in memory and concentration while on treatment. Some women call this “chemo fog” or “chemo brain”. These changes, if they do occur, could be due to a direct toxic effect of chemotherapy on the brain or could be due to factors like depression or anxiety, temporarily influencing brain function.

This study looks at cognitive changes, mood and quality of life in women with early breast cancer receiving chemotherapy compared to women who have undergone similar surgery but no chemotherapy in order to examine the role of mood and treatment in any measurable change.

You will be asked to meet with a research psychologist (Rachel Lacey) for about three hours at three times over the next 12 months. For participants receiving chemotherapy this will be once before treatment, once on completion of treatment and once around 6 months after treatment is completed. For participants who have undergone surgery, this will be approximately 1 month, 6 months and around 12 months after surgery.

At each assessment you will be asked to complete a series of tests including pencil and paper, question and answer or familiar problem-solving tasks looking at how your memory, concentration and planning skills are functioning. You will be asked to complete questions about your feelings of anxiety and depression and how often you have been experiencing memory problems. As people with memory problems can forget such instances, you will also be asked to nominate someone close to you who can complete some questions about your recent memory abilities. This would take them around 5 minutes. They can complete this before your assessment or you can take the questionnaire to them to complete.

In addition, we will require information about your relevant medical history before starting treatment and following the completion of treatment. The information we are interested in includes the standard tests your oncologist will collect as part of routine medical procedure. This information will be extracted from your medical records and will be identified only by a code number. No medical tests will be done that would not be routinely done as part of your medical care.

Your personal information will be held safely and securely in a locked cabinet and will only be used by the research team for the purpose of this study. No personal information will be identifiable in the reporting or presentation of the results.

Your participation in this study is voluntary. Your decision to participate or not in this study will not affect your medical care in any way. If at any stage you wish to withdraw from the study, you may do so without explanation and any previously completed documents will be destroyed. If, in the course of the study, you think that you would like more psychosocial support, then please ask the investigator or your doctor, as this is also available.

Your participation in this research is greatly appreciated. If at any time you would like further information about this evaluation, or if you have any concerns with any aspects of the evaluation, feel free to talk with your doctor or nurse or to speak with A/Prof Robin Stuart-Harris on 6244 2220, Prof Don Byrne on 6125 3974, Dr Anne Aimola Davies on 6125 5545 or Ms Rachel Lacey on 6125 2147.
Approval for this research project has been given by the ACT Department of Health Ethics Committee and the Australian National University Human Research Ethics Committee (and any further relevant hospital ethics committee). Should you have any concerns or queries about the way in which the study is conducted, and you do not feel comfortable contacting the research staff, please contact:

1. the ACT Department of Health Ethics Committee Secretary at 11 Moore St, Canberra City, ACT, 2601 or on phone number (02) 6205 0846, or
2. The ANU Human Research Ethics Committee Secretary, Research Services Office, Chancelry 10B, The Australian National University ACT 0200 or on phone number (02) 6125 7945.
3. (and contact details of any further relevant hospital ethics committee).
B.6. Participant consent form

SCHOOL OF PSYCHOLOGY
BUILDING 39, CANBERRA ACT 0200
www.anu.edu.au
telephone: (02) 6125 9656
facsimile: (02) 6125 0499

Consent Form to Participate in a Research Project

I, ____________________________
(name of participant)
of ____________________________ (street) ____________________________ (suburb/town) ____________________________ (state & postcode)

have been asked to participate in a research project entitled:

COGNITIVE FUNCTION, MOOD AND QUALITY OF LIFE IN WOMEN WITH EARLY BREAST CANCER RECEIVING ADJUVANT CHEMOTHERAPY: A MULTI-CENTRE PROSPECTIVE CONTROLLED STUDY

In relation to this project I have read the Participant Information Sheet and have been informed of the following points:

1. Approval has been given by the ACT Department of Health Ethics Committee and the ANU Human Research Ethics Committee (and any further relevant hospital ethics committee).

2. The aim of the project is to research whether there is any measurable change in memory and problem-solving following adjuvant chemotherapy and whether any changes are due to treatment or the possible effects of mood.

3. The results obtained from the study may or may not be of direct benefit to my medical management.

4. The procedure will involve an interview with a research psychologist for three hours once before chemotherapy and twice after treatment has ceased. I understand that I will be asked some questions about my background, how I have been feeling lately and to complete some questionnaires. I will also be asked to complete a series of pencil and paper, question and answer and problem-solving tasks. I understand that I will also be asked to nominate someone who knows me well to complete a questionnaire taking around 5 minutes rating the instances of minor memory problems that I may have displayed.

5. Should I have any concerns relating to my involvement in this Project, I am aware that I may contact – A/Prof Robin Stuart-Harris on 6244 2220, Prof Don Byrne on 6125 3974, Dr Anne Aimola Davies on 6125 5545 or Ms Rachel Lacey on 6125 2147.
6. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the research staff, I am aware that I may contact the ACT Department of Health Ethics Committee Secretary at 11 Moore St, Canberra City, ACT 2601 or on phone number 02-62050846, or the ANU Human Research Ethics Committee Secretary, Research Services Office, Chancellery 10B, The Australian National University ACT 0200 or on phone number (02) 61257945 or (contact details of any further relevant hospital ethics committee).

7. I can refuse to take part in this project or withdraw from it at any time without affecting my medical care.

8. Participation in this project will not result in any extra medical and hospital costs to me.

9. I understand that the results of the research will be made accessible and that my involvement and my identity will not be revealed.

10. I understand that the information provided by me will be kept confidential so far as the law allows. This form and the data sheets will be stored separately in a locked office at the Australian National University. Data entered onto a computer will be kept in a computer accessible only by password by a member of the research team.

11. ** In giving my consent, I acknowledge that the relevant Research Team directly involved in the study, may examine my medical records only as they relate to this project.

I can specify here if I have any particular concerns regarding the research:

After considering all these points, I accept the invitation to participate in this project.

I also state that I have/have not participated in any other research project in the past 3 months. If I have, the details are as follows:

Date: ___________ Witness: __________________________

(Please print name)

Signature: __________________________ (of participant/volunteer)

_____________________ (of witness)

Investigator's Signature: __________________________

Page 2 of 2
B.7. Informant information sheet

You have a friend or family member who is a participant in a study looking at possible changes to memory, attention and problem solving associated with chemotherapy. You have been asked to provide a comment on this person's functioning to help the investigators understand any changes to memory following treatment. Over recent years, some women receiving chemotherapy for breast cancer have complained of a decrease in memory and concentration while on treatment. Some women call this "chemo fog" or "chemo brain". These changes, if they do occur, could be due to a direct toxic effect of chemotherapy on the brain or could be due to factors like depression or anxiety, temporarily influencing brain function.

This study looks at cognitive changes, mood and quality of life in patients with early cancer receiving chemotherapy compared to patients who have undergone similar surgery but no chemotherapy in order to examine the role of mood and treatment in any measurable change. As people with memory problems can forget such instances, the study participant has been asked to nominate someone close to them who can complete some questions about their recent memory abilities.

You will be asked to complete some questions rating how often your friend or family member has been experiencing minor memory problems. These questions will take you around 5 minutes to complete and you will be asked to complete them 3 times over the next year. If you agree, you can complete the questionnaire before your friend or family member's assessment or you can complete and return it in the stamped addressed envelope provided.

You will not be asked to provide personal information. The information you do provide regarding the study participant will be held safely and securely in a locked cabinet and will only be used by the research team for the purpose of this study. This information will be coded and will not be identifiable in the reporting or presentation of the results.

Your participation in this study is voluntary. Your decision to participate or not in this study will not affect the study participant's medical care in any way. If at any stage you wish to withdraw from the study, you may do so without explanation.

Your participation in this research is greatly appreciated. If at any time you would like further information about this study, or if you have any concerns with any aspects of the study, feel free to talk with your doctor or nurse or to speak with A/Prof Robin Stuart-Harris on 6244 2220, Prof Don Byrne on 6125 3974, Dr Anne Aimola Davies on 6125 5545 or Ms Rachel Lacey on 6125 2147.

Approval for this research project has been given by the ACT Department of Health Ethics Committee and the Australian National University Human Research Ethics Committee (and any further relevant hospital ethics committee). Should you have any concerns or queries about the way in which the study is conducted, and you do not feel comfortable contacting the research staff, please contact:

- the ACT Department of Health Ethics Committee Secretary at 11 Moore St, Canberra City, ACT, 2601 or on phone number (02) 6205 0846, or
- The ANU Human Research Ethics Committee Secretary, Research Services Office, Chancelry 10B, The Australian National University ACT 0200 or on phone number (02) 6125 7945;
- (contact details of any further relevant hospital ethics committee).
B.8. Informant consent form

I, ____________________________ (the study participant) have asked my friend/family member to participate as an informant in the research project to help the investigators understand any changes to my memory following treatment.

________________________________________________________________________

(signature of participant)

Consent Form to Participate as an Informant in a Research Project

I, ____________________________

(name of informant)

of ____________________________

(street) (suburb/town) (state & postcode)

have been asked to provide information on a participant in a research project entitled:

COGNITIVE FUNCTION, MOOD AND QUALITY OF LIFE IN WOMEN WITH EARLY BREAST CANCER RECEIVING ADJUVANT CHEMOTHERAPY: A MULTI-CENTRE PROSPECTIVE CONTROLLED STUDY

In relation to this project I have read the Informant Information Sheet and have been informed of the following points:

1. Approval has been given by the ACT Department of Health Ethics Committee and the ANU Human Research Ethics Committee (and any further relevant hospital ethics committee).

2. The aim of the project is to research whether there is any measurable change in memory and problem-solving following adjuvant chemotherapy and whether any changes are due to treatment or the possible effects of mood. I understand my participation will help the investigators understand my friend or family member’s memory function following treatment.

3. The results obtained from the study may or may not be of direct benefit to my friend or family member’s (the study participant) medical management.

4. I understand I will not be asked to provide personal information but will be asked to rate the instances of minor memory problems that my friend or family member (the study participant) may have displayed. The procedure will involve the completion of a questionnaire three times over a year. This will take around 5 minutes to complete.
5. Should I have any concerns relating to my involvement in this Project, I am aware that I may contact – A/Prof Robin Stuart-Harris on 6244 2220, Prof Don Byrne on 6125 3974, Dr Anne Aimola Davies on 6125 5545 or Ms Rachel Lacey on 6125 2147.

6. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the research staff, I am aware that I may contact the ACT Department of Health Ethics Committee Secretary at 11 Moore St, Canberra City, ACT 2601 or on phone number 02-62050846, or the ANU Human Research Ethics Committee Secretary, Research Services Office, Chancery 10B, The Australian National University ACT 0200 or on phone number (02) 6125 7945 (and contact details of any further relevant hospital ethics committee).

7. I can refuse to take part in this project or withdraw from it at any time without affecting the study participant’s medical care.

8. Participation in this project will not result in any extra medical and hospital costs to the study participant.

9. I understand that the results of the research will be made accessible and that my involvement and my identity will not be revealed.

10. I understand that the information provided by me will be kept confidential so far as the law allows. This form and the data sheets will be stored separately in a locked office at the Australian National University. Data entered onto a computer will be kept in a computer accessible only by password by a member of the research team.

I can specify here if I have any particular concerns regarding the research:

After considering all these points, I accept the invitation to participate as an informant in this project.

Date: / / 

Signature: ________________________________
(of informant/volunteer)

Investigator’s Signature: ________________________________

Page 2 of 2
# B.9. Client demographic form

## CLIENT DEMOGRAPHIC FORM

<table>
<thead>
<tr>
<th>Client ID</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>1 Married/Defacto</td>
<td>2 Widowed</td>
<td>3 Divorced/ Separated</td>
<td>4 Never married</td>
</tr>
<tr>
<td>Cohab status</td>
<td>1 Live with partner</td>
<td>2 Live with someone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of children (no. under 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work over last 12 mths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status (current):</td>
<td>1 Unemployed or not in the labour force (Retired, Voluntary, Student, home, child duties)</td>
<td>2 F/t work (include work for family business)</td>
<td>3 P/T work</td>
<td></td>
</tr>
<tr>
<td>Occupation •</td>
<td>1 Professionals (eg Dr, teacher, scientist)</td>
<td>2 Managers and administrators (eg legislators)</td>
<td>3 Paraprofessionals (eg RN, technicians)</td>
<td>4 Tradesperson (eg hairdresser, dressmaker)</td>
</tr>
<tr>
<td>Years of Formal Education (K+) • location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest qualification achieved •</td>
<td>1 No formal qualification</td>
<td>2 Yr 10 equivalent</td>
<td>3 Year 12 or equivalent</td>
<td>4 Trade/apprenticeship/certificate/diploma</td>
</tr>
<tr>
<td>Country of Birth • (specify):</td>
<td>1 Australia</td>
<td>2 Other ESC (eg UK, NZ, North America)</td>
<td>3 NES – Europe, USSR, Africa, Asia, Middle East</td>
<td></td>
</tr>
<tr>
<td>Usually speak English at home? Age began speaking English</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATSI status •</td>
<td>1 Yes</td>
<td>2 No</td>
<td>3 Unknown</td>
<td></td>
</tr>
<tr>
<td>Handedness •</td>
<td>1 Left</td>
<td>2 Right</td>
<td>3 Ambi</td>
<td>4 Unknown</td>
</tr>
<tr>
<td>Colour blindness •</td>
<td>1 Yes</td>
<td>2 No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision impairment •</td>
<td>1 None</td>
<td>2 Corrected</td>
<td>3 Not corrected</td>
<td></td>
</tr>
<tr>
<td>Hearing impairment •</td>
<td>1 None</td>
<td>2 Corrected</td>
<td>3 Not corrected</td>
<td></td>
</tr>
<tr>
<td>Alcohol • std drink – last 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed medications •</td>
<td>1 Yes</td>
<td>2 No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-prescribed medications •</td>
<td>1 Yes</td>
<td>2 No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **DDMMYYYY**: Date of birth
- **Yrs**: Years of age
- **Married/Defacto**: Marital status
- **Divorced/Separated**: Divorced status
- **Widowed**: Widowed status
- **Never married**: Never married status
- **Live with partner**: Cohab status
- **Live alone**: Cohab status
- **Live with someone**: Cohab status
- **Professionals**: Occupation
- **Managers and administrators**: Occupation
- **Paraprofessionals**: Occupation
- **Tradesperson**: Occupation
- **Clerical/ Sales/ Service worker**: Occupation
- **No formal qualification**: Highest qualification achieved
- **Year 10 equivalent**: Highest qualification achieved
- **University bachelor degree**: Highest qualification achieved
- **Graduate diploma**: Highest qualification achieved
- **Postgraduate degree**: Highest qualification achieved
- **Australia**: Country of Birth
- **Other ESC**: Country of Birth
- **NES – Europe, USSR, Africa, Asia, Middle East**: Country of Birth
- **Yes**: Usually speak English at home?
- **No**: Usually speak English at home?
- **Yes**: ATSI status
- **No**: ATSI status
- **Yes**: Handedness
- **No**: Handedness
- **Yes**: Colour blindness
- **No**: Colour blindness
- **None**: Vision impairment
- **Corrected**: Vision impairment
- **Not corrected**: Vision impairment
- **None**: Hearing impairment
- **Corrected**: Hearing impairment
- **Not corrected**: Hearing impairment
- **usual/day**: Alcohol consumption
- **- maximum**: Alcohol consumption
- **Yes**: Prescribed medications
- **No**: Prescribed medications
- **Yes**: Non-prescribed medications
- **No**: Non-prescribed medications
- **Dose**: Prescribed medications
- **Freq**: Prescribed medications
- **Last use**: Prescribed medications

---

**B-20**
## B.10. Client status form

**CLIENT STATUS FORM (interviewer administered)**

<table>
<thead>
<tr>
<th>Client ID</th>
<th>Session no</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menopausal status</strong></td>
<td></td>
</tr>
<tr>
<td>1. Are you currently taking? (mark one on each line)</td>
<td></td>
</tr>
<tr>
<td>a. Hormone Replacement Therapy (HRT)</td>
<td>Yes □ 1 No □ 2</td>
</tr>
<tr>
<td>b. the oral contraceptive pill</td>
<td>Yes □ 1 No □ 2</td>
</tr>
<tr>
<td>2. Have you: (mark one on each line)</td>
<td></td>
</tr>
</tbody>
</table>
| a. Had a hysterectomy/oophorectomy? | Yes □ 1 No □ 2 [If yes go to 3.]
| b. Had a period or menstrual bleeding in the last 12 months? | Yes □ 1 No □ 2 [If no go to 4.]
| c. Had a period or menstrual bleeding in the last 3 months? | Yes □ 1 No □ 2 |
| 3. Compared with 12 months ago, are your periods: | |
| 1 □ Less frequent 2 □ About the same 3 □ More frequent 4 □ Changeable | |
| 4.a If you have reached menopause, at what age did your periods completely stop? | |
| □ □ years old OR □ no: applicable | |
| b. If you have not reached menopause, do you think you are starting menopause? Yes □ 1 No □ 2 | |
| **Vasomotor symptoms** | |
| 5. Hot flushes | 0 None 1 Mild 2 Moderate 3 Severe |
| 6. Night sweats | 0 None 1 Mild 2 Moderate 3 Severe |
| **Meno Interference** | 7. In general, how much do menopausal symptoms interfere with your day-to-day activities? |
| 0 No interference 1 2 3 4 5 6 7 Extreme interference | |
| **Sleep qual 4 wks** | 1 Very sound 2 Sound 3 Average 4 Restless 5 Very restless |
| **Fatigue interference** | 9. In general, how much does fatigue interfere with your day-to-day activities? |
| 0 No interference 1 2 3 4 5 6 7 Extreme interference | |
| **ECOG Performance status** | |
| Assess client status for the last week | |
| 0 Able to carry out normal activities without restriction | |
| 1 Ambulatory-Capable of light work, restricted with strenuous activity | |
| 2 Ambulatory-Capable of self care, but unable to work | |
| 3 Resting in bed/chair more than half waking hours, only capable of limited self care | |
| 4 Totally confined to bed/chair, not capable of any self care | |
| OFFICE USE ONLY 1a. Surgery (2a-1) 2. Peri (2b-1 + 2c-2 or 3 nc2) 4. HRT (1a-1) | |
| 1b. Post (2b-2) 3. Pre (2b,c-1 + 3-2) 5. Unclassifiable | |
Feedback Summary Report

Confidential
Client: -- Dates of assessment: [Time 1; Time 2]
Age: - years Handedness: Right/Left
Psychologist: Rachel Lacey
Supervisor: Dr Anne Aimola Davies
Location/agency: Rm 220, The Psychology Building, The Australian National University

Nature of the assessment:
The assessment consisted of two sessions on [Time 1] and [Time 2]. You completed a wide range of tasks of varying levels of complexity. Your performance on these tasks was compared to standardized scoring for women of your age and education. Further to this, a comparison of your results at each testing session gave us an idea of whether there had been any changes in your thinking, attention, concentration, memory and other areas of cognitive functioning.

Results of clinical interview:
You presented as well-groomed, alert, intelligent, open and cooperative. You displayed a quick grasp of instructions and good frustration tolerance.

Some of your responses to items suggest that you may be experiencing some symptoms of anxiety. At the initial assessment you described a period in your 30s when you experienced panic attacks. During these attacks you trembled, experienced dry mouth, shortness of breath, discomfort in your stomach, a sense that things around you were unreal and you were afraid you might die. You have not experienced a recent anxiety attack and you were not afraid of having another attack. You also described a recent period of persistent worrying about relationship and financial stresses. You did not consider this worrying excessive or that it interfered with your functioning. While the symptoms you described are characteristic of anxiety you do not meet the diagnostic criteria for a current anxiety or mood disorder.

Overall strengths:
• Your strengths were in verbal working memory and speed of information processing (e.g., the paced auditory serial addition task – 3 secs and 2 secs). Working memory is the ability to temporarily store and manipulate information (e.g., remembering and reversing the order of a string of numbers you hear).
• You also displayed strengths in response inhibition on tasks where you had to name the ink colour rather than read the word.

Improvement from one performance (Time 1) to the next performance (Time 2):
Please note that for the following tasks, your performance was lower than expected initially, but that you demonstrated performance within the expected level of ability at the second testing:
• Category fluency (e.g., generating as many words that begin with a particular category in 60 seconds).
• Verbal learning and memory at both short and long delays (i.e., memory for information you hear, as demonstrated on a shopping list task).
• Visual memory (i.e., memory for patterns or a complex figure you had just seen, and after a long delay). This appeared to be explained by lower than expected visuoconstructional skills (e.g., copying a complex figure) and encoding of visuospatial information.
Deterioration from one performance (Time 1) to the next performance (Time 2):

- Attention functions, including choice reaction time, spatial attention span and spatial working memory and false alarms on a sustained attention task.
- First trial visual immediate memory and visuospatial learning (when remembering up to eight pattern-location associations).
- Spatial recognition memory.
- Executive functions, that is, functions (as listed below) which refer to the control system that manages other cognitive processes:
  - Longer planning times and reduced efficiency (at the highest level of the task) on a planning and problem-solving task (e.g., where you had to copy an arrangement of coloured balls by moving other balls in a set number of moves).
  - Less use of strategy in a spatial working memory task (e.g., remembering and avoiding where a blue token had been found previously in a series of displayed boxes).
  - Reduced cognitive flexibility skills (e.g., switching attention from irrelevant to relevant visual dimensions on the basis of computer feedback).
  - Verbal abstract reasoning skills (e.g., stating the relationship between two words) and verbal paired associate learning in a paired names task.
  - Generating words while switching between two categories (fruits/furniture).

Consistent and intact performance from one assessment (Time 1) to the next (Time 2):

- Language functions (picture naming).
- Motor speed (simple and choice movement times).
- Attention and concentration tasks, including attention span (verbal) and working memory (verbal and visual) and sustained attention (e.g., monitoring changing digits for target sequences of 3 numbers).
- Speed of information processing tasks (simple reaction time and the paced auditory serial addition task – 3 and 2 sec).
- New Learning for information you hear, as demonstrated on a shopping list task. You made good use of effective active learning strategies, like semantic clustering (grouping by category).
- In terms of executive functioning, your response inhibition abilities on tasks where you had to name the ink colour rather than read the word and inhibition abilities whilst switching and your overall planning and problem-solving performances were consistent.

Recommendations:

These described difficulties might impact on every day activities in the following ways:

- Difficulty with recalling new information presented visually, for example, remembering where you have put things or written instructions;
- Concentrating in the midst of distractions.
- Remembering to remember to do things.

If you continue experiencing problems, you might benefit from using some retrieval strategies:

- Repeat content words, or use meaningful associations or categories to aid memory;
- Use a diary, make lists or carry a notebook as memory aids;
- Minimize distractions when you need to complete tasks (in a timely fashion).

Note that many of the cognitive changes you displayed following treatment are subtle, and most often remain within the normal range of functioning. The third assessment will help us to clarify whether these changes are temporary or sustained.
If there are any further questions concerning this summary, please feel free to contact me.

Best regards,

Rachel Lacey
Psychologist
PhD Candidate (Clinical Psychology)
# B.12. Medical information form

Changes in cognitive function associated with treatment in women with early breast cancer (Rachel Lacey)

**ETHICS:** ACT HACC (ETH 9/05.892); ANU HREC (2005/59); CALVARY HC HREC (10-2005); JMJH (28-11-05); NATCAP (23-11-05)

---

**MEDICAL INFORMATION FORM**

<table>
<thead>
<tr>
<th>Item</th>
<th>Data</th>
<th>Fields</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEMOGRAPHICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOB (confirmed)</td>
<td>Yes No</td>
<td>(dd/mm/yyyy)</td>
</tr>
<tr>
<td>DATE OF FORM COMPLETION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Diagnosis:</td>
<td></td>
<td>(dd/mm/yyyy)</td>
</tr>
<tr>
<td>Hospital (where major surgery performed)</td>
<td>1 TCH 2 NATCAP 3 Cal 4 JJ 5 Other</td>
<td></td>
</tr>
<tr>
<td>Hospital (primary treating hospital)</td>
<td>1 TCH 2 NATCAP 3 Cal 4 JJ 5 Other</td>
<td></td>
</tr>
<tr>
<td>Bilateral Breast Cancer</td>
<td>Bilateral Unilateral 1 Left 2 Right 3 Unknown</td>
<td></td>
</tr>
<tr>
<td>Menopausal status:</td>
<td>Pre- Post- Peri- NA</td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td>Average Risk Moderately increased Potentially High Risk</td>
<td></td>
</tr>
<tr>
<td>Past History (Breast Cancer/Other Cancer)</td>
<td>No Previous Cancer Previous DCIS Other Cancer Unknown</td>
<td></td>
</tr>
<tr>
<td><strong>DETECTION/INVESTIGATIONS/PRE-OP MANAGEMENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer Detection (Asymptomatic (includes screen-detected) or Symptomatic)</td>
<td>Asymptomatic: Breast Screen Other Screening Program Other Symptomatic: GP Specialist Other</td>
<td></td>
</tr>
<tr>
<td>Neo-adjuvant Treatment</td>
<td>Yes No Pre-chemo/radio/hormonal</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Mammogram US (Ultrasound) Core/Mammothome Bx FNAC Other (incl. MR)</td>
<td></td>
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<tr>
<td>Clinical stage</td>
<td>T1 T2 T3 T4 TX T0 Tis N0 N1 N2 N3 NX M0 M1 MX Unknown</td>
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<tr>
<td><strong>PROCEDURE</strong></td>
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<tr>
<td>Breast Surgery</td>
<td>Conservation Open Biopsy R L Local Excision R L Re-excision R L Modified radical Simple</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reason for Mastectomy Clinical Indication Patient Choice Recurrent Disease Unknown</td>
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<tr>
<td>Item</td>
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<td>Fields</td>
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<tr>
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<tr>
<td>Axillary Surgery</td>
<td>Nil Sampled</td>
<td>Sentinel node biopsy</td>
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<td></td>
<td></td>
<td>0-4 nodes/level I</td>
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<td></td>
<td></td>
<td>Clearance (level II at least)</td>
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<tr>
<td>Port</td>
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<td>No Date</td>
</tr>
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<td>Anaesthetics</td>
<td>Regional</td>
<td>General</td>
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<tr>
<td>ADJUVANT TREATMENT</td>
<td></td>
<td>Order of treatment</td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td>Yes</td>
<td>No Offered but refused</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCF (Supraclavicular)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chest Wall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IMN (Int. mammary)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axilla</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Adjuvant Radiotherapy</td>
<td>Yes</td>
<td>No Offered but refused</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCF (Supraclavicular)</td>
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<tr>
<td></td>
<td></td>
<td>Chest Wall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IMN (Int. mammary)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axilla</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
<td>Yes</td>
<td>No Offered but refused</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type, # cycles, order</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CMF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC or EC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC or EC + CMF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC or EC + Taxane or TAC</td>
</tr>
<tr>
<td></td>
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<td>FEC/FAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Herceptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Adjuvant Hormonal Therapy</td>
<td>Yes</td>
<td>No Offered but refused</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamoxifen</td>
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<td></td>
<td></td>
<td>Aromatase Inhibitor (Anastrozole/ Arimidex</td>
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<td></td>
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<td>Zoladex</td>
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<tr>
<td></td>
<td></td>
<td>Oopherectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
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<tr>
<td>Clinical Trial</td>
<td>Yes</td>
<td>No Specify</td>
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<tr>
<td>CO-MEDICATIONS</td>
<td></td>
<td>Anti-emetic</td>
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<tr>
<td>Co-medications (prescribed)</td>
<td>Yes</td>
<td>No</td>
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<td></td>
<td>Ondonestron 1 2 3 4 5 6</td>
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<td></td>
<td></td>
<td>Dexamethasone 1 2 3 4 5 6</td>
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<td></td>
<td></td>
<td>Anxiolytic</td>
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<td></td>
<td></td>
<td>Antidepressant</td>
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<td>Other</td>
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<td>TOXICITY</td>
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<td>Complications noted on file</td>
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<td></td>
<td>Yes</td>
<td>No</td>
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<td></td>
<td>Hospital readmission?</td>
<td>Yes No</td>
</tr>
<tr>
<td></td>
<td>Reason</td>
<td>Dates</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>Yes No</td>
</tr>
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<td></td>
<td>Dates/cycles</td>
<td>Other</td>
</tr>
<tr>
<td>PATHOLOGY</td>
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<td>Focality</td>
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<tr>
<td></td>
<td>Unifocal</td>
<td>Multifocal/Multicentric</td>
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<tr>
<td>Tumour (principal)</td>
<td>Size</td>
<td>0-10mm</td>
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<td></td>
<td>11-20mm</td>
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<td></td>
<td></td>
<td>21-50mm</td>
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<td></td>
<td></td>
<td>&gt;50mm</td>
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<tr>
<td></td>
<td></td>
<td>Unknown</td>
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<tr>
<td>Tumour (principal)</td>
<td>Site</td>
<td>UOQ</td>
</tr>
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<td></td>
<td></td>
<td>UIQ</td>
</tr>
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<td></td>
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<td>Central</td>
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<td>Multiple quadrants</td>
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<tr>
<td>Item</td>
<td>Data</td>
<td>Fields</td>
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<td>----------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Invasive Cancer</td>
<td>Invasive Ductal (NOS)</td>
<td>Infiltrating Lobular Cancer Special (Specify)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other invasive (Specify)</td>
</tr>
<tr>
<td>Non-invasive Cancer</td>
<td>DCIS comedo (with necrosis)</td>
<td>DCIS non-comedo (no necrosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other non-invasive subtype:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LCIS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Histological Grade (Invasive)</td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Unknown/NA</td>
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<tr>
<td>Nuclear Grade (non-invasive)</td>
<td>Low</td>
<td>Medium</td>
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<td></td>
<td>High</td>
<td>Unknown/NA</td>
</tr>
<tr>
<td>Margin</td>
<td>0</td>
<td>&lt;5mm</td>
</tr>
<tr>
<td></td>
<td>5-10mm</td>
<td>&gt;10mm</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Vessel Invasion</td>
<td>Present</td>
<td>Absent</td>
</tr>
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<td></td>
<td></td>
<td>Unknown/equivocal</td>
</tr>
<tr>
<td>Number of axillary nodes examined</td>
<td>0</td>
<td>1-4</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Number of nodes involved</td>
<td>0</td>
<td>1-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA (0 exam)</td>
</tr>
<tr>
<td>Oestrogen Receptor Status</td>
<td>Positive</td>
<td>Negative</td>
</tr>
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<td></td>
<td></td>
<td>Unknown</td>
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<tr>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Progesterone Receptor status</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
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<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Her-2/neu receptor status</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>CURRENT STATUS</td>
<td>Disease free</td>
<td>With disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dead</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Patient Died</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Date of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td>Death due to breast cancer</td>
<td>Died without breast cancer</td>
</tr>
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<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Recurrence</td>
<td>No evidence of recurrence</td>
<td>Loco-regional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loco-regional + distant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Appendix C

Individual measures

Language, Motor and Visuoconstruction skills

Appendix C presents the means and standard deviations for both raw scores and standardized scores for each measure of language (Table C1), motor (Table C4) and visuoconstruction skills (Table C7). Also included are the latent vector loadings for the first two principal components from the Principal Components Analysis of all measures within the language domain (Table C2) and all measures within the motor domain (Table C5). Individual measures use age-standardized z-scores derived from relevant test norms. Figures and p-value summary tables are presented that were obtained from individual ANOVAs adjusted for between and within subject variation. The performance profile of the summary measure for each grouping (name italicized) in language skills and motor skills is compared with each of the individual measures that contribute to that grouping.
### Table C1a

**Variable Names for Measures of Language**

<table>
<thead>
<tr>
<th>Variable ID</th>
<th>Test</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>cw1cnz</td>
<td>D-KEFS</td>
<td>¹CW1 colour naming speed</td>
</tr>
<tr>
<td>GNTza</td>
<td>CANTAB</td>
<td>Graded Naming Test</td>
</tr>
<tr>
<td>VFcftcz</td>
<td>D-KEFS</td>
<td>²VF category fluency correct</td>
</tr>
</tbody>
</table>

¹Color-Word Interference. ²Verbal Fluency.

Table C1b

**Raw Score Means (and SDs)¹ for Measures of Language by Group over Time**

<table>
<thead>
<tr>
<th>Name</th>
<th>Time 1 (n = 30)</th>
<th>Time 2 (n = 30)</th>
<th>Time 3 (n = 29)</th>
<th>Time 1 (n = 15)</th>
<th>Time 2 (n = 16)</th>
<th>Time 3 (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>cw1cnz</td>
<td>29</td>
<td>5</td>
<td>29</td>
<td>6</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>5</td>
<td>29</td>
<td>6</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>GNTza</td>
<td>21</td>
<td>4</td>
<td>22</td>
<td>4</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>1.02</td>
<td>21</td>
<td>4</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>VFcftcz</td>
<td>46</td>
<td>9</td>
<td>47</td>
<td>8</td>
<td>44</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>8</td>
<td>50</td>
<td>9</td>
<td>48</td>
<td>11</td>
</tr>
</tbody>
</table>

Table C1c

**Standardized Means (and SDs)¹ for Measures of Language by Group over Time**

<table>
<thead>
<tr>
<th>Name</th>
<th>Time 1 (n = 30)</th>
<th>Time 2 (n = 30)</th>
<th>Time 3 (n = 29)</th>
<th>Time 1 (n = 15)</th>
<th>Time 2 (n = 16)</th>
<th>Time 3 (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>cw1cnz</td>
<td>.12</td>
<td>.69</td>
<td>.12</td>
<td>.84</td>
<td>.01</td>
<td>.82</td>
</tr>
<tr>
<td></td>
<td>1.02</td>
<td>.37</td>
<td>.97</td>
<td>.53</td>
<td>1.03</td>
<td>.62</td>
</tr>
<tr>
<td>GNTza</td>
<td>.22</td>
<td>1.14</td>
<td>.49</td>
<td>1.18</td>
<td>1.03</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>1.51</td>
<td>.91</td>
<td>2.02</td>
<td>1.67</td>
<td>1.28</td>
<td></td>
</tr>
</tbody>
</table>

¹Raw and standardized scores based on scoring guides in test manuals.

²Descriptive names in the same order are presented in Table C1a.
Table C2

*Latent Vector Loadings of the First Two Principal Components obtained from Principal Components Analysis of All Measures of Language*

<table>
<thead>
<tr>
<th>Measure</th>
<th>PC 1</th>
<th>PC 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>cw1cnz</td>
<td>0.4346</td>
<td>-0.7923</td>
</tr>
<tr>
<td>GNTza</td>
<td>0.5605</td>
<td>0.6102</td>
</tr>
<tr>
<td>VFcftcz</td>
<td>0.7049</td>
<td>0.0032</td>
</tr>
</tbody>
</table>

*Descriptive names in same order are presented in Table C1a.*

*First principal component (accounts for 42% of variance).* *Second principal component (accounts for 33% of variance)*
Figure C1. Means (± SEM) of summary score and individual measures of language over time by breast cancer treatment group.

Table C3

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Language Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>Visual/Verbal</td>
<td>0.075</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>^cw1cnz</td>
<td>Verbal</td>
<td>0.879</td>
<td>0.312</td>
</tr>
<tr>
<td>^GNTza</td>
<td>Verbal</td>
<td>0.185</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>^VFctcz</td>
<td>Verbal</td>
<td>0.083</td>
<td>0.004**</td>
</tr>
</tbody>
</table>

^CWI Colour naming speed. ^bGraded Naming Test total correct. ^VF Category Fluency Total Correct. *Significant at: *p < 0.05; ** p < 0.01; *** p < 0.001 (boldface).
Table C4a

 Variable Names for Measures of Motor Skills

<table>
<thead>
<tr>
<th>Variable ID</th>
<th>Test</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLCMCLz</td>
<td>CANTAB</td>
<td>1BLC mean correct latency</td>
</tr>
<tr>
<td>MOTMEza</td>
<td>CANTAB</td>
<td>2MOT mean errors</td>
</tr>
<tr>
<td>MOTMLza</td>
<td>CANTAB</td>
<td>MOT mean latency</td>
</tr>
<tr>
<td>RTI5mtza</td>
<td>CANTAB</td>
<td>3RTI 5-choice movement time</td>
</tr>
<tr>
<td>RTlsmtza</td>
<td>CANTAB</td>
<td>RT1 simple movement time</td>
</tr>
</tbody>
</table>

1Big Little Circle. 2Motor Screening Test. 3Reaction Time Test.

Table C4b

Raw Score Means (and SDs)1 for Measures of Motor Skills by Group over Time

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy group</th>
<th>No-chemotherapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
</tr>
<tr>
<td>Name2</td>
<td>M (n=30)</td>
<td>M (n=30)</td>
</tr>
<tr>
<td>BLCMCLz</td>
<td>754.7</td>
<td>701.4</td>
</tr>
<tr>
<td>MOTMEza</td>
<td>5.8</td>
<td>6.1</td>
</tr>
<tr>
<td>MOTMLza</td>
<td>934.9</td>
<td>901.1</td>
</tr>
<tr>
<td>RTI5mtza</td>
<td>441.6</td>
<td>412.2</td>
</tr>
<tr>
<td>RTlsmtza</td>
<td>427.9</td>
<td>387.1</td>
</tr>
</tbody>
</table>

1Raw and age standardized scores based on scoring guides in test manuals.
2Descriptive names in the same order are presented in Table C2a.
3Measured in milliseconds.

Where data missing on measure: a n=28; b n=14.

Table C4c

Standardized Means (and SDs)1 for Measures of Motor Skills by Group over Time

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy group</th>
<th>No-chemotherapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1 (n=30)</td>
<td>Time 2 (n=30)</td>
</tr>
<tr>
<td>Name2</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>BLCMCLz</td>
<td>.26</td>
<td>.56</td>
</tr>
<tr>
<td>MOTMEza</td>
<td>.93</td>
<td>.56</td>
</tr>
<tr>
<td>MOTMLza</td>
<td>.43</td>
<td>.42</td>
</tr>
<tr>
<td>RTI5mtza</td>
<td>.35</td>
<td>1.00</td>
</tr>
<tr>
<td>RTlsmtza</td>
<td>.49</td>
<td>.95</td>
</tr>
</tbody>
</table>

1Raw and age standardized scores based on scoring guides in test manuals.
2Descriptive names in the same order are presented in Table C2a.
3Measured in milliseconds.

Where data missing on measure: a n=28; b n=14.
Table C5

*Latent Vector Loadings of the First Two Principal Components obtained from Principal Components Analysis of All Measures of Motor Skills*

<table>
<thead>
<tr>
<th>Measure&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PC 1&lt;sup&gt;1&lt;/sup&gt;</th>
<th>PC 2&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT15mtza</td>
<td>0.57545</td>
<td>0.26845</td>
</tr>
<tr>
<td>RT1smtza</td>
<td>0.60613</td>
<td>0.19158</td>
</tr>
<tr>
<td>BLCMCLz</td>
<td>0.39472</td>
<td>-0.34180</td>
</tr>
<tr>
<td>MOTMEza</td>
<td>-0.04749</td>
<td>-0.75450</td>
</tr>
<tr>
<td>MOTMLza</td>
<td>0.37869</td>
<td>-0.45292</td>
</tr>
</tbody>
</table>

<sup>a</sup> Descriptive names in same order are presented in Table C2a.

<sup>1</sup> First principal component (accounts for 40% of variance).

<sup>2</sup> Second principal component (accounts for 22% of variance).
Figure C2. Means (± SEM) of summary score and individual measures of motor skills over time by breast cancer treatment group.

*Big Little Circle mean correct latency.  2Motor Screening Test mean errors (adjusted).
3Motor Screening Test mean latency (adjusted).  4RTI 5-choice movement time.  5RTI simple choice movement time.
Table C6

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Motor Skills Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal/Motor</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor skills</td>
<td>Visual-motor</td>
<td>0.972</td>
<td>&lt;.001***</td>
<td>0.983</td>
</tr>
<tr>
<td>aBLCMCLz</td>
<td>Visual-motor</td>
<td>0.923</td>
<td>&lt;.001***</td>
<td>0.199</td>
</tr>
<tr>
<td>bMOTMEza</td>
<td>Visual-motor</td>
<td>0.170</td>
<td>0.070</td>
<td>0.275</td>
</tr>
<tr>
<td>cMOTMLza</td>
<td>Visual-motor</td>
<td>0.936</td>
<td>0.262</td>
<td>0.834</td>
</tr>
<tr>
<td>dRTISmtza</td>
<td>Visual-motor</td>
<td>0.752</td>
<td>0.016*</td>
<td>0.959</td>
</tr>
<tr>
<td>eRTISmtza</td>
<td>Visual-motor</td>
<td>0.824</td>
<td>0.005**</td>
<td>0.834</td>
</tr>
</tbody>
</table>

aBig Little Circle mean correct latency. bMotor Screening Test mean errors (adjusted).
cMotor Screening Test mean latency (adjusted). dRTI 5-choice movement time. eRTI simple choice movement time.

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).
Table C7a

*Variable Name for Measure of Visuoconstruction*

<table>
<thead>
<tr>
<th>Variable ID</th>
<th>Test</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>cftcyz</td>
<td>CFT</td>
<td>CFT Copy total correct</td>
</tr>
</tbody>
</table>

*Complex figure test.*

Table C7b

*Raw Score Mean (and SD)* for Complex Figure Copy Accuracy by Group over Time

<table>
<thead>
<tr>
<th>Chemotherapy group</th>
<th>No-chemotherapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1 (n = 30)</td>
</tr>
<tr>
<td>Name*2</td>
<td>Mean</td>
</tr>
<tr>
<td>CFTcyrs*4</td>
<td>30.7</td>
</tr>
</tbody>
</table>

Table C7c

*Standardized Mean (and SD)* for Complex Figure Copy Accuracy by Group over Time

<table>
<thead>
<tr>
<th>Chemotherapy group</th>
<th>No-chemotherapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1 (n = 30)</td>
</tr>
<tr>
<td>Name*2</td>
<td>Mean</td>
</tr>
<tr>
<td>CFTcyra*3</td>
<td>-1.85</td>
</tr>
</tbody>
</table>

*Raw and age standardized scores based on scoring guides in test manuals.*

*Descriptive names in the same order are presented in Table C3a.*
Appendix D

Complex figure test results

1.1 Introduction

The Complex Figure test (Corwin & Bylsma, 1993; Hubley & Tremblay, 2002; Meyers & Meyers, 1995; Rey, 1941) is sensitive to mild neuropsychological impairment in a variety of clinical populations, including high functioning patients with Parkinson's disease or early stage Alzheimer's disease, detoxified alcoholics and patient who have suffered a mild traumatic brain injury or frontal lobe lesions (Lezak, et al., 2004).

Poor performance on the individual complex figure measures has been used to identify specific areas of cognitive dysfunction. Taking a long time to copy the figure is indicative of speed of processing deficits or perfectionism. Poor copy accuracy is associated with visuoconstructional or organizational problems; poor recall is sensitive to visual memory deficits; poor recognition with visual encoding problems and poor organizational approach is an indicator of executive dysfunction (Strauss, et al., 2006).

![Figure D.1. The Rey complex figure. Reprinted from stimulus card (Meyers & Meyers, 1995). Copyright 1995 by Psychological Assessment Resources, Inc.](image)

In this section, some examples are presented of types of approaches found to the copy task employing the Rey complex figure (Figure D.1), along with a description of the individual approach and the corresponding performance on recall and other complex figure measures post surgery. This is followed by an examination of trends over time in the main...
complex figure measures (Recognition, Copy accuracy, Copy Organization, Immediate recall and Delayed recall) for each treatment group, as well as an examination of the association between variables at each timepoint for each group.

1.2 Types of approach to copy

An examination was made of the copy figures in the complex figure tests as well as approaches to determine pattern profiles. As performance on the copy task can be influenced by organizational approach, this was recorded by the examiner at the time of administration, reproducing the examinee’s drawing on a separate sheet using coloured pencils, changing colours for each detail/element in the construction of the figure, noting the order of the colours. While not a formal part of the test administration, Meyers and Meyers (1995) suggest this procedure in order to provide a detailed record of the respondent’s organizational approach. This enabled later quantitative scoring, following the five configural elements defined by Binder (1982) (see Figure D.2b and Chapter 3.4.7g for further details). Some representative examples of copies of the Rey complex figure are presented along with descriptions of the approaches and the recall performance at Time 1 (prior to chemotherapy and/or post surgery) and Time 3 (around 10 months after the completion of chemotherapy and/or 15 months from Time 1) to illustrate change in figure copy performance and impact on recall.

a. Accurate copy of the complex figure

Rey (1941; translated by Corwin and Bylsma, 1993) asserted that copying the complex figure does not require a high level of drawing ability, as each of the details is simple to reproduce separately and the difficulty of the task is in the arrangement of the elements. Meyers and Meyers (1995) reported they had studied the copy drawings of 100 healthy normal subjects to establish normal variability. Some degree of variability in the accuracy and placement of the copy drawings was observable in all subjects. They measured the distance of error (i.e. the distance from correct accuracy or placement) of the drawings and averaged this across subjects and scoring elements to develop normative criteria. They established that units of drawings that deviated from accurate reproduction by 3 mm\(^4\) or less or deviated from correct placement by 6mm or less were considered within normal limits.

At Time 1, 37% \((n = 11)\) of the chemotherapy group and 53% \((n = 8)\) of the no-chemotherapy group displayed copy figures that were accurate and within the normal

\(^4\) Imperial units of measurement used in the manual were converted to metric for the purposes of consistency.
At Time 2, 43% \((n = 13)\) of the chemotherapy group and 56% \((n = 9)\) of the no-chemotherapy group displayed copy figures that were in the normal range. At Time 3, considerably fewer of the chemotherapy group \((28\%; \ n = 8)\) and slightly fewer of the no-chemotherapy group \((50\%; \ n = 8)\) displayed copy figures that were in the normal range. Overall, the copy performances of the no-chemotherapy group \((53\%; \ n = 25)\) were more likely to be in the normal range than the chemotherapy group \((36\%; \ n = 32)\) with this approaching, but not quite reaching significance, \(\chi^2(1, \ N = 136) = 3.753, \ p = 0.053\).

**Figure D.2.** The Rey complex figure (a) and the configural elements (b).

Most accurate copies in the study displayed a configural approach to the copy task, involving a reproduction of structural and main elements first or as a whole unit (i.e., base rectangle, diagonal cross, horizontal midline, vertical midline and large triangle as shown in Figure D.2 (b), as opposed to a local, detail-oriented approach. However, there were some complete and accurate copies that displayed good visuoconstructional accuracy but did not use a global, configural approach.

In Figure D.2a is a representative example of a complete and accurate copy of the Rey complex figure at Time 1 that did not use a configural approach to the copy. This participant (Case 10) obtained a perfect Copy raw score of 36.0, which, along with her copy speed, fell in the normal range (>16th percentile). Her approach to copying the figure was systematic but not configural. She started with the vertical cross and then completed each quadrant of the rectangle counterclockwise, starting from the top left quadrant, and filling in the details. She then completed the elements below the left half of the rectangle (square and horizontal cross) before completing the right half of the rectangle, followed by the triangles. All elements were drawn accurately and correctly placed, displaying excellent visuospatial construction skills. Her approach, though, became more integrated and globally organized at recall (see Figure D.3b and c).
This was characterised by drawing the base rectangle and configural elements first and then the details, with the figure elements again all accurate and correctly placed. This respondent displayed Extremely High levels of Immediate and Delayed recall at Time 1, with Average Recognition of material. At the Time 3 assessment, she displayed similar Copy accuracy (Raw score = 35.0) and Copy speed that were again within the normal range. Her overall copy of the complex figure was well planned and executed (Figure D.3d) starting with the base rectangle and configural elements. She maintained her Extremely High level of Immediate and Delayed Recall performances (Figure D.3e and f). Recognition of material was the same.

<table>
<thead>
<tr>
<th>a. Time 1 Copy</th>
<th>d. Time 3 Copy</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="a.png" alt="Image" /></td>
<td><img src="d.png" alt="Image" /></td>
</tr>
<tr>
<td>b. Time 1 Recall (3 mins)</td>
<td>e. Time 3 Recall (3 mins)</td>
</tr>
<tr>
<td><img src="b.png" alt="Image" /></td>
<td><img src="e.png" alt="Image" /></td>
</tr>
<tr>
<td>c. Time 1 Recall (30 mins)</td>
<td>f. Time 3 Recall (30 mins)</td>
</tr>
<tr>
<td><img src="c.png" alt="Image" /></td>
<td><img src="f.png" alt="Image" /></td>
</tr>
</tbody>
</table>

*Figure D.3. Case 10: Copy and Recall of Complex Figure at Time 1 and Time 3.*

This pattern of normal copy and good recall demonstrates that organizational approach and visuospatial constructional skills are not synonymous constructs, as shown in this example (Figure D.3a) involving a completely accurate copy without using a configural.
approach. This respondent did use a global, configural approach on further trials and this is consistent with other respondents who produced accurate copies using locally oriented approaches initially. Most participants who displayed consistently accurate copies over the course of assessments demonstrated a configural approach by the delayed recall trial at Time 1. This suggests that while a configural approach was not the only way of achieving an accurate reproduction; it was found to be a more efficient approach to completing an accurate copy.

Thirteen percent of participants \((n = 6)\) maintained copy scores within the normal range at all assessments, with proportionally more of the no-chemotherapy group \((25\%; n = 4)\) than the chemotherapy group \((7\%; n = 2)\) maintaining performances within the normal range. There was no significant difference, though, in the probability of maintaining normal copy performances between treatment groups, \(p = 0.163\) (Fisher’s exact test).

Seventeen percent of participants \((n = 8)\) displayed copy performances that improved from outside the normal range at Time 1 to within the normal range \((>16^{th}\) percentile) by Time 2 or Time 3, not indicating an underlying deficit. More of the chemotherapy group \((20\%; n = 6)\) demonstrated this improvement than the no-chemotherapy group \((12.5\%; n = 2)\), although there was no significant difference in the likelihood of this profile between treatment groups, \(p = 0.694\) (Fisher’s exact test).

b. *Deterioration in copy accuracy of the complex figure*

Over one-quarter of participants \((26\%; n = 12)\) displayed a decline in their copy performance from the normal range at Time 1 to below the normal range at Time 2 and/or Time 3.

In Figure D.4 is an example of a participant (Case 29) whose copy performance deteriorated from the normal range at Time 1 to below this at follow-up. She made a complete copy of the Rey complex figure \((\text{Raw score } = 34)\) at Time 1 (see Figure D.4a) that was within the normal range \((>16^{th}\) percentile). Her Copy speed was also in the normal range. Her approach to copying the figure was well organized, starting with the base rectangle, then the diagonals and midlines, with the figure accurate apart from the small rectangle within the large rectangle being drawn as a square, and the diamond not being attached to the large triangle. This participant displayed *Well Above Average* Immediate and Delayed Recall at Time 1 (see Figure D.4b and c), with *High Average* Recognition of material.

At the Time 3 assessment this respondent displayed more problems in her copy performance. She obtained a Copy raw score of 31.0, which corresponded to the 11-16th
percentile range. Her Copy speed was in the normal range, indicating adequate speed of processing. Her approach to copying the figure was less spatially organized with the figure not fitting on the page (Figure D.4d), indicating more visuospatial construction problems. She again began her copy with the rectangle, followed by the midlines, and the large triangle. She then drew the diagonal lines as the vertex of a triangle in each half of the rectangle and filled in the details.

<table>
<thead>
<tr>
<th>a. Time 1 Copy</th>
<th>d. Time 3 Copy</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b. Time 1 Recall (3 mins)</th>
<th>e. Time 3 Recall (3 mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>c. Time 1 Recall (30 mins)</th>
<th>f. Time 3 Recall (30 mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
</tbody>
</table>

Figure D.4. Case 29: copy and recall of complex figure at Time 1 and Time 3.

Most errors incurred in this copy involved relationship and placement errors: the height of the vertical cross extended > 12mm above the horizontal midline; the small horizontal line above the small rectangle was not discontinuous with a segment of the four parallel lines; the diamond was not attached to the vertex of the large triangle; the horizontal cross was not within 6mm of connecting to the midpoint of the right side of the small square;
and the square below the large rectangle was not drawn as a square and the width was not within 6mm of the approximate width of the small rectangle (see Figure D.4).

This participant displayed poorer recall of the overall figure than at the initial assessment, illustrated in Figure D.4e and f, with her Immediate and Delayed recall scores dropping from the Well Above Average to the border of the High Average range. This was not explained by her encoding (Recognition) of material, which remained the same. This profile suggests some deterioration in visuospatial constructional performance.

More of the chemotherapy group (30%; \( n = 9 \)) demonstrated a deterioration profile (from normal range to below the normal range) than the no-chemotherapy group (17%; \( n = 3 \)), although there was no significant difference in the probability between treatment groups, \( p = 0.498 \) (Fisher's exact test).

c. **Inaccurate copies below the normal range**

Thirty percent of participants \( (n = 14) \) displayed copy performance below the normal range at all assessments, with more of the chemotherapy group (33%; \( n = 10 \)) than the no-chemotherapy group (25%; \( n = 4 \)). The Fisher's exact test yielded no significant difference, though, in the likelihood of this profile between treatment groups, \( p = 0.739 \).

Unexpectedly, 65% of participants \( (n = 30) \) displayed Copy performance profiles over the course of assessments that involved either deterioration to below the normal range by the final assessment or sustained problems in the copy task below the normal range over the course of the assessments. This impairment profile suggests some visuoconstructional and/or organizational deficits. More of the chemotherapy group (73%; \( n = 22 \)) than the no-chemotherapy group (50%; \( n = 8 \)) displayed this impairment profile, although there was no significant difference in the probability of this profile between treatment groups, \( \chi^2(1, N = 46) = 2.504, p = 0.114 \) (Pearson's chi-square).

There were two main profiles found that were associated with copy performances that were not within the normal range. The first involved inaccurate, distorted copying, suggesting visual perception or visuoconstruction difficulties. The other involved fragmented, piecemeal copies, indicating more visuoconstruction or organization problems. Examples of these types of poor copy performance profiles will be presented.

d. **Distorted copy of the complex figure**

Some copies were copied carefully but were poorly executed due to distortions made in the reproduction of the key elements, including visuospatial relationship errors. These
types of distorted copies can be indicative of visual perception or visuospatial constructional problems (Meyers & Meyers, 1995).

An example of a participant's copy (Case 14) at Time 1 is presented in Figure D.5a, where the main structural elements are copied carefully but there are distortions in the reproduction of key figural elements. She obtained a Copy raw score of 27.5, which corresponded to the ≤1st percentile. Her approach involved: drawing the left side of the large rectangle and the small square; completing the rectangle starting from the top left corner; drawing the vertical midline and the isosceles triangle, drawing the horizontal midline and the large triangle; and filling in the details.

Figure D.5. Case 14: copy and recall of complex figure at Time 1 and Time 3.
The base configural unit of the rectangle was distorted, leading to other distortions and misplacement errors (Figure D.5a). In recall, she recalled the key structural elements but omitted the details and made misplacement errors. Her Immediate and Delayed recall performances (Figure D.5b and c) were both within the *Well Below Average* range, reflecting problems with retrieval and this was not explained by her speed of processing (time to copy) which was in the normal range or encoding (Recognition) performance which was in the *Average* range.

At the *Time 3* follow-up assessment, this respondent continued to display marked impairments in her visuoconstruction skills on the Rey copy trial (Figure D.5d), with the Copy raw score of 21.5 remaining in the ≤1st percentile. Her approach to the copy this time was more disorganized. Her copy proceeded with: a line near the apex of the large triangle; recommenced from the top of the isosceles triangle; completed the outside of the large triangle; the bottom left half of the rectangle to the vertical midline; the vertical line in the large triangle; the other half of the rectangle; the horizontal cross; the horizontal midline; and one diagonal line in the rectangle. The left diagonal was started from the intersection of the horizontal and vertical midline, with the diagonal in the top left quadrant drawn after other details were completed. The base rectangle was drawn more accurately than previously but other structural elements showed distortions and relationship errors, including the off-centred placement of both midlines, leading to a distortion in the large triangle and omission of details.

Her Immediate and Delayed recall performances deteriorated further to the *Extremely Low* range (Figure D.5e and f). These indicated underlying visuoconstruction problems not explained by her speed of processing (Time to copy), which was in the normal range, or encoding (Recognition) performance, which was in the *High Average* range.

e. *Fragmented copy of the complex figure*

Performance on the copy task is also influenced by organizational ability, considered to be an executive function. Drawing the figure more globally and organizing it into meaningful perceptual units during encoding is known to enhance recollection accuracy (Shorr, Delis, & Massman, 1992). According to Meyers and Meyers (1995), healthy normal subjects tend to copy the figure in a more integrated, global approach with the design being more configural, rather than drawn in isolated elements. These copies tend to draw the main structural elements (base rectangle, diagonals, horizontal/vertical midline) as whole units and place them in reference to each other. According to Osterrieth (Corwin & Bylsma, 1993; 1944), 83% of adults adopt a configural approach and 13% adopt a fragmented, piecemeal approach.
In Figure D.6a is an example of a participant’s copy at *Time 1* where the figure is reproduced in a fragmented, piecemeal fashion. Her approach to copying the figure was characterized by drawing triangles, segments and small rectangles and adding internal details to make up the large rectangle. As can be seen, this led to significant errors in the reproduction.

<table>
<thead>
<tr>
<th>a. <em>Time 1 Copy</em></th>
<th>d. <em>Time 3 Copy</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Time 1 Copy" /></td>
<td><img src="image2" alt="Time 3 Copy" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b. <em>Time 1 Recall (3 mins)</em></th>
<th>e. <em>Time 3 Recall (3 mins)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Time 1 Recall 3 mins" /></td>
<td><img src="image4" alt="Time 3 Recall 3 mins" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>c. <em>Time 1 Recall (30 mins)</em></th>
<th>f. <em>Time 3 Recall (30 mins)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image5" alt="Time 1 Recall 30 mins" /></td>
<td><img src="image6" alt="Time 3 Recall 30 mins" /></td>
</tr>
</tbody>
</table>

*Figure D.6. Case 44: copy and recall of complex figure at *Time 1* and *Time 3*.*

There were numerous accuracy errors, including all angles of the large rectangle not being at 90 degrees, lines under or overshooting, vertical and horizontal cross overshooting.
circles being drawn instead of dots within the small circle as well as an additional 'hair', and a rectangle being drawn rather than a small square. The retracing and dark lines may be an indicator of uncertainty. Her Copy raw score of 27.0 was in the ≤1st percentile. Her copy speed fell in the normal range. Her Immediate and Delayed Recall fell within the Extremely Low range (Figure D.6b and c). These scores indicate a mild-to-moderate level of impairment of visual memory skills. She obtained a Recognition total correct raw score of 18, which was in the Well Below Average range. This score is considered mild-to-moderately impaired (Meyers & Meyers, 1995).

This profile indicates a visuospatial construction and organization impairment leading to problems encoding and retrieving visuospatial material. This is supported by the lack of improvement in this respondent's copying of the figure at Time 3 (Figure D.6d). Her approach was even more piecemeal. Her Copy raw score of 18.5 was in the ≤1st percentile. Her Immediate recall improved to the border of the Well Below Average range while her Delayed recall remained within the Extremely Low range (see Figure D.6e and f). Her Recognition raw score remained the same.

1.3  Complex figure test analysis

To examine whether visuoconstructional accuracy or organizational approach had an influence on efficient encoding and/or visual recall, the mean standardized scores for the Complex Figure Copy accuracy, Copy organization, Immediate and Delayed Recall and Recognition were compared over the assessments for each group, to examine trends over time. Following this, a multivariate analysis was conducted to examine associations between variables over the course of the assessments.

1.3.1  Comparing trends over time

α. Comparing trends for the no-chemotherapy group over time

The average z-scores for the Complex Figure Copy accuracy, Organization, Immediate and Delayed Recall and Recognition are presented in Figure D.7 for the no-chemotherapy group to examine the trends over time in these measures.

Both the Immediate and Delayed Recall of the no-chemotherapy group showed an improvement in performance from Time 1 to Time 2, although immediate recall was more marked, improving from the Average to the High Average range. While Delayed Recall performance plateaued at Time 3, Immediate Recall performance declined slightly to the bottom of the High Average range.
Copy organization showed improvement over time, while remaining within the *Average* range. Recognition, a test of visual encoding, showed similar performance over time, with a slight deterioration between *Time 1* and *Time 2*, and a corresponding slight improvement between *Time 2* and *Time 3*, all within the *Average* range.

![Graph showing performance over time](image)

**Figure D.7.** Mean complex figure standard scores for the no-chemotherapy group over time. *Time 1* = Post-surgery; *Time 2* = 6 months from *Time 1*; *Time 3* = 15 months from *Time 1*.

Copy accuracy performance was, on average, at least one standard deviation poorer than other measures. The trend, though, was akin to Recognition, as Copy accuracy performance was similar over time. There was a slight deterioration between *Time 1* and *Time 2*, and a plateau in performance between *Time 2* and *Time 3*, all within the *Well Below Average* range.

### f. Comparing trends for the chemotherapy group over time

The average z-scores for the Complex Figure Copy accuracy, Organization, Immediate and Delayed recall and Recognition are presented in Figure D.8 for the chemotherapy group over the course of the assessments.

For the chemotherapy group, Immediate and Delayed recall performances were very similar in both values and trends over time. Immediate and Delayed recall performances improved at a corresponding rate between *Time 1* and *Time 2*. While Delayed Recall remained in the *Average* range, Immediate recall moved just over the border into the *High Average* range. Both recall performances deteriorated from *Time 2* to *Time 3*, although not below initial performance, remaining within the *Average* range.
Copy organization performance for the chemotherapy group showed a similar trend to the no-chemotherapy group, as performance improved over time, within the Average range.

Recognition performance by the chemotherapy group also showed a similar trend to the no-chemotherapy group over the assessments, with deterioration between Time 1 and Time 2, and corresponding improvement between Time 2 and Time 3, all within the Average range.

![Figure D.8. Mean complex figure standard scores for the chemotherapy group over time.](image)

*Time 1 = Post-surgery and pre-chemotherapy; Time 2 = Post-chemotherapy (6 months from Time 1); Time 3 = 15 months from Time 1.*

Copy accuracy performance was, on average, at least one and a half standard deviations poorer than other measures. The Copy accuracy trend displayed over the assessments was unlike that shown for the no-chemotherapy group. It was also different to other Complex Figure measures for the chemotherapy group, although it was more like the trend displayed in the recall measures. Copy accuracy improved slightly between Time 1 and Time 2 but then deteriorated markedly from Time 2 to Time 3, below initial performance, from the Well Below Average to the Extremely Low range.

### 1.3.2 Associations between variables

Principal components analyses, using a correlation matrix, were conducted on all five Complex Figure measures at each time for each group. Principal components analysis was used as a statistical visualization tool to explore the relationships between variables across individuals within each group at each timepoint. The biplots for each treatment
group at each timepoint are presented for comparison in Figure D.9. Variable names are presented in the colours shown in the biplot to aid interpretation.

a. **Associations between variables for the no-chemotherapy group over time.**

For the no-chemotherapy group at Time 1, the Immediate and Delayed Recall measures (CFTirz and CFTdrz) demonstrated high correlation (Figure D.9d). They were clearly separate from the other measures, Recognition (CFTrez), Copy accuracy (CFTcyz) and Copy organization (CFTorgz), in the top right quadrant. By Time 3, Recognition (CFTrez) shifted its relative position and was now closely associated with the Recall measures (CFTirz and CFTdrz) (Figure D.9f). This indicates that, at Time 3, individual Recognition scores in the no-chemotherapy group showed higher association with individual Immediate and Delayed Recall scores. Copy accuracy (CFTcyz) and Organization (CFTorgz) were also more closely associated at Time 3 than at Time 1 or Time 2.

b. **Associations between variables for the chemotherapy group over time.**

For the chemotherapy group, at Time 1 (Figure D.9a), Immediate and Delayed recall (CFTirz and CFTdrz) were highly associated. Copy accuracy (CFTcyz) and Organization (CFTorgz) also showed a high correlation. Recognition (CFTrez), though, was clearly separate from all other measures, near the vertical midline. The associations between variables become more diffuse by Time 2, so there were not clearly defined associations between variables by Time 3.

c. **Comparing associations between variables between groups over time**

Both Recall measures (CFTirz and CFTdrz) provided very similar information across each timepoint. This was more tightly consistent within the no-chemotherapy group, as opposed to the chemotherapy group where these measures became more disassociated over each time. The high correlation of both Recall measures in the no-chemotherapy group across time was consistent with previous findings from normative samples. Meyers and Meyers (1995) correlated Complex Figure test measures from 601 normal adults and found that the largest correlation was between Immediate recall and Delayed recall \( r = 0.88 \). Recognition (CFTrez), the measure of visual encoding, became more closely related to Recall over time, especially in the no-chemotherapy group. A respondent is highly likely to recognize a scoring unit in the recognition trial if they correctly recalled it (Meyers & Meyers, 1995). Meyers and Meyers found lower but significant correlations in the adults sample between Recall measures and Recognition scores \( r = 0.15 \), suggesting that they are assessing different aspects of memory.
Figure D.9. Biplots of the complex figure measures by group and time.

CFTrcz = CFT Recognition; CFTcyz = CFT copy accuracy; CFTorgz = CFT copy organization;
CFTirz = CFT immediate recall; CFTdrz = CFT delayed recall
The converging associations between these test measures could also reflect that, on repeated administration, the Complex Figure test assesses intentional recall and encoding rather than the incidental recall and encoding that is assessed on first encounter. In the administration of the copy instructions there is no forewarning that the respondent will be asked to recall the figure. At the first administration, being asked to recall the figure previously copied is an incidental or implicit recall task. On re-testing, respondents can be aware they will need to recall the figure and, therefore, their recognition and recall scores may reflect their intentional encoding abilities associated with intentional recall. Interestingly, when seen together with the overall trends over time, recall scores did not demonstrate continued improvement after Time 2, indicating that, while chemotherapy respondents recognized similar rates of scoring units to their recall of these units, they recalled less detail correctly at Time 3 than at Time 2.

Copy organization (CFTorgz) and Copy accuracy (CFTcyz) were closely related at Time 1. This was the same for both groups, meaning that for many individuals the more organized their approach to copying the figure, the more accurate it was (Figure D.9a and c). These measures were not overlapping, indicating that they assessed different constructs. For the no-chemotherapy group, these measures maintained a grouping a similar distance apart at Time 3 when compared to Time 1, meaning these measures maintained a consistent association (Figure D.9f). For the chemotherapy group, these measures became increasingly disassociated at each subsequent time. By Time 3, Copy accuracy (CFTcyz) had shifted away from Copy organization (CFTorgz) and was more closely related to the Recall (CFTlrz and CFTdrz) and Recognition measures (CFTrcz) (Figure D.9c).

1.4 Summary

In this appendix, a detailed examination was made of results from one widely used visual memory test, the Complex Figure test. Firstly, representative examples were presented of typical approaches to the copy task found in this study, alongside the individual performance on other complex measures at the Time 1 and Time 3 assessments. These prototypical examples of approaches to the copy task were categorized as:

- consistently accurate over time;
- accurate but with deterioration at follow-up;
- distorted; or
- fragmented.
Accurate copies tended to use a more global or configural approach, as recorded by the examiner, which was consistent with previous findings. One copy example was presented, though, of a respondent who produced a completely accurate copy using a more careful, local approach, indicating the use of excellent visuospatial construction skills. This illustrated how copy organization and copy accuracy are not the same construct. However, where copies were consistently accurate, respondents who had previously used a more local approach generally adopted a global, configural approach on subsequent trials, suggesting that this approach was a more efficient way of producing an accurate copy.

Distorted copies tended to be copied carefully but showed visuospatial inaccuracies in the copying of the elements or the placement or the relationship between the elements. Fragmented or piecemeal copies demonstrated a more disorganized approach to copying the figure.

While the proportion of accurate copies was higher in the no-chemotherapy group (53% compared to 36%) and the proportion of deteriorating or consistently inaccurate copies was higher in the chemotherapy group (73% compared to 50%), there was a trend but no significant difference found in the probability of these profiles between treatment groups, $\chi^2(1, N = 136) = 3.753, p = 0.053$ and $\chi^2(1, N = 46) = 2.504, p = 0.114$ respectively.

Further analyses were conducted in order to examine the trends and relationships between variables associated with treatment in more detail. The average standardized scores for each of the main complex measures were compared for each treatment group over each assessment to assess trends over time. Principal components analyses were conducted on all five Complex Figure measures for each treatment group at each timepoint to examine the association between variables over time.

Although Immediate and Delayed recall were similar in values and trends over time for both groups, the pattern of association between variables over time was different. The association between Recall measures remained close and consistent for the no-chemotherapy group across time, whereas it became more dissociated for the chemotherapy group following the receipt of chemotherapy.

Copy organization also showed similar trends over time for both groups, with organization performance improving over time. Copy accuracy performances, though, were one to one-and-a-half standard deviations poorer than other measures for each group. While Copy accuracy performance in the no-chemotherapy group was fairly consistent over time, it differed in the chemotherapy group, improving slightly and then
deteriorating below performance at Time 1. The pattern of association between Copy organization and Copy accuracy measures over time showed a similar pattern to Recall. The association between Copy organization and Copy accuracy measures remained consistent for the no-chemotherapy group across time, whereas it became more dissociated for the chemotherapy group following the receipt of chemotherapy.

Recognition, the measure of visual encoding, showed a similar trend across time for each group. There was a decline in Recognition performance between Time 1 and Time 2, and a corresponding improvement between Time 2 and Time 3. When comparing the associations between variables over time, Recognition became more closely related to Recall over time, especially in the no-chemotherapy group. This may reflect the closer association of intentional encoding abilities with intentional recall that is assessed on repeated test administration.

This analysis included: detailed descriptions of the typical approaches to copying the complex figure; a comparison of trends over time in the complex figure measures between treatment groups; and a comparison of the associations between variables over time between groups. This allowed a more detailed picture to emerge of the subtle differences in ways of responding to this test between the groups and over time.
Appendix E

Individual measures results

Attention and Speed of Processing

Appendix E presents the means and standard deviations for both raw scores and standardized scores for each measure of attention and speed of processing (Tables E1b and E2). Also included are the latent vector loadings for the first two principal components from the Principal Components Analysis of all measures within the Attention and Speed of Processing domain (Table E3). Individual measures use age-standardized z-scores derived from relevant test norms. Figures and p-value summary tables are presented that were obtained from individual ANOVAs adjusted for between and within subject variation. The performance profile of the summary measure for each grouping (name italicized) in Attention and Speed of Processing is compared with each of the individual measures that contribute to that grouping.
<table>
<thead>
<tr>
<th>Variable ID</th>
<th>Test</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSSb</td>
<td></td>
<td>Digit Supraspan Backward, longest span length</td>
</tr>
<tr>
<td>DSSL</td>
<td></td>
<td>Digit Supraspan Forward, longest span length</td>
</tr>
<tr>
<td>Dspt</td>
<td>WAIS-III</td>
<td>Digit Span Total</td>
</tr>
<tr>
<td>PRMdML</td>
<td>CANTAB</td>
<td>PRM delay, mean latency for correct responses</td>
</tr>
<tr>
<td>PRMiML</td>
<td>CANTAB</td>
<td>PRM immediate, mean latency for correct response</td>
</tr>
<tr>
<td>RTI5rt</td>
<td>CANTAB</td>
<td>5-choice reaction time</td>
</tr>
<tr>
<td>RTIlsrt</td>
<td>CANTAB</td>
<td>RTI Simple reaction time</td>
</tr>
<tr>
<td>RVPA</td>
<td>CANTAB</td>
<td>RVP A' (A prime)</td>
</tr>
<tr>
<td>RVPMPL</td>
<td>CANTAB</td>
<td>RVP mean latency</td>
</tr>
<tr>
<td>RVPJFA</td>
<td>CANTAB</td>
<td>RVP total false alarms</td>
</tr>
<tr>
<td>RVPJHT</td>
<td>CANTAB</td>
<td>RVP total hits</td>
</tr>
<tr>
<td>RVPJcR</td>
<td>CANTAB</td>
<td>RVP correct rejections</td>
</tr>
<tr>
<td>SRMMCL</td>
<td>CANTAB</td>
<td>SRM mean latency for correct responses</td>
</tr>
<tr>
<td>SSPbSL</td>
<td>CANTAB</td>
<td>SSP backward, longest span length</td>
</tr>
<tr>
<td>SSPfSL</td>
<td>CANTAB</td>
<td>SSP backward, longest span length</td>
</tr>
<tr>
<td>cw2wr</td>
<td>D-KEFS</td>
<td>CWI word reading speed</td>
</tr>
<tr>
<td>pas2</td>
<td>PASAT</td>
<td>2 second pacing, total correct</td>
</tr>
<tr>
<td>pas3</td>
<td>PASAT</td>
<td>3 second pacing, total correct</td>
</tr>
</tbody>
</table>

1Pattern Recognition Memory. 2Reaction Time Test. 3Rapid Visual Information Processing. 4Spatial Recognition Memory. 5Spatial Span. 6Color-Word Interference. 7Paced Auditory Serial Addition Test.
Table E1b

Raw Score Means (and SDs)\(^1\) for Measures of Attention and Speed of Processing by Group over Time

<table>
<thead>
<tr>
<th>Name(^2)</th>
<th>Chemotherapy group</th>
<th></th>
<th></th>
<th></th>
<th>No-chemotherapy group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1 ((n = 30))</td>
<td>Time 2 ((n = 30))</td>
<td>Time 3 ((n = 25))</td>
<td>Time 1 ((n = 15))</td>
<td>Time 2 ((n = 16))</td>
<td>Time 3 ((n = 16))</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>DSSbrs</td>
<td>5.90</td>
<td>1.71</td>
<td>5.80</td>
<td>1.52</td>
<td>5.62</td>
<td>1.40</td>
<td>5.33</td>
<td>1.29</td>
</tr>
<tr>
<td>DSSfrs</td>
<td>6.93</td>
<td>1.28</td>
<td>7.00</td>
<td>1.36</td>
<td>7.21</td>
<td>1.40</td>
<td>7.07</td>
<td>1.03</td>
</tr>
<tr>
<td>Dsp_trs</td>
<td>19.33</td>
<td>4.74</td>
<td>19.47</td>
<td>4.34</td>
<td>19.48</td>
<td>4.58</td>
<td>18.60</td>
<td>3.72</td>
</tr>
<tr>
<td>PRMdMCL(^3)</td>
<td>2285.65</td>
<td>513.88</td>
<td>2112.2</td>
<td>425.62</td>
<td>2259.1</td>
<td>590.81</td>
<td>2015.5</td>
<td>501.61</td>
</tr>
<tr>
<td>PRMIMCL(^3)</td>
<td>2345.32</td>
<td>475.41</td>
<td>2056.4</td>
<td>384.83</td>
<td>2146.5</td>
<td>668.54</td>
<td>2303.5</td>
<td>832.80</td>
</tr>
<tr>
<td>RT1Srt(^4)</td>
<td>360.63</td>
<td>46.15</td>
<td>346.0</td>
<td>35.17</td>
<td>357.09</td>
<td>37.80</td>
<td>370.33</td>
<td>51.95</td>
</tr>
<tr>
<td>RT1Srt(^5)</td>
<td>315.82</td>
<td>43.16</td>
<td>316.8</td>
<td>38.16</td>
<td>329.53</td>
<td>52.60</td>
<td>326.19</td>
<td>57.10</td>
</tr>
<tr>
<td>RVPA(^6)</td>
<td>0.93</td>
<td>0.03</td>
<td>0.95</td>
<td>0.03</td>
<td>0.95</td>
<td>0.04</td>
<td>0.92</td>
<td>0.04</td>
</tr>
<tr>
<td>RVPTMCL(^3)</td>
<td>420.73</td>
<td>63.05</td>
<td>411.14</td>
<td>59.16</td>
<td>413.71</td>
<td>73.69</td>
<td>473.11</td>
<td>72.47</td>
</tr>
<tr>
<td>RVPTHT</td>
<td>20.03</td>
<td>3.54</td>
<td>21.70</td>
<td>3.34</td>
<td>22.24</td>
<td>3.74</td>
<td>18.53</td>
<td>4.09</td>
</tr>
<tr>
<td>RVPTFA</td>
<td>1.30</td>
<td>1.58</td>
<td>1.07</td>
<td>1.39</td>
<td>0.86</td>
<td>1.48</td>
<td>1.60</td>
<td>1.84</td>
</tr>
<tr>
<td>RVPTCR</td>
<td>256.57</td>
<td>7.74</td>
<td>260.7</td>
<td>7.18</td>
<td>261.66</td>
<td>8.16</td>
<td>253.00</td>
<td>9.80</td>
</tr>
<tr>
<td>SRMMCL(^3)</td>
<td>2054.</td>
<td>407.7</td>
<td>2133.</td>
<td>559.8</td>
<td>2072.</td>
<td>515.9</td>
<td>2144.</td>
<td>564.8</td>
</tr>
<tr>
<td>SSPisL</td>
<td>5.83</td>
<td>1.18</td>
<td>6.33</td>
<td>1.30</td>
<td>6.28</td>
<td>1.31</td>
<td>5.93</td>
<td>1.03</td>
</tr>
<tr>
<td>SSPisL</td>
<td>6.13</td>
<td>1.31</td>
<td>6.00</td>
<td>1.44</td>
<td>6.34</td>
<td>1.49</td>
<td>5.20</td>
<td>1.15</td>
</tr>
<tr>
<td>ctw2wrs(^6)</td>
<td>22.20</td>
<td>3.60</td>
<td>22.73</td>
<td>3.66</td>
<td>22.55</td>
<td>4.56</td>
<td>21.27</td>
<td>3.47</td>
</tr>
<tr>
<td>pas2rs</td>
<td>36.37</td>
<td>7.76</td>
<td>38.03</td>
<td>10.55</td>
<td>39.90</td>
<td>9.16</td>
<td>36.87</td>
<td>8.62</td>
</tr>
<tr>
<td>pas3rs</td>
<td>48.97</td>
<td>8.98</td>
<td>51.13</td>
<td>9.35</td>
<td>50.76</td>
<td>7.86</td>
<td>49.20</td>
<td>7.49</td>
</tr>
</tbody>
</table>

\(^1\) Raw scores based on scoring guides in test manuals.
\(^2\) Descriptive names in the same order are presented in Table E1a.
\(^3\) Measured in milliseconds.
\(^4\) Measured in seconds.

Where data missing on measure: \(^*\) \(n = 27\); \(^*\) \(n = 29\); \(^*\) \(n = 28\).
Table E2

Standardized Means (and SDs)\(^1\) for Measures of Attention and Speed of Processing by Group over Time

| Name\(^2\) | Chemotherapy group | | | | No-chemotherapy group | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Time 1 (n = 30) | Time 2 (n = 30) | Time 3 (n = 29) | Time 1 (n = 15) | Time 2 (n = 16) | Time 3 (n = 16) |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| DSSbza | .81 | 1.15 | .74 | 1.02 | .62 | .83 | .42 | .89 | .81 | .75 | .82 | .84 |
| DSSfz | .30 | .95 | .35 | 1.00 | .53 | .98 | .44 | .76 | .57 | .75 | .59 | 1.08 |
| Dspitzza | 3.03 | 1.68 | 3.08 | 1.54 | 3.08 | 1.63 | 2.78 | 1.36 | 3.02 | 1.24 | 3.20 | 1.56 |
| PMdMLaza | -.14 | .88 | .18 | .78 | -.12 | 1.09 | .30 | .90 | .45 | .86 | .16 | .55 |
| PRMIIMaza | -.25 | .84 | .26 | .69 | .10 | 1.20 | -.25 | 1.35 | .40 | .81 | .48 | .96 |
| RTIsrTza | -.01 | .79 | .28 | .66 | .11 | .75 | -.01 | .90 | .54 | .71 | .28 | .82 |
| RTIsrTza | .09 | .69 | .10 | .68 | -.05 | .82 | .02 | .83 | .34 | .46 | .16 | .60 |
| RVPAa | .26 | .69 | .59 | .63 | .69 | .71 | .04 | .83 | .25 | .83 | .25 | .85 |
| RVPMLaza | .74 | .62 | .84 | .58 | .81 | .72 | .23 | .71 | .54 | .64 | .40 | .82 |
| RVPTFaza | .07 | .67 | .17 | .59 | .25 | .63 | -.03 | .79 | .12 | .75 | .17 | .63 |
| RVPHTTza | .37 | .74 | .72 | .70 | .83 | .78 | .14 | .88 | .37 | .85 | .35 | .93 |
| RVPCTaza | .50 | .69 | .87 | .64 | .96 | .72 | .25 | .89 | .50 | .85 | .48 | .86 |
| SMMMCza | .47 | .46 | .40 | .58 | .48 | .56 | .46 | .62 | .76 | .49 | .50 | .80 |
| SSPoSFLza | .35 | 1.04 | .20 | 1.10 | .55 | 1.17 | -.19 | .85 | .26 | .68 | -.11 | 1.11 |
| SSPoSFLza | .15 | .87 | .50 | .96 | .50 | 1.11 | .43 | 1.05 | .05 | 1.40 | .82 | 1.22 |
| cw2wrz | .13 | .62 | .82 | .66 | .16 | .84 | .40 | .52 | .43 | .52 | .44 | .42 |
| pas2z | -.05 | .70 | .04 | .99 | .22 | .86 | -.21 | .90 | .05 | .89 | -.25 | 1.06 |
| pas3z | -.01 | .86 | .23 | .89 | .21 | .77 | -.09 | .82 | .28 | .58 | .12 | .93 |

\(^1\) Age standardized z-scores based on relevant test norms.

\(^2\) Descriptive names in the same order are presented in Table E1a.

Where data missing on measure: \(^a\) n = 27; \(^b\) n = 29; \(^c\) n = 28.
Table E3

Latent Vector Loadings of the First Two Principal Components obtained from Principal Components Analysis of All Measures of Executive Functions

<table>
<thead>
<tr>
<th>Measure^a</th>
<th>PC 1^b</th>
<th>PC 2^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSSbz</td>
<td>0.26977</td>
<td>0.03295</td>
</tr>
<tr>
<td>DSSFz</td>
<td>0.25792</td>
<td>0.07290</td>
</tr>
<tr>
<td>DspLta</td>
<td>0.32969</td>
<td>0.06722</td>
</tr>
<tr>
<td>PRMdMLza</td>
<td>0.04494</td>
<td>0.28845</td>
</tr>
<tr>
<td>PRMiMLza</td>
<td>0.11555</td>
<td>0.38207</td>
</tr>
<tr>
<td>RT15rtza</td>
<td>0.11848</td>
<td>0.46178</td>
</tr>
<tr>
<td>RT1srtza</td>
<td>0.08715</td>
<td>0.48879</td>
</tr>
<tr>
<td>RVPAza</td>
<td>0.36769</td>
<td>-0.19499</td>
</tr>
<tr>
<td>RVPMLza</td>
<td>0.19660</td>
<td>-0.00705</td>
</tr>
<tr>
<td>RVPTFaza</td>
<td>0.21831</td>
<td>-0.21427</td>
</tr>
<tr>
<td>RVPTHTza</td>
<td>0.36149</td>
<td>-0.18301</td>
</tr>
<tr>
<td>RVPTcRza</td>
<td>0.37435</td>
<td>-0.22313</td>
</tr>
<tr>
<td>SRMMCLz</td>
<td>0.11324</td>
<td>0.28167</td>
</tr>
<tr>
<td>SSPbSLza</td>
<td>0.20008</td>
<td>0.07046</td>
</tr>
<tr>
<td>SSPfSLza</td>
<td>0.15807</td>
<td>0.11223</td>
</tr>
<tr>
<td>cw2wrz</td>
<td>0.15242</td>
<td>0.22541</td>
</tr>
<tr>
<td>pas2z</td>
<td>0.26442</td>
<td>-0.06727</td>
</tr>
<tr>
<td>pas3z</td>
<td>0.22735</td>
<td>-0.05597</td>
</tr>
</tbody>
</table>

^a Descriptive names in same order are presented in Table E1a.
^b First principal component (accounts for 26% of variance).
^c Second principal component (accounts for 14% of variance)
Spatial span and working memory

Figure E1. Means (± SEM) of summary score and individual measures for spatial span and working memory over time by breast cancer treatment group.

Table E4

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Score of the Spatial Span and Working Memory Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial span and working memory</td>
<td>Visuospatial</td>
<td>0.268</td>
<td>0.022*</td>
<td>0.425</td>
</tr>
<tr>
<td>aSSPfSLza</td>
<td>Visuospatial</td>
<td>0.843</td>
<td>0.083</td>
<td>0.051</td>
</tr>
<tr>
<td>bSSPbSLza</td>
<td>Visuospatial</td>
<td>0.035*</td>
<td>0.118</td>
<td>0.723</td>
</tr>
</tbody>
</table>

*CANTAB Spatial span (forward), bSpatial span (reverse).

*significant at p < 0.05 (boldface)
Auditory span and working memory

Figure E2. Means (± SEM) of summary score and individual measures for auditory attention span and working memory over time by breast cancer treatment group.

aDigit supraspan (bwd). bDigit supraspan (fwd). cDigit span total. dPaced auditory serial addition test (2 seconds). ePASAT (3 seconds).
Table E5

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Score of the Auditory Attention Span and Working Memory Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Variable ID</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
<td></td>
<td>0.927</td>
<td>0.042*</td>
<td>0.361</td>
</tr>
<tr>
<td>Auditory</td>
<td></td>
<td>0.970</td>
<td>0.723</td>
<td>0.071</td>
</tr>
<tr>
<td>Auditory</td>
<td></td>
<td>0.567</td>
<td>0.156</td>
<td>0.678</td>
</tr>
<tr>
<td>Auditory</td>
<td></td>
<td>0.953</td>
<td>0.501</td>
<td>0.572</td>
</tr>
<tr>
<td>Auditory</td>
<td></td>
<td>0.378</td>
<td>0.145</td>
<td>0.091</td>
</tr>
<tr>
<td>Auditory</td>
<td></td>
<td>0.859</td>
<td><strong>0.006</strong></td>
<td>0.696</td>
</tr>
</tbody>
</table>

*Digit supraspan (backwards). bDigit supraspan (forwards). cDigit span total.
 dPaced auditory serial addition test (2 seconds).
 ePaced auditory serial addition test (3 seconds).
 *Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).
Figure E3. Means (± SEM) of summary score and individual measures for sustained attention over time by breast cancer treatment group.

\(^a\)CANTAB Rapid visual information processing (RVP) A' (A prime). \(^b\)RVP mean correct latency. \(^c\)RVP Total correct rejections. \(^d\)RVP Total false alarms. \(^e\)RVP total hits.
Table E6

P values for Group, Time and Interaction effects obtained from ANOVAs of the Sustained Attention Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Variable ID</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained attention</td>
<td>Visual</td>
<td>0.045*</td>
<td>0.001**</td>
<td>0.648</td>
</tr>
<tr>
<td>aRVPA za</td>
<td>Visual</td>
<td>0.079</td>
<td>0.003**</td>
<td>0.584</td>
</tr>
<tr>
<td>bRVPMCLz</td>
<td>Visual</td>
<td>0.023*</td>
<td>0.256</td>
<td>0.671</td>
</tr>
<tr>
<td>cRVPTcRza</td>
<td>Visual</td>
<td>0.062</td>
<td>&lt;.001***</td>
<td>0.587</td>
</tr>
<tr>
<td>dRVPTFAza</td>
<td>Visual</td>
<td>0.575</td>
<td>0.186</td>
<td>0.971</td>
</tr>
<tr>
<td>eRVPTHTza</td>
<td>Visual</td>
<td>0.081</td>
<td>0.004**</td>
<td>0.568</td>
</tr>
</tbody>
</table>

aCANTAB Rapid visual information processing (RVP) A' (A prime). bRVP mean correct latency. cRVP Total correct rejections. dRVP Total false alarms. eRVP total hits.

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).
Speed of Processing

![Graph](image_url)

*Figure E4a.* Means (± SEM) of summary score for speed of processing over time by breast cancer treatment group.

Individual measures are presented on the following page.

Table E7

*P values for Group, Time and Interaction effects obtained from ANOVAs of Speed of Processing Grouping and Individual Measures*

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of processing</td>
<td>Visual-verbal</td>
<td>0.234</td>
<td>&lt;.001***</td>
<td>0.253</td>
</tr>
<tr>
<td>cw2wrz</td>
<td>Visual-verbal</td>
<td>0.092</td>
<td>0.456</td>
<td>0.457</td>
</tr>
<tr>
<td>PRM1MLza</td>
<td>Visual</td>
<td>0.432</td>
<td>0.003**</td>
<td>0.543</td>
</tr>
<tr>
<td>PRM2MLza</td>
<td>Visual</td>
<td>0.130</td>
<td>0.107</td>
<td>0.820</td>
</tr>
<tr>
<td>RTlsrtzia</td>
<td>Visual</td>
<td>0.476</td>
<td>0.180</td>
<td>0.257</td>
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<tr>
<td>RTlsrtzia</td>
<td>Visual</td>
<td>0.420</td>
<td>0.010*</td>
<td>0.699</td>
</tr>
<tr>
<td>SRMCLza</td>
<td>Visuospatial</td>
<td>0.404</td>
<td>0.629</td>
<td>0.175</td>
</tr>
</tbody>
</table>

*D-KEFS Color Word Interference test, Word reading speed.
* CANTAB Pattern recognition memory (immediate), mean correct latency.
* Pattern recognition memory (delayed), mean correct latency.
* Spatial recognition memory, mean correct latency. Simple reaction time. Choice reaction time.
* Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).
Figure E4b. Mean age-standardized scores for individual measures of speed of processing over time by breast cancer treatment group.

\textsuperscript{a}D-KEFS Color Word Interference test, Word reading speed. \textsuperscript{b}CANTAB Pattern recognition memory (immediate), mean correct latency. \textsuperscript{c}Pattern recognition memory (delayed), mean correct latency. \textsuperscript{d}Spatial recognition memory, mean correct latency. \textsuperscript{e}Simple reaction time. \textsuperscript{f}5-choice reaction Time.
Individual measures results

Learning and Memory measures

Appendix F presents the means and standard deviations for both raw scores and standardized scores for each measure of learning and memory (Tables F1b and F2). Also included are the latent vector loadings for the first two principal components from the Principal Components Analysis of all measures within the Learning and Memory domain (Table F3). Individual measures use age-standardized z-scores derived from relevant test norms. Figures and p-value summary tables are presented that were obtained from individual ANOVAs adjusted for between and within subject variation. The performance profile of the summary measure for each grouping (name italicized) in Learning and Memory is compared with each of the individual measures that contribute to that grouping.
<table>
<thead>
<tr>
<th>Name</th>
<th>Measure</th>
<th>Test</th>
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<tbody>
<tr>
<td>CFTdrrz</td>
<td>Delayed recall</td>
<td>CFT</td>
</tr>
<tr>
<td>CFTirz</td>
<td>Immediate recall</td>
<td>CFT</td>
</tr>
<tr>
<td>CFTrctz</td>
<td>Recognition correct</td>
<td>CFT</td>
</tr>
<tr>
<td>Catrcz</td>
<td>Across trial recall consistency, Trials 1-5</td>
<td>CVLT-2</td>
</tr>
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<td>Ccorimz</td>
<td>Average immediate recall, Trials 1-5</td>
<td>CVLT-2</td>
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<tr>
<td>Ccorlcz</td>
<td>Long delayed cued recall correct</td>
<td>CVLT-2</td>
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<td>Ccorlfz</td>
<td>Long delayed free recall correct</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Ccorscz</td>
<td>Short delayed cued recall correct</td>
<td>CVLT-2</td>
</tr>
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<td>Ccorsfz</td>
<td>Short delayed free recall correct</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Ccort1z</td>
<td>List A First trial memory (word span)</td>
<td>CVLT-2</td>
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<td>List A trial 2 total correct</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Ccort3z</td>
<td>List A trial 3 total correct</td>
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<tr>
<td>Ccort4z</td>
<td>List A trial 4 total correct</td>
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</tr>
<tr>
<td>Ccort5z</td>
<td>List A trial 5 total correct</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Ccortb2z</td>
<td>List B total correct (interference trial)</td>
<td>CVLT-2</td>
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<tr>
<td>Cordz</td>
<td>Cued recall discriminability (List A vs Int, Cued recall trials)</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Cdrdz</td>
<td>Delayed recall discriminability (List A vs Int., Delay recall trials)</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Cfrdz</td>
<td>Free recall discriminability (List A vs Intrusions, Free recall trials)</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Cmddpz</td>
<td>% recall from middle region of list, Trials 1-5</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Cnrdsz</td>
<td>Novel recognition discriminability</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Cprimpz</td>
<td>% Recall from Primacy Region of List</td>
<td>CVLT-2</td>
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<tr>
<td>Cridimz</td>
<td>Immediate Recall Discriminability, Trials 1-5</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Crdicz</td>
<td>Recall Discriminability, Long Delay Cued Recall</td>
<td>CVLT-2</td>
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<td>Crdifz</td>
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<td>Crcdsz</td>
<td>Recall Discriminability, Short Delay Cued Recall</td>
<td>CVLT-2</td>
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<td>Crcdfs</td>
<td>Recall Discriminability, Short Delay Free Recall</td>
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<tr>
<td>Crdt5z</td>
<td>Recall Discriminability, Trial 5</td>
<td>CVLT-2</td>
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<tr>
<td>Crdz</td>
<td>Total recall discriminability (List A, All trials vs Total intrusions)</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Crecpz</td>
<td>% Recall from Recency Region of List</td>
<td>CVLT-2</td>
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<td>Csbbcz</td>
<td>Subjective Clustering Bidirectional (chance adj), t1-5</td>
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<td>Csecaimz</td>
<td>Semantic clustering (chance adj) Trials 1-5</td>
<td>CVLT-2</td>
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<tr>
<td>Csecafsz</td>
<td>Semantic clustering (chance adj), Short Delay free recall</td>
<td>CVLT-2</td>
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<tr>
<td>Csemc5z</td>
<td>Semantic clustering (chance adj), Trial 5</td>
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<tr>
<td>Csecafsz</td>
<td>Semantic clustering (chance adj), Long Delay free recall</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Csrdsz</td>
<td>Source recognition discriminability (Recog List A hits v List B)</td>
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<tr>
<td>Cthitsz</td>
<td>Recognition trial (total hits)</td>
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<tr>
<td>Cintz</td>
<td>Total intrusions</td>
<td>CVLT-2</td>
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<tr>
<td>Ctotspsz</td>
<td>Total learning slope (adjusted for ceiling and trial 1)</td>
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</tr>
<tr>
<td>Ctdrz</td>
<td>Total recognition discriminability (hits v false positives)</td>
<td>CVLT-2</td>
</tr>
<tr>
<td>Ctrpz</td>
<td>Total repetitions</td>
<td>CVLT-2</td>
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<tr>
<td>VPAn1z</td>
<td>T1-4 Immediate recall</td>
<td>VPA</td>
</tr>
<tr>
<td>VPAn2z</td>
<td>Long delay recall</td>
<td>VPA</td>
</tr>
<tr>
<td>VPAnprtz</td>
<td>Percent Retention</td>
<td>VPA</td>
</tr>
<tr>
<td>VPAn1tz</td>
<td>Trial 1 recall</td>
<td>VPA</td>
</tr>
<tr>
<td>VPAn2tz</td>
<td>Trial 2 recall</td>
<td>VPA</td>
</tr>
<tr>
<td>VPAn3tz</td>
<td>Trial 3 recall</td>
<td>VPA</td>
</tr>
<tr>
<td>VPAn4tz</td>
<td>Trial 4 recall</td>
<td>VPA</td>
</tr>
<tr>
<td>VPAnisz</td>
<td>Learning slope (adjusted)</td>
<td>VPA</td>
</tr>
<tr>
<td>PALM1Ma</td>
<td>First trial memory (visuospatial span)</td>
<td>PAL</td>
</tr>
<tr>
<td>PALMESz</td>
<td>Mean errors to success</td>
<td>PAL</td>
</tr>
<tr>
<td>PALMTsz</td>
<td>Mean trials to success (adjusted)</td>
<td>PAL</td>
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<td>PALS1sz</td>
<td>Stages completed on first trial (adjusted)</td>
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<td>PALTsz</td>
<td>Total errors, 6 shapes</td>
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<tr>
<td>PALTsz</td>
<td>Total errors (adjusted)</td>
<td>PAL</td>
</tr>
<tr>
<td>PALTTsz</td>
<td>Total trials (adjusted)</td>
<td>PAL</td>
</tr>
<tr>
<td>PRMdzsz</td>
<td>Delayed recognition memory % correct</td>
<td>PRM</td>
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<tr>
<td>PRMdzsz</td>
<td>Immediate recognition memory % correct</td>
<td>PRM</td>
</tr>
<tr>
<td>SRMdzsz</td>
<td>Immediate recognition memory % correct</td>
<td>PRM</td>
</tr>
</tbody>
</table>

1Complex figure test 2 California Verbal Learning Test-2 3 Verbal paired associates (names) 4 CANTAB Paired associates learning 5 CANTAB Pattern recognition memory 6 CANTAB Spatial recognition memory
Table Flb
Raw Score Means (and SDs)1 for Measures of Learning and Memory by Group over Time
Chemotherapy
Name

Time 1 (n
M

= 30)

Time 2 (n
SO
M

CFTdrrs
CFTirrs
CFTrcrs
Catrcr

18.72
19.40
20 .63
85 .93

6.22
6.48
2.04
8.52

21 .10
21 .60
20 .30
87 .03

Ccorimt
Ccorlcrs
Ccorlfrs
Ccorscrs
Ccorsfrs

56 .27
12.80
12.00
12.60
11.40

9.26
2.30
2. 72
2.42
2.82

56.43
13.00
12.33
12.93
12.40

Ccort1 rs
Ccort2rs
Ccort3rs
Ccort4rs
Ccort5rs

6.60
17.10
11.97
12.67
13.23

1.90

6.83
14.30
12.17
12.97
13.40

Ccortbrs
Ccrdr
Cdrdr
Cfrdr
Cmiddpr

6.20
2.55
2.49
2.24
44.80

Cnrdr
Cprimpr
Crdiimr
Crdilcr
Crdilfr

3.10
27 .70
2.30
2.53
2.48

Crdiscr
Crdisfr
Crdit5r
Crdr
Crecpr
Csbcbiz
Csecaimr
Csecasfr
Csemca5r
Csecalfr

= 30)
SO
6.30
6.28
1. 95

7.52
8.48
2.51

2.55
2. 16
2. 75

No-chemotherapy
Time 3 (n
M
19.84
20 .34
20 .52
86 .90
58 .97
13.17
12.90
13.00
12.24

2.27

7.59
16.48
12.59
12.76
13.38

6.70
2.69
2.66
2.37
43.03

2.22
.67
.65
.39
4.56

7.07
2.52
2.52
2.32
44 .90

.43

.66
.60

3.28
29.40
2.41
2.67
2.56

3.28
28 .28
2.39
2.53
2.55

2.57
2.39
2.87
2.30
27.47

.67
.67
.57
.42
5. 75

2.70
2.68
2.93
2.41
27 .73

.52
1.75
2.92
2.62
3.30

1.09

3.23

.75
1.97
3.62
3.35
3.63

2.06
3.45
3.90
3.38

1.10
3.27
4.58
4.28
4 .83

8. 16
2.22
2.56
2. 14
1.86
.64
.58
.37
6.45
.51
4.59
.39

1.94
3. 17
3.62

1.72
8. 16
1.97
2.08

4.08
.38

. 76
.65
.63
. 71

.62
.43
4.32
1. 16

2.53
2.45
2.77
2.36
26 .79

C~rdr
Cthitsr
Ctintr
Ctotslpr
Crdr

3.13
14.90
3.93
1.59
2.30

. 72
1.24
3.30
.65
.42

3.25
14.97
2.33
1.61
2.41

.52
1.27
2. 94
. 61
.43

3.26
14.69
6.31
1.29
2.36

Ctrepr
VPAn1rs
VPAn1rs
VPAn2rs
VPAnprp

5.87
20 .04
20 .04
6.56
92 .90

4.53

5.33
20 .52
20 .52
6.62
89 .93

4. 12

4.00
18.89
18.89
5.67
86 .38

VPAnt1 rs
VPAnt2rs
VPAnt3rs
VPAnt4rs
VPAnlsr

2.84
4.64
6.12
6.48
1.53

6. 18
6. 18
1.85
12.78
1.93
1.89
1. 76

1.76
.89

PAL 1M
PALMES
PALMTS
PALSCm1
PALTEa6

19.21
1.47
1.49
6.00
2.93

3.82

PALTEa
PALTTa
PRMd %c
PRMi %c
SRM%c

11.45
11 .69
83 .33
93 .33
85 .00

8. 70

1.12
.35
1.10
3.86

2. 71
10.26
8.59
7.97

2.76
4.97
6.03
6.79
1.66

6.07
6. 07
1.90
16.93
1.60
2.24
1.74
1.42

.88

14.07
2.61
1.84
3.13
2.93

3.43

12.63
9.07
88 .33
95 .56
77.41

10.75

2.50
.61
.63
2.45
2. 70
13. 77
6.09
11 . 70

2.48
4.37
5.85
6.19
1.54
15.00
1.88
1.70
3.10
3.10
9.41
8.48
89 .37
95 .69
76 .96

=29)
SO

Time 1 (n
M

= 15)
SO

6.60
6.35
2.41
9.03

18.53
18.67
20.40
83 .60

5.40

9.20
2.21

2.27
2.59
2.94
2. 16

8. 96
2.01

2. 71
2.06
1.96
.82

. 77
.51
5.43
. 71
3.64
.51

.88
.70
.83
.85

. 70
.54
4.34
1.46
2.47
3.27
3.44
3.06
.68
2.83
8.46
. 68
.54
3.32
6.31
6.31

1. 86
20.81
1.53
1.96
1.90
1.88
.82
2.43
1.09
.36
.49

2.77
5.45
1.82
8 00
6.54
11 .89

Time 2 (n
M

= 16)
SO
4. 73

2. 03
8.36

20 .09
21.44
19.94
86 .13

54 .60
12.07
11 .00
12.40
10.80

9.09
2.52
2.67
2.26
2. 18

53 .25
12.63
12.00
12.69
11 .69

9.21

6.60
16.80
11 .33
12.40
12.53

1.45

1.96

6.00
16.44
11.44
12.00
13.19

6.73
2.34
2.25
2.15
43.73

2.02
.77
.61
.36
4.04

7.13
2.53
2.50
2.22
43 .88

2.89
27 .73
2.27
2.21
2.14

.56
4.03
.38
.85
.53

2.46
2.17
2.61
2.19
28.40

Time 3 (n
M

= 16)
SO

20.25
20 .28
20 .19
89.38

6.25
5. 17
2.43
7.46

60 .06
12.94
12.88
12.94
12.44

11 .07

7.94
17 .19
12.50
12.81
13.81

2.41

1.89

4.53

7.13
2.65
2.65
2.42
43 .19

3.19
28 .63
2.24
2.46
2.48

.50
5.49
.43
.83
.59

3.48
28 .81
2.48
2.66
2.70

. 76
. 54
.50
.42
5. 14

2.61
2.44
2.78
2.27
27 .62

.87

2.62
2.64
2.94
2.46
28 .06

.03
1.50
3.04
2.03
3.40

.95
1.40
2.57
2.59
2.32

.38
1.87
3.61
2.94
4.30

3.05
14.53
5.07
1.43
2.19

.49

3.29
15.00
3.44
1.69
2.27

5.28
.48

3.46
15.50
4.06
1.29
2.46

5.00
20 .75
20 .75
6.31
86 .25

2. 80
7.35
7.35
2.27
25.25

5.44
20 .19
20 .19
5.69
81 .10

31 .93

2.69
5.25
6.25
6.56
1.61

2.09
2.29
1.84
1.93
.82

2.75
4.88
5.81
6.62
1.47

2.29
2.50
2.23
1.59
.53

15.38
2.60
1.78
3.50
2.13

3.76

15.88
1.76
1.68
3.31
2.75

2.94

.60
2.65

8.81
8.38
88 .02
94 .27
76 .25

7.62
2.31
11 .37
7.89
10.25

4.93
18.54
18.54
6.38
89.28
2.15
4.62
5.46
6.31
1.47

5.48

10.96

2. 69
2.41

1. 19
5.44
.41
.42

3. 75
6.50
6.50
2.36
27.42
1.41

2.06
2. 15
1. 75
.66

18.40
1.50
1.47
5.87
3.13

3.56

11 .27
11 .40
82 .78
92 .78
80 .33

5.31

.88
.22
.99
2. 17
1. 72

9. 16
9.38

7.67

13.31
9.44
89 .06
92 .71
73 .13

4.47
3.38
6.47
2. 16
2.03

2.55
2.39
1.83
10. 11

2.66
1.86
1.68
1.93
.83
.68
.44

.66
.57
.48
6.98
.59
1.88

2.69
3.45
2. 19
.46
1. 10
.47

2.69
.57
. 97
2. 16
13.29

2. 78
8.45
9.07
13. 15

1.03
2.59
4.78
4.13
5.44

2.52
2.55
2.49
2.94
9.74

2.92
2.32
1.72
.79
.73
.53
8.60
.31
3.56
.54
.82
.73

.79
.71
.59
.57
7.04
1.38
2.23

2.97
3. 15
2.78
.45
.73
6. 17
.54
.57
4.91
7.85
7.85
2.68

1.52
.46

F-3


Table F2
Standardized Means {and SDs) 1 for Measures of Learning and Memory by Group over Time
Chemotherapy group

=16)

=16)

Time 1 (n = 30)

Time 2 (n = 30)

Time 3 (n = 29)

Time 1 (n = 15)

Time 2 (n

Name

Mean

50

Mean

50

Mean

50

M ea n

50

Mean

50

Mean

50

CFTdrrz

-0 .14

1.25

0.40

1.26

0.09

1.25

0.18

1.25

0.43

1.05

0.44

1.39

CFTirz

-0 .03

1.29

0.51

1.20

0.19

1.22

0.20

1.24

0.73

0.96

0.54

1.15

CFTrcz

-0 .01

1.15

-0 .21

1.07

-0 .01

1.21

-0 .04

1.12

-0.12

1.39

-0 .01

1.26

Catrcz

0.57

0.64

0.53

0.56

0.58

0.64

0.41

0.68

0.53

0.43

0.75

0.63

Ccorimz

0.63

0.93

0.64

0.85

0.90

0.92

0.39

0.91

0.33

0.92

1.01

1. 11

Ccorlcz

0.18

0.85

0.25

0.95

0.31

0.84

0.04

0.93

0.16

0. 77

0.16

1.00

Ccorlfz

0.17

0.99

-0.07

0.92

0.13

0.82

-0.11

0.87

0.03

0.62

0.22

0.89

Ccorscz

0.20

0.97

0.32

0.97

0.28

1. 11

0.13

0.95

0.19

1.09

0.25

1.17

Ccorsfz

0.20

0.89

0.32

1. 12

0.30

1. 12

0.03

0.78

0.16

0.81

0.41

1. 17

Ccort1 z

-0 .03

1. 10

0.00

0.86

0.44

1.08

-0.08

0.77

-0.28

0.98

0.53

1. 13

Ccort2z

0.30

0.76

0.32

0.83

0.83

0.91

0.25

0.94

0.03

1.09

0.94

1.18

Ccort3z

0.50

0.97

0.52

0.84

0.76

0.70

0.12

1.05

0.28

0.95

0 .72

1. 14

Ccort4z

0.35

1. 11

0.50

0.93

0.37

1.22

0.20

1.07

0.13

0. 70

0.44

1.00

Ccort5z

0.18

0.91

0.25

0.98

0.22

0.83

-0 .06

0. 77

0.25

0.66

0.44

0.70

Ccortbz

0.03

0.96

0.25

1.06

0.40

0.98

0.30

0.94

0.47

0.88

0.47

0.85

Ccrdz

0.30

0.84

0.30

1.06

0.01

1.28

0.07

0.94

0.19

1. 15

0.28

1. 14

Cdrdz

0.32

0.85

0.37

0.99

0.14

1. 17

0.03

0.92

0.25

0.95

0.41

1.00

Cfrdz

0.38

0.85

0.65

0.87

0.48

1. 14

0.20

0. 77

0.38

0.81

0.81

1.12

-0.17

1.00

0.08

0. 70

0.31

0. 79

-0 .28

0.65

0.25

0. 73

0.09

1.32

Cnrdz

0.17

0.77

0.38

0.60

0.32

1. 13

-0 .18

0.88

0.22

0. 75

0.66

0.47

Cprimpz

0.00

0.91

-0.08

0.82

-0 .23

0. 74

-0 .01

0.82

-0 .19

1.06

-0.22

0.75

Crdiimz

0.42

0.99

0 .72

0.97

0.64

1.33

0.29

0.90

0.34

0.98

0.91

1.25

Crdilcz

0.25

0.76

0.22

0.96

-0 .07

1. 13

-0 .10

0.99

-0.03

0.96

0.22

1.03

Crdilfz

0.25

0.79

0.25

0.83

0.13

0.90

-0 .24

0.65

0.16

0. 70

0.44

0.81

Crdiscz

0.33

0.86

0.38

0.99

0.07

1.31

0.20

0.98

0.31

1.21

0.28

1. 15

Crdisfz

0.32

1.07

0.57

1.26

0.13

1.52

0.01

0.90

0.19

0.95

0.56

1.22

Crdit5z

0.43

0.85

0.58

0.99

0.16

1. 13

0.02

0.89

0.34

0.92

0.56

0.93

Crdz

0.40

0.87

0.43

0.94

0.30

1. 18

0.23

0.82

0.13

0.90

0.56

1.22

Crecpz

-0.15

0.86

-0.25

0.63

-0.34

0.70

-0.07

0.81

-0.22

1.02

-0.22

1.10

Csbcbiz

0.52

1.09

0.75

1.16

0.96

1.48

0.07

0.95

0.38

0.59

1.03

1.38

Csecaimz

0.47

1.20

0.43

1.24

1.19

1.49

0.38

0.90

0.44

1. 14

0.84

1.25

Csecasfz

0.32

1.36

0.1 8

1.42

0.59

1.36

0.40

1.36

0.28

1.21

0.88

1.32

Csemca5z

0.17

1.36

0.22

1.49

0.52

1.27

-0 .07

0.97

0.13

1.32

0.59

1. 11

Csemcalfz

0.20

1.21

-0 .02

1.25

0.38

1. 12

0.17

0.84

0.22

0. 71

0.63

0.94

Csrdz

0.18

1.00

0.35

0.65

0.29

0.89

0.17

0.58

0.34

0.60

0.63

0.53

Cthitsz

-0 .20

0.78

-0 .12

0.72

-0 .12

1.09

-0 .40

0.66

-0 .16

0.63

0.16

0.44

Cmiddpz

1

No-chemotherapy group
Time 3 (n

Ctintz
Ctotslpza

0.02

0. 65

-0 .23

0. 75

0.68

1.66

0.26

1.24

0.00

1.37

0.09

1.45

0.21

1.45

0.23

1.23

0.32

1.91

-0 .09

0.80

0.23

0.85

0.04

1. 14

Ctrdz

0.32

0.98

0.62

0 77

0.65

1.05

0.08

0.80

0.59

0. 76

0.97

0.69

Ctrepz

0.22

0.88

0.15

0.83

-0 .16

0.75

0.03

0.87

0.19

0.70

0.28

1.03

VPAn1z

-0 .08

0.89

0.02

0.90

-0 .27

0.94

-0 .05

1.04

0.22

1. 17

0.13

1.24

VPAn2z

0.19

0.88

0.16

0.89

-0 .27

0.88

0.15

1. 14

0.05

1. 10

-0 .25

1.29

VPAnprtz

0.33

0.58

0.10

0.81

-0 .14

0.99

0.17

1.22

-0 .08

1. 13

-0 .32

1.45

VPAnt1z

0.0

1.03

0.01

0.89

-0 .21

0.81

-0.17

0.82

0.13

1.23

0.16

1.32

VPAnt2z

-0.13

0.84

0.12

1.02

-0 .31

0.88

-0 .12

1.02

0.30

1. 12

0.13

1.24

VPAnt3z

0.03

0.93

-0 .03

0.96

-0 .18

1.02

-0.15

1. 13

0.21

0.95

-0.02

1. 15

VPAnt4z

-0.09

1.03

0.09

0.86

-0.25

1. 12

-0.01

1.01

0.09

1. 12

0.13

0.90

VPAnlsz

0.02

1. 15

0.11

1.07

-0.11

1.00

-0.11

0.88

0.14

1.08

-0.04

0.67

PAL1Mza

0.16

1.07

-1 .31

1.00

-0.99

0.75

0.49

0.66

-0.95

1. 10

-0.56

0.83

PA LMESza*

0.28

0.85

-0 .63

1. 74

-0 .05

0.96

0.63

0.36

-0.42

1. 72

0.28

0.94

PA LMTSza

0.44

0. 71

-0.42

1.34

-0.06

1.06

0.78

0.30

0.02

0.93

0.28

0. 70

PALSC1za

0.26

1. 12

-2.66

0.65

-2 .71

0.59

0.47

0.62

-2.42

0.69

-2.42

0.65

PALTEza *

0.32

0. 73

0.20

0. 75

0.46

0.51

0.55

0.28

0.33

0. 74

0.66

0.42

PALTE6za *

0.29

1.05

0.4 1

0.50

0.36

0.60

0.50

0.36

0.58

0.37

0.56

0.29

PALTTza

0.49

0.67

1.19

0.69

1.37

0.61

0.70

0.29

1.25

0.61

1.45

0.47

PRMd ¾ cza

-0. 29

1.03

0.24

1.31

0.27

0.80

-0.36

0.89

0.31

0.82

0.20

1. 13

PRM i¾cza

0.69

0.85

0.94

0.62

0.94

0.63

0.67

0.87

0.71

0.91

0.82

0.76

SRM ¾corz

0. 34

0.73

-0 .38

1. 15

-0.28

1.04

0.16

0.63

-0.73

1. 19

-0 .39

0.93

Age -adjusted z-scores

F- 4

* These scores

showed non-random distribution in residuals and were later transformed .


### Table F3

**Latent Vector Loadings of the First Two Principal Components obtained from Principal Components Analysis of Learning and Memory Measures**

<table>
<thead>
<tr>
<th>Measure</th>
<th>PC 1 1</th>
<th>PC 2 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTdrrz</td>
<td>0.08201</td>
<td>0.13146</td>
</tr>
<tr>
<td>CFTirz</td>
<td>0.09445</td>
<td>0.11310</td>
</tr>
<tr>
<td>CFTcz</td>
<td>0.06702</td>
<td>0.19750</td>
</tr>
<tr>
<td>Catrcz</td>
<td>0.13726</td>
<td>-0.10704</td>
</tr>
<tr>
<td>Ccorimz</td>
<td>0.17184</td>
<td>-0.13802</td>
</tr>
<tr>
<td>Ccorcz</td>
<td>0.18189</td>
<td>0.02041</td>
</tr>
<tr>
<td>Ccorlfz</td>
<td>0.18309</td>
<td>-0.02926</td>
</tr>
<tr>
<td>Ccorscz</td>
<td>0.18113</td>
<td>-0.01588</td>
</tr>
<tr>
<td>Ccorsfz</td>
<td>0.19117</td>
<td>-0.07804</td>
</tr>
<tr>
<td>Ccort1z</td>
<td>0.07070</td>
<td>-0.13963</td>
</tr>
<tr>
<td>Ccort2z</td>
<td>0.11997</td>
<td>-0.11264</td>
</tr>
<tr>
<td>Ccort3z</td>
<td>0.15258</td>
<td>-0.12357</td>
</tr>
<tr>
<td>Ccort4z</td>
<td>0.16464</td>
<td>-0.10486</td>
</tr>
<tr>
<td>Ccort5z</td>
<td>0.18139</td>
<td>-0.10119</td>
</tr>
<tr>
<td>Ccortbz</td>
<td>0.07538</td>
<td>-0.02199</td>
</tr>
<tr>
<td>Ccrdz</td>
<td>0.19401</td>
<td>0.03719</td>
</tr>
<tr>
<td>Cdrdz</td>
<td>0.20170</td>
<td>0.01846</td>
</tr>
<tr>
<td>Cfrdz</td>
<td>0.20103</td>
<td>-0.07222</td>
</tr>
<tr>
<td>Cmiddpz</td>
<td>0.10726</td>
<td>-0.10124</td>
</tr>
<tr>
<td>Cnrdz</td>
<td>0.13301</td>
<td>0.00507</td>
</tr>
<tr>
<td>Cprimpz</td>
<td>-0.03037</td>
<td>0.08437</td>
</tr>
<tr>
<td>Crdiiimz</td>
<td>0.18994</td>
<td>-0.11867</td>
</tr>
<tr>
<td>Crdilcz</td>
<td>0.18335</td>
<td>0.04181</td>
</tr>
<tr>
<td>Crdilfz</td>
<td>0.19043</td>
<td>0.01131</td>
</tr>
<tr>
<td>Crdiscz</td>
<td>0.18530</td>
<td>0.02997</td>
</tr>
<tr>
<td>Crdisfz</td>
<td>0.18850</td>
<td>-0.04089</td>
</tr>
<tr>
<td>Cridtz</td>
<td>0.18663</td>
<td>-0.06629</td>
</tr>
<tr>
<td>Crdz</td>
<td>0.20941</td>
<td>-0.03731</td>
</tr>
<tr>
<td>Crecpz</td>
<td>-0.07832</td>
<td>0.02369</td>
</tr>
<tr>
<td>Csbbcz</td>
<td>0.13700</td>
<td>-0.04501</td>
</tr>
<tr>
<td>Csecaimz</td>
<td>0.15041</td>
<td>-0.14408</td>
</tr>
<tr>
<td>Csecafsz</td>
<td>0.16300</td>
<td>-0.10923</td>
</tr>
<tr>
<td>Csemca5z</td>
<td>0.12995</td>
<td>-0.14886</td>
</tr>
<tr>
<td>Csemcaifz</td>
<td>0.15621</td>
<td>-0.08119</td>
</tr>
<tr>
<td>Csrtdz</td>
<td>0.13722</td>
<td>0.02951</td>
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<tr>
<td>Cthitsz</td>
<td>0.12368</td>
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<tr>
<td>Ctrdz</td>
<td>-0.09441</td>
<td>-0.07408</td>
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<tr>
<td>Ctrotpza</td>
<td>0.10056</td>
<td>0.00009</td>
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<tr>
<td>Ctrdz</td>
<td>0.15094</td>
<td>0.02857</td>
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<tr>
<td>Ctrpz</td>
<td>-0.03792</td>
<td>-0.02589</td>
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<tr>
<td>VPAn1z</td>
<td>0.11188</td>
<td>0.22220</td>
</tr>
<tr>
<td>VPAn2z</td>
<td>0.10117</td>
<td>0.22482</td>
</tr>
<tr>
<td>VPAnprtz</td>
<td>0.07512</td>
<td>0.16340</td>
</tr>
<tr>
<td>VPAnt1z</td>
<td>0.08257</td>
<td>0.18924</td>
</tr>
<tr>
<td>VPAnt2z</td>
<td>0.11287</td>
<td>0.17229</td>
</tr>
<tr>
<td>VPAnt3z</td>
<td>0.10943</td>
<td>0.21177</td>
</tr>
<tr>
<td>VPAnt4z</td>
<td>0.08544</td>
<td>0.20421</td>
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<td>VPansz</td>
<td>0.05567</td>
<td>0.08863</td>
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<tr>
<td>PAL1Mza</td>
<td>0.01007</td>
<td>0.23639</td>
</tr>
<tr>
<td>PALMESza</td>
<td>0.05556</td>
<td>0.28915</td>
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<td>PALMTSza</td>
<td>0.04201</td>
<td>0.28564</td>
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<td>PALSC1za</td>
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<td>PALTE6za</td>
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<td>0.19614</td>
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<td>0.06068</td>
<td>0.29105</td>
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<tr>
<td>PALTtaza</td>
<td>0.06496</td>
<td>0.15501</td>
</tr>
<tr>
<td>PRMd%za</td>
<td>0.03790</td>
<td>0.04084</td>
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<tr>
<td>PRMi%za</td>
<td>0.04098</td>
<td>0.04174</td>
</tr>
<tr>
<td>SRM%orz</td>
<td>0.06374</td>
<td>0.16421</td>
</tr>
</tbody>
</table>

---

1 See Table F1a for measure details.  
2 First principal component accounts for 35% of variance.  
3 Second principal component accounts for 9.6% of variance.
**Figure F1.** Means (± SMD) of summary score and individual measures for verbal memory encoding over time by breast cancer treatment group.

Table F4

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Verbal Memory Encoding Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory encoding</td>
<td>Verbal</td>
<td>0.870</td>
<td></td>
<td>0.021*</td>
<td>0.093</td>
</tr>
<tr>
<td>Cnrdz(^a)</td>
<td>Encoding</td>
<td>Verbal</td>
<td>0.771</td>
<td>0.011*</td>
<td>0.039*</td>
</tr>
<tr>
<td>Csrdz(^b)</td>
<td>Encoding</td>
<td>Verbal</td>
<td>0.579</td>
<td>0.170</td>
<td>0.328</td>
</tr>
<tr>
<td>Cthitsz(^c)</td>
<td>Encoding</td>
<td>Verbal</td>
<td>0.782</td>
<td>0.395</td>
<td>0.164</td>
</tr>
<tr>
<td>Ctrdz(^d)</td>
<td>Encoding</td>
<td>Verbal</td>
<td>0.925</td>
<td>&lt;.001***</td>
<td>0.124</td>
</tr>
</tbody>
</table>

\(^a\)CVLT-2 novel recognition discriminability (hits v novel word distractors).
\(^b\)CVLT-2 source recognition discriminability (hits v List B distractors).
\(^c\)CVLT-2 recognition trial (total hits).
\(^d\)CVLT-2 total recognition discriminability (hits v total false positives).

*Significant at: *p < 0.05; ** p < 0.01; *** p < .001 (boldface).
Verbal immediate recall and learning

Figure F2a. Means (± SEM) of summary score and individual measures of verbal immediate memory and learning over time by breast cancer treatment group.

a CVLT-2 across trial recall consistency, t1-5.
b CVLT-2 average immediate recall, t1-5.
c CVLT-2 List A t1 correct.
d CVLT-2 List A t2 correct.
e CVLT-2 List A t3 correct.
Figure F2b. Mean z-scores (± SEM) for individual measures of verbal immediate memory and learning over time by breast cancer treatment group.

**f** CVLT-2 List A t4 correct. **g** CVLT-2 List A t5 correct. **h** CVLT-2 List B correct (interference trial).

**i** CVLT-2 % recall from middle region of list, t1-5. **j** CVLT-2 Immediate Recall Discriminability, t1-5.

**k** CVLT-2 Subjective Clustering Bidirectional (chance adj), t1-5.
Figure F2c. Mean z-scores (± SEM) for individual measures of verbal immediate memory and learning over time by breast cancer treatment group.

CVLT-2 Semantic clustering (chance adj) t1-5. CVLT Semantic clustering (chance adj), Short Delay free recall. CVLT Semantic clustering (chance adj), t5. CVLT Semantic clustering (chance adj), Long Delay free recall.
Table F6

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Verbal Immediate Memory and Learning Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
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</thead>
<tbody>
<tr>
<td>Catrica</td>
<td>Immediate Recall</td>
<td>Verbal</td>
<td>0.767</td>
<td>&lt;.001***</td>
<td>0.406</td>
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<tr>
<td>Cconimz</td>
<td>Immediate recall</td>
<td>Verbal</td>
<td>0.978</td>
<td>0.345</td>
<td>0.225</td>
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<tr>
<td>Ccort1z</td>
<td>Immediate word span</td>
<td>Verbal</td>
<td>0.580</td>
<td>0.003**</td>
<td>0.169</td>
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<tr>
<td>Ccort2z</td>
<td>Immediate recall</td>
<td>Verbal</td>
<td>0.751</td>
<td>&lt;.001***</td>
<td>0.554</td>
</tr>
<tr>
<td>Ccort3z</td>
<td>Immediate recall</td>
<td>Verbal</td>
<td>0.754</td>
<td>&lt;.001***</td>
<td>0.332</td>
</tr>
<tr>
<td>Ccort4z</td>
<td>Immediate recall</td>
<td>Verbal</td>
<td>0.367</td>
<td>0.007**</td>
<td>0.424</td>
</tr>
<tr>
<td>Ccort5z</td>
<td>Immediate recall</td>
<td>Verbal</td>
<td>0.537</td>
<td>0.854</td>
<td>0.473</td>
</tr>
<tr>
<td>Ccortbzh</td>
<td>Immediate recall</td>
<td>Verbal</td>
<td>0.967</td>
<td>0.252</td>
<td>0.227</td>
</tr>
<tr>
<td>Cmidddz</td>
<td>Learning strategy</td>
<td>Visual</td>
<td>0.429</td>
<td>0.161</td>
<td>0.819</td>
</tr>
<tr>
<td>Crdiimz</td>
<td>Recall accuracy</td>
<td>Visual</td>
<td>0.790</td>
<td>0.068</td>
<td>0.134</td>
</tr>
<tr>
<td>Csbcbiz</td>
<td>Learning strategy</td>
<td>Verbal</td>
<td>0.355</td>
<td>0.013*</td>
<td>0.443</td>
</tr>
<tr>
<td>Csecaimz</td>
<td>Learning strategy</td>
<td>Verbal</td>
<td>0.647</td>
<td>&lt;.001***</td>
<td>0.643</td>
</tr>
<tr>
<td>Csecasfz</td>
<td>Learning strategy</td>
<td>Verbal</td>
<td>0.660</td>
<td>0.045*</td>
<td>0.846</td>
</tr>
<tr>
<td>Csemca5z</td>
<td>Learning strategy</td>
<td>Verbal</td>
<td>0.789</td>
<td>0.068</td>
<td>0.767</td>
</tr>
<tr>
<td>Csecaelfz</td>
<td>Learning strategy</td>
<td>Verbal</td>
<td>0.599</td>
<td>0.028*</td>
<td>0.627</td>
</tr>
</tbody>
</table>

*CVLT-2 across trial recall consistency, (t1-5).  †CVLT-2 average immediate recall, t1-5.
‡CVLT-2 List A t1 correct.  §CVLT-2 List A t2 correct.  ‡CVLT-2 List A t3 correct.
| CVLT-2 List A t4 correct.  ^CVLT-2 List A t5 correct.  ‡CVLT-2 List B correct (interference trial).  
CVLT-2 % recall from middle region of list, t1-5.  †CVLT-2 Immediate Recall Discriminability, t1-5.
| CVLT-2 Subjective Clustering Bidirectional (chance adj), t1-5.  ‡CVLT-2 Semantic clustering (chance adj) t1-5.  ‡CVLT Semantic clustering (chance adj), Short Delay free recall
| CVLT Semantic clustering (chance adj), t5.  ‡CVLT Semantic clustering (chance adj), Long Delay free recall.

*Significant at:  *p < 0.05;  **p < 0.01;  ***p < .001 (boldface).
Figure F3. Means (± SEM) of summary score and individual measures for verbal delayed recall over time by breast cancer treatment group.

aCVLT-2 long delayed cued recall, total correct. bCVLT-2 long delayed free recall, total correct. cCVLT-2 short delayed cued recall, total correct. dCVLT-2 short delayed free recall, total correct.
### Table F7

**P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Verbal Delayed Recall Grouping and Individual Measures**

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal delayed recall</td>
<td>Verbal delayed recall</td>
<td>Verbal</td>
<td>0.742</td>
<td>0.547</td>
<td>0.777</td>
</tr>
<tr>
<td>Ccortcz&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Delayed recall (long delay, cued)</td>
<td>Verbal</td>
<td>0.583</td>
<td>0.541</td>
<td>0.963</td>
</tr>
<tr>
<td>Ccorlfz&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Delayed recall (long delay, free)</td>
<td>Verbal</td>
<td>0.897</td>
<td>0.340</td>
<td>0.299</td>
</tr>
<tr>
<td>Ccorscz&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Delayed recall (short delay, cued)</td>
<td>Verbal</td>
<td>0.779</td>
<td>0.799</td>
<td>0.951</td>
</tr>
<tr>
<td>Ccorflsfz&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Delayed recall (short delay, free)</td>
<td>Verbal</td>
<td>0.771</td>
<td>0.421</td>
<td>0.615</td>
</tr>
</tbody>
</table>

<sup>a</sup>CVLT-2 long delayed cued recall, total correct.  
<sup>b</sup>CVLT-2 long delayed free recall, total correct.  
<sup>c</sup>CVLT-2 short delayed cued recall, total correct.  
<sup>d</sup>CVLT-2 short delayed free recall, total correct.
**Figure F4a.** Means (± SEM) of summary score and individual measures for verbal recall discriminability over time by breast cancer treatment group.

- CVLT-2 cued recall discriminability (List A v Intrusions, cued recall trials).
- CVLT-2 delayed recall discriminability.
- CVLT-2 free recall discriminability (List A v Intrusions, free recall trials).
- CVLT-2 recall discriminability, Trial 5.
- CVLT-2 recall discriminability, long delay cued recall.
Figure F4b. Mean z-scores (± SMD) of individual measures for verbal recall discriminability over time by breast cancer treatment group.

1CVLT-2 recall discriminability, long delay free recall. 2CVLT-2 recall discriminability, short delay cued recall. 3CVLT-2 recall discriminability, short delay free recall. 4CVLT-2 total recall discriminability (List A, All trials vs total intrusions).
Table F8

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Verbal Recall Discriminability Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Variable ID</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal recall discriminability</td>
<td>Verbal recall discriminability</td>
<td>Verbal</td>
<td>0.807</td>
<td>0.623</td>
<td>0.038*</td>
</tr>
<tr>
<td>Ccrdz$^a$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.935</td>
<td>0.509</td>
<td>0.208</td>
</tr>
<tr>
<td>Cdrdz$^b$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.858</td>
<td>0.663</td>
<td>0.122</td>
</tr>
<tr>
<td>Cfrdz$^c$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.838</td>
<td>0.074</td>
<td>0.065</td>
</tr>
<tr>
<td>Crdit5z$^d$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.765</td>
<td>0.344</td>
<td>0.045*</td>
</tr>
<tr>
<td>Crdilcz$^e$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.696</td>
<td>0.685</td>
<td>0.056</td>
</tr>
<tr>
<td>Crdifz$^f$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.661</td>
<td>0.341</td>
<td>0.006**</td>
</tr>
<tr>
<td>Crdiscz$^g$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>1.000</td>
<td>0.402</td>
<td>0.554</td>
</tr>
<tr>
<td>Crdisfz$^h$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.781</td>
<td>0.446</td>
<td>0.066</td>
</tr>
<tr>
<td>Crdz$^i$</td>
<td>Recall discriminability</td>
<td>Verbal</td>
<td>0.795</td>
<td>0.864</td>
<td>0.069</td>
</tr>
</tbody>
</table>

$^a$CVLT-2 cued recall discriminability (List A v Intrusions, cued recall trials).
$^b$CVLT-2 delayed recall discriminability
$^c$CVLT-2 free recall discriminability (List A v Intrusions, free recall trials).
$^d$CVLT-2 recall discriminability, Trial 5
$^e$CVLT-2 recall discriminability, long delay cued recall.
$^f$CVLT-2 recall discriminability, long delay free recall.
$^g$CVLT-2 recall discriminability, short delay cued recall.
$^h$CVLT-2 recall discriminability, short delay free recall.
$^i$CVLT-2 total recall discriminability (List A, All trials v total intrusions).

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).
Verbal primacy/recency and recall errors

Figure F5. Means (± SEM) of summary score and individual measures for verbal primacy/recency and recall errors over time by breast cancer treatment group.

aCVLT-2 % Recall from Recency Region of Word List. bCVLT-2 % Recall from Primacy Region of Word List. cCVLT-2 total intrusions. dCVLT-2 total repetitions
Table F9

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Verbal Primacy/Recency and Recall Errors Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal primacy/recency recall and recall errors</td>
<td>Verbal primacy/recency recall</td>
<td>0.800</td>
<td>0.967</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>Crecepz^a</td>
<td>Recency recall</td>
<td>Verbal</td>
<td>0.704</td>
<td>0.417</td>
<td>0.952</td>
</tr>
<tr>
<td>Cprimpzb</td>
<td>Primacy recall</td>
<td>Verbal</td>
<td>0.901</td>
<td>0.242</td>
<td>0.895</td>
</tr>
<tr>
<td>Cintzc</td>
<td>Errors (intrusions)</td>
<td>Verbal</td>
<td>0.908</td>
<td>0.005**</td>
<td>0.059</td>
</tr>
<tr>
<td>Ctrepz^d</td>
<td>Errors (perseverative)</td>
<td>Verbal</td>
<td>0.600</td>
<td>0.444</td>
<td>0.137</td>
</tr>
</tbody>
</table>

^aCVLT-2 % Recall from Recency Region of Word List. ^bCVLT-2 % Recall from Primacy Region of Word List. ^cCVLT-2 total intrusions. ^dCVLT-2 total repetitions

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).
Figure F6. Means (± SMD) of summary score and individual measures for visuospatial memory encoding over time by breast cancer treatment group.

Table F10

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Visuospatial Memory Encoding Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visuospatial memory encoding</td>
<td>Visuospatial</td>
<td>0.719</td>
<td>&lt;.001***</td>
<td>0.969</td>
<td></td>
</tr>
<tr>
<td>SRM%corz(^a)</td>
<td>Encoding</td>
<td>0.423</td>
<td>&lt;.001***</td>
<td>0.730</td>
<td></td>
</tr>
<tr>
<td>CFTrcz(^b)</td>
<td>Encoding</td>
<td>0.944</td>
<td>0.578</td>
<td>0.946</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)CANTAB Spatial recognition memory % correct. \(^{b}\)Complex figure test, recognition trial, total correct.

*Significant at: *\(p<0.05\); **\(p<0.01\); ***\(p<0.001\) (boldface).
Figure F7. Means (± SMD) of summary score and individual measures for visuospatial span over time by breast cancer treatment group.

Table F11

*P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Visuospatial Span Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visuospatial span performance</td>
<td>Visuospatial</td>
<td>0.034*</td>
<td>&lt;.001***</td>
<td>0.971</td>
<td></td>
</tr>
<tr>
<td>PALSC1za&lt;sup&gt;a&lt;/sup&gt;</td>
<td>First trial performance</td>
<td>Visuospatial</td>
<td>0.035*</td>
<td>&lt;.001***</td>
<td>0.982</td>
</tr>
<tr>
<td>PAL1Mza&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Visuospatial span</td>
<td>Visuospatial</td>
<td>0.062</td>
<td>&lt;.001***</td>
<td>0.970</td>
</tr>
</tbody>
</table>

<sup>a</sup>CANTAB PAL Stages completed on first trial (adjusted). <sup>b</sup>CANTAB PAL First trial total correct (visuospatial span).

*Significant at: *p < 0.05; **p < 0.01; ***p < 0.001 (boldface).
Verbal paired associates learning

Figure F8a. Means (± SEM) of summary score and individual measures for verbal paired associates learning over time by breast cancer treatment group.

a Verbal paired associates (names) (VPAn), t1-4 Immediate recall.
b VPAn, Long delay, total correct.
c Verbal paired associates (names), % Retention.
d Verbal paired associates (names), t2 total correct.
e Verbal paired associates (names), t1 total correct.
Figure F8b. Mean (± SEM) z-scores of individual measures for verbal paired associates learning over time by breast cancer treatment group.

- Verbal paired associate (names), t3 total correct.
- Verbal paired associate (names), t4 total correct.
- Verbal paired associate (names), Learning slope (adjusted for ceiling and t1 correct).

Table F12

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Verbal Paired Associates Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name Function</th>
<th>Visual / Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal paired associates learning</td>
<td>Verbal</td>
<td>0.658</td>
<td>0.054</td>
<td>0.480</td>
</tr>
<tr>
<td>VPA, t3z</td>
<td>Immediate Recall</td>
<td>Verbal</td>
<td>0.455</td>
<td>0.171</td>
</tr>
<tr>
<td>VPA, t2z</td>
<td>Delayed recall</td>
<td>Verbal</td>
<td>0.876</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>VPA, prtz</td>
<td>Retention</td>
<td>Verbal</td>
<td>0.446</td>
<td><strong>0.041</strong></td>
</tr>
<tr>
<td>VPA, t1z</td>
<td>First trial recall</td>
<td>Verbal</td>
<td>0.665</td>
<td>0.702</td>
</tr>
<tr>
<td>VPA, t2z</td>
<td>Immediate Recall</td>
<td>Verbal</td>
<td>0.223</td>
<td>0.175</td>
</tr>
<tr>
<td>VPA, t3z</td>
<td>Immediate Recall</td>
<td>Verbal</td>
<td>0.777</td>
<td>0.416</td>
</tr>
<tr>
<td>VPA, t4z</td>
<td>Immediate Recall</td>
<td>Verbal</td>
<td>0.557</td>
<td>0.378</td>
</tr>
<tr>
<td>VPA, tsz</td>
<td>Learning slope</td>
<td>Verbal</td>
<td>0.960</td>
<td>0.515</td>
</tr>
</tbody>
</table>

*Verbal paired associate (names) (VPA), t1-4 Immediate recall, VPA, Long delay, total correct. **Verbal paired associate (names), % Retention. ***Verbal paired associate (names), t1 total correct. ****Verbal paired associate (names), t2 total correct. ****Verbal paired associate (names), t3 total correct. *****Verbal paired associate (names), t4 total correct. ******Verbal paired associate (names), Learning slope (adjusted for ceiling and t1 correct).

*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).
Figure F9. Means (± SMD) of summary score and individual measures for visual paired associates learning over time by breast cancer treatment group.

a CANTAB Paired Associates Learning (PAL) Mean errors to success (LOG).
b CANTAB PAL Total errors, 6 shapes (LOG).
c CANTAB PAL Total errors (adjusted) (LOG).
d CANTAB PAL Mean trials to success (adjusted).

RL = Natural log transformation with reflection conducted on data to correct for skew and non-random distribution in residuals prior to ANOVA.
Table F13

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Visual Paired Associates Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual paired associate learning</td>
<td>Paired associates learning/recall</td>
<td>Visual spatial</td>
<td>0.176</td>
<td><strong>0.003</strong></td>
<td>0.976</td>
</tr>
<tr>
<td>PALMESza(^a)</td>
<td>Paired associates</td>
<td>Visual spatial</td>
<td>0.247</td>
<td>&lt;.001***</td>
<td>0.866</td>
</tr>
<tr>
<td>PALTE6za(^b)</td>
<td>Paired associates</td>
<td>Visual spatial</td>
<td>0.240</td>
<td>0.891</td>
<td>0.928</td>
</tr>
<tr>
<td>PALTEza(^c)</td>
<td>Paired associates</td>
<td>Visual spatial</td>
<td>0.256</td>
<td>0.011*</td>
<td>0.858</td>
</tr>
<tr>
<td>PALMTSza(^d)</td>
<td>Paired associates</td>
<td>Visual spatial</td>
<td>0.113</td>
<td>&lt;.001***</td>
<td>0.937</td>
</tr>
</tbody>
</table>

\(^a\)CANTAB Paired Associates Learning (PAL) Mean errors to success (LOG). \(^b\)CANTAB PAL Total errors, 6 shapes (LOG). \(^c\)CANTAB PAL Total errors (adjusted) (LOG). \(^d\)CANTAB PAL Mean trials to success (adjusted).

*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).
Figure F10. Means (± SD) of summary score and individual measures for visual memory over time by breast cancer treatment group.

aComplex figure test, long delay, total correct. bComplex figure test, short delay (3 minutes), total correct. cCANTAB Pattern recognition memory (immediate) % correct. dCANTAB Paired associate learning, total trials completed (adjusted). eCANTAB Pattern recognition memory (delayed) % correct.
Table F14

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Visual Memory Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual memory</td>
<td></td>
<td>Visuospatial</td>
<td>0.590</td>
<td>&lt;.001***</td>
<td>0.719</td>
</tr>
<tr>
<td>CFTdrzz&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Recall (LD)</td>
<td>Visuospatial</td>
<td>0.503</td>
<td>0.018**</td>
<td>0.528</td>
</tr>
<tr>
<td>CFTirz&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Recall (SD)</td>
<td>Visuospatial</td>
<td>0.424</td>
<td>0.002**</td>
<td>0.878</td>
</tr>
<tr>
<td>PRMi%cza&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Recog. memory (IR)</td>
<td>Visual</td>
<td>0.480</td>
<td>0.249</td>
<td>0.762</td>
</tr>
<tr>
<td>PALTtza&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Learning and recall</td>
<td>Visuospatial</td>
<td>0.432</td>
<td>&lt;.001***</td>
<td>0.729</td>
</tr>
<tr>
<td>PRMd%cza&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Recog. memory (LD)</td>
<td>Visual</td>
<td>0.919</td>
<td>0.001***</td>
<td>0.909</td>
</tr>
</tbody>
</table>

SD = Short delay. LD = Long delay. IR = Immediate recall.
<sup>a</sup>Complex figure test, long delay, total correct. <sup>b</sup>Complex figure test, short delay (3 minutes), total correct. <sup>c</sup>CANTAB Pattern recognition memory (immediate) % correct. <sup>d</sup>CANTAB Paired associate learning, total trials completed (adjusted). <sup>e</sup>CANTAB Pattern recognition memory (delayed) % correct.
<sup>*</sup>Significant at: *p < 0.05; ** p < 0.01; *** p < .001 (boldface).
Appendix G

Individual measures results

Executive functions

In Appendix G are presented the means and standard deviations for both raw scores and standardized scores for each measure of executive functions (Tables G1b and G2). Also included are the latent vector loadings for the first two principal components from the Principal Components Analysis of all measures within the Executive Functions domain (Table G3). Individual measures use age-standardized z-scores derived from relevant test norms. Figures and p-value summary tables are presented that were obtained from individual ANOVAs adjusted for between and within subject variation. The performance profile of the summary measure for each grouping (name italicized) in Executive Functions is compared with each of the individual measures that contribute to that grouping.
Table G1a

**Variable Names for Measures of Executive Functions**

<table>
<thead>
<tr>
<th>Variable ID</th>
<th>Test</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTcorg6z</td>
<td>CFT</td>
<td>CFT organization</td>
</tr>
<tr>
<td>CFTcytza</td>
<td>CFT</td>
<td>CFT Copy time</td>
</tr>
<tr>
<td>IEDEDSEz</td>
<td>CANTAB</td>
<td>IED Extra-dimensional (ED) shift</td>
</tr>
<tr>
<td>IEDSCmz</td>
<td>CANTAB</td>
<td>IED stages completed</td>
</tr>
<tr>
<td>IEDTEaz</td>
<td>CANTAB</td>
<td>IED total errors (adjusted)</td>
</tr>
<tr>
<td>IEDTTaz</td>
<td>CANTAB</td>
<td>IED total trials (adjusted)</td>
</tr>
<tr>
<td>IEDpDEEz</td>
<td>CANTAB</td>
<td>IED pre-ED shift errors</td>
</tr>
<tr>
<td>SOCMi3za</td>
<td>CANTAB</td>
<td>SOC initial planning speed (3 moves)</td>
</tr>
<tr>
<td>SOCMi4za</td>
<td>CANTAB</td>
<td>SOC initial planning speed (4 moves)</td>
</tr>
<tr>
<td>SOCMi5za</td>
<td>CANTAB</td>
<td>SOC initial planning speed (5 moves)</td>
</tr>
<tr>
<td>SOCMm5za</td>
<td>CANTAB</td>
<td>SOC mean moves (5 moves)</td>
</tr>
<tr>
<td>SOCMs5za</td>
<td>CANTAB</td>
<td>SOC subsequent planning speed (5 moves)</td>
</tr>
<tr>
<td>SOCPmiza</td>
<td>CANTAB</td>
<td>SOC problems solved in minimum moves</td>
</tr>
<tr>
<td>SWMBE8za</td>
<td>CANTAB</td>
<td>SWM Between errors (8 boxes)</td>
</tr>
<tr>
<td>SWMBEza</td>
<td>CANTAB</td>
<td>SWM Between errors</td>
</tr>
<tr>
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<td>CANTAB</td>
<td>SWM Double errors (8 boxes)</td>
</tr>
<tr>
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<td>CANTAB</td>
<td>SWM Double errors</td>
</tr>
<tr>
<td>SWMStrza</td>
<td>CANTAB</td>
<td>SWM Strategy</td>
</tr>
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<td>SWM Total errors</td>
</tr>
<tr>
<td>SWMW8eza</td>
<td>CANTAB</td>
<td>SWM Within errors (8 boxes)</td>
</tr>
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<td>CANTAB</td>
<td>SWM Within errors (WE)</td>
</tr>
<tr>
<td>VFcspsz</td>
<td>D-KEFS</td>
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<td>D-KEFS</td>
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<td>D-KEFS</td>
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</tr>
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</tr>
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<td>Vfslez</td>
<td>D-KEFS</td>
<td>VF set loss errors</td>
</tr>
<tr>
<td>cw3iz</td>
<td>D-KEFS</td>
<td>CWI inhibition speed</td>
</tr>
<tr>
<td>cw4isz</td>
<td>D-KEFS</td>
<td>CWI inhibition/switching speed</td>
</tr>
<tr>
<td>cwistez</td>
<td>D-KEFS</td>
<td>CWI inhibition errors</td>
</tr>
<tr>
<td>cwitez</td>
<td>D-KEFS</td>
<td>CWI inhibition/switching errors</td>
</tr>
</tbody>
</table>

1Complex figure test. 2Intra-Extra Dimensional Shift. 3Stockings of Cambridge. 4Spatial Working Memory. 5Verbal Fluency. 6Color-Word Interference.
Table G1b

Raw Score Means (and SDs)\(^1\) for Measures of Executive Functions by Group over Time

<table>
<thead>
<tr>
<th>Name(^2)</th>
<th>Chemotherapy group</th>
<th>No-chemotherapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1 (n = 30)</td>
<td>Time 2 (n = 30)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>CFTclys</td>
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<td>CFTcys7</td>
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<tr>
<td>IEDEDSE</td>
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<td>9.32</td>
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<td>IEDSm</td>
<td>8.48</td>
<td>0.83</td>
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<tr>
<td>IEDTea</td>
<td>26.69</td>
<td>19.7</td>
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<tr>
<td>IEDTta</td>
<td>98.72</td>
<td>34.9</td>
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<tr>
<td>IEDPDE</td>
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<td>7.35</td>
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<td>5654</td>
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<td>9092</td>
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<td>15035</td>
<td>10821</td>
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<td>SOCMMv5</td>
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<td>SOCMMst</td>
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<td>5300</td>
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<td>SOCpmin</td>
<td>9.13</td>
<td>1.83</td>
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<td>2.19</td>
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<td>SWMBME</td>
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<td>VFCsps</td>
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<td>VFHctcs</td>
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<td>Vfiers</td>
<td>1.77(^4)</td>
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<td>VFslers</td>
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<tr>
<td>CW3irs(^3)</td>
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<td>CW4irs(^3)</td>
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<tr>
<td>Cwisters</td>
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</table>

\(^1\) Raw scores based on scoring guides in test manuals.
\(^2\) Descriptive names in the same order are presented in Table E1a.
\(^3\) Measured in seconds. \(^4\) Measured in milliseconds.
Where data missing on measure: \(^6\) n = 27; \(^5\) n = 29; \(^7\) n = 28; \(^8\) n = 14.

G-3
### Table G2

Standardized Means (and SDs) for Measures of Executive Functions by Group over Time

<table>
<thead>
<tr>
<th>Name</th>
<th>Chemotherapy group</th>
<th>No-chemotherapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1 (n = 30)</td>
<td>Time 2 (n = 30)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>CFTcorg6z</td>
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<td>0.84</td>
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<tr>
<td>CFTcyt2za</td>
<td>0.92</td>
<td>0.66</td>
</tr>
<tr>
<td>IEDED5Ez</td>
<td>-0.20</td>
<td>1.26</td>
</tr>
<tr>
<td>IEDSCmz</td>
<td>-0.12</td>
<td>0.79</td>
</tr>
<tr>
<td>IEDTEaz</td>
<td>-0.06</td>
<td>0.71</td>
</tr>
<tr>
<td>IEDTAz</td>
<td>-0.13</td>
<td>0.76</td>
</tr>
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<td>IEDpDEez</td>
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<td>SOCMM3za</td>
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<tr>
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<td>1.00</td>
</tr>
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<tr>
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<td>0.47</td>
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<tr>
<td>cwitez</td>
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1. Age standardized z-scores based on relevant test norms.
2. Descriptive names in the same order are presented in Table E1a.
Where data missing on measure: a n = 27, b n = 29, c n = 28, d n = 14.
Table G3

**Latent Vector Loadings of the First Two Principal Components obtained from Principal Components Analysis of All Measures of Executive Functions**

<table>
<thead>
<tr>
<th>Measurea</th>
<th>PC 1(^1)</th>
<th>PC 2(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTcorgöz</td>
<td>0.06432</td>
<td>0.03176</td>
</tr>
<tr>
<td>CFTcytza</td>
<td>-0.01361</td>
<td>-0.02532</td>
</tr>
<tr>
<td>IEDDSEz</td>
<td>0.03151</td>
<td>-0.02158</td>
</tr>
<tr>
<td>IEDSCmz</td>
<td>0.22049</td>
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</tr>
<tr>
<td>IEDTEaz</td>
<td>0.21895</td>
<td>-0.32090</td>
</tr>
<tr>
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<td>0.18634</td>
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<tr>
<td>IEDpEDEz</td>
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<tr>
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<td>0.09225</td>
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<td>SOCMi5za</td>
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<tr>
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<td>0.07914</td>
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<td>SOCMS5za</td>
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<tr>
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<td>0.10343</td>
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<td>0.31998</td>
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<td>0.32236</td>
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<td>0.32205</td>
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<tr>
<td>cwitez</td>
<td>0.00636</td>
<td>0.21266</td>
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\(^1\)Descriptive names in same order are presented in Table E1a.

\(^2\)First principal component (accounts for 21% of variance). Second principal component (accounts for 11% of variance)
Figure G1a. Means (± SEM) of summary score and individual measures of verbal fluency, flexibility and reasoning over time by breast cancer treatment group.

*a Verbal Fluency (VF) Letter Fluency Total Correct. bVF Category Switching Percent Switching.

*VF Category Switching Total Correct. cVF Category Switching Total Switching. dVF Total set-loss errors. eVRz
Figure G1b. Mean z-scores (± SEM) for individual measure of verbal fluency, flexibility and reasoning over time by breast cancer treatment group.

Table G4

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Verbal Fluency, Flexibility and Reasoning Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency, Flexibility and Reasoning</td>
<td>Verbal</td>
<td>0.032*</td>
<td>0.054</td>
<td>0.154</td>
</tr>
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<td>aVF1ftcz</td>
<td>Verbal</td>
<td>0.025*</td>
<td>0.394</td>
<td>0.466</td>
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<tr>
<td>bVFcspz</td>
<td>Verbal</td>
<td>0.217</td>
<td>&lt;.001***</td>
<td>0.301</td>
</tr>
<tr>
<td>cVFcstcz</td>
<td>Verbal</td>
<td>0.175</td>
<td>0.006**</td>
<td>0.363</td>
</tr>
<tr>
<td>dVFcstsz</td>
<td>Verbal</td>
<td>0.129</td>
<td>0.433</td>
<td>0.363</td>
</tr>
<tr>
<td>eVFslez</td>
<td>Verbal</td>
<td>0.905</td>
<td>0.113</td>
<td>0.138</td>
</tr>
<tr>
<td>fVRz</td>
<td>Verbal</td>
<td>0.014*</td>
<td>0.001***</td>
<td>0.777</td>
</tr>
</tbody>
</table>

aVerbal Fluency (VF) Letter Fluency Total Correct. bVF Category Switching Percent Switching. 
 cVF Category Switching Total Correct. dVF Category Switching Total Switching. 
 eVF Total set-loss errors. fVerbal reasoning total score. 

*Significant at: *p < 0.05; ** p < 0.01; *** p <.001 (boldface).
Figure G2. Means (± SEM) of summary score and individual measures of verbal inhibition over time by breast cancer treatment group.

- a Color-word interference (CWI) trial 3 inhibition total correct.
- b CWI trial 4 inhibition/switching total correct.
- c CWI trial 4 total errors.
- d CWI trial 3 total errors.
Table G5

*P* values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Verbal Inhibition Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition</td>
<td>Verbal-visual</td>
<td>0.388</td>
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<td>0.441</td>
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<tr>
<td>cw3iz</td>
<td>Verbal-visual</td>
<td>0.543</td>
<td>0.883</td>
<td>0.505</td>
</tr>
<tr>
<td>cw4iz</td>
<td>Verbal-visual</td>
<td>0.534</td>
<td>0.211</td>
<td>0.327</td>
</tr>
<tr>
<td>cwistez</td>
<td>Verbal-visual</td>
<td>0.140</td>
<td>0.771</td>
<td>0.637</td>
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<tr>
<td>cwitez</td>
<td>Verbal-visual</td>
<td>0.666</td>
<td>0.110</td>
<td>0.227</td>
</tr>
</tbody>
</table>

*a* Color-word interference trial 3 inhibition total correct.

*b* Color-word interference trial 4 inhibition/switching total correct.

*c* Color-word interference trial 4 total errors.

*d* Color-word interference trial 3 total errors.
Figure G3a. Means (± SEM) of summary score and individual measures of planning and strategy over time by breast cancer treatment group.

1 Complex Figure Test total organization score. 2 ED Extra Dimensional Shift Total Errors.
3 Stockings of Cambridge (SOC) mean moves (5 move problems).
4 SOC mean subsequent move (after initial move) planning time (5 move problem). 5 SOC problems solved in minimum moves.

6 SWMStrza 7 Vfrez
Figure G3b. Mean z-scores (± SEM) for individual measure of planning and strategy over time by breast cancer treatment group.

Table G6

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning and strategy</td>
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<td></td>
<td>0.003**</td>
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<tr>
<td>CFTcorg6z</td>
<td>Visuospatial</td>
<td>0.955</td>
<td>0.233</td>
<td>0.907</td>
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<tr>
<td>IEDEDSez</td>
<td>Visual</td>
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<td>0.228</td>
<td>0.823</td>
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<tr>
<td>SOCMMm5za</td>
<td>Visual</td>
<td>0.038*</td>
<td>0.190</td>
<td>0.385</td>
</tr>
<tr>
<td>SOCMs5za</td>
<td>Visual</td>
<td>0.199</td>
<td>0.057</td>
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<tr>
<td>SOCpmiza</td>
<td>Visual</td>
<td>0.720</td>
<td>0.003**</td>
<td>0.074</td>
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<td>Visuospatial</td>
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<td>0.137</td>
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<tr>
<td>Vfrez</td>
<td>Verbal-visual</td>
<td>0.543</td>
<td></td>
<td>0.021*</td>
</tr>
</tbody>
</table>

*a Complex Figure Test total organization score. *b IED Extra Dimensional Shift Total Errors.

c Stockings of Cambridge (SOC) mean moves (5 move problems).
d SOC mean subsequent planning time (5 move problem). e SOC problems solved in minimum moves.
f Spatial Working Memory (SWM) strategy score. g Verbal Fluency total repetition errors.

*Significant at: *p < 0.05; **p < 0.01; ***p< .001 (boldface).
Figure G4a. Means (± SEM) of summary score and individual measures of spatial working memory over time by breast cancer treatment group.

a SWM between errors. b SWM between errors at 8 box (highest) level.
c SWM double errors. d SWM double errors at 8 box (highest) level. e SWM total errors.
Figure G4b. Mean z-scores (± SEM) for individual measure of spatial working memory over time by breast cancer treatment group.

Table G7

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Spatial Working Memory Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial working memory</td>
<td>Visuospatial</td>
<td>0.390</td>
<td>0.940</td>
<td>0.819</td>
</tr>
<tr>
<td>³SWMBEza</td>
<td>Visuospatial</td>
<td>0.330</td>
<td>0.428</td>
<td>0.490</td>
</tr>
<tr>
<td>⁴SWMBE8za</td>
<td>Visuospatial</td>
<td>0.227</td>
<td>0.539</td>
<td>0.339</td>
</tr>
<tr>
<td>⁵SWMDEza</td>
<td>Visuospatial</td>
<td>0.449</td>
<td>0.883</td>
<td>0.438</td>
</tr>
<tr>
<td>⁶SWMDE8za</td>
<td>Visuospatial</td>
<td>0.637</td>
<td>0.712</td>
<td>0.366</td>
</tr>
<tr>
<td>⁷SWMTEza</td>
<td>Visuospatial</td>
<td>0.519</td>
<td>0.385</td>
<td>0.574</td>
</tr>
<tr>
<td>⁸SWMWEza</td>
<td>Visuospatial</td>
<td>0.398</td>
<td>0.890</td>
<td>0.459</td>
</tr>
<tr>
<td>⁹SWMWE8za</td>
<td>Visuospatial</td>
<td>0.617</td>
<td>0.726</td>
<td>0.293</td>
</tr>
</tbody>
</table>

³Spatial Working Memory (SWM) between errors. ⁴SWM between errors at 8 box (highest) level.
⁵SWM double errors. ⁶SWM double errors at 8 box (highest) level. ⁷SWM total errors.
⁸SWM within errors. ⁹SWM within errors at 8 box (highest) level.
Figure G5. Means (± SEM) of summary score and individual measures of cognitive flexibility over time by breast cancer treatment group.

*aED pre-Extra dimensional shift total errors. bED Mean Stages Completed. cED Total errors (adjusted). dED Total trials (adjusted).
Table G8

P values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Cognitive Flexibility Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive flexibility</td>
<td>Visual</td>
<td>0.496</td>
<td><strong>0.031</strong></td>
<td>0.130</td>
</tr>
<tr>
<td>a^IEDpEDSez</td>
<td>Visual</td>
<td>0.395</td>
<td><strong>0.006</strong></td>
<td>0.734</td>
</tr>
<tr>
<td>b^IEDSCmz</td>
<td>Visual</td>
<td>0.563</td>
<td>0.134</td>
<td>0.084</td>
</tr>
<tr>
<td>c^IEDTEaz</td>
<td>Visual</td>
<td>0.475</td>
<td>0.088</td>
<td>0.123</td>
</tr>
<tr>
<td>d^IEDTTaz</td>
<td>Visual</td>
<td>0.611</td>
<td>0.074</td>
<td>0.092</td>
</tr>
</tbody>
</table>

^a^IED pre-Extra dimensional shift total errors. ^b^IED Mean Stages Completed. ^c^IED Total errors (adjusted). ^d^IED Total trials (adjusted).

*Significant at: *p < 0.05; **p < 0.01; ***p < .001 (boldface).
**Figure G6.** Means (± SEM) of summary score and individual measures of planning speed over time by breast cancer treatment group.

- Stockings of Cambridge (SOC) mean initial planning speed (3 moves).
- SOC mean initial planning speed (4 moves).
- SOC mean initial planning speed (5 moves).
- Complex figure copy speed.
Table G9

*P* values for Group, Time and Interaction effects obtained from ANOVAs of Summary Scores of Planning Speed Grouping and Individual Measures

<table>
<thead>
<tr>
<th>Name</th>
<th>Visual/Verbal</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning Speed</td>
<td>Visuospatial</td>
<td>0.287</td>
<td>&lt;.001***</td>
<td>0.450</td>
</tr>
<tr>
<td>^aSOCMi3za</td>
<td>Visuospatial</td>
<td>0.541</td>
<td>0.071</td>
<td>0.251</td>
</tr>
<tr>
<td>^bSOCMi4za</td>
<td>Visuospatial</td>
<td>0.333</td>
<td>0.012*</td>
<td>0.277</td>
</tr>
<tr>
<td>^cSOCMi5za</td>
<td>Visuospatial</td>
<td>0.753</td>
<td>0.245</td>
<td>0.471</td>
</tr>
<tr>
<td>^dCFTcytza</td>
<td>Visuospatial</td>
<td>0.186</td>
<td>&lt;.001***</td>
<td>0.888</td>
</tr>
</tbody>
</table>

^a^ Stockings of Cambridge (SOC) mean initial planning speed (3 moves).
^b^ SOC mean initial planning speed (4 moves).
^c^ SOC mean initial planning speed (5 moves).
^d^ Complex figure copy speed.

*Significant at: ^* *p* < 0.05; ** *p* < 0.01; *** *p* < .001 (boldface).