LONG-TERM EFFECTS OF IMATINIB ON COGNITION IN CHRONIC MYELOID LEUKAEMIA

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ABSTRACT

Imatinib was successfully introduced into haematology-oncology practice in 2001 and rapidly endorsed as a first line treatment for chronic myeloid leukaemia (CML) in the chronic, accelerated, and blastic phases. The survival advantage demonstrated by this target kinase inhibitor has meant that patients are now treated with this agent on a long-term basis. There is a growing literature on the potential toxic effects of chronic imatinib use (Fruttiger et al., 1999; Grove et al., 2004). A safety sub-study undertaken by the Australasian Leukaemia and Lymphoma Group (ALLG) identified a range of subtle effects consistent with the inhibition of targeted kinases in the immunological, respiratory, endocrine, and reproductive systems (Seymour et al., 2004). To date, there has been no attempt to elucidate possible neuropsychological sequelae of chronic imatinib use. However concerns exist about the potential neurotoxic effects of this agent, given that the inhibition of protein kinase in animal studies has been associated with a range of deleterious consequences, such as impaired learning and memory, and reduced synaptic efficacy (Grove et al., 2004; Moresco et al., 2003).

The purpose of the current study was to monitor the neuropsychological function of a group of adult CML patients' newly prescribed imatinib. A baseline assessment occurred prior to commencing treatment, and subsequent review assessments took place at six and twelve months. Multiple measures were employed to monitor changes in attention and working memory, motor and processing speed, verbal learning and verbal memory, and executive function. Levels of psychological distress and fatigue were also documented at each study point in order to understand their potential impact on cognition. The study aimed to investigate possible changes in verbal learning and memory, and other measures of cognitive function by six and twelve months. Any relationship between imatinib dose and performance would also be examined. The final aim of the current study was to elucidate the relationship between cognitive function and other demographic variables, mood, affect, and fatigue. Twelve participants completed the full research protocol, which included subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III), Logical Memory from the Wechsler Memory Scale – Third Edition (WMS-III), the Rey Auditory Learning Test (RAVLT), the Trailmaking Test, the Verbal Fluency and Sorting Test from the Delis-Kaplan Executive Functioning System (D-KEFS), the

Beck Depression Inventory – Second Edition (BDI-II), the State Trait Anxiety Inventory (STAI), and the Functional Assessment of Cancer Therapy – Leukemia Module (FACT-LEU). Data analysis shows no decline in cognitive function across the three assessments. In fact, significant increases were seen on measures of verbal memory and there was a trend towards improvement in processing speed, verbal learning, verbal recognition, and executive function. The vital issue of a suitable control group for comparison and the consequences for determining the impact of mood and the extent of practice effects are discussed.

STATEMENT OF AUTHORSHIP

"I, *Kerrie Shiell,* declare that the Doctor of Psychology (Clinical Neuropsychology) thesis entitled *Long-Term Effects of Imatinib on Cognition in Chronic Myeloid Leukaemia* is no more than 40,000 words in length, exclusive of tables, figures, appendices, references, and footnotes. This thesis contains no material that has been previously submitted, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work".

Signature: …… **Date:** ……/...../…..….

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TABLE OF CONTENTS

Abstract i
Statement of Authorship iii
Acknowledgements iv
Table of Contents v
Table of Tables viii
Table of Figures ix
List of Appendices x

1. INTRODUCTION 1

1.1 OVERVIEW OF THE RESEARCH ISSUE 1

1.2 HAEMATOLOGICAL MALIGNANCIES 2
1.2.1 The Leukaemias 2
1.2.2 Chronic Myeloid Leukaemia (CML) 3

1.3 TREATMENT EFFICACY IN CML: AN OVERVIEW 6

1.4 TRADITIONAL CML TREATMENTS: EARLY ATTEMPTS, EFFICACY, AND ADVERSE EFFECTS 7
1.4.1 Early History 7
1.4.2 Cytotoxic Treatments (Conventional Chemotherapy) 8
1.4.2.1 Bulsulfan 8
1.4.2.2 Hydroxyurea 9
1.4.3 Interferon Alpha 10
1.4.4 Stem Cell Transplantation 12
1.4.4.1 Allogeneic Stem Cell Transplantation 12
1.4.4.2 Autologous Stem Cell Transplantation 14

1.5 TARGET KINASE INHIBITIORS: ACTION, EFFICACY, AND ADVERSE EFFECTS 15
1.5.1 Action of Imatinib 15
1.5.2 Efficacy 16
1.5.3 Adverse effects 18

1.6 TREATMENT EFFECTS: COGNITION, EMOTION, AND QUALITY OF LIFE 20
1.6.1 Transplant Therapies 20
1.6.1.1 Impact of Preparative Regimes for ASCT 21
1.6.2 Non-transplant Therapies 23
1.6.2.1 The impact of Imatinib on CNS functioning 25

1.7 DEMOGRAPHIC VARIABLES, AFFECT, AND COGNITION 27
1.7.1 Mood 27
1.7.2 Affect 27
1.7.3 Socio-economic Status 28
1.7.4 Educational Attainment and IQ 28

1.8 DISEASE-EFFECTS AND COGNITION 29
1.8.1 Fatigue and Cognition 29
1.8.2 Concomitant Medication and Cognition 30

1.9 NEUROPSYCHOLOGICAL MEASUREMENT ISSUES 31
1.9.1 Assessment of Neuropsychological Sequelae of Traditional Non-transplant Treatments 31
1.9.2 Evaluating the Neuropsychological Impact of Transplant Treatments 33
1.9.3 A Best Practice Approach for Investigating the Neuropsychological Effects of Imatinib 34
1.9.3.1 Considerations for Study Design 34

1.9.3.2 Cognitive Measures to Assess the Impact of Cancer Treatment....35
1.9.3.3 Measures of Mood and Affect....39
1.9.3.4 Measures of Fatigue and Quality of Life....40

1.10 RATIONALE....40

1.11 AIMS OF THE PRESENT STUDY....42

2. METHOD....43

2.1 PARTICIPANTS....43

2.2 MATERIALS....44
2.2.1 Cognitive Tasks....44
2.2.1.1 Intellectual Function....44
2.2.1.2 Attention and Working Memory....44
2.2.1.3 Motor and Processing Speed....45
2.2.1.4 Verbal Memory....45
2.2.1.5 Executive Function....47
2.2.2 Measures of Mood and Affect....48
2.2.3 Measure of Socio-economic Status....50
2.2.4 Measures of Disease-related Variables....50
2.2.5 Measures of Response to Therapies/Aversive Events....50

2.3 PROCEDURE....52

2.4 ETHICS APPROVAL....55

3. RESULTS....56

3.1 DATA ANALYSIS....56

3.2 DEMOGRAPHIC VARIABLES....56

3.3 MOOD-RELATED VARIABLES AND FATIGUE....57

3.4 DISEASE-RELATED VARIABLES....58

3.5 VERBAL LEARNING AND VERBALMEMORY....60
3.5.1 Statistical Tests for Aim 1....60

3.6 OTHER COGNITIVE MEASURES....63
3.6.1 Statistical Tests for Aim 2....63

3.7 RELATIONSHIP BETWEEN COGNITION, DEMOGRAPHICS, AND AFFECT....66
3.7.1 Statistical Tests for Aim 3....66
3.7.1.1 Verbal Learning and Memory....66
3.7.1.2 Other Cognitive Tasks....68

3.8 RELATIONSHIP BETWEEN DOSE AND COGNITION....69
3.8.1 Statistical Tests for Aim 4....69
3.8.1.1 Verbal Learning and Memory....69
3.8.1.2 Other Cognitive Tasks....69

3.9 AN EXAMINATION OF INDIVIDUAL PERFORMANCES……....70
3.9.1 Case Study 1: ‘Marie’……...70
3.9.2 Case Study 2: 'Tom'……..72
3.9.3 Case Study 3: 'Jane' ...…….....74

4. DISCUSSION 76

4.1 STATISTICAL METHODS USED TO TESTS AIMS 1 AND 2 76

4.2 VERBAL LEARNING AND MEMORY 76
4.2.1 Comparisons with Baseline Performances 76

4.3 OTHER COGNITIVE MEASURES 83
4.3.1 Comparison with Baseline Performances 83

4.4 DEMOGRAPHICS, AFFECT, FATIGUE, AND COGNITION 85
4.4.1 Verbal Learning and Memory 86
4.4.1.1 Mood, Affect, and Verbal Memory 86
4.4.1.2 Fatigue and Verbal Memory 87
4.4.1.3 FSIQ and Verbal Memory 88
4.4.1.4 Demographics and Verbal Memory 89
4.4.2 Other Cognitive Functions 90

4.5 DOSE AND COGNITION 90
4.5.1 Verbal Learning and Memory 90
4.5.2 Other Cognitive Measures 91

4.6 EMOTIONAL FUNCTIONING 91

4.7 QUALITY OF LIFE 92

4.8 LIMITATIONS AND FUTURE DIRECTIONS 93

4.9 CONCLUSIONS 97

5. REFERENCES 99

6. APPENDICES 131

TABLE OF TABLES

		Page
Table 1.	Response assessment in CML…….	6
Table 2.	Adverse effects of bulsulfan ……...	9
Table 3.	Adverse effects associated with hydroxyurea …….…...	10
Table 4.	Adverse effects associated with interferon alpha ……...	12
Table 5.	Adverse effects associated with allogeneic bone marrow tranplant……...	14
Table 6.	Summary of the pharmacological properties of imatinib…..……...	16
Table 7.	Comparison of response to imatinib vs. interferon plus cytarabine.……...	17
Table 8.	Adverse effects associated with imatinib use …….	19
Table 9.	Adverse cognitive effects associated with medication use…….	31
Table 10.	Test selection and order across assessments ……..	54
Table 11.	Demographic Information ……..	57
Table 12.	Analysis of verbal memory performances over time using repeated measures ANOVA and effect size.…….	61
Table 13.	Analysis of other cognitive measures over time using repeated measures ANOVA and effect size ……..……...	64
Table 14.	Bivariate correlations between mood, fatigue, and verbal memory……	66
Table 15.	Intercorrelations between verbal memory function and demographic variables……..	67
Table 16.	Intercorrelations between verbal memory function and dose …..……..	69

TABLE OF FIGURES

		Page
Figure 1.	Chromosomal translocation in CML……..	4
Figure 2.	Incidence of grade 3 or 4 non-haematological adverse events ……..	18
Figure 3.	Subjective cognitive and emotional effects of cancer related fatigue…….	30
Figure 4.	The incidence and severity of self-reported depressive symptoms…….	57
Figure 5.	Self-reported adverse effects of CML participants ……	59
Figure 6.	Classification and frequency of concomitant medication use in the study….	59
Figure 7.	Mean verbal memory performances across the three occasions of assessment……...	62
Figure 8.	Mean performances on other measures of cognitive function across the three occasions of assessment ……..…….…….	65
Figure 9.	Verbal memory results for the participant with the pre-morbid FSIQ closest to the population mean …….……	70
Figure 10.	Performance on other cognitive measures for the participant with the FSIQ closest to the population mean….	71
Figure 11.	Verbal Memory results for the participant with highest pre-morbid FSIQ ……..…….	72
Figure 12.	Performance on other cognitive measures for the participant with the highest pre-morbid FSIQ……	73
Figure 13.	Verbal Memory results for the participant with lowest pre-morbid FSIQ ……..…….	74
Figure 14.	Performance on other cognitive measures for the participant with the lowest pre-morbid FSIQ…….	75

LIST OF APPENDICES

	Page
Appendix A: Trail-making Test (including Trails A & B) ……	131
Appendix B: Rey Auditory Verbal Learning Test (Form 1)……..	134
Appendix C: Auditory Verbal Learning Test (Alternate Version) ……	136
Appendix D: Delis-Kaplan Executive Functioning System - Verbal Fluency (Standard Form) – letter fluency condition……..	138
Appendix E: Delis-Kaplan Executive Function System - Verbal Fluency (Alternate Form) – letter fluency condition ..……...	140
Appendix F: Delis-Kaplan Executive Functioning System - Sorting Test (Standard Form) – free sort condition……...	142
Appendix G: Delis-Kaplan Executive Functioning System- Sorting Test (Alternate Form) – free sort condition ……..…….	146
Appendix H: Functional Assessment of Cancer Therapy –Leukaemia Module……	150
Appendix I: Case Report Form ……..	154
Appendix J: NIH/NCI Common Terminology Criteria for Adverse Events……..	156
Appendix K: Ethics Approval Form ……..	161
Appendix L: Results of Repeated Measures ANOVA …….	165
Appendix M: Recall and Recognition Scores on the Standard and Alternate Forms of the Auditory Verbal Learning Test...……	179

1. INTRODUCTION

1.1 OVERVIEW OF THE RESEARCH ISSUE

As Paracelsus, the 16th Century alchemist and physician first said, "all substances are poisons, there is none which is not a poison. The right dose differentiates a poison and a remedy". With this in mind, the therapeutic benefits of any new agent must be weighed up against its potentially adverse effects. Recent advances in haematology-oncology practice have led to concerns about the chronic toxicity of new molecular therapies, such as imatinib, designed to inhibit the aberrant kinase activity in chronic myeloid leukaemia (CML). Preliminary research indicates that the destruction of target kinases in mice adversely affects specific body systems (Fruttiger et al., 1999; Grove et al., 2004). Subtle effects have also been noted in humans, specifically in the immunological, respiratory, endocrine and reproductive systems (Seymour et al., 2004), however research is yet to investigate possible neuropsychological sequelae.

The potential for adverse neuropsychological sequelae may compromise the benefits of otherwise successful cancer treatment. In the recent past, enthusiasm for the effectiveness of prophylactic cranial irradiation in the treatment of childhood leukaemia was replaced by major concerns about cognitive impairment in survivors (Langer et al., 2002). Similar issues have been reported in the adult population, particularly with higher dose/fraction/field and older age (Laack & Brown, 2004). Verbal learning, memory, attention, and speed of processing deficits were also identified in a recent review of chemotherapy (McAllister et al., 2004) and cognitive declines have been noted in patients six months after treatment with myeloablative therapy followed by allogenic stem cell transplantation (Syrjala, Dikmen, Langer, Roth-Roerner & Abrams, 2004).

In regard to CML, the lack of longitudinal support behind the newer molecular therapies also raises potential for concern. In particular, issues have arisen in relation to imatinib because the different types of protein kinase inhibited by this agent *in vitro* (including PDGF-R and B, KIT, ABL and ARG) may have an important role in neuropsychological function (Grove et al., 2004; Moresco, Scheetz, Bornmann,

Koleske & Fitzsimonds, 2003). For example, ABL and ARG regulate the neuronal cytoskeleton, and modulate synaptic efficacy, important in memory (Moresco et al., 2003). Mice deficient in ABL-interactor proteins show deficits in learning and memory (Grove et al., 2004). Separately, activation of KIT enables repair of brain damage (Sun, Lee, & Fine, 2004), and enhances survival of the central nervous system (CNS) stem cells (Erlandsson, Larsson & Forsberg-Nilsson, 2004). Hence, long-term neuropsychological assessment of patients on imatinib may be important in order to determine whether the agent is causing similar sequelae in humans. This need has also been highlighted by reports of acute cerebral oedema in CML patients treated with imatinib, although the incidence is extremely rare (Ebnoether, Stentoft, Ford, Buhl & Gratwohl, 2002).

The current study seeks to assess the neuropsychological functioning of a group of adult CML patients' newly prescribed imatinib and followed up over one year. An initial baseline assessment took place prior to the commencement of treatment; and subsequent assessment took place six and twelve months after the start of treatment. An evaluation of the patient's level of overall cognitive functioning, attention and working memory, motor and processing speed, verbal memory, executive functioning, mood, anxiety and fatigue was conducted.

The aim of the present study is to monitor the cognitive function of patients prescribed imatinib treatment for CML. In order to ascertain whether these changes were associated with imatinib therapy, a range of demographic and mood-related variables were also monitored (e.g., FSIQ; years of education; socio-economic status (SES); mood; anxiety; fatigue). A systematic review of the diverse literature relevant to this area forms the context of this empirical research study.

1.2 HAEMATOLOGICAL MALIGNANCIES

1.2.1 The Leukaemias

The leukaemias are a heterogeneous group of malignant blood disorders that result from the overproduction of immature mutated white cells in the bone marrow and blood. These mutations give rise to four classifications of leukaemia including the acute and

chronic leukaemias, which are further subdivided into either the lymphoid or myeloid leukaemias (i.e., Acute Lymphoblastic Leukaemia (ALL), Acute Myeloid Leukaemia (AML), Chronic Lymphocytic leukaemia (CLL), and CML). In 2005 it was projected that 3,003 people in Australia, including 213 children (0-14 years) would be diagnosed with leukaemia in 2008 (Australian Institute of Health and Welfare, 2005). According to the Australian Institute of Health and Welfare (2005), CLL and AML will continue to be the most prevalent forms of leukaemia in adults, whilst ALL will not only remain the most common leukaemia in children but also the most prevalent childhood cancer.

In all forms of leukaemia, symptoms arise for one of two reasons; the infiltration of abnormal cells into organs such as the spleen, liver, lymph nodes, and brain, and in association with bone marrow failure (i.e., anaemia, neutropenia, and thrombocytopenia) (Hoffbrand, Pettit & Moss, 2005). The aetiology of these disorders is largely unknown, although it is likely to be a multi-step process involving acquired cytogenetic abnormalities and other predisposing factors, such as ionizing radiation exposure, previous chemotherapy, occupational chemical exposure, viral infection, and cigarette smoking (Corso et al., 1995; Geary, 2000; Souhami & Tobias, 2005). Whilst the underlying cause is not well understood, research has shown that leukaemic cells arise from mutations in the chromosomal structure of undifferentiated blood cells (i.e., haematopoietic stem cells) (Howard & Hamilton, 2002). These 'chromosomal translocations' occur when a fragment from one chromosome is broken away and donated to another chromosome, which then responds by reciprocating with a fragment of its own (Howard & Hamilton, 2002).

1.2.2 Chronic Myeloid Leukaemia (CML)

A classic example of 'chromosomal translocation' occurs in >95% of all cases of CML. In this example, a segment from the ABL gene on chromosome 9 combines with a portion of the BCR gene on chromosome 22 (Faderl et al., 1999). This translocation forms a shortened chromosome, known as the 'Philadelphia chromosome (Ph+)', which harbours the mutated 'BCR-ABL' fusion gene (See Figure 1).

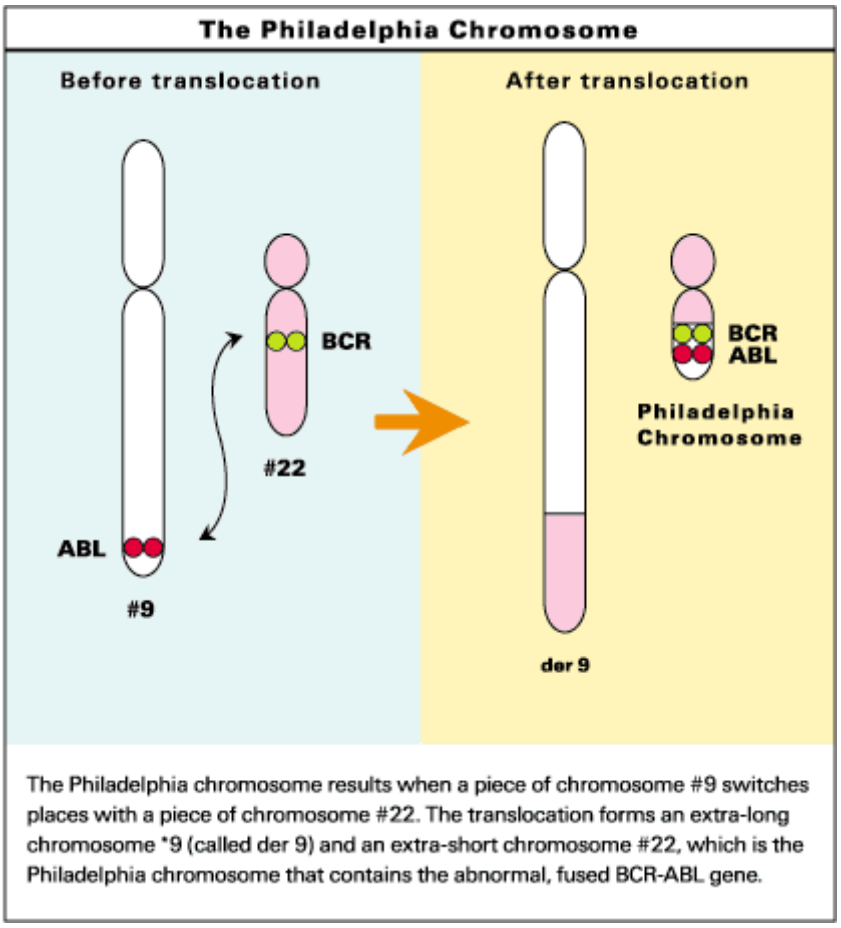


Figure 1. Chromosomal translocation in CML (Antigenics Inc., 2008)

This BCR-ABL gene mutation is thought to play an essential role in the over production of mutated white blood cells in CML. Prior to the fusion of the BCR-ABL gene, the ABL acts as a chemical messenger or 'protein tyrosine kinase', which is considered to be integral to the activation of cell division and growth, and apoptosis or programmed necrosis. The activity of this ABL tyrosine kinase is intensified by the fusion of the BCR-ABL gene (Deininger & Druker, 2003; Hoffbrand, Pettit & Moss, 2005; Ren, 2002). In the case of CML, this heightened activity impairs apoptosis and results in the relentless proliferation of specific elements contained within the white blood cells of the bone marrow called neutrophils and the neutrophil precursors. The gross over production of neutrophils and their precursor cells in CML then suppress and impair normal bone marrow function (Marieb, 1989).

The annual incidence of CML is around 1 in 100,000 worldwide (Ghanei & Vosoghi, 2002), and although it can occur at any stage, it is very uncommon in children under ten

years and typically presents between the ages of 40 and 60 years. The disease affects males and females in similar numbers, with 1.4 males for every one female diagnosed. CML consists of three distinct phases, including a relatively benign chronic phase, followed by an accelerated phase, and an almost inevitably fatal acute leukaemic phase known as 'blast crisis' (Howard & Hamilton, 2002).

The initial or chronic phase is insidious and typically characterised by vague feelings of ill health, weight loss, fever, or symptoms of anaemia. Pain associated with an enlargement of the spleen is the most common physical finding in CML, however patients occasionally present with gout and hyperviscosity (Howard & Hamilton, 2002; Souhami & Tobias, 2005; Woodliff & Hermann, 1976). Symptoms generally arise due to a lack of red blood cells, normal white cells, and platelets, which result in increased fatigue, and a heightened susceptibility to infection, bleeds, and bruising (Leukaemia Foundation, 2005). In some cases, patients are asymptomatic and 50% of cases are discovered during a routine blood test (Faderl et al., 1999). Symptoms are more obvious in the accelerated phase, with pain generally accompanying further splenic enlargement. In this phase, immature blast cells comprise between 10% and 30% of blood cells in the marrow. The final blast phase is more rapid and aggressive, with the presence of 30% or more leukaemic cells in peripheral blood or bone marrow (Faderl et al.). In both the accelerated and blast phase, new chromosomal abnormalities emerge and the disease process becomes more difficult to treat (Faderl et al.; Hoffbrand et al., 2005). Death usually occurs from terminal transformation from CML into AML or ALL, intercurrent haemorrhage, or infection.

The diagnosis is confirmed through a multi-step process. A routine blood screen showing elevated white cell counts is typically followed by a bone marrow biopsy and chromosome analysis, which will generally be positive for the Ph+. Further molecular testing occurs on blood or bone marrow, and diagnosis is made if the bcr-abl gene is identified (Diagnosing CML for Healthcare Professionals, 2006).

Prior to the introduction of tyrosine kinase inhibitors, patients were typically treated with interferon alpha in cases where allogeneic stem-cell transplantation was not an option. At this stage, 20-30% of patients died within two years of diagnosis, and a further 25% of patients died every year after (Howard & Hamilton, 2002). Since the

introduction of new treatments that inhibit tyrosine kinase activity, such as imatinib, the median survival rate has increased to well in excess of six years (approximately 90% survival at six years (Hochhaus et al., 2007).

1.3 TREATMENT EFFICACY IN CML: AN OVERVIEW

Three hierarchical levels of disease control have been described in CML. The first stage of disease control involves the 'complete haematological response' (CHR). For the patient to achieve a CHR, blood counts and white cells must return to normal levels, and all symptoms and signs of the disease must disappear (e.g., splenomegaly) (See Table 1) (Deininger & Druker, 2003). The CHR is considered the lowest level of treatment response. If the patient fails to achieve CHR, then the disease will progress and patient will ultimately die (Schiffer, Hehlmann & Larson, 2003).

The second level of response involves a 'complete cytogenic response' (CCR). Different levels of response are defined by the percentage of Ph+ in the marrow (See Table 1). Van Rhee et al. (1997) claimed that a complete and durable cytogenic response was the most important factor in achieving long-term disease control.

Table 1
Response Assessment in CML (Schiffer et al., 2003)

Haematological Response	Cytogenetic Response	
Complete response	Complete response	0% Ph + cells
Normal peripheral blood count	Major (partial) response	1-34% Ph +
White blood count < 10 x 10^9/1	Minor response	35-95 % Ph +
Platelet count < 450 x 10^9/1	No response	≥ 96% Ph +
No palpable splenomegaly		

The third level of response is the quantification of the BCR-ABL transcript in the blood or bone marrow. For the patient to achieve complete 'molecular remission', there must be no BCR-ABL fusion genes detected during molecular testing. As per the cytogenic response, a partial response can be recorded if low levels of BCR-ABL are seen on testing.

1.4 TRADITIONAL CML TREATMENTS: EARLY ATTEMPTS, EFFICACY, AND ADVERSE EFFECTS

1.4.1 Early History

John Hughes Bennett and Robert Virchow described the first cases of CML in 1845 (Geary, 2000). Initial attempts to control the disease using iron and quinine proved unsuccessful, however a number of positive treatment effects were seen after the administration of various arsenic preparations, such as 'Fowler's solution' (Deininger & Druker, 2003). Lissauer was the first to use this popular tonic for the treatment of CML in 1865 (Geary, 2000). Although it was necessary to induce a mild state of arsenic poisoning to produce a significant haematological response, Lissauer reported a range of positive treatment effects including reduced spleen size and white blood cell count, and an improvement in anaemia and overall sense of well being. This state was maintained for a number of months but the disease ultimately became refractory to treatment.

Physicians continued to employ such preparations until the advent of radiotherapy in 1903. Splenic radiation emerged as the most popular treatment option in CML, after its efficacy was demonstrated by Professor Nicholas Senn. Senn (as cited in Geary, 2000) described a series of cases in which spleen size was reduced and white blood cell counts decreased following irradiation. Treatment effects were immediate, with many patients reportedly returning to near normal function for weeks to months, and occasionally years. Unfortunately patients ultimately relapsed, and although further remissions were possible with additional therapy, the disease eventually became resistant to treatment (Geary, 2000). Radiation protocols expanded over the proceeding years, with further attempts to improve efficacy by targeting bone marrow in the axial skeleton, the limb bones, the abdomen, and the whole body. In spite of this, numerous trials undertaken by 1950 suggested that, although radiation improved quality of life and offered symptom relief, it probably did not prolong life (Bolin, Robinson, Sutherland & Hamman, 1982; Deininger & Druker, 2003; Geary, 2000).

1.4.2 Cytotoxic Treatments (Conventional Chemotherapy)

1.4.2.1 Bulsulfan

Bulsulfan was the first synthetic compound to be used in the treatment of CML (Deininger & Druker, 2003). This alkylating agent was initially tested on animal tumours (Haddow & Timmus, 1953), and after some early success, human trials commenced in 1953 (as cited in Geary, 2000). Successive trials confirmed the toxicity of this agent at the stem cell level (Deininger & Druker, 2003; Medical Research Council's Working Party for Therapeutic Trials in Leukemia, 1968), and established its ability to control the related signs and symptoms in 95% of CML patients over the first three months.

More recent studies have identified bulsulfan's role in depressing white cell counts, maintaining counts at normal levels in the chronic stage, reducing splenic size, and limiting hypermetabolic symptoms (Cortes et al., 1996; Sawyers, 1999). Superior efficacy and a lower incidence of adverse reactions were demonstrated when compare to radiotherapy (Medical Research Council's Working Party for Therapeutic Trials in Leukemia, 1968). The emerging evidence in support of bulsulfan's efficacy, together with its relative convenience and cost-effectiveness, made it the mainstay of CML treatment for over 35 years.

Ninety percent of patients treated with bulsulfan achieved haematological remission (Sawyers, 1999), whilst the mean duration of the chronic phase was 37 months and the overall length of survival was 45 months (Cortes et al., 1996). However, these apparent improvements were not accompanied by a significant reduction in the percentage of cells bearing the Ph+ chromosome. Therefore while disease control was achieved, the duration of disease control before transformation to the acute stage was unchanged (Cortes et al.). In fact, Bolin et al. (1982) claimed that any increased survival was probably not associated with the treatment but rather earlier diagnosis and improvements in managing complications.

Bulsulfan's efficacy was further limited by the long list of frequent and serious adverse effects associated with its use (Silver et al., 1999) (See Table 2). Ultimately bulsulfan

was displaced by treatments with greater therapeutic benefits and fewer adverse consequences.

Table 2
Adverse Effects associated with Bulsulfan (Australian Medicines Handbook, 2005)

Common Side Effects	Rare Side Effects
Low Dose mild nausea and vomiting; diarrhoea; anorexia; weight loss; hyperpigmentation of the skin, myelosuppression.	*Low Dose* Addison-like syndrome; pulmonary fibrosis; erythema nodosum; erythema multiforme; cataracts; gynaecomastia.
High Dose hepatic veno-occlusive disease; tumour lysis syndrome; alopecia; amenorrhoea; myelosuppression; mild nausea and vomiting; stomatitis; diarrhoea or constipation; dry mouth, oesophagitis; dyspepsia; dizziness; blurred vision; intermittent muscle twitching; seizure; insomnia; confusion; delirium; hyperglycaemia; hypokalaemia; hypocalcaemia; skin reactions with intercurrent radiotherapy.	*High Dose* raised hepatic enzymes; pulmonary fibrosis; cardiovascular effects; dyspnoea and cough; interstitial pneumonitis; increase serum creatinine; graft versus host disease.

1.4.2.2 Hydroxyurea

Hydroxyurea, a ribonucleotide reductase inhibitor, emerged as a popular replacement for bulsulfan because of its swift action and low level of adverse effects: 15.8 % versus 24.2 % with bulsulfan (Hehlmann et al., 1993). Virtually no 'serious' side effects were observed in patients treated with hydroxyurea, and Hehlmann et al. (1993) postulated that hydroxyurea's lower toxicity might enable more intensive treatment leading to better treatment outcomes. (See Table 3 for a listing of possible adverse effects associated with hydroxyurea).

Support for hydroxyurea's superiority over bulsulfan was established after a randomised comparison study identified a longer mean duration of the chronic phase (47 months compared to 35 months in bulsulfan, $p = 0.04$) and increased overall survival (58 months compared with 45 months, $p = 0.08$) (Cortes et al., 1996). This was further supported by further meta-analytic studies that demonstrated a significant survival advantage for Hydroxyurea (Chronic, Myeloid Leukemia Trialists' Collaborative Group, 1997).

Unfortunately, hydroxyurea was not curative and very few patients achieved cytogenic remission. As per bulsulfan, improvements were not associated with a decrease in the number of cells bearing the Ph+ chromosome, and therefore treatment had no effect on the rate of progression to blast crisis (Cortes et al., 1996; Sawyer, 1999).

Table 3
Adverse Effects associated with Hydroxyurea (Australian Medicines Handbook, 2005)

Common Side Effects	Infrequent Side Effects	Rare Side Effects
myelosuppression; haemolyosis; anorexia; stomatitis; mild nausea and vomiting; constipation; diarrhoea; maculopapular rash; facial erythema; itch.	hyperpigmentation; atrophy of skin and nails; cutaneous leg ulcers.	alopecia; skin cancer; dysuria; elevated serum creatinine; fever; chill; malaise; oedema; elevation of liver enzymes; acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dysponea.

1.4.3 Interferon Alpha

In the mid 1990's interferon alpha emerged as the treatment of choice for those patients not eligible for allogeneic transplantation (Sawyer, 1999). This treatment was the first agent to irrefutably delay the onset of blast crisis, and prolong survival (Talpaz, McCredie, Mavligit & Gutterman, 1983). Haematological remission was reported in more than 70% of patients, whilst 15-20% of patients achieved a complete cytogenic response (Hehlmann et al., 1994; Talpaz, Kantarjian, Kurzrock, Trujillo & Gutterman, 1991). The drug offered a distinct survival advantage over its predecessors, with 5 year survival rates of 57% compared to 42% for hydroxyurea and bulsulfan combined ($p = 0.001$) (Chronic Myeloid Leukaemia Trialists' Collaborative Group, 1997). Controlled studies suggested an increase in life expectancy by a median of approximately 20 months (Guilhot et al., 1997; Hehlmann et al., 1997). Almost all patients in the chronic phase experienced a range of clinical and haematological improvements. Splenic size and white blood cell counts commonly reduced, and improved bone marrow function and rising haemaglobin levels were associated with less fatigue (Souhami & Tobias,

2005). Unfortunately, interferon alpha has been shown to have little impact once patients progress to the accelerated phase of the disease (Kantarjian, Giles, O'Brien & Talpaz, 1998).

The precise activity of interferon alpha in CML is unknown. Bhatia and Verfaillie (1998) have claimed that the agent probably intervenes on multiple levels by indirectly inhibiting leukemic cells and by reducing BCR-ABL transcription. Recent studies indicated that interferon alpha has a role in activating factors that regulate myeloid cell growth and anti-tumour immunity (Cornelissen et al., 1998; Gordon et al., 1998; Ren, 2002).

In spite of the drug's encouraging treatment outcomes, serious complications are more common with interferon alpha than bulsulfan and hydroxyurea (Silver et al., 1999). Virtually all patients experience some adverse effects (Table 4), and between 4 to 18% discontinue treatment compared with 1% of patients receiving hydroxyurea (Vial & Descotes, 1994). Homewood, Watson, Richards, Halsey and Shepherd (2003) suggested that the toxic effects of interferon compromised patients' quality of life to a greater extent than other treatments. In particular, patients' described poorer levels of emotional, social, and cognitive functioning, heightened pain and dysponea ($p = 0.01$) and marginally worse fatigue, nausea, and vomiting ($p = 0.05$). Significant cognitive and mood changes have been described in the literature (Meyers, Scheibel & Forman, 1991; Licino, Kling & Hauser, 1998; Scheibel, Valentine, O'Brien & Meyers, 2004; Valentine, Meyers, Kling, Richelson & Hauser, 1998). The details of these changes will be described in more detail in Section 1.6 Treatment Effects: Cognition and Emotion.

Recent studies have investigated the effectiveness of interferon alpha in combination with cytarabine (Goldman & Melo, 2003; Kantarjian et al., 1999). Although an increased rate of haematological and cytogenic response (94% and 74% respectively) was observed (Kantarjian et al.), these improvements reportedly coincided with increased neurotoxicity (Silver et al., 1999).

Table 4
Adverse Effects associated with Interferon Alpha (Australian Medicines Handbook, 2005)

Common Side Effects	Infrequent Side Effects*	Rare Side Effects
flu-like symptoms; anorexia; nausea; diarrhoea; abdominal pain; weight loss; alopecia; anaemia; transient leucopenia; hypotension; hypertension; palpitations; arrhythmias; arthralgia; myalgia; fatigue; headache.	dizziness; somnolence; confusion; severe depression; paraesthesia; nervousness; neuropathy; taste disturbance; diarrhoea; elevated liver enzymes; cardiomyopathy; thyroid dysfunction; thyrombocytopenia. **Occurs more frequently in patients 60 years +*	pneumonitis; pulmonary infiltrates; hepatic dysfunction; liver failure; retinopathy; seizures; coma; peripheral neuropathy; renal impairment; impaired glucose tolerance; hypertriglyceraemia; aplastic anaemia; rhabdomyolysis; autoimmune disease, e.g., vasculitis, hypersensitivity including anaphylaxis.

1.4.4 Stem Cell Transplantation

1.4.4.1 Allogeneic Stem Cell Transplantation

In 2005, over 45,000 patients underwent allogeneic stem cell transplantation (ASCT) worldwide (Syrjala, Langer, Abrams, Storer & Martin, 2005). ASCT has long been regarded as the only curative treatment for CML. Moderate to high levels of long-term disease free survival (50-80%) have been described in the literature (Deininger & Druker, 2003), with relapse reportedly occurring in less than 20% of patients (Silver et al., 1999). Higher rates of cytogenic and molecular remission have also been seen following ASCT in comparison to the conventional chemotherapies described above (Silver et al.).

Only 15 to 20 % of CML patients are eligible for ASCT (Sawyers, 1999). Access to the procedure is limited by the availability of a Human Leukocyte Antigen (HLA)-matched sibling, age considerations, and the patient's ability to sustain the rigorous preparative regime, which can include whole body irradiation and high dose chemotherapy (Deininger & Druker, 2003; Schiffer, Hehlmann & Larson, 2003). The use of less toxic or 'non-myeloblative' preparative regimes, which emphasize the use of immunosuppressants, may increase the pool of suitable candidates (Goldman & Melo, 2003). However it is unclear if the long-term survival rates associated with these preparative regimes are comparable to that of the more toxic conventional myeloblative regimes (Bornhauser et al., 2001).

The use of matched unrelated donors increases the number of potential candidates for ASCT to 30% (O'Brien, 1997). However lower two year disease free survival rates (37-45%) are consistently reported with the use of such donors (McGlave et al., 1993; McGlave, Kollman & Shu, 1996). Comparable results to these have been obtained with mismatched family donors (de Witte et al., 2001), with higher rates of graft failure described for both mismatched and unrelated but matched donor groups (Beelen, Graeven & Elmaagacli, 1995).

In addition to donor type, four other pre-transplant risk factors were found to influence patient outcomes (Gratwohl et al., 1998). These factors included "stage of disease at the time of transplantation, recipient age, donor-recipient sex combination, and the interval from diagnosis to transplantation". The best outcomes were achieved in patients younger than 20 years of age; with higher rates of long-term disease free survival (60-70%), and the lowest incidence of complications (10%) and relapse (20%) (Gratwohl et al., 1993). A rise in the frequency of treatment-related mortality was described with increasing age, with some centres refusing to perform the procedure on patients over 55 years of age (Schiffer et al., 2003). Gender also impacted treatment outcome, with "male recipients of female blood or bone marrow grafts at greater risk of treatment related mortality" (Gratwohl et al., 2001, p. 363).

Higher survival rates have been described in patients who undergo transplantation during the chronic phase (Horowitz, Rowlings & Passweg, 1996). Over 50% of patients in the chronic phase achieve long-term survival, in comparison to 15-40% of patients receiving transplants during the accelerated phase and less than 15% in blast crisis (Biggs et al., 1992). Finally, transplantation in the first year after diagnosis is also associated with increased rates of long-term disease free survival (Horowitz et al., 1996).

However controversy exists regarding the true survival advantage of ASCT over other treatments. Silver et al. (1999) suggested that increased long-term survival might be related to the selection criteria required for treatment rather than the treatment itself (i.e., better health status, younger age, less time from diagnosis). Further to this, high rates of transplant related mortality are reported in the literature (Table 5) (Silver et al.),

particularly in patients receiving transplants from mismatched or unrelated donors and treated in the 1980s (Silver et al.). According to Gale et al. (1998), treatment related mortality rates are higher in ASCT compared with other treatments (hydroxyurea and interferon alpha) in the first 18 months. Similar mortality rates are reported between 18-56 months, however a distinct survival advantage is described for ASCT after 56 months. As per interferon, cognitive and emotional changes are reported following ASCT. The details of these changes will be described in more detail in Section 1.6 Treatment Effects: Cognition and Emotion.

Table 5
Adverse Effects with Allogeneic Bone Marrow Transplants (Silver et al., 1999)

Complications	Incidence Rates %
Transplant-related mortality (all causes)	18-68
Grade II-IV acute GVHD	8-63
Chronic GVHD	4-75
GVHD (fatal)	1-12
Acute GVHD (fatal)	2-12
Chronic GVHD (fatal)	8-10
Mucositis, oral	48
Pulmonary	
Interstitial pneumonitis	8-28
Interstitial pneumonitis (fatal)	4-32
ARDS (fatal)	2
Obstructive bronchitis (fatal)	2
Pulmonary oedema	2
Pulmonary embolism	2
Infection/sepsis (fatal)	3-24
Veno-occlusive disease	7-43
Veno-occlusive disease (fatal)	1-4
Haemorrhagic cystitis	12
Haemorrhage (fatal)	1-2
Second malignancy (fatal)	2
Cardiac failure (fatal)	2
Cerebral bleeding (fatal)	2
Haemolytic uremic syndrome (fatal)	1
Hepatotoxicity (fatal)	6

1.4.4.2 Autologous Stem Cell Transplantation

Autologous stem cell transplantation may be considered a second line treatment for patients without matched sibling donors. In this procedure, early progenitor cells unaffected by the BCR-ABL gene are taken from the patient during a process known as leukapheresis (Cortes et al., 1996). These cells are then collected and later re-infused into the patient. A number of methods have been described to minimise the chance of

harvesting Ph+ cells, however the details of these procedures are beyond the scope of this review.

This process is capable of restoring a complete cytogenic response in 50% of patients and prolonging survival (Carella et al., 1997). Up to 70% of patients survive beyond five years (Reiffers, Goldman, Meloni, Cahn & Gratwohl, 1994) and lower rates of treatment related mortality are described when compared to allogeneic transplants using unmatched family donors (de Witte et al., 2001). However the procedure is not curative, and although many patients experience a good response initially, this response tends to be transitory and patients ultimately relapse (Talpaz et al., 1995).

1.5 TARGET KINASE INHIBITIORS: ACTION, EFFICACY, AND ADVERSE EFFECTS

1.5.1 Action of Imatinib

As researchers began to understand the molecular basis of CML, efforts turned towards identifying agents that blocked or altered the action of the BCR-ABL oncogene (Sawyers, 1999). By the mid 1990's, Buchdunger and colleagues had described a range of agents that inhibited the action of ABL and the platelet derived growth factor receptor (PDGF-R) (Deininger & Druker, 2003). After an exhaustive investigation, the team identified a particular compound, which displayed a weak inhibitory action against this protein kinase. This discovery was the impetus for further research to identify related compounds with greater potency.

A small molecule called STI571 (now known as Imatinib, Gleevec or Glivec), derived from 2-phenylaminopyrimidine, emerged as the most promising compound. Early research confirmed its ability to inhibit the kinase activity of proteins containing ABL, ABL-related gene (ARG) protein, PDGF-R, and the c-KIT receptor (Buchdunger et al., 1996). This compound was found to be highly specific against cells affected by BCR-ABL in pre-clinical animals studies and in vitro (Deininger, Goldman, Lydon & Melo, 1997; Druker et al., 1996; Le Coutre et al., 1999). Further research has identified imatinib's wide-ranging haematological benefits (See Table 6) and this along with its

limited toxicity resulted in its consideration for therapeutic use and ultimately its endorsement as a first line treatment for CML and gastrointestinal stromal tumours.

Table 6

Summary of the Pharmacological Properties of Imatinib (Moen, McKeage, Plosker & Siddiqui, 2007).

- Inhibits proliferation and induces apoptosis in Ph+ CML cells expressing BCR-ABL
- Potently inhibits fresh leukaemia cells in vitro
- Demonstrates anti-tumour activity in murine models against BCR-ABL positive tumour cells
- Inhibits receptor tyrosine kinases for platelet-derived growth factor (PDGFR) and stem cell factor
- Down regulates telomerase activity, thereby inhibiting proliferation in telomerase-expressing cell lines
- Inhibits vascular endothelial growth factor by targeting Sp1 and Sp3 DNA-binding activity
- Stimulates mitochondrial glucose metabolism while inhibiting glycolytic activity
- Normalises bone marrow vascularity in CML patients
- Reduces myelofibrosis in CML patients

1.5.2 Efficacy

Imatinib's efficacy was established through a series of large-scale randomised control studies (Guilhot et al., 1997, Sawyers et al., 2002; Talpaz et al., 2002). One such study compared the therapeutic benefits of imatinib with the first line non-transplant treatment option of the day (i.e., interferon alpha plus low dose cytarabine) (Guilhot et al., 1997). Imatinib demonstrated superior rates of complete haematological remission, major cytogenic remission, and complete cytogenic response (See Table 7). The imatinib cohort also experienced a significantly higher incidence of disease free survival at 18 months. These findings lead the FDA to approve imatinib as a first line treatment for Ph+ CML in the chronic phase, accelerated phase or blastic crisis in December 2001 (Deininger & Druker, 2003; Moen et al., 2007).

Table 7

Comparison of Response to Imatinib vs. Interferon plus Cytarabine (O'Brien et al., 2003).

	Complete Haematological Response	Major Cytogenic Response	Complete Cytogenic Response	Progression-Free Survival (14 months)
Imatinib (n=553)	95.3%	85.2%	73.8%	92.1%
Interferon-α + Cytarabine (n=553)	55.5%	22.1%	8.5%	73.5%
p =	0.001	0.001	0.001	0.001

According to Kantarjian et al. (2002), imatinib's therapeutic response was dependent upon the stage of the disease, with the best results seen in patients in the chronic phase. In this phase, a rapid and complete haematological response was reported in 95% of patient, whilst 60% experienced a major cytogenic response, and 41% achieved a complete cytogenic response (Kantarjian et al.). Unfortunately even patients with complete cytogenic responses, still exhibited low levels of BCR-ABL on investigation (Merx et al., 2002).

Prior to the introduction of imatinib, non-transplant treatments had proven ineffective in the accelerated phase and during blast crisis. However unlike conventional chemotherapies and interferon, imatinib demonstrated some therapeutic benefit in the accelerated phase (Kantarjian, Giles, O'Brien & Talpaz, 1998; Talpaz et al., 2002). Up to 34% of patients achieved complete haematological remission, whilst 17% experienced a complete cytogenic response (Talpaz et al.). Kantarjian et al. (2005) reported a significant survival advantage in the accelerated stage when compared to other therapies ($p < 0.0001$); stating that an estimated 53% of patients taking imatinib would survive beyond four years, compared to 42% of patients on interferon alpha, and <25% for other therapies (Kantarjian & Giles, et al.).

Although successful treatment in the blastic phase remains somewhat elusive, imatinib has demonstrated some impact on the course and progression of the disease during this phase. Up to 8% of patients achieved a completed haematological response, whilst 7% experienced a complete cytogenic remission (Sawyers et al., 2002). A durable haematological response was associated with increased survival times (i.e., surviving

19 months with a sustained haematological response; 6 months with an unsustained response; 3 months with no response). However patients rapidly developed drug resistance in blast crisis due to additional mutation of the BCR-ABL gene (Gorre et al., 2001).

1.5.3 Adverse effects

Not only did imatinib prove to be more effective than interferon plus low dose cytarabine, it was also shown to be less toxic. In a series of large-scale investigations (Druker et al., 2006; O'Brien et al., 2003), imatinib demonstrated consistently less frequent and less severe adverse effects than previous first line treatments (See Figure 2).

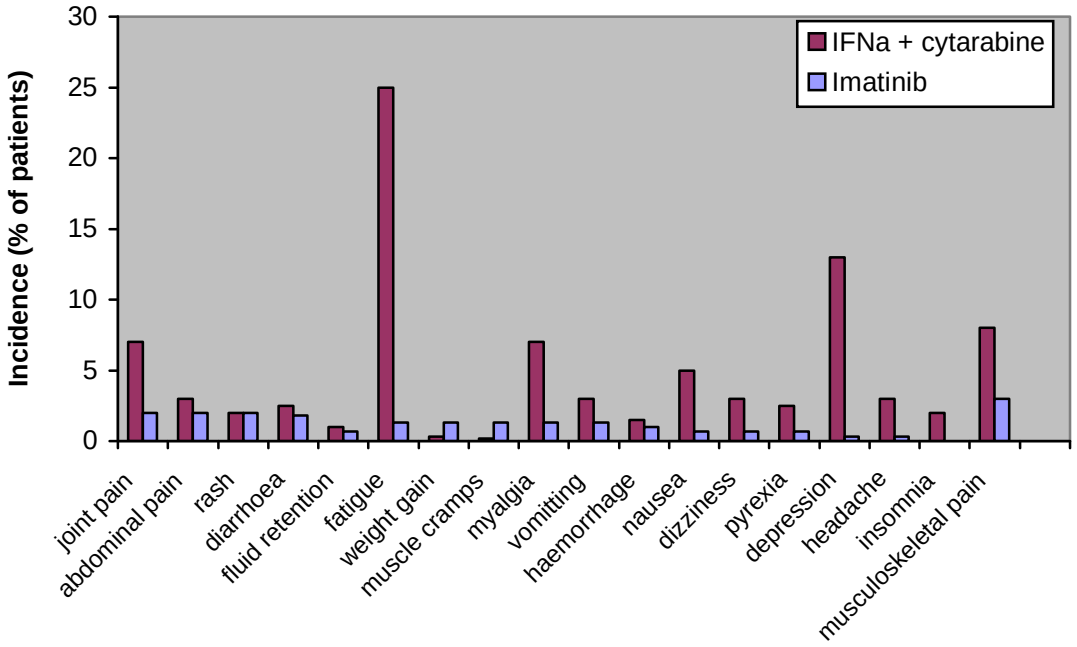


Figure 2. Incidence of grade 3 or 4 (Common Toxicity Criteria see Appendix J) non-haematological adverse events (Moen et al., 2007).

Although side effects are still relatively common in the imatinib cohort, they are generally mild (See Table 8). The range and underlying etiology of a number of these adverse effects is discussed in more detail below.

Table 8

Adverse Effects associated with Imatinib Use (Adapted from Moen et al., 2007)

Common Side Effects		Infrequent Side Effects	Rare Side Effects	
Superficial oedema	58%	Neutropenia	Cardiac failure	0.04%
Nausea	47%	*12% in chronic phase; 3% in accelerated phase*	Pleural effusion	
Muscle cramps	43%		Renal failure	
Musculoskeletal pain	39%			
Diarrhoea	39%	Thrombocytopenia		
Rash	37%	*8% in chronic phase; 0.2% in accelerated phase*		
Fatigue	37%			
Headache	34%			

Periorbital oedema is the most frequent form of fluid retention, however pleural and pericardial effusions, pulmonary oedema, ascites, and anasarca have been reported infrequently. Ebnoether et al. (2002) described two cases of cerebral oedema; one resolved after withdrawal of treatment and the other proved fatal. Although the underlying etiology is not well understood, it is thought to be related to the inhibition of PDGF-R as mice with deletions of this kinase experience oedema as a result of defective blood vessels (Lindahl, Johansson, Leveen & Betscholtz., 1997).

Gastrointestinal complaints such as nausea and diarrhoea are also common, and thought to be due to the local irritant effects of imatinib (Deininger & Druker, 2003). In contrast, changes in skin pigmentation and a darkening of hair colour, reported in rare cases, are considered to be indirectly associated with the inhibition of c-KIT (Etienne, Cony-Makhoul & Mahon, 2002). More serious adverse consequences include one reported case of liver failure, although a direct causal link was not firmly established (Deininger & Druker, 2003), and severe congestive heart failure and left ventricular dysfunction, which was described in ten patients with pre-existing cardiac risk factors (Kerkelä et al., 2006). Recent attempts have been made to re-engineer imatinib to decrease its potential cardiotoxicity (Demetri, 2007). Further to this, Seymour et al. (2004) described subtle changes in fertility, immunological, and pulmonary function.

1.6 TREATMENT EFFECTS: COGNITION, EMOTION, AND QUALITY OF LIFE

1.6.1 Transplant Therapies

A range of cognitive and mood changes have been associated with both allogeneic and autologous stem cell transplantation. Whilst the majority of patients experience a return to baseline cognitive function within a year of treatment, a subset of patients continue to perform more poorly on measures of verbal fluency, attentional switching, and/or memory (Ahles, Tope, Furstenberg, Hans & Mills, 1996; Syrjala et al., 2004). Interestingly, Syrjala et al. reported that a return to baseline levels might not reflect a genuine return to 'normal' function, as a high percentage of patients consistently perform below expectation during the baseline assessment. Andrykowski, Brady and Henslee-Downey (1994) and others (Baker et al., 2004) claimed that these pre-transplant related deficits were probably associated with myeloblative preparative regimes, i.e., the use of high dose chemotherapy (but not hydroxyurea) and total body irradiation prior to treatment. The impact of these regimes will be discussed in more detail later in this section. Ahles (2004) also suggested that the use of baseline measures were problematic, as the stress of the patients' recent diagnosis could impact their baseline levels of cognitive function.

A number of additional neurosensory and neuromotor deficits have also been reported post-treatment. Baker et al. (2004) indicated that patients were 2.8 times more likely to experience an abnormal or lost sense of taste, touch or smell than the general population. Balance problems, tremor or weakness was also 4.4 times more likely, and patients continued to report reduced grip strength and motor dexterity one year after transplantation (Baker et al; Syrjala et al., 2004).

Mood disturbance is also commonly observed after ASCT. Almost 20% of patients describe symptoms in the initial period following treatment, whilst anti-depressant and anti-anxiolytic use remains higher than the general population even 10 years after transplantation (Syrjala et al., 2005). Lowered mood is intricately linked to reports of reduced social function and poorer quality of life following ASCT. However these factors are also thought to be associated with the intensity and toxicity of preparatory

regimes, prolonged hospitalisations and recovery, and risk of mortality (Ahles et al., 1996).

Lowered mood has also been associated with reduced survival, as depressed patients are three times more likely to die in the first year after transplant (Loberiza et al., 2002). Andrykowski et al. (1994) claimed that individuals with an "anxious preoccupation" about their treatment were more prone to relapse. The authors proposed a biological basis for this phenomenon, suggesting that ongoing anxiety would lead to over activity of hypothalamo-pitutitary-adrenal axis and the sympathoadrenomedullary axis. This prolonged activation would suppress the immune system, thereby increasing the patient's susceptibility to relapse (Andrykowski et al.). Previous research has also identified a link between increased survival and either a 'fighting-spirit' or denial, whilst a sense of hopelessness or resignation was associated with a higher likelihood of death (Andrykowski et al.).

In spite of the greater incidence of mood disturbance following ASCT, patients also described more positive psychological and interpersonal growth than the general population. In particular, studies have reported an increased tendency towards improved interpersonal relationships, greater self-esteem, a renewed and enhanced appreciation of life, and a heightened spirituality (Andrykowski et al., 2005).

1.6.1.1 Impact of Preparative Regimes for ASCT

Toxic regimes such as high dose chemotherapy and whole brain irradiation typically occur prior to ASCT as a preparative measure to reduce the numbers of leukaemic cells in the system. The impact of radiation on cognition has been well documented in the literature (Andrykowski et al., 1992; Laack & Brown, 2004; Peper et al., 2000). Much of the research has focused on the impact of radiotherapy in childhood, and therefore this literature is beyond the scope of this thesis. Instead this discussion will focus primarily on the adult literature, given that CML typically affects individuals during this stage of life.

Laack & Brown (2004) claimed that cranial irradiation is more likely to cause cognitive deficits with increasing dose, fraction, field, and older age. Neurological changes

associated with treatment are typically classified into acute effects, subacute encephalopathy, and late delayed effects (Moretti et al., 2005). Both the acute and subacute responses are reversible but residual deficits are common with late delayed effects. The acute stage, which is traditionally characterised by drowsiness, headache, and nausea, is believed to be secondary to increased focal oedema (Sheline, Wara & Smith, 1980). In contrast, the subacute response, which includes somnolence, fatigue, and deterioration of pre-existing symptoms, is thought to result from diffuse demyelination within the CNS (van der Kogel, 1986). The final, and more concerning late delayed response tends to be irreversible and progressive (Kramer, 1968). Schultheiss, Kun, Ang and Stephens (1995) claimed that deficits were mediated by CNS white matter changes associated with vascular insult, demyelination, and necrosis. The extent of cognitive deterioration varies in accordance with the severity and location of white matter damage (Correa et al., 2004; Delano-Wood et al., 2008), and as such symptoms may range from mild fatigue to executive dysfunction and significant memory impairment (Moretti et al., 2005; Schultheiss et al., 1995).

Although research into the psychological impact of hydroxyurea and busulfan is lacking, attempts have been made to define the adverse cognitive sequelae associated with chemotherapy in general. These attempts have been somewhat controversial, as research efforts have attempted to generalise findings from different chemotherapy agents. Furthermore, much of the research has focused on cognitive impairment in middle-aged female breast cancer patients (Pedersen et al., 2009) and studies have typically failed to account for pre-treatment cognitive dysfunction associated with the disease process (Wefel, Witigert & Meyers, 2008). Given the role of chemotherapy in preparative regimes for ASCT, the current literature regarding its impact on cognition will be briefly discussed in the following review.

A profile of subtle but durable and disabling cognitive deficits has been described in much of the literature (Vardy, Wefel, Ahles, Tannock & Schagen, 2008). Recent large-scale longitudinal studies have identified a pattern of attentional deficits, poor processing speed, impaired memory retrieval, and executive dysfunction (Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006; Scherwath et al., 2006; Wefel, Lenzi, Theriault, Davis & Meyers, 2004). In contrast, Pedersen et al. (2009) claimed that this profile of deficits could not be generalised across cancer groups or treatments,

as patients receiving chemotherapy for testicular cancer did not differ from controls on a range of cognitive measures.

In spite of this, Ingaki et al. (2007) and others (Saykin, Ahles, & McDonald, 2003; Saykin, Ahles & Schoenfield, 2003; Stemmer, Stears, Burton, Jones & Simon, 1994) claimed that chemotherapy resulted in visible cortical changes on neuroimaging. In particular, MRI brain scans have identified white matter insults, and reduced volumes in the frontal cortex and diffuse gray matter. Decreased metabolic activity in the bilateral prefrontal gyrus, Broca's area and its contralateral structure, also correlated highly ($p < 0.02$) with impaired performance on working memory tasks (Silverman, Castellon & Abraham, 2003).

The underlying neuropathological processes are not well understood. However a number of hypotheses have been proposed including damage to the endothelium of blood vessels causing increased blood clotting and enhancing the risk of micro-infarcts (Levine, Gent & Hirsh, 1988), direct neurotoxic effects to neurons and white matter (Saykin et al., 2003), and the release of cytokines (Ahles & Saykin, 2007). Ahles et al. (2003) claimed that not all patients experienced these cognitive deficits, and suggested that there may be a genetic predisposition, with carriers of the e4 allele of apoliprotein significantly more likely to perform poorly on measures of cognitive function.

1.6.2 Non-transplant Therapies

Prolonged survival was the sole focus of early cancer treatment efforts. As such, there is no research on the specific cognitive and mood effects of conventional chemotherapies such as bulsulfan and hydroxyurea. As cancer therapies improved, research efforts turned towards the impact of treatment on quality of life and general functioning.

Interferon alpha was the first non-transplant treatment to be scrutinized, given its reported survival advantage and apparent neurotoxicity. According to Pavol et al. (1995) patients treated with interferon alpha exhibited higher levels of cognitive and affective disturbance than might be expected in the general population or a group of terminally ill patients. Even healthy volunteers subjectively reported a reduction in the

level of alertness after a single dose (Valentine et al., 1998). Impaired memory function, reduced processing speed, and executive dysfunction, as evidenced by poor problem-solving skills and an inability to shift mental set, was consistently reported across studies (Meyers, Scheibel & Forman, 1991; Pavol et al.; Scheibel, Valentine, O'Brien & Meyers, 2004). Scheibel and colleagues (1991) claimed that the extent of these deficits was more than might be expected from depression alone.

Extrapyramidal signs have also been described in a number of patients including tremor, masked faces, and rigidity. In most cases, the type and severity of these symptoms impacted the patient's ability to maintain their usual work (Meyers et al., 1991).

Molignier, Allo, Zittoun and Gout (2002) described the case of a woman who presented with progressive personality change, short-term memory loss, and choreiform movements two years after commencing treatment with interferon alpha. An MRI brain scan undertaken during this time was reported to show bilateral widening of the ventricles, and EEG was disorganised with diffuse slow waves. Over the next six months the patient's condition declined to the point where she was bedridden and scoring 5/30 on the mini-mental state examination (MMSE). Interferon treatment was discontinued. The choreic movements disappeared and cognitive function improved (MMSE of 26/30). Six months after discontinuation of treatment, the patient's cognitive profile and EEG results had returned to normal levels. According to Valentine et al. (1998) neurotoxic symptoms generally resolve within two to three weeks of discontinuing therapy. In contrast, Meyers et al. (1991) described persistent neurotoxicity long after treatment was discontinued. However these findings were based on the longtidunal follow-up of four cancer patients with different malignancies. These patients were assessed between 18 to 240 days after the discontinuation of interferon. It is anticipated that the findings would be differentially impacted by practice, and that participants would be at different stages in the disease process and/or undergoing a variety of treatments for cancer.

The profile of cognitive deficits described in the literature is consistent with a pattern of frontal-subcortical dysfunction (Pavol et al., 1995). However neuroimaging studies and EEG findings have failed to clearly support this finding. In a series of MRI and CT

brain scans of patients with interferon-induced cognitive deficits, 40% of scans were reportedly normal, whilst 50% showed marked atrophy and 30% displayed white matter change (Meyers et al., 1991). Further to this, EEG studies have consistently shown a pattern of diffuse slowing (Amodio et al., 2005; Meyers et al.).

Interferon alpha has also been associated with significant affective and psychiatric disturbance in patients with no previous history. Depressive symptoms are reported to occur in 8 to 48% of patients (Malek-Ahmadi & Hilsabeck, 2007), with the variation in rates most likely due to a lack of standardized methods of investigation (Amodio et al., 2005). Heightened anxiety and mania were also described both during and after discontinuation of treatment (Amodio et al., Carpiniello, Orru, Baita, Pariante & Farci, 1998; Kingsley, 1999). Although uncommon, a number of cases of attempted and completed suicide have been attributed to interferon use (Janssen, Brouwer, van der Mast & Schalm, 1994). Fattovich, Giustina, Favarato and Ruol (1996) claimed that approximately 1% of patients experience psychosis, and isolated cases of homicidal ideation (James & Savini, 2001) and PTSD (Maunder, Hunter & Feinman, 1998) have been described in the literature. The risk of these types of disturbance, along with the potential for cognitive decline increases with higher dosage, longer treatment duration, older age, and the presence of a pre-existing neurological or psychiatric disorder (Hensley et al., 2000; Poynard et al., 1996; Valentine et al., 1998).

A number of mechanisms have been proposed to explain these cognitive and psychiatric changes, however the process is not well understood. Cognitive changes are thought to be associated with the reduced movement of calcium into the hippocampus, given this regions primary role in memory function. In addition to this, hypothalamic structures have been implicated, as this structure acts to allow interferon into the brain but also has important interconnections with the frontal lobes and brain stem. Finally, interferon effects dopaminergic activity that in turn impacts subcortical function and neuroendocrine hormones, which may indirectly affect memory (Pavol et al., 1995).

1.6.2.1 The impact of Imatinib on CNS functioning

At present no systematic studies have been undertaken to investigate the impact of chronic imatinib usage on cognition and affect. However, improved quality of life has

been reported with imatinib use, as the drug can be self-administered on an outpatient basis (Deininger & Druker, 2003). Hahn et al. (2003) Indicated that patients reported significantly better quality of life, physical functioning, and well being when compared to interferon alpha plus cytarabine (p= 0.001).

The impact of imatinib on cognition is not yet understood, however adverse effects may be expected given the role of protein kinase in the CNS. The various protein kinase inhibited by imatinib *in vitro* (including PDGF-R and B, KIT, ABL and ARG) are responsible for a range of diverse neurological activities. The ABL, ARG, and KIT kinase play an important role in regulating the neuronal cytoskeleton and modulating synaptic efficacy, and is implicated in the consolidation and retention of memories (Moresco et al., 2003; Tzingounis & Nicoli, 2006). The inhibition of such kinase is most significant in areas with a high concentration of synapses, such as the hippocampus; a region intimately involved with learning and memory (Katafuchi, Li, Hirota, Kitamura & Hori, 2000; Moresco et al., 2003). This was effectively demonstrated in a series of animal studies, which showed impaired learning and memory in mice deficient in the ABL-interactor protein (Grove et al., 2004), ARG (Tzingounis & Nicoli, 2006) and KIT (Katafuchi et al., 2000).

The inhibition of particular kinase may also leave the CNS more susceptible to insult. For example, the protein kinase KIT is intricately involved in the repair of brain damage (Sun, Lee & Fine, 2004) and prolongs the survival of stem cells in the CNS (Erlandsson, Larsson & Forsberg-Nissen, 2004). In contrast, the inhibition of PDGF in mice has been shown to profoundly effect the expression of oligodendrocyctes and myelin, particularly in the cerebellum and spinal cord (Fruttiger et al., 1999). However in clinical practice imatinib has demonstrated low CNS permeability (0.7-2.5%), leaving the brain as a potential sanctuary for the BCR-ABL gene (Wolff, Richardson, Egorin & Ilaria, 2003).

Interestingly, a number of positive findings have been reported following imatinib use. Alvarez, Sandoval, Leal, Castro, and Kosik (2004) claimed that the inhibition of ABL by imatinib halts neuronal cell death triggered by beta-amyloid (as occurs in Alzheimer disease). Further to this, the inhibition of PDGF by imatinib resulted in fewer complications and reduced damage to the blood brain barrier after haemorrhagic stroke

in mice (Rieckmann, 2008). Newer kinase inhibitors now in clinical trials may have higher CNS permeability, which whilst more effective in eradicating leukemic cells from the CNS, risk higher CNS toxicities (Porkka et al., 2008).

1.7 DEMOGRAPHIC VARIABLES, AFFECT, AND COGNITION

1.7.1 Mood

Heightened anxiety and lowered mood is not uncommon following a diagnosis of CML. The potential for affective disturbance is an important consideration, as changes in mood may impact cognition. However there is little consensus about the specific profile of cognitive deficits associated with mood disturbance, even amongst large-scale meta-analytic studies. Veiel (1997) claimed that mental flexibility, visual scanning, and visual spatial functions were most affected by lowered mood. However, Zakzanis, Leach and Kaplan (1998) described a pattern of reduced psychomotor speed, sustained attention, and encoding or retrieval of episodic memories. The greatest impairment was reportedly seen on memory tasks that required more effortful encoding of information. In contrast, deficits in attention, psychomotor speed, working memory, and executive functioning have also been reported in the literature (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari & Lönnqvist, 2008; Liotto & Mayberg, 2001). The variation in findings has been associated with the heterogeneous nature of the study samples, including the presence of co-morbid disorders, differences in physical well being and medication use, and a raft of methodological issues (Castaneda et al., 2008; Ottowitz, Dougherty, & Savage, 2002; Veiel, 1997).

Various neuroanatomical substrates have been implicated in depression. Liotti and Mayberg (2001) reported PET resting state abnormalities in the dorsal prefrontal cortex and anterior cingulate (particularly in the right hemisphere). Ottowtiz et al. (2002) described atrophy in the hippocampus, amygdala and caudate nucleus, and reduced blood flow to the anterior temporal, anterior cingulate, and inferior frontal cortices.

1.7.2 Affect

Acute stress and anxiety may also impact an individual's cognitive abilities. Airaksinen, Larsson and Forsell (2005) reported significant episodic memory and

executive functioning deficits associated with anxiety. Ransom (2008) claimed that anxiety had a greater impact on executive function than depression (Airaksinen et al., 2005; Toren et al., 2000; Yan, Wang, and Cui, 2007; Yun-fei, 2005).

Acute stress reactions have also been shown to negatively compromise working memory capacity (Ashcraft, 2002) processing speed (Crowe et al., 2001), impair learning (Keinan & Friedland, 1984), and reduce an individual's ability to inhibit irrelevant stimuli (Keinan, Friedland, Kahneman & Roth, 1999).

Castaneda et al. (2008) claimed that the profile of deficits is dependent on the anxiety disorder subtype. An analysis of separate subtypes revealed that individuals with social phobia were more likely to exhibit episodic memory deficits, whilst panic disorder was associated with declines in executive function and memory. No consistent profile of deficits has been reported in individuals with generalized anxiety and specific phobias (Airaksinen et al., 2005).

1.7.3 Socio-economic Status

An individual's SES is said to mediate the extent of recovery from brain insult (Ponsford, 2004). Long term neuropsychological outcomes following brain injury (regardless of severity) are better for people from higher socio-economic groups, with superior performances reported on measures of overall cognitive function, verbal ability, and visual perceptual skills (Catroppa & Anderson, 2003). Arango-Lasprillo et al. (2007) claimed that people from lower socio-economic backgrounds tend to receive fewer therapy services and are required to wait longer to see a physician, whilst a higher SES has been associated with better access to resources (Taylor, Schatschneider & Rich, 1992).

1.7.4 Educational Attainment and IQ

Premorbid ability and education are considered significant predictors of outcome following brain insult (Putman et al., 2007; Starr & Lonie, 2008). Bigler (1995) claimed that these personal variables modulate the degree of cognitive impairment after closed head injury. Although the underlying mechanisms are not well understood,

Banich (2004) and others (Satz, 1993) proposed a number of explanations. Firstly, individuals with greater intellectual ability have a larger reserve of capacity, which will help buffer them against the full impact of brain injury. Sohlberg and Mateer (2001) claimed that the challenges associated with higher education also enhanced one's 'cognitive reserve' by contributing to increased neural connectivity, particularly in language areas (Jacobs, Schall & Scheibel, 1993). Secondly, intelligent individuals may be more able to learn and develop strategies to compensate for their disability (Banich, 2004).

1.8 DISEASE-EFFECTS AND COGNITION

1.8.1 Fatigue and Cognition

Fatigue has now been acknowledged as a significant and potentially disabling consequence of most cancers and cancer treatment. Cancer-related fatigue evolves over time, compromising physical energy and mental capacity (Iop, Manfredi & Bonura, 2004) and can by differentiated from normal fatigue, as it is refractory to rest (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre & Morrow, 2007).

Often it is difficult to differentiate cancer-related fatigue from treatment-related fatigue. However, Savage, Szydlo and Goldman (1997) reported fatigue as a common symptom of CML, which is typically present at diagnosis and persists at some levels throughout the course of the disease. Recent research efforts have endeavoured to describe the subjective behavioural and psychological consequences of this symptom (Hofman et al., 2007). See figure 3.

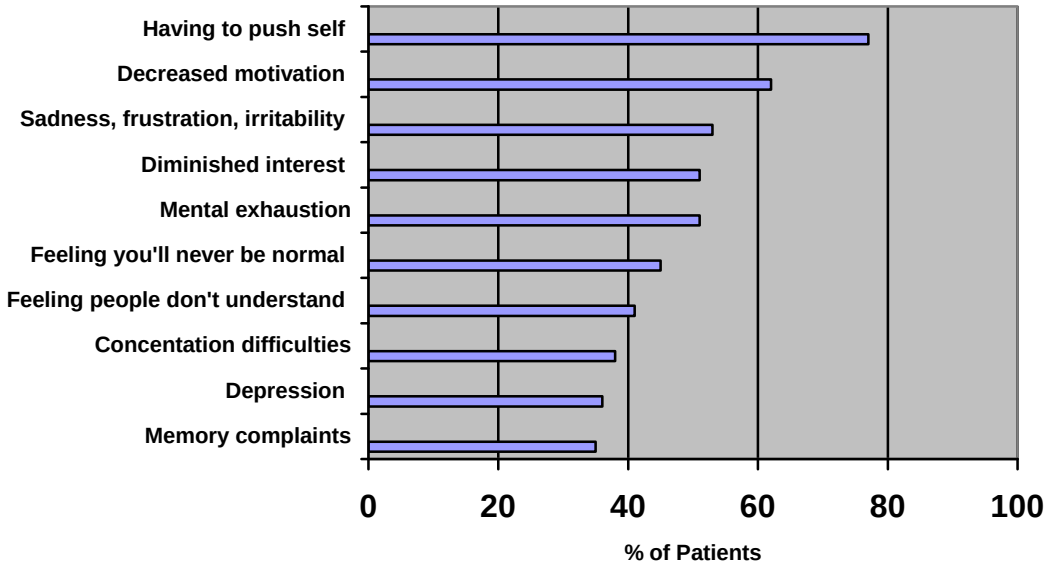


Figure 3. Subjective cognitive and emotional effects of cancer-related fatigue (Curt et al., 2000)

Heightened fatigue is commonly associated with reduced processing and motor speed, along with other deficits in sustained attention, concentration, and reaction time (Groopman, 1998, Michiels, de Gucht, Cluydts & Fischler, 1999; Tiersky, Johnson, Lange, Natelson, & DeLuca, 1997). This pattern of deficits is evident across cancer treatments (Caraceni et al., 1998; Jacobsen, et al., 1999; Valentine et al., 1998) and disease populations, including cancer, multiple sclerosis, and chronic fatigue syndrome (Diamond et al., 2008; Michiels et al., 2008; Meyers, 2000).

1.8.2 Concomitant Medication and Cognition

Specific medications can differentially impact cognition and behaviour, and alter neuropsychological assessment findings (Bjorkman, Fastbom, Schmidt & Bersten, 2002). Drugs associated with the most adverse effects include anti-cholinergics, benzodiazepines, narcotics, neuroleptics, anti-epileptic drugs, and sedative-hypnotics (Meador, 1998; Stein & Strickland, 1998). A brief summary of these agents and their impact on cognition is outlined in Table 9.

Table 9

Adverse Cognitive Effects associated with Medication Use (Adapted from Moore & O'Keefe, 1999)

Drug Class	Potential Adverse Effects
Anti-cholinergic agents (e.g.,) Anisotropine, Atropine, Belladonna, Clidinium, Dicyclomine, Glycopyrrolate, Homatropine, Hyoscyamine, Mepenzolate, Methantheline, Methscopolamine, Pirenzepine, Propantheline	▪ Linked to memory impairment in healthy ▪ Increased likelihood of developing delirium.
Anticonvulsants (e.g.,) Phenobarbital, Primidone, Clonazepam, Valproic Acid, Carbamazepine, Phenytoin	▪ Greatest impact with phenobarbital, primidone, & clonazepam
Antidepressants (e.g.,) Tricyclics Pamelor, Norpramin, Vivactil, Elavil, Adapin, Tofranil SSRI's *Prozac, Paxil, and Zoloft*	▪ Impaired memory, reaction time, retrieval and information processing, disorientation and delirium possible with tricyclics.
Antiparkinsonian agents (e.g.,) Amantadine, Pergolide, Levodopa, Selegiline carbidopa	▪ Possible delirium ▪ Hallucinations
Antipsychotics (e.g.,) Risperidone, Quetiapine, Ziprasidone, Clozapine and Olanzapine	▪ Delirium ▪ Possible accelerated cognitive decline
Antibiotics/anti-infective agents (e.g.,) Penicillin	▪ Can induce psychosis and encephalopathy
Hypnotics/Sedative agents (e.g.,) Benzodiazepines, diazepam, temazepam	▪ Impaired learning, memory, and psychomotor speed
Cardiac medications /Antihypertensive Agents (e.g.,) Statins Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin, Cerivastatin, Rosuvastatin Antirrhythmics Digoxin, Amiodarone, Lidocaine Antihypertensives Beta-blockers, Propranolol, Methyldopa, Clonidine	▪ Impaired memory and cognition ▪ Psychiatric problems ▪ Methyldopa associated with decreased visual motor performance ▪ Digoxin toxicity associated with delirium and dementia
Corticosteriod Agents Dexamethasone, Prednisone, Betamethasone, Prednisolone	▪ Delirium ▪ Psychosis

1.9 NEUROPSYCHOLOGICAL MEASUREMENT ISSUES

1.9.1 Assessment of Neuropsychological Sequelae of Traditional Non-transplant Treatments

Researchers have endeavoured to characterise the cognitive and affective sequelae of cancer therapies. The success or otherwise of investigating treatment-related effects has varied according to the chosen research methods employed. The following section includes a brief review of the methodological approaches used in recent non-transplant-related studies.

Pavol et al. (1994) conducted a cross-sectional investigation in order to ascertain the impact of interferon on cognition and behaviour in CML. No pre-treatment assessment was undertaken, and therefore it was not possible to determine whether mood disturbance or cognitive impairment was present prior to commencement of treatment. The participants were in different phases of the disease, and had received interferon treatment for varying periods of time (ranging from 1 week to 84 months). Although treatment dose and time since diagnosis were considered in the overall analysis, the impact of disease progression and treatment chronicity were not analysed.

In contrast, Meyers et al. (1991) completed a longitudinal study of individuals on interferon to determine the impact of treatment over time. Unlike the previous investigation, the authors performed repeat assessments on a limited number of participants. However the sample included participants with a range of malignancies, and the neuropsychological test inventory varied between individuals given the diversity of ages in the study and the availability of age norms for various tests. The heterogeneity of the sample and the different test inventories employed raises questions about one's ability to draw firm conclusions from the data.

In a more recent review, Scheibel et al. (2004) performed serial neuropsychological assessments with 30 CML patients prior to commencing treatment and during treatment with interferon. The authors gave due consideration to the period of time since diagnosis and treatment dose, as these important factors may influence treatment response, potential neurotoxicity, and disease progression. A short inventory of six tests measuring graphomotor speed, verbal learning and memory, visual motor/sequencing skills, and verbal fluency was used to assess changes in cognition over time. Tests were chosen, based on the expectation that they would be sensitive to the cognitive effects of interferon. However this is potentially problematic, as it increases the potential for 'confirmatory bias' in which researchers utilise measurements techniques to derive data that is consistent with their hypothesis whilst failing to identify other potential sequelae (Dawes, Faust & Meehl, 1989).

1.9.2 Evaluating the Neuropsychological Impact of Transplant Treatments

Similar issues and developments have been seen in the investigation of transplant-related effects on cognition. Ahles et al. (1996) examined the impact of ASCT on 55 candidates with a variety of malignancies before treatment, one to three days after transplantation, and within two days of discharge. On all three occasions, assessments included measures of mood, affect, and cognition. It is crucial that participant's affective state is assessed on each occasion, as lowered mood or increased anxiety at the baseline assessment may depress cognitive function and therefore influence the examiner's interpretation of results on subsequent assessments. Limitations identified in the study include the rapid succession of assessments, leading to an increased risk of practice effects and the lack of longitudinal follow up. The authors reported that any further assessments should include a measure of the participant's quality of life in order to understand the impact of cognitive impairment on daily living.

Finally Syrjala et al. (2004) examined the impact of allogeneic SCT on cognition by undertaking assessments before treatment, at 80 days, and one year after treatment. Adult patients completed a brief assessment of selected cognitive domains including motor strength, speed, and dexterity; attention and processing speed; verbal fluency and memory; and executive function. The Information subtest from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) was used as an estimate of premorbid ability. However the authors acknowledged that a more robust and thorough measure (e.g., Full-scale IQ) would be required to obtain a better understanding of the person's baseline function. Alternate tests were utilised during the course of assessment to minimise practice effects. However the authors still described this as an area of ongoing concern as the participants increased familiarity with the test procedure might lead to improved performance. Finally, a one standard deviation drop in performance was utilised as an indication of statistically significant change. However, Keith et al. (2002) argued that this criterion is quite liberal, as a "*one standard deviation decrement would be expected to occur by chance alone with about a 14% likelihood"* (p. 412). Alternate statistical analyses for assessing change are discussed in more detail in section 3.1 Data Analysis.

1.9.3 A Best Practice Approach for Investigating the Neuropsychological Effects of Imatinib

1.9.3.1 Considerations for Study Design

The International Cognition and Cancer Task Force (ICCTF) recently established a best practice approach to assess cognitive changes associated with cancer treatment (Vardy et al., 2008). This model emphasised the use of longitudinal approaches over cross-sectional designs in order to assess adverse effects over time. This is particularly relevant for younger people as cognitive deficits may evolve as they grow and serial assessment will assist to plot the course of deterioration (Anderson & Moore, 1995).

The ICCTF also favoured the use of thorough test inventories, which assess multiple cognitive domains and have the capacity to detect subtle deficits. Whilst this is considered best practice, it may have other practical implications for study design and statistical analysis. That is, large test inventories with multiple dependent variables require a greater number of participants in order to reduce the potential for type I errors.

Given the strong emphasis on serial assessment, the ICCTF state that these assessment tools should have high test-retest reliability and strive to minimise the potential for practice effects through such means as alternate forms (Vardy et al., 2008). Parth, Dunlop, Kennedy, Lane and Ordy (1989) asserted that inventories should also consider confounding variables such as motivation and fatigue, which are known to influence performance on cognitive measures. In addition to this, researchers should aim to monitor the use of concomitant medication, and obtain a measure of premorbid ability and SES as these factors have the potential to impact and mediate cognitive changes (Schagen et al., 2002). Pre-morbid intellectual capacity is an important variable, particularly when serial assessments are undertaken, as intelligent people will often benefit more from practice (Rapport, Brines, Axelrod & Thiesen, 1997). Therefore, measuring an individual's pre-morbid intellectual function may help to determine whether there has been any real change in performance over time. Wefel et al. (2008) indicates that it is equally important to obtain a pre-treatment measure of one's cognition, as the disease process itself may impact cognitive function. Therefore, this assessment may help to differentiate the effects of the disease process from the effects of the treatment.

The ICCTF briefly address the issue of control groups and state that studies should aim to utilise controls that closely resemble patients. Previous studies into the effects of chemotherapy in breast cancer have recruited age and gender-matched participants' receiving different treatments in order to differentiate the impact of the disease from the impact of the treatment (Ahles et al., 2002). Unfortunately in CML, imatinib is the first line treatment regardless of the stage of the disease and therefore it is difficult to identify a perfect comparator group.

1.9.3.2 Cognitive Measures to Assess the Impact of Cancer Treatment

Taking into consideration the guidelines developed by the ICCTF, a thorough test inventory should establish the patients' overall cognitive ability prior to commencement of treatment, and then review a range of domains in subsequent assessments. Although ideally a broad and detailed assessment should be undertaken at the very least the assessment should cover; attention and working memory; motor and processing speed; verbal learning and memory; and executive function as these domains have been previously identified in the literature as potentially susceptible to cancer treatments. The following is a brief review of up-to-date and reliable measures that may be used to effectively investigate the participant's cognition over time.

Pre-morbid Ability

The Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997a) is one of the most reliable, valid, and well-regarded measures of adult intelligence and therefore would provide an accurate estimate of one's baseline ability.

Attention and Working Memory

Digit Span subtest

The 'digits forward' component of the Digit Span subtest from the WAIS-III (Wechsler, 1997a) is considered a sound measure of one's immediate auditory attention span, which is dependent upon a short-term phonologically based storage system (Vallar & Baddeley, 1984). In contrast, the 'digits backwards' component of this test is regarded as one of the most sensitive measures of working memory, as it requires the

participant to hold and manipulate information in their mind and visually scan sequences of numbers internally (Baron, 2004).

Motor and Processing Speed

Digit Symbol Coding subtest

The Digit Symbol Coding subtest from the WAIS-III effectively measures both motor and processing speed (Wechsler, 1997a), and serves as a good tool for serial assessments given its high test-retest reliability (0.82 – 0.88) (Matarazzo & Hermann, 1984; Wechsler, 1981) and modest practice effects (McCaffery, Duff, & Westervelt, 2000). It is regarded as highly sensitive to a range of neurological disease processes (Lezak, Howieson, & Loring, 2004), with performance likely to be affected even with minimal brain damage. The Digit Symbol Coding subtest has proven to be a more effective measure of processing and motor speed in serial assessments than other popular tests, such as Part A of the Trail-making test, as "Trails A" is prone to significant practice effects (Lezak, 1982).

Verbal Learning and Memory

Logical Memory subtest

Considered the purest measure of episodic memory (Woodard, Goldstein, Roberts, & McGuire, 1999), the Logical Memory subtest from the Wechsler Memory Scale-Third Edition (WMS-III) (Wechsler, 1997b) provides the best estimate of one's everyday verbal memory capacity for meaningful verbal information. Given that the amount of material presented is beyond one's normal immediate memory span, the Logical Memory subtest helps to clarify the impact of data overload on cognitive abilities. The comparison between one's recall of a prose passage and a list of unrelated words also emphasises the importance of context and meaning in memory function (Lezak et al., 2004). In addition, the second presentation of this information is designed to minimise the amount of overwhelm experienced by the subject (Lezak et al., 2004).

Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT is considered one of the most sensitive measures of verbal memory function (Lezak et al., 2004). This supraspan word list-learning task was originally developed by Rey (1958) but revised by Lezak (1983), and yields an estimate of verbal learning, verbal recall, and verbal recognition (as cited in Lezak et al., 2004). Whilst

various measures may be derived from this test, some measures such as the post-interference trial (i.e., Trial 6) have proven to be more sensitive to neuropsychological insult than others (Geffen, Butterworth, Forrester & Geffen, 1994). In addition to this, the participants' total learning across the first five trials is considered one of the most reliable measures (Strauss et al., 2006), with low learning curves seen in most patients with brain disorders (Lezak et al., 2004). Furthermore, participants' performance on the verbal recognition trial enables the examiner to identify specific deficits in retrieval, which may be common after brain injury (Strauss et al., 2006).

Given that significant practice effects have been noted on repeat assessments of the RAVLT (McCaffrey et al., 2000), comparable alternate forms have been devised for serial assessments (Geffen, Butterworth & Geffen, 1994). The form follows the same format but utilises different words from the original list, the interference list, and the recognition task.

Executive Function

The Delis-Kaplan Executive Functioning System (D-KEFS) incorporates a range of traditional executive function tests, which have been revised and re-normed in order to increase their sensitivity to mild brain damage. Additional features or tasks have been added to these measures to assess cognitive flexibility, a key deficit in frontal lobe pathology (Delis, Kaplan & Kramer, 2001). In addition, the processing demands of many of the tests were increased in order to enable subtle deficits to emerge (Delis et al., 2001).

Verbal Fluency Test

The Verbal Fluency subtest from the D-KEFS is an executive functioning task, which is typically sensitive to changes in the CNS. The D-KEFS provides the most up-to date normative data for this commonly used measure (Delis et al., 2001). A decline in one's performance on the letter fluency component of this task is often indicative of diffuse brain insult or frontal lobe pathology, with left frontal and bilateral lesions resulting in lower word production than right frontal lesions (Lezak et al., 2004). The letter fluency component is commonly regarded as a more difficult task than the category fluency condition of this test (Lezak et al., 2004), which correlates more highly with posterior

cerebral function (Baron, 2004). Given this, the letter fluency condition of this task may serve as a more useful and sensitive measure of cerebral pathology. Alternate forms are available for this measure, making it appropriate for serial assessments and moderate to high correlations have been reported between the standard and alternate forms of the test (Delis et al., 2001).

Sorting Test

The Sorting Test from the D-KEFS was originally developed as the California Card Sort test in the late 1980's. This measure of executive function is sensitive to the effects of frontal lobe pathology (Delis, Squires, Birhle & Massman, 1992; Dimitrov, Grafman, Soares & Clarke, 1999). Again, an alternate form has been developed for serial assesments to reduce the potential impact of practice effects. However, low to moderate correlations have been reported between the two forms (Delis et al., 2001). This test derives four primary measures, however as with many other measures the free sort condition would be considered more demanding than the recognition format (Johnson, 1990).

Trails B

Finally the Trails B component of the Trail-Making subtests has been described as a sound measure of executive function. This test forms one half of an assessment tool originally devised by Partington and Leiter in 1938, as 'Partington's Pathways' or the 'Divided Attention Test' and later included in the 'Army Individual Test Battery' (1944) (as cited in Strauss et al., 2006). This test shares some similarities with Part A of the Trail-making subtest; also requiring adequate motor speed, agility, and visual scanning for its successful completion (Schear & Sato, 1989; Shum, McFarland & Bain, 1990). However the attentional switching component of the task places additional demands on cognitive flexibility, and probes one's ability to deal with multiple stimuli or thoughts at once (Arbuthnott & Frank, 2000; Kortte, Horner, Johnson & Windham, 2002; Eson, Yen & Bourke, 1978). There have been inconsistent findings about the psychometric properties of the test. Durvasula et al. (1996) reported significant practice effects when the test was administered in six-month intervals, yet in contrast Lezak (1982) identified no improvements over the same time course. Modest to high retest reliabilities have also been identified across studies, with coefficients ranging between .67 and .83 (Goldstein & Watson, 1989; Lezak, 1982).

1.9.3.3 Measures of Mood and Affect

Measures of mood and affect are crucial to any assessment of cancer-related cognitive impairment. This is particularly pertinent at the baseline assessment, as the stress associated with receiving a diagnosis may influence test performance and alter one's perceptions of the patient's pre-morbid ability (van Dam et al., 1998).

Researchers have attempted to identify 'gold standards' for the assessment of affective disturbance (Antony & Rowa, 2005; Gass, 2002**;** Joiner, Walker, Pettit & Perez, 2005). Gass (2002) claimed that direct observation was problematic, as clinicians could make inferences and over-generalisations based on a limited sampling of behaviour. In addition, informant reports have been criticised, as family members lack objectivity and may seek to portrait the patient in a more favourable light.

Much of the research has endorsed the use of semi-structured interviews and self-report inventories (Antony & Rowa, 2005; Joiner et al., 2005; Wilder & Douglas, 2005). Researchers have claimed that these techniques provide a more valid and reliable means to systematically and comprehensively assess psychopathology (Widiger & Samuel, 2005).

Mood

Beck Depression Inventory – Second Edition (BDI-II)

The BDI-II is a self-report inventory that was originally developed over 35 years ago. This instrument's psychometric properties have been well established, with retest reliabilities reported to be in the high eighties to low nineties in both clinical and non-clinical populations (Beck, Steer & Brown, 1996; Beck, Steer & Garbin, 1988).

Affect

State Trait Anxiety Inventory (STAI)

With over 3000 studies and reviews reported in the literature and strong psychometric qualities, the STAI is a self-report inventory designed to assess both state and trait anxiety (Spielberger, Gorsuch, Vagg & Jacobs, 1983). Modest to good test-retest reliability have been reported for questions tapping trait anxiety (r = .65 to .75), whilst state anxiety is changeable across assessments due to the transitory nature of one's

emotional state in a given situation (Spielberger et al., 1983).

1.9.3.4 Measures of Fatigue and Quality of Life

Quality of Life

Functional Assessment of Cancer Therapy-Leukaemia module (FACT-Leu)

The FACT-Leu measure was developed in 2002 in response to a growing need for a disease-specific quality of life and fatigue questionnaire in both acute and chronic leukaemia populations (Webster et al., 2002). The current twenty-seven item self-report inventory was derived from an extensive literature search, together with semi-structured interviews of patients and experts from across nine countries.

Functional Impact of Disease

The Eastern Cooperative Oncology Group Performance Status Scale (ECOG)

The ECOG (Oken et al., 1982) is completed by the examiner to capture the functional implications of the disease or treatment at each time point in a study.

1.10 RATIONALE

There is increasing interest surrounding the impact of cancer therapies on quality of life, mental health, and cognition. Patients treated with some of the conventional chemotherapies for other cancers are reported to suffer subtle but durable cognitive deficits, which persist long after treatment concludes (Freeman & Broshek, 2002). The adverse cognitive and affective changes associated with earlier non-transplant and transplant therapies for CML, such as interferon and ASCT, are well documented in the literature. Impairments in memory, processing speed, and executive function have been consistently reported following interferon use (Meyers et al., 1991; Pavol et al., 1995; Scheibel et al., 2004) and persistent memory complaints and executive dysfunction is described after ASCT (Syrjala et al, 2005). Up to 48% of patients taking interferon also experience depression, whilst 20% of patients report depression following ASCT (Malek-Ahmadi & Hilsabeck, 2007; Syrjala et al., 2005). Heightened anxiety, mania, and isolated cases of suicidal and homicidal ideation have also been linked to interferon use in the literature (Amodio et al., 2005; Carpiniello et al., 1998; James & Savini, 2001; Janssen et al., 1994; Kingsley, 1999).

In 2001 imatinib was introduced into haematology-oncology practice and rapidly endorsed as a first line treatment for CML in the chronic, accelerated, and blastic phase. The survival advantage demonstrated by this target kinase inhibitor has meant that patients are now treated with the agent on a long-term basis. However, there is a growing body of literature on the potential toxic effects of chronic imatinib use (Fruttiger et al., 1999; Grove et al., 2004). A safety sub-study undertaken by the Australasian Leukaemia and Lymphoma Group (ALLG) identified a range of subtle effects consistent with the inhibition of targeted kinases in the immunological, respiratory, endocrine, and reproductive systems (Seymour et al., 2004). To date, there has been no attempt to elucidate possible neuropsychological sequelae of chronic imatinib use.

However concerns exist about the potential neurotoxic effects of this agent, given that the inhibition of protein kinase in animal studies has been associated with a range of deleterious consequences, such as impaired learning and memory, and reduced synaptic efficacy (Grove et al., 2004; Moresco et al., 2003). Furthermore, research has identified the important role specific protein kinase play in repair after brain insult, prolonged survival of CNS stem cells, and regulation of the neuronal cytoskeleton (Erlandsson et al., 2004; Moresco et al; Sun et al., 2004). Therefore, the inhibition of protein kinase may have potential effects on the cognitive function of CML patients. However any investigation into the neuropsychological sequelae of long-term imatinib use must also consider the influence of mood, affect, and fatigue given their potential to impact cognitive function (Ashcraft, 2002; Buck-Gengler & Healy, 2001; Zakzanis et al., 1998).

At a methodological level there is a strong case for a wide-ranging assessment of cognitive functioning. Accordingly, the domains of attention and working memory, motor and processing speed, verbal memory, and executive function will be investigated. However this must be balanced with the practical implications of recruiting participants, given that CML is a relatively uncommon condition. From a study design perspective only the most sensitive measures in each of these domains will be utilised, in order to reduce the number of dependent variables and strengthen data analysis.

Fatigue, mood, and affect will also be monitored to elucidate their potential impact on assessment and cognition. In approaching the current study, attempts were made to enrol an appropriate control group for comparison. Unfortunately, it was not possible to recruit a comparable group for this study during the two and half years of data collection. This complex issue will be discussed in further detail in chapter four.

1.11 AIMS OF THE PRESENT STUDY

The aims of current study are:

Aim 1: To examine the verbal learning and verbal memory of adult CML patients over the course of 12 months. Results on verbal learning and memory tasks, completed 6 and 12 months after commencing imatinib, will be compared to baseline performances.

Aim 2: To monitor the cognitive function of a sample of adult CML patients over a 12 month period. Results on other cognitive measures (excluding verbal learning and memory tasks), completed 6 and 12 months after commencing imatinib, will be compared to baseline performances in order to identify potential changes.

Aim 3: To examine whether changes in verbal learning and memory, and other cognitive measures were related to mood and affect, demographics (FSIQ, SES, educational attainment), and fatigue. Variations in cognitive function and their relationship to the above-mentioned variables will be assessed at baseline, six months, and twelve months.

Aim 4: To investigate whether any identified changes in verbal learning and memory, and other cognitive measures were related to imatinib dose. The relationship between participants' performance on cognitive measures and medication dose will be investigated at baseline, six months, and twelve months.

2. METHOD

2.1 PARTICIPANTS

Male and female patients from four of the major oncology departments in the state of Victoria, Australia were invited to participate in the study if they were between the ages of 16 to 75 years inclusive, if they were able to give written voluntary consent, had a life expectancy beyond 12 months, and were fluent in English. Patients were recruited with the assistance of haematologists from the Diagnostic Haematology Department and Medical Oncology at the Royal Melbourne Hospital, Parkville, Victoria; the Andrew Love Cancer Centre at Barwon Health, Geelong, Victoria; the Bone Marrow Transplant Service at the Alfred Hospital, Melbourne, Victoria; and the Peter MacCallum Cancer Centre, Melbourne, Victoria.

The study involved 12 adult male and female participants aged between 24 and 75 years inclusive with newly diagnosed CML not involving the central nervous system, who were about to commence treatment with the tyrosine kinase inhibitor, Imatinib. Another participant was initially enrolled in the study but died in the months after his baseline assessment. In all cases, CML was established through blood chemistry results, followed by a bone marrow biopsy to confirm diagnosis. Once confirmed, subjects were invited to participate in the study and provided with a verbal and written explanation of the study requirements by the author. Participants were excluded prior to study entry if they were known to have central nervous system disease associated with the CML or an uncontrolled co-morbid condition. Two participants were excluded from the present sample on the basis of these criteria. The first was excluded due to concerns about the impact of their limited English skills on the reliability of testing. The second individual was already in blast crisis at the point of diagnosis and required more aggressive therapy. Four of the seventeen CML patients who initially expressed an interest in the study, later declined. There were a number of reasons given why patients chose not to participate. One participant reportedly felt overwhelmed about the prospect of having her thinking and memory skills examined, whilst others reported the length of time involved as the primary reason for declining, particularly as they had already spent considerable time at the hospital during the initial period for blood tests and bone marrow biopsies.

2.2 MATERIALS

2.2.1 Cognitive Tasks

2.2.1.1 Intellectual Function

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III)

A baseline measure of general intellectual functioning was completed through the use of the Wechsler Adult Intelligence Scale – Australian Adaptation – 3rd Edition (WAIS-III) (Wechsler, 1997a). The WAIS-III subtest administration followed the standard administration, as described by Wechsler (1997a). The WAIS-III comprises 14 subtests, including eleven core components and three supplementary tests. Each of the individual subtests has a mean of 10 and a standard deviation of 3. Two intelligence quotients are obtained by calculating performances across verbal and visual perceptual domains (Verbal Intelligence Quotient – VIQ and Performance Intelligence Quotient – PIQ). These composite scores of verbal and visual perceptual ability are then combined to obtain an overall measure of intellectual function (Full Scale Intelligence Quotient – FSIQ). Each of these quotients has a mean of 100 and a standard deviation of 15.

Participants completed nine subtests from the WAIS-III, including five verbal subtests (Information, Digit Span, Vocabulary, Similarities, Letter Number Sequencing) and four visual perceptual subtests (Picture Completion, Block Design, Digit Symbol, and Matrix Reasoning).

2.2.1.2 Attention and Working Memory

Digit Span Subtest

Immediate attention span and working memory was assessed using the Digit Span subtest from the WAIS-III (Wechsler, 1997a). The subtest consists of a 'digits forward' and 'digits backwards' stage. In the 'digits forward' component the participant is asked to verbally recite a string of numbers in the same order in which they are presented by the examiner. The examiner reads aloud the digits at a rate of one digit per second and then the participant is required to repeat the sequence verbatim. There are two trials for each digit string length, starting with two digits to a maximum of ten digits. The digits sequence increases in length until the participant fails two

sequences of the same length or reaches the maximum length of ten digits. 'Digits backwards' follows a similar format, except that participants are required to recite the digits presented by the examiner in the reverse order. This subtest was administered in accordance with the standard administration procedures, as described in the WAIS-III manual (Wechsler, 1997a).

2.2.1.3 Motor and Processing Speed

Digit Symbol Coding Subtest

The Digit Symbol Coding subtest from the WAIS-III was chosen to assess motor and processing speed (Wechsler, 1997a). As per the other tests, the Digit Symbol Coding subtest was administered according to guidelines set out in the WAIS-III manual (Wechsler, 1997a).

This subtest requires the participant to quickly transcribe a series of symbols from a key at the top of the page to the response section below. The key includes numbers one to nine and each of the numbers is assigned a specific symbol. The response section consists of a series of rows with numbers in the top section of the row and an empty square below each number. The participant is required to use the key and copy the symbol that is assigned to the specific number in the empty square below. The participant is given a short practice trail before being asked to fill in as many squares as possible, one after another without skipping any squares. The participant is required to work as quickly as possible without making any mistakes. The subtest ends after 120 seconds and the raw score is tallied according to the number of symbols correctly copied within the time limit.

2.2.1.4 Verbal Memory

Logical Memory Subtest

Verbal memory function was examined using the Logical Memory subtest from the WMS-III (Wechsler, 1997b). This subtest was administered in accordance with the guidelines presented in the WMS-III manual (Wechsler, 1997b).

In this test the examiner reads two short stories to the participant in their natural

speaking voice. Immediately after each reading the participant is encouraged to freely recall as much of the story as possible. Once the two stories have been presented the examiner re-reads the second story and the participant is encouraged to freely recall the story once more. The participant is then instructed to remember both stories, as they will be required to recall them again following a delay. Twenty-five to thirty-five minutes after the initial presentation, the participant is again asked to freely recall each of the stories. The examiner may provide limited prompting with set cues for each story. A forced choice recognition test then follows, with fifteen yes/no answers provided for each of the two stories. The subtest yields a measure of immediate and delayed verbal recall (i.e., Logical Memory I and II).

Rey Auditory Learning Test (RAVLT) and Auditory Learning Test (AVLT)

The RAVLT and an alternate version (AVLT) was utilised to assess verbal learning and memory function (Geffen et al., 1994; Lezak, 1983) (See Appendix B and C). Subtest administration followed the standard administration guidelines as set out by Geffen, Moar, O'Hanlan, Clark and Geffen (1990) in Strauss et al. (2006) page 784.

In this task, the examiner recites a list of 15 unrelated words, with a one second interval between each word. The participant is required to listen carefully and recite as many words as they can recall, in any order, immediately after the list is presented. Five consecutive trials are administered one after the other, and the participant is asked to recall as many of the words they remember, including words recalled in previous trials, on each occasion. After the list is presented five times, a single interference list is administered, which is followed by an immediate recall of the original word list and an uncued delayed recall of the original list approximately 20 minute later. A forced choice recognition test is then presented. In this task, the participant is presented with a longer list that contains words from the original list (presented five times), the interference trial, and a selection of new words. The list is read aloud by the examiner, and the subject is asked to identify whether the word was from the first list, the second list, or is a new word.

Each phase of the assessment measures different components of the memory system. Thus, failure at differing points is suggestive of different forms of neuropsychological dysfunction. For example, the difference between the fifth trial and the post

interference trial shows the impact of retroactive interference. Summing trials one to five gives a measure of the individual's total learning, whilst the individual's performance on trial seven shows their retention of this unrelated verbal information after a delay.

2.2.1.5 Executive Function

Specific conditions in the Verbal Fluency test and Sorting Test from the D-KEFS and the Trail-making test Part B (Trails B) were used to assess different aspects of executive function (Delis et al., 2001; Wechsler, 1997a).

Verbal Fluency subtest (Standard and Alternate Form)

Verbal fluency and mental flexibility were measured using both the standard and alternate versions of the Verbal Fluency subtest from the D-KEFS (Delis et al., 2001) (See Appendix D). The test derives measures for phonemic fluency, semantic fluency, and semantic switching (i.e., the individual's ability to generate words starting with a given letter and a given category, and their ability to switch between two semantic categories respectively). The phonemic or letter fluency score was the focus of assessment in the present study as this measure has proven to be more sensitive to neuropsychological insult (Lezak et al., 2004). Furthermore, there is controversy about whether the switching condition is a true measure of executive function (Baldo, Shimamura, Delis, Kramer & Kaplan, 2001).

Standard administration procedures were followed, as described in Delis et al. (2001). In the letter fluency task, the participant is given 60 seconds to say as many words as possible beginning with a specific letter. The examinee completes three trials with different letters. The commonly used letters F-A-S were employed in this assessment task (See Appendix E).

Sorting Test (Standard and Alternate Form)

Concept formation and problem-solving behaviour was assessed through the use of both the standard and alternate forms of the D-KEFS Sorting test (Delis et al., 2001) (See Appendix F and G). As per the previous subtest, this measure was administered according to the standard administration guidelines set out by Delis et al. (2001).

Whilst the D-KEFS Sorting Test consists of three measures; 'free sorting', 'confirmed sorts', and 'sort recognition', the free sort condition was the focus of assessment as it is more demanding than the recognition format (Johnson, 1990). The free sorting task requires the participant to group a series of cards on the basis of their perceptual features or the verbal/semantic information written on the cards. The participant is then required to describe the concepts employed to generate each sort. A maximum of four minutes is given in order to identify the eight different sort options. In this condition the participant receives a score for the number of sorts accurately identified (confirmed sorts).

Trail-Making Test – Part B

Part B of the Trail-making test was utilised to measure a component of executive function – mental flexibility (Strauss et al., 2006) (See Appendix A). This measure was administered according to the guidelines set out in the Compendium of Neuropsychological Tests – Third Edition (Strauss et al., 2006, page 656). In this task the participant draws a line to connect twenty-five consecutive numbers and letters randomly placed on a single page. The examinee starts with the lowest numbers and then alternates between consecutive numbers and letters, as quickly as possible without making any mistakes or lifting the pencil from the page.

This test shares some similarities with Part A of the Trail-making subtest; also requiring adequate motor speed, agility, and visual scanning for its successful completion (Schear & Sato, 1989; Shum et al., 1990). However the attentional switching component of the task places additional demands on cognitive flexibility, and probes one's ability to deal with multiple stimuli or thoughts at once (Arbuthnott & Frank, 2000; Kortte et al., 2002; Eson et al., 1978).

2.2.2 Measures of Mood and Affect

Mood was assessed using two self-reported measures of mood symptoms. The Beck Depression Inventory – Second Edition (BDI-II) (Beck et al., 1996) and the State Trait Anxiety Inventory - Form Y (STAI) (Spielberger et al., 1983).

Mood

Beck Depression Inventory – Second Edition (BDI-II)

As one of the most widely accepted measures of depression, the BDI-II was utilised to monitor the presence and severity of mood symptoms (Beck et al., 1996). The BDI-II is a 21-item self-report questionnaire, with items corresponding to the criteria for the diagnosis of depression, as outlined in the American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV-TR, 2000). Items tap areas such as sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping pattern, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, and loss of interest in sex. Statements of varying severity are included under each of these areas, and participants are asked to choose the statement that best describes how they have been feeling in the past fortnight including today. Administration followed the standard administration procedures, as described by Beck et al. (1996).

Affect

Spielberger State-Trait Anxiety Inventory – Form Y (STAI)

With over 3000 studies and reviews reported in the literature and strong psychometric qualities, the STAI was chosen to assess state and trait anxiety in study population (Spielberger et al., 1983). This self-reported measure provides an indication of an individual's general level of anxiety (or trait anxiety), along with an estimate of one's emotional state during the assessment process (state anxiety). The participant is required to rate the frequency in which they experience feelings of apprehension, tension, nervousness, and worry either at the time of the assessment or in general. The STAI was administered in accordance with the guidelines provided in the STAI-Form Y manual (Spielberger et al).

2.2.3 Measure of Socio-economic Status

Australian Version of the International Socioeconomic Index (ANU_4 Scale)

Socio-economic status (SES) was measured using the Australian version of the International Socio-economic Index (ANU_4 Scale) (Jones & McMillan, 2001). This scale rates SES using an ordinal rating system, with the highest ranks representing the most prestigious positions (e.g., 100.0 Medical Practitioner) and the lowest ranks reflecting lower prestige roles (e.g., 0.0 Agricultural and related labourers).

2.2.4 Measures of Disease-related Variables

Quality of Life and Fatigue

Functional Assessment of Cancer Therapy-Leukemia module (Fact-Leu)

Quality of life and fatigue was assessed using the Functional Assessment of Cancer Therapy-Leukemia module (Fact-Leu) (Webster et al., 2002) (See Appendix H). This self-report questionnaire comprises 17 physical symptoms (fevers, bleeding, general pain, stomach pain, chills, night sweats, bruising, lymph node swelling, weakness, tiredness, weight loss, appetite change, shortness of breath, functional ability, diarrhoea, concentration, and mouth sores) and 10 emotional/social concerns (frustration with activity limitation, discouraged by illness, uncertainty in future planning, worry about illness, emotional lability, isolation, infertility concern, family worry, and worry about infection (Webster et al.). The scale derives three measures including an estimate of the participant's physical/functional status, an indication of social/emotional wellbeing, and a composite measure of the overall impact of the disease.

The questionnaire requires participants to indicate how much they had been bothered by specific symptoms or concerns over the past week on a five point Likert scale ranging from 'Not at all' (rated as 0) to 'Very Much' (rated as 4).

2.2.5 Measures of Response to Therapies/Aversive Events

Eastern Cooperative Oncology Group Performance Status Scale (ECOG)

The impact of the disease process on daily living was assessed using the Eastern Cooperative Oncology Group Performance Status Scale (ECOG) (Oken et al., 1982). This scale was developed in 1982 by the Eastern Cooperative Oncology Group in 1982,

one of the earliest cooperatives to perform multi-centre cancer clinical trials. The ECOG performance status scale is also widely used by physicians and researchers alike to determine the progression of the disease.

The participants functional capacity is rated on a five point scale, with a score of zero indicating no change in capacity and a score of four reflecting complete dependence and disability (See below).

Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Adverse Events

Information about every adverse event was recorded on the Case Report Form (See Appendix I). Adverse events included undesirable signs, symptoms or medical conditions that occurred after commencing treatment. Any medical conditions present before starting treatment were only recorded if they subsequently worsened.

Adverse events were recorded on the Case Report Form and followed up carefully by the treating doctor until they resolved. As far as possible, each adverse event was described by:

1. Duration (start and end dates)
2. Severity grade (according to National Cancer Institute/National Institute of Health Common Toxicity Criteria severity grades 1-4. Appendix J)
3. Relationship to the study drug (suspected, not suspected)
4. Action(s) taken.

2.3 PROCEDURE

Recruitment

Participants in the clinical group were recruited over a twenty month period, from May 2006 to January 2008. Participants were only approached after cytogenic and molecular confirmation of the disease process through blood tests and bone marrow biopsy.

A diverse source of referrals was sought to maximise recruitment given the rarity of the condition. The sample was recruited from the Peter MacCallum Hospital, Royal Melbourne Hospital, Barwon Health, and Alfred Hospital, all in the state of Victoria, Australia. Informed consent was obtained by the treating doctor to allow the examiner to contact the patient in writing. If the patient was agreeable, the Patient Information and Consent form was sent to their home address, with a cover note explaining that they would be contacted by telephone within the week to discuss the study in more detail and address any concerns or queries. The timing of this follow-up discussion occasionally occurred more quickly if the patient required treatment urgently. If, after these discussions, the patient was in agreement, the initial assessment was scheduled to occur within the neuropsychiatry unit at the Royal Melbourne Hospital. Participants were reimbursed for parking costs, however no other expenses were met.

Consent

Before any formal testing commenced, the Patient Information and Consent form was completed. This was followed by a thirty minute screening interview to gather demographic information, along with details of their current medication regime, past medical history, mood, current complaints, functional capacity (using the ECOG performance status scale), height, and weight.

Baseline Assessment

Assessments were conducted individually in a quiet, well-lit office on hospital grounds. The initial assessment was completed over approximately a four hour period and generally commenced in the morning. Participants were given a long rest period for lunch after approximately two hours to minimise fatigue.

Prior to commencement of treatment, all participants completed a thorough baseline assessment of their general intellectual function, which included nine subtests from the WAIS-III. Participants were asked to complete three verbal tasks (Information, Vocabulary, Similarities) and three visual perceptual subtests (Picture Completion, Block Design, and Matrix Reasoning) from the WAIS-III in order to obtain a composite measure of verbal skills (Verbal Comprehension Index) and visual perceptual abilities (Perceptual Organisation Index). Results from these subtests were combined with results from the Digit Span, Digit Symbol Coding, and Letter Number Sequencing subtests from the WAIS-III to calculate an estimate of cognitive function (pro-rated Full Scale IQ score from the WAIS-III). In addition to the indices from the WAIS-III, the initial assessment focused on measures in specific domains. Motor and processing speed was examined using Digit Symbol Coding from the WAIS-III; attention & working memory were assessed using the Digit Span subtest from the WAIS-III; a measure of verbal memory was obtained using the Rey Auditory Verbal Learning Test and the Logical Memory subtest from the WMS–III; and executive function was evaluated through the Trail Making Test Part B, and subtests from the D-KEFS, including the free sort condition from the Sorting Test and letter fluency component of the Verbal Fluency test. Confounding factors such as mood, affect, and fatigue were also examined using the following measures; mood was monitored via the BDI–II; anxiety was measured through the STAI; and fatigue was assessed using the FACT–Leu. These measures combined to form an overall impression of the participant's neuropsychological function prior to commencing treatment. Given the variety of tests used, a summary of the type and order of tests on each tests occasion is included in Table 10.

Review Assessments

Shorter review assessments were conducted six and twelve months after commencing treatment. These assessments were completed over approximately two hours, and included further history taking to obtain reports of subjective cognitive and physical complaints, changes in medication and functional capacity (again using the ECOG performance status scale), weight, and adverse effects of the medication, along with an abbreviated cognitive assessment. At this time selected subtests from the WAIS-III were given, together with other standardised measures to tap specific cognitive

domains; attention & working memory (Digit Span subtest from the WAIS-III); motor and processing speed (Digit Symbol Coding from the WAIS-III); verbal memory (Rey Auditory Verbal Learning Test and Logical Memory subtest from the WMS – III); executive function (Trail Making Test-Part B, the free sort component of the Sorting Test, and the letter fluency condition of the Verbal Fluency test from the D-KEFS). Alternate versions of the RAVLT and D-KEFS Verbal Fluency and Sorting Tests were also utilised at the six month review to minimise the impact of practice. The results of the latter assessments were then compared to the baseline assessment to evaluate potential change in cognitive function over time. Mood, affect, and fatigue were also examined at each time point using the BDI-II for mood, STAI for anxiety, and the FACT-Leu for fatigue and quality of life. These factors were examined at each point in the study in order to examine their potential impact on cognitive functioning.

Following the second assessment, a brief report of the results of the baseline and review assessments was sent to each participant. Participants were given the option to discuss these results with the examiner in greater detail. If high levels of anxiety/depression were reported, participants were offered access to appropriate psychological support services within the hospital system.

Table 10

Tests Selection and Order across Assessments

Baseline Assessment	6 Month Review	12 Month Review
➢ Picture Completion (WAIS-III) ➢ Vocabulary (WAIS-III) ➢ Coding (WAIS-III) ➢ Logical Memory I (WMS-III) ➢ RAVLT ➢ Similarities (WAIS-III) ➢ Block Design (WAIS-III) ➢ Digit Span (WAIS-III) ➢ Logical Memory II (WMS-III) ➢ Logical Memory Recognition (WMS-III) ➢ RAVLT – Delayed and Recognition Trial ➢ Matrix Reasoning (WAIS-III) ➢ Information (WAIS-III) ➢ Letter Number Sequencing (WAIS-III) ➢ Trailmaking Test ➢ Verbal Fluency (D-KEFS) ➢ Sorting (D-KEFS) ➢ BDI-II ➢ STAI ➢ -LEU	➢ Digit Span (WAIS-III) ➢ Coding (WAIS-III) ➢ Logical Memory I (WMS-III) ➢ AVLT (Alternate Form) ➢ Trailmaking Test ➢ Verbal Fluency – Alternate Form (D-KEFS) ➢ Logical Memory II (WMS-III) ➢ Logical Memory Recognition (WMS-III) ➢ AVLT (Alternate Form)– Delayed and Recognition Trial ➢ Sorting – Alternate Form (D-KEFS) ➢ BDI-II ➢ STAI ➢ FACT-LEU	➢ Digit Span (WAIS-III) ➢ Coding (WAIS-III) ➢ Logical Memory I (WMS-III) ➢ RAVLT ➢ Trailmaking Test ➢ Verbal Fluency (D-KEFS) ➢ Logical Memory II (WMS-III) ➢ Logical Memory Recognition (WMS-III) ➢ RAVLT – Delayed and Recognition Trial ➢ Sorting (D-KEFS) ➢ BDI-II ➢ STAI ➢ FACT-LEU

2.4 ETHICS APPROVAL

The research reported in this thesis was conducted in accordance with the principles of ethical treatment of human participants as set out by the National Health and Medical Research Committee. The current study has been approved by the Melbourne Health Human Research Ethics Committee and the Victoria University Human Research Ethics Committee (See Ethics Approval Appendix K).

3. RESULTS

3.1 DATA ANALYSIS

A series of repeated measures ANOVAs were used to assess changes in the mean performance of individuals across the three assessments. Given that multiple assessments were undertaken, Bonferroni's correction was employed to calculate the approximate alpha level for the given pairwise tests (Field, 2005). Given that ten pairwise tests were completed an alpha level of 0.005 was employed as an indicator of significance for all of the repeated measures ANOVAs. The 'partial eta squared (η^2)' statistic was used to examine the magnitude of these differences, as this analysis quantifies the likelihood of detecting a real effect given the small sample size. Finally, bivariate correlations were performed to examine whether statistically significant changes were related to mood, demographics, or treatment-related variables. These analyses were all conducted using the SPSS Version 16 computer package.

3.2 DEMOGRAPHIC VARIABLES

The main demographic information for the sample group is outlined in Table 11. In addition to the information provided below, none of the participants had completed a neuropsychological or more limited cognitive assessment in the past. Of the 12 subjects, two reported a positive family history of neurodegenerative disease (16.67%). Eight (66.67%) of the participants described themselves as non-smokers and non-drinkers, two participants drank alcohol and smoked (16.67%), and two smoked but did not drink (16.67%).

Table 11
Demographic Information

Variable	No. of Participants
N	12
Age (Mean years)	51.5
Range	24 –71
Gender	
Male	8
Female	4
Education (Mean years)	11.3
Range	7-15
SES (Mean)	39.19
Range	12.4 – 83.6
Ethnicity	
Australia-born	8
*Other * (NESB)*	4
Marital Status	
Married	7
Single	2
Divorced	3
Co-Morbidities	
MTBI	2
Vascular problems	3

** Eight participants were Australian born (66.67%), three were of Greek descent (25%), and one participant was from the Cook Islands (8.3%).*

3.3 MOOD-RELATED VARIABLES AND FATIGUE

The incidence and severity of depressive symptoms, as assessed by the Depression Index Score on the BDI-II, were recorded at each of the three assessments. A graph of levels of the Depression Index Score as a function of occasion of assessment is shown in figure 4.

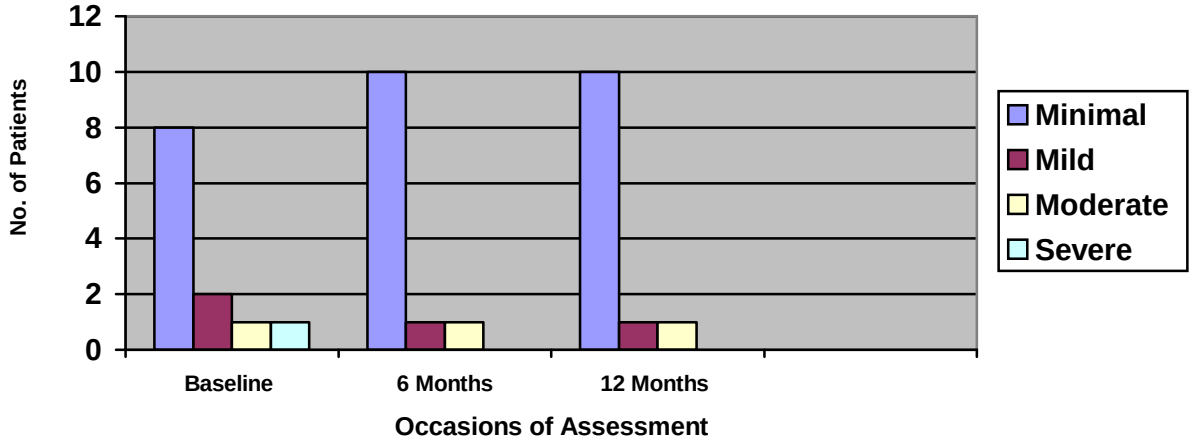


Figure 4. The incidence and severity of self-reported depressive symptoms

The frequencies shown in this graph indicate a general improvement in mood over time, with more participants reporting fewer depressive symptoms at the six month and one year assessments.

Results from the repeated measures ANOVA showed a subtle but non-significant decline in participants' overall level of state anxiety over the three assessments, dropping from a mean state anxiety score at baseline of 58.25 to a mean of 49.83 at six months, and 44.50 at twelve months (See Appendix L). A similar non-significant trend was evident in measures of fatigue, overall well-being, and quality of life (as measured by the FACT-Leu questionnaire). A mean of 124.97 at the baseline assessment, increased to a mean of 135.22 at six months and remained steady at 132.10 at one year (See Appendix L). Note: an increase in the value represents a reported lessening in fatigue and related-physical symptoms.

3.4 DISEASE-RELATED VARIABLES

Seven participants received the lowest dosage of imatinib at 400mg (58.3%), two participants were prescribed 600mg (16.67%), and the remaining three participants took 800mg (25%). By 12 months, 10 participants had achieved a cytogenic response (83.3%), whilst two had achieved a molecular response (16.67%). At baseline, all 12 participants were fully active in spite of reportedly high levels of fatigue. However at 6 and 12 months, only ten participants continued to describe themselves as 'fully active' (83.3%), whilst two participants were undertaking lighter activities (16.67%).

Participants reported a range of mild adverse effects throughout the course of the study. For a graphical representation of the type and frequency of these effects see figure 5.

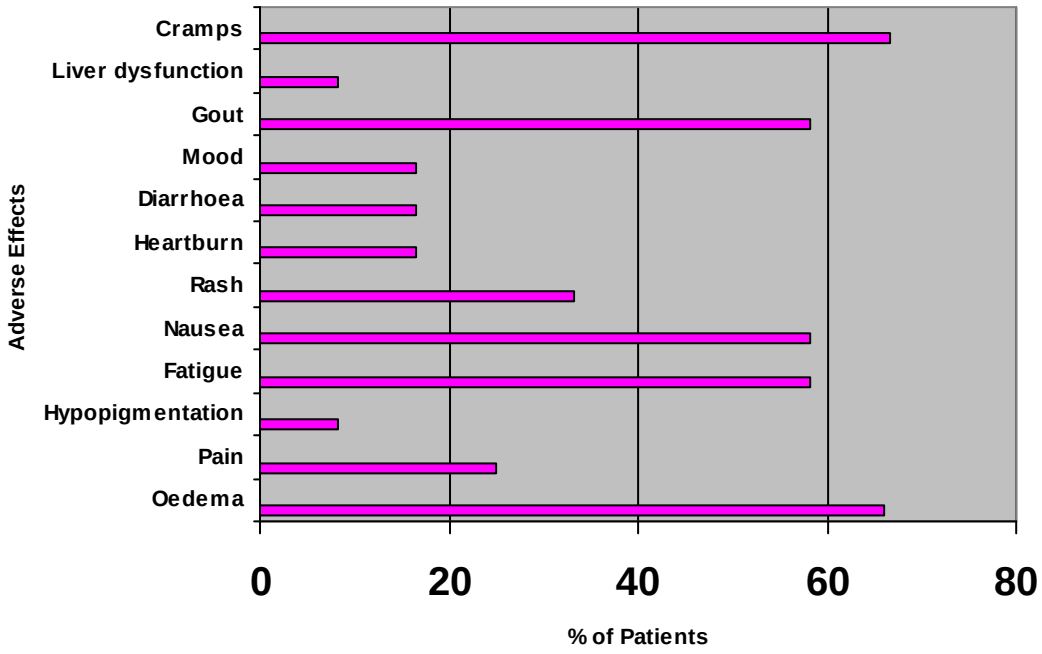


Figure 5. Self-reported adverse effects of CML participants

In addition to this, participants used a variety of different medications to manage adverse effects and co-morbid conditions. Figure 6 broadly outlines the class and frequency of medication used in the study group.

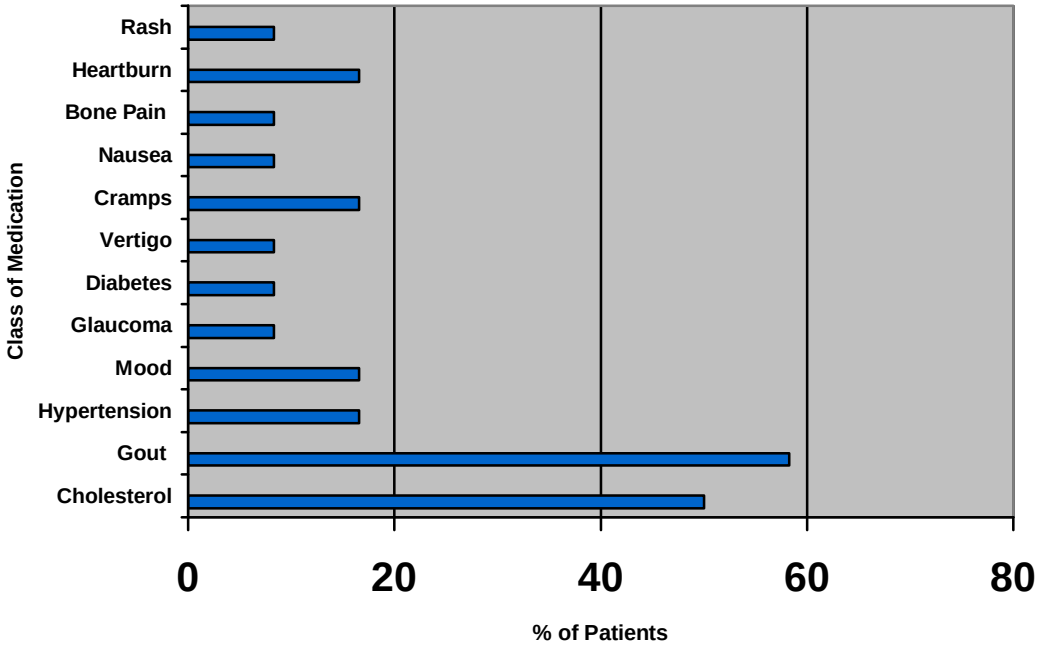


Figure 6. Class and frequency of concomitant medication use in the study group

3.5 VERBAL LEARNING AND MEMORY

3.5.1 Statistical Tests for Aim 1

Aim 1: To examine the verbal learning and verbal memory of adult CML patients over the course of 12 months. Results on verbal learning and memory tasks, completed 6 and 12 months after commencing imatinib, will be compared to baseline performances.

Repeated Measures ANOVA and Effect Size

A series of repeated measures ANOVAs were conducted to investigate changes in the participants' performance on verbal learning and memory tasks across the three assessments. The following assumption was employed in order to determine which statistic should be used to identify statistical significance. When 'Mauchly's test of sphericity' was non-significant, the sphericity statistic was utilized to determine whether there was a change in performance across time (Francis, 2007). In contrast, a significant result on Mauchly's test of sphericity indicated that 'the difference scores for each pair of treatments (did not) come from populations with the same variance' (Francis, 2007, p. 69). When this occurred the Greenhouse Geisser adjustment was used to detect significant change over time (Francis, 2007). Further to this, a Bonferroni's correction was employed, given the number of dependent variables and the small sample size. Given that ten dependent variables were analysed, an alpha level of 0.005 was set to minimise the potential for Type I errors.

The magnitude of differences between baseline verbal memory performances and performances at the 6 and 12 month review were examined through the 'partial eta squared (η^2)' statistic. Cohen (1988) proposed a set of parameters to determine the size of effect, suggesting that r = .01 represents a small effect size, r =0.3 represents a moderate effect size, and r = 0.5 represents a large effect size. The results of each repeated measures ANOVA and the effect size for any significant change are shown in Table 12.

Table 12
Analysis of Verbal Memory Performances over time using Repeated Measures ANOVA and Effect Size

Variable	Time 1	Time 2	Time 3	T1-T2		T1-T3	
	M (SD)	M (SD)	M (SD)	F	η^2	F	η^2
Verbal Memory							
Logical Memory I	10.67 (3.06)	11.25 (3.02)	12.42 (3.58)	1.67		13.36**	(*.55)*
Logical Memory II	10.36 (2.64)	12.42 (3.37)	12.92 (3.55)	9.14		14.44**	(*.57)*
RAVLT Trial 6	0.52 (0.99)	0.17 (0.96)	1.10 (0.78)	1.88		5.57**	(*.37)*
Verbal Recognition							
RAVLT Recognition	0.863 (0.43)	-0.48 (1.77)	0.80 (0.46)	6.14*	*(.36)*	0.09	
Verbal Learning							
RAVLT Total Learning	0.73 (0.94)	0.19 (1.39)	1.31 (0.83)	1.87		10.18*	*(.48)*

Note: Logical Memory I = immediate recall trial; Logical Memory II = delayed recall trial
* 0.005> p<0.01
** Significant to 0.005

Logical Memory Subtest

For this sample of 12 participants, there was a significant improvement in the mean immediate recall of prose (i.e., immediate recall on the Logical Memory task) when the baseline performance was compared to the 12 month assessment F (1,11)= 13.36, p < 0.005 (p=0.004). Further improvements were also identified in the participants delayed recall on the Logical Memory subtest at 12 months, as participants' mean performance was significantly higher than the mean baseline performance F (1,11)= 14.44, p <0.005 (p = 0.003). Large effect sizes were evident across these measures of verbal memory.

RAVLT

A repeated measures ANOVA was also employed to compare participants' total verbal learning, immediate verbal recall, and verbal recognition on the RAVLT. A review of the results revealed an increase in the mean verbal recall score (i.e., Trial 6 of the RAVLT) by the 12 month assessment F (1,11)=5.57, p ≤0.005 (p = 0.005). This represented a moderate effect size. In contrast, there was a subtle but non-significant decline in participants' overall verbal recognition by the 6 month assessment F (1,11)= 6.14, p <0.01 (p= 0.007). There was no indication of decline when the participants' mean baseline performance was compared to their performance at the 12 month assessment. Finally, there was a non-significant trend towards improvement in participants' mean total learning by the 12 month review F (1,11)= 10.18, p <0.01 (p = 0.009).

Trends in Verbal Memory Performance

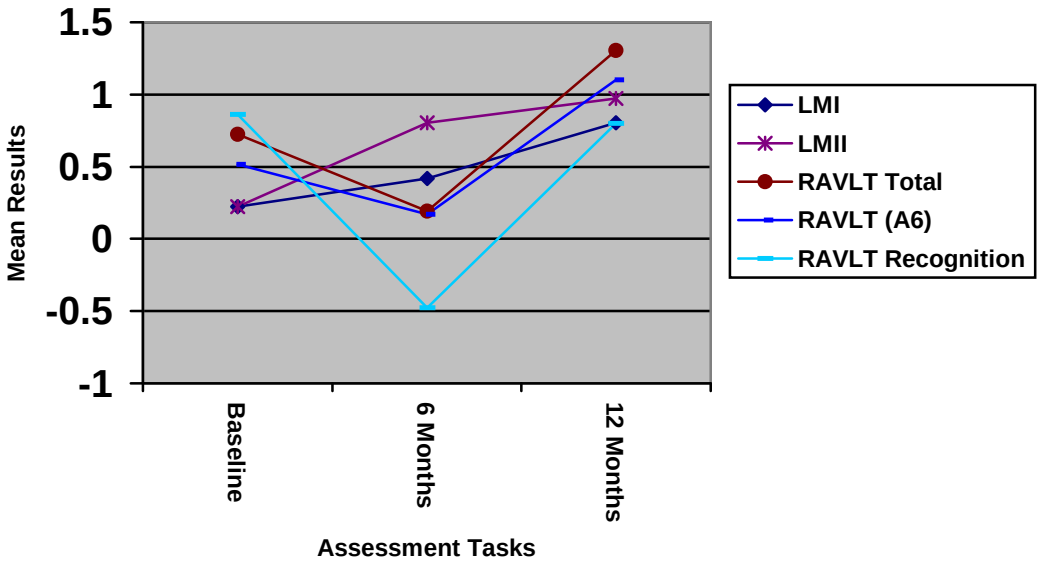


Figure 7. Mean verbal memory performances across the three occasions of assessment

According to figure 7, there was an overall trend towards improvement when performances from the twelve month review were compared with the baseline assessment. Participants demonstrated a steady pattern of improvement on both Logical Memory tasks over time. However this pattern was not consistently apparent on the RAVLT. Whilst participants ultimately demonstrated subtle improvements in immediate recall and total learning over time, there was a tendency for participants to perform more poorly when the alternate version of the RAVLT was used at the six month review. In contrast, there was no improvement in verbal recognition on the RAVLT by twelve months, and considerable decline in performance at the six month assessment.

Summary of Results for Aim 1

In summary, there was no decline on any measure of verbal learning and memory by the six or twelve month review. In fact there was a significant improvement in participants' performance on most verbal memory tasks by one year. According to the repeated measures ANOVA, there was a large improvement in participants' immediate and delayed recall of a prose passage (i.e., Logical Memory I and II) by twelve months,

and a moderate but significant improvement in recall following distraction (i.e., Trial 6 on the RAVLT) by the final review.

In addition to this, a subtle but non-significant decline in participants' verbal recognition was evident at the six month assessment. However this trend was no longer apparent at the one year review. Finally, there was a further trend, albeit non-significant, towards improved verbal learning by the final assessment (See Appendix L).

3.6 OTHER COGNITIVE MEASURES

3.6.1 Statistical Tests for Aim 2

Aim 2: To monitor the cognitive function of a sample of adult CML patients over a 12 month period. Results on other cognitive measures (excluding verbal learning and memory tasks), completed six and twelve months after commencing treatment with imatinib, will be compared to baseline performances in order to identify potential changes.

Repeated Measures ANOVA and Effect Size

A series of repeated measures ANOVA's were calculated to compare performances across time on various measures of attention and working memory, processing and motor speed, and executive function. As before, Bonferroni's correction was employed and an alpha level of 0.005 was again used to determine significance. There was no significant difference on any measure across time. However there was a trend towards improvement on the Digit Symbol Coding subtest and free sort condition of the Sorting Test.

The 'partial eta squared (η^2)' statistic was again used to investigate the magnitude of the difference between performances at baseline, six months, and one year. The same parameters, as described above, were used to determine the extent of the effect size (r = .01 signifies a small effect, r = 0.3 represents a moderate effect, and r = 0.5 indicates a large effect) (Cohen, 1988). The results for each of the repeated measure ANOVAs and the effect sizes for any significant changes are shown in Table 13.

Table 13
Analysis of Other Cognitive Performances over time using Repeated Measures ANOVA and Effect Size

Variable	Time 1 M (SD)	Time 2 M (SD)	Time 3 M (SD)	T1-T2 F	η^2	T1-T3 F	η^2
Attention / Working Memory							
Digit Span	10.42 (3.32)	10.83 (3.19)	10.67 (3.34)	1.00		0.51	
Motor/Processing Speed							
Digit Symbol Coding	11.08 (4.25)	11.58 (4.08)	12 (4.02)	3.00		8.59 *	*(.49)*
Executive Function							
Letter Fluency	8.92 (3.87)	9.17 (3.54)	9.92 (3.48)	0.19		3.00	
Free Sorts	9.83 (4.55)	11.08 (2.58)	12.08 (3.18)	2.29		6.66*	(*.38)*
Trails B	-0.49 (1.57)	-0.24 (1.66)	0.03 (1.61)	0.83		7.74	

* $0.005 > p < 0.05$

Attention and Working Memory

Digit Span Subtest

There were no significant differences on the Digit Span subtest across the three assessments.

Motor/Processing Speed

Digit Symbol Coding Subtest

A subtle but non-significant improvement was evident in the Digit Symbol Coding measure when the 12 month assessment results were compared to the baseline performance $F(1,11) = 8.59$, $p>0.05$ ($p=0.014$).

Executive Function

Sorting Test – free sort condition

For this sample of participants', there was a subtle, albeit non-significant, increase in the mean number of free sorts on the Sorting Test at baseline by the 12 month assessment $F(1,11) = 6.66$, $p <0.05$ ($p = 0.026$). No other significant changes in performance were evident on other measures of executive function (i.e., Letter Fluency subtest, Trails B subtest).

Trends in Performance on Other Cognitive Measures

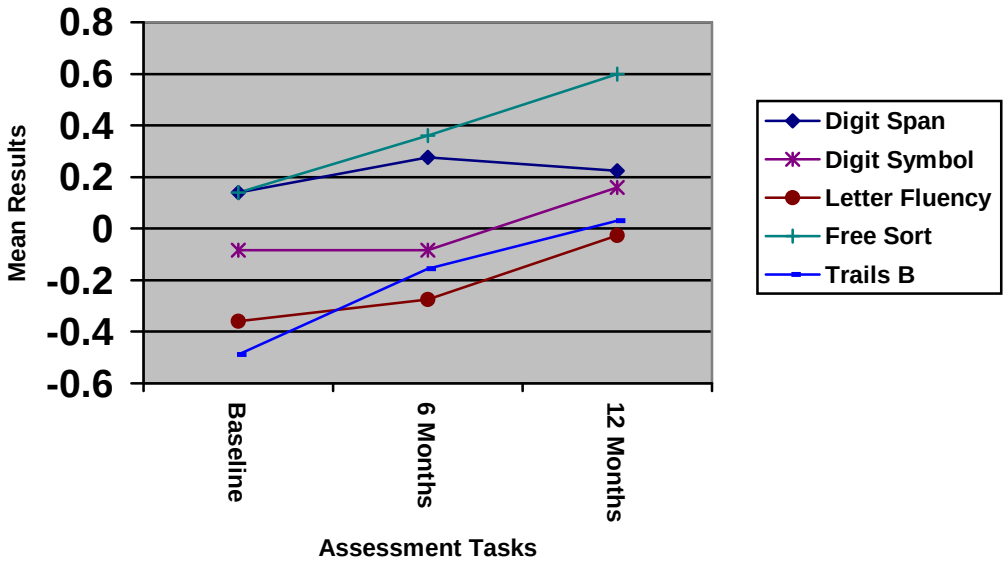


Figure 8. Mean performances on other measures of cognitive function across the three occasions of assessment

According to figure 8, there was a trend towards improved performance on all measures when the baseline results were compared to the twelve month review. There was steady improvement on most measures, with the least improvement apparent on the Digit Span subtest and the greatest amount of improvement seen on the Trails B tests and the free sort condition of the Sorting Test.

Summary of Results for Aim 2

Similar to the previous analysis for Aim 1, there was no significant decline on any measure of cognitive functioning by the six or twelve month review. On the basis of the repeated measures ANOVA, there was a trend towards improvement on the Digit Symbol Coding subtest and the free sort condition from the Sorting Test. However these trends failed to reach significance.

3.7 RELATIONSHIP BETWEEN COGNITION, DEMOGRAPHICS, AND AFFECT

3.7.1 Statistical Tests for Aim 3

Aim 3: To examine whether changes in cognitive function correlate with other factors, such as FSIQ, educational attainment, SES, mood, anxiety, or fatigue. Variations in cognitive function and their relationship to the above-mentioned variables will be assessed at baseline, six months, and twelve months.

3.7.1.1 Verbal Learning and Memory

Bivariate Correlations Between Mood, Fatigue, and Verbal Memory

Intercorrelations between demographics, mood, fatigue, and verbal memory are presented in Table 14 and 15.

Table 14
Intercorrelations between Verbal Memory Function and Mood and Fatigue

Variable	Mood			State Anxiety			Fatigue		
	0mths	6mths	1Yr	0mths	6mths	1Yr	0mths	6mths	1Yr
Verbal Learning									
LMI (0mths)	-.792 **			-.440			.253		
LMI (6mths)		-.329			-.670*			.198	
LMI (1yr)			-.488			-.249			.409
LMII (0mths)	-.782**			-.295			.125		
LMII (6mths)		-.284			-.695*			.078	
LMII (1yr)			-.460			-.213			.280
RAVLT Trial 6 (0mths)	.027			.275			-.203		
RAVLT Trial 6 (6mths)		.261			-.327			-.663	
RAVLT Trial 6 (1yr)			.441			-.406			.712**

Note: LMI = Logical Memory I (immediate recall); LMII = Logical Memory II (delayed recall)
* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

The correlations in table 14 indicate that there is a strong, and significant linear relationship between the participants' mood and their baseline immediate and delayed recall of prose (e.g., Logical Memory I and II), r = -0.792, N=12, p=0.002; and r = -0.782, N=12, p=0.003 respectively. Higher levels of reported mood disturbance tend to negatively impact on immediate and delayed recall. This relationship between mood and verbal recall was no longer apparent at the 12 month review. A moderate linear relationship was evident between state anxiety and immediate and delayed recall on the Logical Memory subtest at six months, r = -0.670, N=12, p=0.017; and r = -0.695,

N=12, p= 0.012 respectively. People who experienced greater anxiety at the time of testing tend to recall less verbal information. Fatigue was not significantly related to the participants' performance on Logical Memory tasks.

A strong, significant linear relationship was also evident between fatigue and immediate recall following distraction (i.e., RAVLT trial 6) at the twelve month assessment, r = 0.712, N=12, p = 0.009. (Note: higher scores on a measure of fatigue represent a decline in reported levels of fatigue and increased physical well being). Lower levels of fatigue are associated with better recall of unrelated verbal information following distraction. No other significant relationships were identified between verbal memory and mood/fatigue variables.

Bivariate Correlations Between Demographic Variables, FSIQ, and Verbal Memory

Table 15
Intercorrelations between Verbal Memory Function and Demographic Variables

Variable	FSIQ	SES	Years of Education
LMI (Baseline)	.877**	.544	.008
LMI (6 mths)	.878**	.708**	.303
LM I (1 Year)	.829**	.608*	.236
LMII (Baseline)	.818**	.482	-.010
LMII (6 mths)	.723**	.608*	.382
LMII (1 Year)	.772**	.501	.255
RAVLT Trial 6 (Baseline)	.126	.146	.403
RAVLT Trial 6 (6 mths)	-.041	.141	.718*
RAVLT Trial 6 (1 Year)	.703*	.630*	.390

Note: LMI = Logical Memory I (immediate recall); LMII = Logical Memory II (delayed recall)
* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

The correlational method used to analyse SES in table 15 was Spearman's rank, given that the SES variable is an interval scale. All other bivariate correlations were calculated using Pearson's method. The correlations reported in table 15 indicate a strong, significant linear association between immediate recall on the Logical Memory subtest at baseline, six months and one year and full-scale IQ (FSIQ), r = 0.877, N=12, p= 0.000; r = 0.878, N=12, p = 0.000; and r = 0.829, N=12, p = 0.001 respectively. This suggests that participants' with higher IQ's tend to immediately recall more verbal

information on the Logical Memory subtest. This continued to be the case 6 and 12 months after commencing treatment.

FSIQ was also strongly associated with the delayed recall of a prose passage during the Logical Memory subtest at the baseline assessment, and 6 and 12 month review, r = 0.818, N=12, p = 0.001; and r = 0.723, N=12, p = 0.008; r = 0.772, N=12, p = 0.003 respectively. Individuals' with higher IQ have a greater tendency to recall more verbal information after a delay.

A strong, significant linear relationship was also evident at the one year review between FSIQ and immediate recall of verbal information following a distraction (i.e., RAVLT trial 6), r = 0.703, N=12, p = 0.011. Thus, individuals' with higher IQ's generally recall more verbal information after a distraction than people with lower IQ's. This trend was only apparent 12 months after commencing treatment with imatinib.

Socio-economic status was also positively related to some measures of verbal memory but not others. There was a moderate, albeit significant, linear correlation between SES and Logical Memory I at baseline, and 6 and 12 months, r = 0.584, N=12, p =0.046; r =0.670, N=12, p = 0.017; and r = 0.620, N=12, p = 0.031 respectively. The same trend was apparent between SES and delayed recall (Logical Memory II) at the 6 and 12 month assessments, r = 0.614, N=12, p=0.034; and r = 0.579, N=12, p = 0.048. Participants' with a higher SES tend to recall more prose both before and after commencing treatment with imatinib.

Bivariate correlations revealed a strong linear relationship between years of education and immediate recall following a distraction at 6 months (i.e., Trial 6 on RAVLT), r = 0.718, N=12, p = 0.009. Individuals' with higher levels of educational attainment tended to recall more verbal information after a distraction. This trend was only apparent at the six month review.

3.7.1.2 Other Cognitive Tasks

Based on an alpha level of 0.005, there was no significant change in performance on any measure of attention and working memory, motor and processing speed, and

executive function. Although there was a trend towards improvement on the Digit Symbol Coding subtest and free sort condition of the Sorting Test, the relationship between these measures and other demographic and mood-related variables will not be further investigated given that this trend failed to reach significance.

3.8 RELATIONSHIP BETWEEN DOSE AND COGNITION

3.8.1 Statistical Tests for Aim 4

Aim 4: To investigate whether any identified changes in verbal learning and memory, and other cognitive measures are related to imatinib dose. The relationship between participants' performance on various cognitive measures and medication dose will be investigated at baseline, six months, and twelve months.

3.8.1.1 Verbal Learning and Memory

Bivariate Correlations Dose and Verbal Memory

Table 16
Intercorrelations between Verbal Memory Function and Dose

Variable	Dose
Logical Memory (6 mths)	.088
Logical Memory I (1 Year)	.031
Logical Memory II (6 mths)	-.124
Logical Memory II (1 Year)	-.122
RAVLT Trial 6 (6 mths)	-.121
RAVLT Trial 6 (1 Year)	-.188

* Correlation is significant at the 0.05 level (2-tailed)

According to the correlations outlined in table 16, there was no significant relationship between medication dose and any of these measures of verbal memory.

3.8.1.2 Other Cognitive Tasks

As mentioned previously, there was no significant change in performance on any measure of attention and working memory, motor and processing speed, and executive function. Therefore the relationship between other cognitive measures and dose will not be further investigated given that this trend failed to reach significance.

3.9 AN EXAMINATION OF INDIVIDUAL PERFORMANCES

3.9.1 Case Study 1: 'Marie'

Marie was 62 years and 11 months when she was diagnosed with CML following a routine blood screen to investigate the basis of increased fatigue. She was born in the United Kingdom and immigrated to Australia approximately thirty years ago. Marie was in formal education until form five and worked in various administrative and reception positions throughout her employment. At the initial assessment, she indicated that she was married and reported minimal depressive symptoms on the BDI-II but moderate symptoms of anxiety on the STAI. Her baseline FSIQ at this assessment was 102 (average range), her verbal comprehension index was 94 (average range) and her perceptual organisation index was 105 (average range). Marie's FSIQ was closer to the population mean than any other participant in the sample.

Marie was initially prescribed 400mg of imatinib, and achieved both a haematological and cytogenic response by the six month review. Although she maintained this therapeutic response at one year, her dosage was increased to 800mg prior to the final review. Her fatigue improved over the same period. She continued to report minimal depressive symptoms but described subtle increases in anxiety by the six and twelve month reviews. Figures 9 and 10 show the pattern of performance in verbal memory and other cognitive measures across the three assessments.

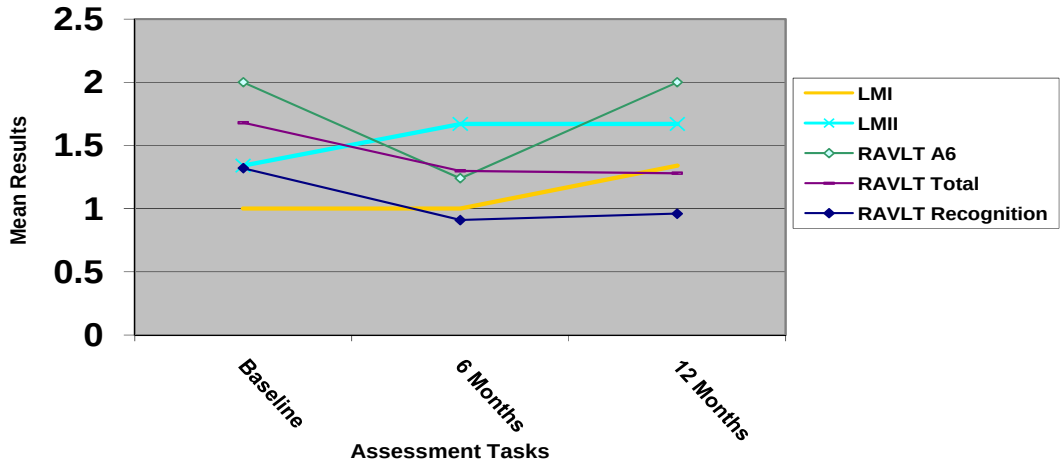


Figure 9. Verbal memory results for the participant with the pre-morbid FSIQ closest to the population mean

According to figure 9, Marie's baseline verbal memory function was above the population mean (i.e., mean result of zero). She demonstrated a slight improvement in her immediate and delayed recall on the Logical Memory subtest by 12 months, however there was no improvement in her immediate recall on the RAVLT over the same time period. In fact her performance on this measure deteriorated at the six month review but returned to baseline levels by one year. Further to this, her total learning on the RAVLT and verbal recognition declined by the six month assessment. This finding was broadly maintained at the twelve month review.

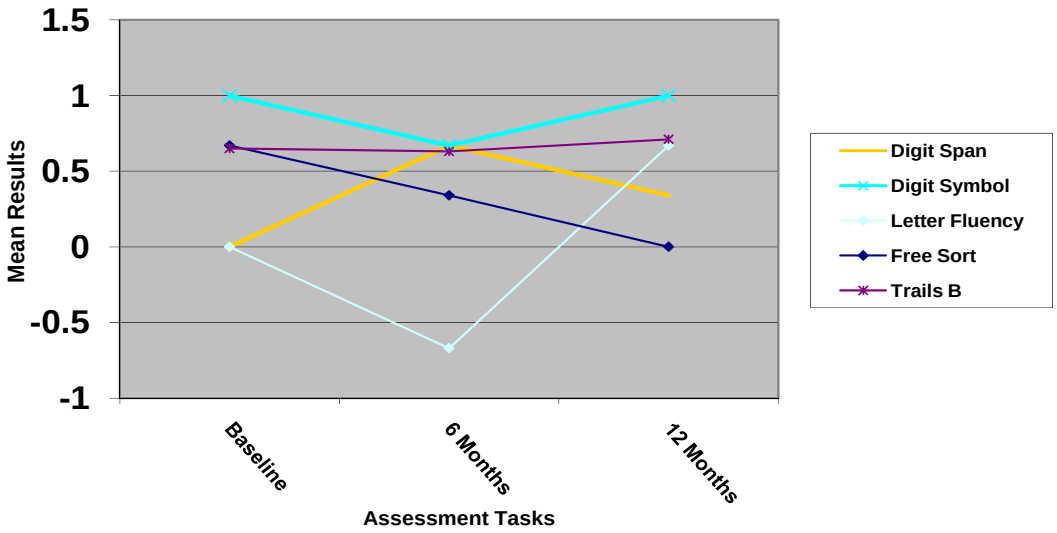


Figure 10. Performance on other cognitive measures for the participant with the FSIQ closest to the population mean

Based on results shown in figure 10, Marie demonstrated a variable pattern of performance across the three assessments. Her letter fluency deteriorated at six months, however she performed well beyond baseline levels by the final review. There was a subtle improvement on the Digit Span subtest over time. Her performance on the Trails B test and Digit Symbol Coding subtest was broadly unchanged across the three assessments. In contrast, she demonstrated a decline on the free sort condition of the Sorting test at both the six and twelve month reviews. In summary, Marie failed to make the expected gains on measures of mental flexibility and some verbal memory tasks. However she demonstrated improvement on timed processing speed measures.

3.9.2 Case Study 2: 'Tom'

At the time of his diagnosis, Tom was 24 years and 2 months. He had completed twelve years of education and was working as a truck driver with the armed services. At the time of the baseline assessment, he was married and had a two month old daughter and described minimal symptoms of depression on the BDI-II. He reportedly became severely depressed several months after his diagnosis, and was placed on anti-depressant medication. By the 6 month review his mood was improving (scored in minimal range on BDI-II) but he was still on modified duties and hours at work. By one year, his mood symptoms had further improved. He had increased his duties and hours at work, and reported improvements in quality of life. His FSIQ at the initial assessment was 126 (superior range), whilst his verbal comprehension index was 136 (very superior range) and his perceptual organisation index was 121 (superior range). Tom had the highest pre-morbid FSIQ in the sample.

Tom was prescribed 800mg of imatinib, and achieved both a haematological and cytogenic response by the six month review. Figures 11 and 12 illustrate the pattern of performance in verbal memory and other cognitive measures across the three assessments.

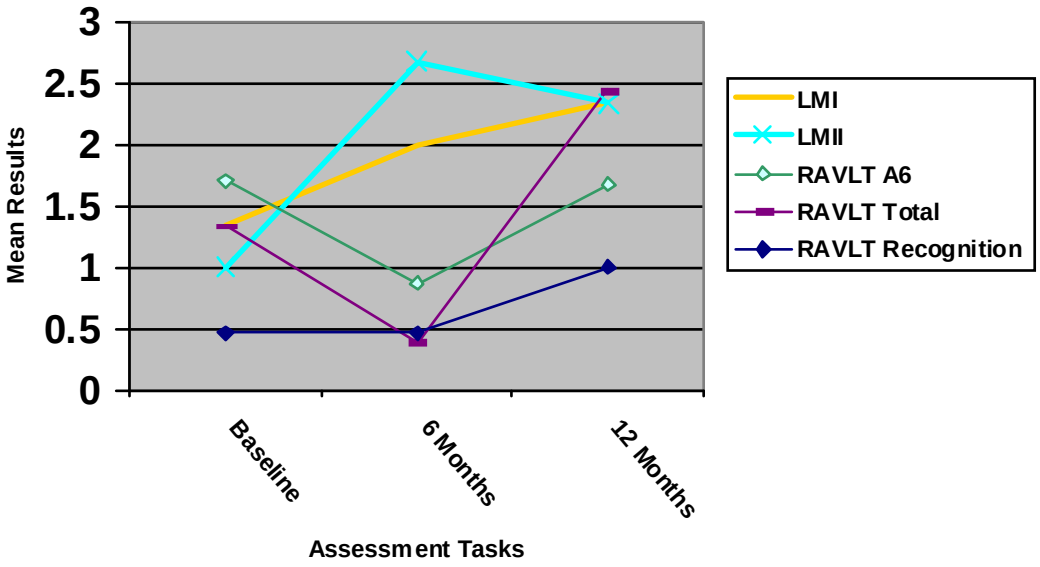


Figure 11. Verbal memory results for the participant with highest pre-morbid FSIQ

Tom demonstrated a variable pattern of performance across the three assessments. However there was a definite trend toward improvement on most measures when his performance at 12 months was compared with his baseline performance. His immediate recall on the RAVLT was the only exception, as his performance at 12 months was broadly comparable to his original performance. His improvement on other verbal memory tasks varied from .5 of a standard deviation to almost 1.5 standard deviations. In general, Tom demonstrated considerable improvement over time and appeared to benefit more from repeated exposure to the verbal memory tasks than Marie.

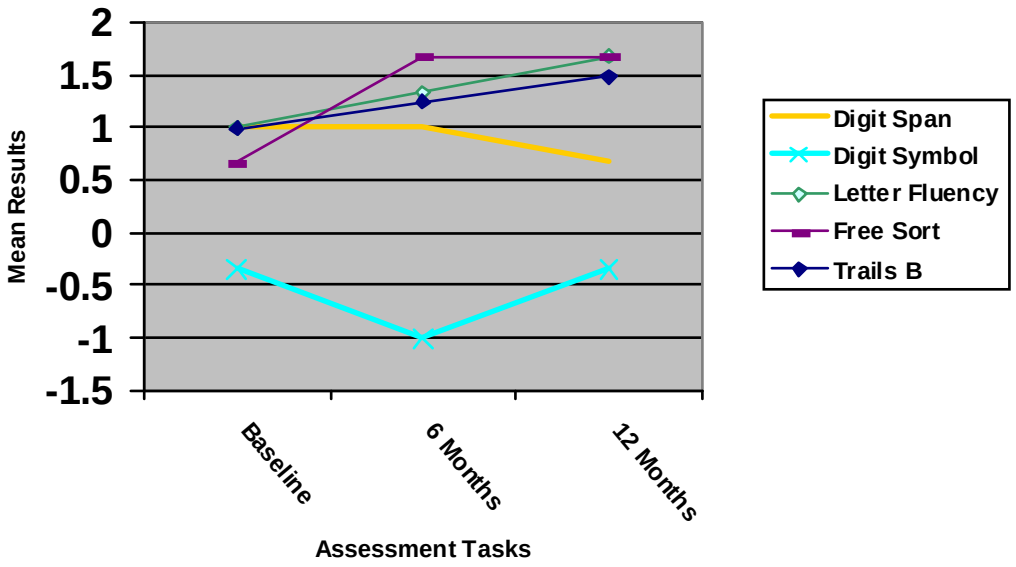


Figure 12. Performance on other cognitive measures for the participant with highest pre-morbid FSIQ

Tom's performance on other cognitive tasks was more variable. He demonstrated a subtle improvement in his performance on the letter fluency task, Trails B, and the free sort condition of the Sorting Test across the three assessments. In contrast, his performance on the Digit Span subtest deteriorated, albeit mildly, by the final review. His processing speed was an area of relative weaknesses across the three assessments. However he did not demonstrated any decline or improvement over time, as his performance in the 12 month assessment was comparable to his baseline performance.

3.9.3 Case Study 3: 'Jane'

At the time of her diagnosis, Jane was 42 years and 7 months. She immigrated to Australia from the Cook Island eight years ago, and she stated that English was her second language. Jane reported that she completed eleven years of education and worked in a range of unskilled positions such as cleaning and factory work. At the time of the baseline assessment, she was separated but in a new relationship and described herself as severely depressed on the BDI-II. Her FSIQ at the initial assessment was 72 (borderline range), whilst her verbal comprehension index was 63 (extremely low range) and her perceptual organisation index was 91 (average range). Jane had the lowest pre-morbid FSIQ in the sample.

Jane was prescribed 800mg of imatinib, and achieved both a haematological and cytogenic response by the six month review. Her mood also improved over the same period, and she reported minimal depressive symptoms at both six months and one year. Figures 13 and 14 illustrate the pattern of performance in verbal memory and other cognitive measures across the three assessments.

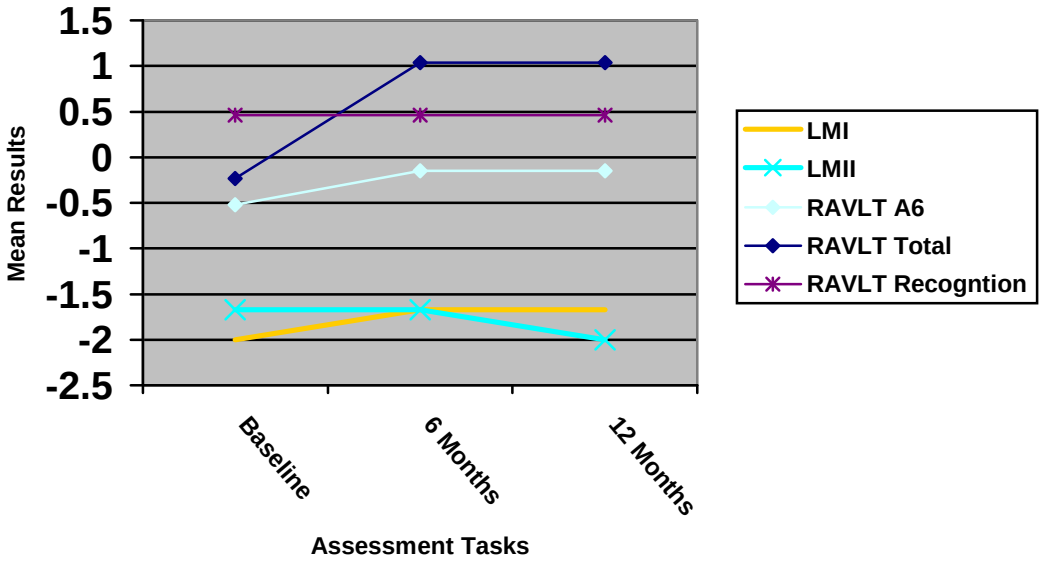


Figure 13. Verbal memory results for the participant with lowest pre-morbid FSIQ

According to figure 13, Jane demonstrated a slight improvement in her immediate recall on both the Logical Memory subtest and RAVLT by 12 months, however there was no improvement in her delayed recall of prose (i.e., Logical Memory II) or verbal recognition on the RAVLT over time. In contrast her total verbal learning on the

RAVLT had improved considerably by the six month assessment. The timing of this improvement coincided with improvements in mood.

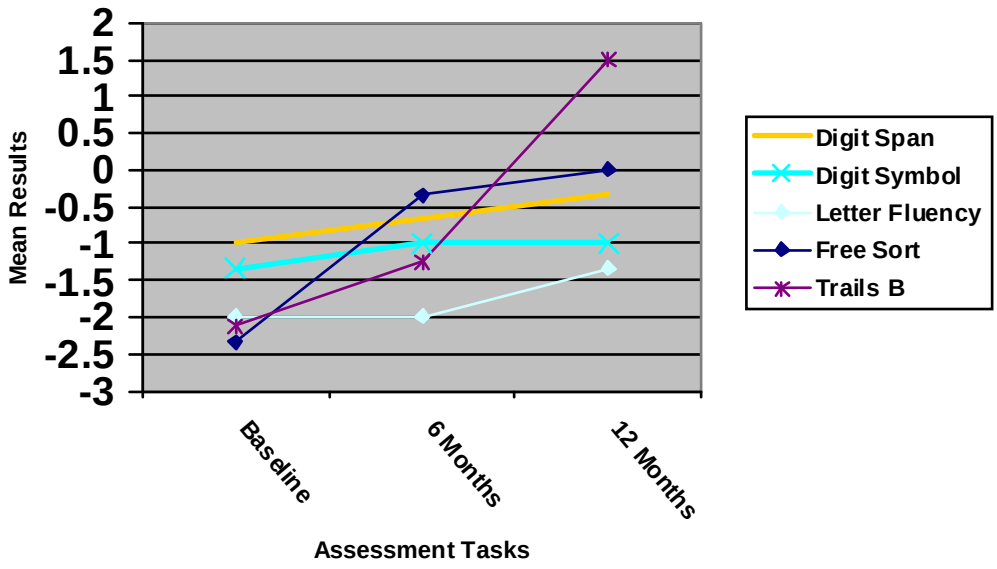


Figure 14. Performance on other cognitive measures for the participant with lowest pre-morbid FSIQ

Based on results shown in figure 14, Jane demonstrated a range of improvements on other measures of cognitive function. Subtle improvements were seen in the Digit Symbol Coding subtest, Digit Span subtest, and the letter fluency condition of the Verbal Fluency test. In contrast, marked improvements were evident on the Trails B test and free sort component of the Sorting Test. In summary, Jane demonstrated the greatest improvement on measures involving mental flexibility but failed to consistently improve across verbal memory tasks. The lack of improvement in her verbal memory across the three assessments may be associated with the fact the English is her second language. The difficult issue of cross-cultural bias in neuropsychological assessment will be discussed in more detail in Section 4.8 (Limitations and Future Directions).

4. DISCUSSION

4.1 STATISTICAL METHODS USED TO TEST AIMS 1 AND 2

A series of repeated measures ANOVA's were conducted to investigate changes in the overall performance of the sample over time. Bonferroni's correction was employed given the large number of dependent variables and the small sample size in order to calculate the appropriate alpha level for the given pairwise tests. Given that ten dependent variables were analysed, an alpha level of 0.005 was required for statistical significance. The 'partial eta squared (η^2)' statistic was used to determine the magnitude of any significant changes. These statistical methods were employed to assess both verbal learning and memory, along with other cognitive measures.

4.2 VERBAL LEARNING AND MEMORY

4.2.1 Comparisons with Baseline Performances

The first aim of the present study was to investigate the verbal learning and memory function of adult CML patients. Participants' performances on specific cognitive measures, completed six and twelve months after commencing imatinib treatment, were compared to baseline performances. Participants' completed the baseline assessment in the days or weeks following diagnosis, and prior to starting imatinib therapy.

Consistent with findings described by Pedersen et al. (2009) in his study on the effects of chemotherapy in testicular cancer, there was no significant decline in any area of verbal learning or memory. Several different areas of verbal memory function were examined in the current study. However, only the most sensitive measures were chosen for analysis. Participants' episodic memory was investigated through the immediate and delayed recall of a prose passage (i.e., Logical Memory I and II subtests from the WMS-III). Verbal learning and memory, together with verbal recognition were also examined using the RAVLT (i.e., Trial 6, Recognition, and Total Learning). Contrasts between performances on the Logical Memory subtest and the RAVLT were useful to emphasise the importance of context and meaning in memory function (Lezak et al., 2004).

Logical Memory (WMS-III)

A comparison of the central trends in the data revealed no significant decline in participants' immediate and delayed recall of prose by twelve months. In fact, participants' performance on both measures had significantly improved by the one year review. The size of effect was large. Although this could still be a chance finding associated with the small sample size (i.e., "sampling error"), the magnitude of this effect is notable. Interestingly, two of the three participants who improved the most on the Logical Memory subtest had FSIQs within the superior range, and therefore might be expected to benefit more from repeated exposure to this information over time (See 3.9.2: Case Study 2).

At the outset of this study there was no strong research evidence to suggest whether there should be a decline, an improvement, or stability in patient's verbal learning and memory following treatment with imatinib. There was some indication from animal studies (Grove et al., 2004; Katafuchi et al., 2000; Tzingounis & Nicoli, 2006) and previous anecdotal reports to suggest that deterioration may occur following the commencement of imatinib treatment. However the present systematic investigation supports no deterioration in verbal memory function, and instead demonstrates a consistent trend towards improvement over time.

The findings in the current study are not consistent with previous patient reports from the Royal Melbourne Hospital. Prior to the commencement of the current study, a number of patients at the hospital expressed concerns about their memory function following treatment with imatinib. Interestingly, when the matter was discussed in detail with the participants in the current study, none of them noticed a decline in any aspect of their cognition over the time of the assessment. It is possible that previous reports of deteriorating memory function may reflect the impact of other psychological/non-cognitive problems, such as fatigue, mood, and affect. The relationship between these psychological variables and cognition will be discussed in more detail in Section 4.4 (Demographics, Affect, Fatigue, and Cognition).

This pattern of retained or improved function was also inconsistent with previous animal studies, which showed that the inhibition of specific protein kinase (namely

ABL-interactor protein, ARG, and the KIT protein) resulted in impaired learning and memory (Grove et al., 2004; Katafuchi et al., 2000; Tzingounis & Nicoli, 2006). However there are difficulties associated with the methodologies used in these animal studies, which make it difficult to translate the findings to humans. In previous studies using mice and rats, kinase was either deleted from the hippocampus, or imatinib was directly injected into the brain. In the current study participants ingested imatinib orally, which is likely to have far less impact on the brain, given the agents low CNS penetration (Wolff et al., 2003). As a result, the protein kinase in the CNS may be partially protected from the adverse effects of imatinib. However there is still cause for concern, as new molecular therapies now in clinical trials may have higher CNS permeability (Porkka et al., 2008), which whilst more effective in eradicating leukaemic cells, risk higher neurotoxicity.

Imatinib's low CNS penetration has been well-documented in the literature (Wolff et al., 2003), and it now appears that the agent's limited permeability minimises potential neurotoxic effects. At present there are no prospective studies which document or seek to explain the cognitive improvements seen in the current study. However there is emerging evidence of imatinib's role in minimising the impact of brain injury and neurodegenerative disease. As Alvarez et al. (2004) claimed that imatinib lessens the behavioural deficits associated with Alzheimer's disease by halting the progression of neuronal cell death, whilst Rieckmann (2008) suggested that imatinib may reduce damage to the blood brain barrier after stroke. At a cellular level this may be the basis of the improved memory function found in the current study.

In addition to these findings, improvements in the current study may also be partially attributed to the effects of practice. Benedict and Zgaljardic (1998) indicated that practice effects are common in serial memory assessments, as repeated exposure to the same information leads to learning in all but the most seriously impaired individuals. In contrast, Martin et al. (2002) demonstrated in his study of 42 patients with temporal lobe epilepsy that practice effects are not always apparent in patient groups. Thus, the evidence of improved memory function in the current study argues against the possibility of clinically significant learning or memory difficulties in CML patients prescribed imatinib.

Certainly there were strong indications that participants in the current study were retaining details from the Logical Memory subtest between assessments. Many of the participants' asked about the stories and also the word lists from the RAVLT prior to commencing formal testing at the six and twelve month review. In fact, a number of participants even mentioned specific details from the stories before commencing the subtest, for example '*I have been trying to remember that story about Joe Garcia*'. This finding was particularly evident by the final review.

RAVLT

A measure of verbal learning, verbal recall, and verbal recognition were derived from the RAVLT. Unlike the Logical Memory subtest, an alternate version of this task was used at the six month review to minimise potential practice effects. The post-interference trial (i.e., Trial 6) of the RAVLT was analysed as it is considered highly sensitive to neurological insult (Geffen, Butterworth, Forrester & Geffen, 1994). This measure examines the impact of distraction on the immediate recall of unrelated verbal information. Again, a comparison of the central tendencies within the data revealed a significant improvement in immediate verbal recall by the twelve month assessment. The magnitude of this change, as measured by the effect size, was in the moderate range.

Participants did not show significant change in total learning and verbal recognition across the assessment period. However, there was a tendency, albeit non-significant, towards improved total verbal learning by the twelve month assessment. Furthermore, there was a non-significant decline in participants' overall verbal recognition at six months, which was no longer apparent by the final review. This decline in verbal recognition may reflect the use of an alternate form at the six month assessment. Geffen et al. (1994) reported poor test-retest reliability for the verbal recognition measure on the alternate form. Therefore this measure is not highly comparable to the verbal recognition measure on the standard form of the RAVLT ($r = 0.38$) (See Appendix M). Thus the decision to use alternate forms to minimise practice effects may introduce further error into the assessment process.

In addition, it is likely that improvements on the RAVLT may still be partially attributed to practice even though alternate forms were utilised. Whilst alternate forms minimise the potential to learn the content of tests, they do not control for procedural learning (Chelune, 2002; Uchimaya, D'Elia, Dellinger, & Becker, 1995). Benedict and Zgaljardic (1998) contend that participants acquire a general 'test-wiseness' from repeated exposure to the test protocol. In later assessments, participants may arrive at strategies more quickly to aid their learning, or recall details of the test process, which may assist their performance (Lezak et al., 2004). For example, participants are not advised that they will be required to recall the words from the RAVLT after a delay. However on review, even with an alternate form, participants may recall the test format and therefore place more emphasis on retaining this information over time. Participants' ability to benefit from practice in the current study, again argues against the presence of any clinically significant memory disturbance in CML patients prescribed imatinib.

Significant attempts were made to address the issue of practice through the use of a control group. There was rigorous discussion about the most appropriate cohort. Whilst healthy controls might elucidate any practice effect, they would not control for the psychological distress associated with the diagnosis, the possible deterioration from the condition alone, or the impact of treatment. The use of another condition with a comparatively grave prognosis might control for factors such as psychological distress, however it is likely that such a group would require treatment with other chemotherapies and/or irradiation. It was agreed that the best comparator group (whilst still imperfect) would comprise participants with other haematological malignancies not requiring chemotherapy. It was anticipated that this group would serve to control for the effects of the disease and the effects of the treatment. Sex and aged matched participants with newly diagnosed Chronic Lymphocytic Leukaemia (CLL) or Low Grade Non-Hodgkin's Lymphoma (NHL) were considered the most comparable group. It was hoped that the introduction of such a group would control for practice effects but also isolate the effect of the disease from the effect of the treatment. Attempts were made to recruit participants to this group over a twelve month period. By the end of this period only one control participant was enrolled in the study. Approximately four other patients who initially reported some interest, ultimately declined. Each of these patients described the time commitment (i.e., approximately eight hours of assessment

across one year) as the primary reason for declining, particularly given that they had already spent considerable time at the hospital undertaking other diagnostic investigations. This trend was not apparent in the CML group, as these patients were overwhelmingly interested in participating in the study. Although it is purely speculative, it appeared that the gravity of the diagnosis influenced their willingness to become involved. For example, patients receiving a less grave diagnosis (i.e., CLL, NHL) tended to resume their normal activities as quickly as possible, whilst the CML patients appeared more likely to take up all the services and supports available to them; which included the research.

Ultimately the baseline assessment was utilised as a control measure to gain an understanding of participants' normal function prior to the introduction of treatment. Fortunately, the samples overall baseline performance appeared to be reasonably representative of the normal population (i.e., Mean FSIQ = 101.92, SD = 18.33). This suggests that the lack of decline across assessments cannot be attributed to a floor effect. When this occurs, the poor baseline performance of the sample makes it difficult to demonstrate further decline over time. Given that participants' FSIQs in the current study ranged from the borderline to superior range, there was opportunity for deterioration to be observed during the course of the treatment. Further issues associated with the use of the baseline measure as a control will be discussed in more detail in section 4.3.1.1.

In summary, there was significant improvement across many measures of verbal learning and memory on the RAVLT. There was no clear indication of decline over time. Other than the issues mentioned previously regarding the potential neuroprotective qualities of imatinib, a possible inflation of deficits in animal studies, the low CNS permeability, and practice effect, one might argue that the results of the current study may also be an artefact of the small sample size. Only thirteen participants were enrolled in the study over almost two years of recruitment through four of the main cancer treatment centres in the state of Victoria. (This total includes one participant who died in the months after his baseline assessment). This sample represented almost all new patients from at least three of the four cancer centres over that time, and therefore highlights the rarity of the condition. Initially, it was considered a realistic goal to recruit 15 participants in a 12 month period. However

only nine participants were recruited over this period, and it took another eight months to recruit the additional four participants. In total the data collection phase of this study was completed over approximately two and a half years. The recruitment was ultimately ceased for a number of reasons. Logistically it was no longer practical to extend the recruitment period further given that any new patients would need to be followed up for a further 12 months. This decision was also made in light of the emerging trend in participants' performance, which appeared to indicate improvement rather than decline over time.

Given the rarity of this condition, it is likely that issues of recruitment and limited sample size will continue to hamper research efforts in this area. The challenges associated with this are further complicated by best practice recommendations from the International Cognition and Cancer Task Force (ICCTF), which indicate that test inventories should assess a broad range of cognitive domains (Vardy et al., 2008). This presents a number of research design issues, as each additional dependent variable requires a larger sample size to ensure that inferential statistical tests will have sufficient power to detect a real difference. In the current study, a number of different statistical methods were employed to address concerns associated with the limited sample size. Only the most sensitive measures in each test were chosen for analysis to limit the potential for type I errors. Furthermore, Maxwell and Delaney (1990) contend that univariate approaches, such as the repeated measures ANOVA, are more powerful when the sample size is small (as cited in Field, 2005). Finally, a measure of effect size was used to identify the strength of any mean change in performance.

Ideally, with a larger sample size additional dependent variables may have been assessed including visual memory. The current study sought to assess verbal memory function as it is commonly described as an area of deficit following treatment with chemotherapy (Schagen et al., 2006; Scherwath et al., 2006; Wefel et al., 2004). However it may be interesting to determine whether the treatment has any lateralising effects, as many of the animal studies mentioned earlier assessed visual spatial memory (Grove et al., 2004; Katafuchi et al., 2000; Tzingounis & Nicoli, 2006).

4.3 OTHER COGNITIVE MEASURES

4.3.1 Comparison with Baseline Performances

The second aim of the current study was to monitor the cognitive function of a sample of adult CML patients over a twelve month period. Participants' performances on measures of attention and working memory, motor and processing speed, and executive function, completed six and twelve months after commencing imatinib treatment, were compared to baseline performances. Participants' completed the baseline assessment in the days or weeks following diagnosis, and prior to starting imatinib therapy.

There was no significant decline in any area of attention and working memory, motor and processing speed, or executive function. This is consistent with the samples self-report, as no patient described any concerns about their cognition at the six or twelve month review. Furthermore, the lack of decline is concordant with findings described by Pedersen et al. (2009) in his study of the long-term cognitive effects of chemotherapy in testicular cancer but contradicted previous longitudinal oncology research that identified subtle but enduring deficits in attention, processing speed, and executive function (Schagen et al., 2006; Scherwath et al., 2006; Wefel et al., 2004). However, much of this research focused on cognition in breast cancer patients treated with different chemotherapy agents. Pedersen et al. (2009) argued that findings from these earlier studies might not be generalisable to different cancer groups and treatments. Furthermore, many chemotherapy treatments are not highly specific and risk damage to otherwise healthy tissue (Wefel et al., 2008). Therefore, patients receiving traditional chemotherapy agents might experience greater adverse consequences than patients receiving highly targeted molecular therapies such as imatinib. Given the difference between these medications, there is no human comparison for the current research findings and as such the results of the present study act as an important baseline for ongoing research in this domain to clarify these issues further. In this next section, the trends in the data will be discussed in more detail.

Attention and Working Memory

Digit Span Subtest (WAIS-III)

A comparison of the central trends in the data indicated that there was no significant change in participants' performance on the Digit Span subtest by the six or twelve

month review. Often improvement is expected as a result of repeated exposure to the same material, however practice effects for this measure are reported to be negligible (McCaffrey, Duff & Westervelt, 2000).

Motor and Processing Speed

Digit Symbol Coding Subtest (WAIS-III)

There was no significant decline on this measure of processing and motor speed. In fact, the analysis of group trends revealed a non-significant tendency towards improvement on the Digit Symbol Coding subtest by the twelve month assessment. Whilst a lack of improvement with repeated exposure to the same measure can be clinically meaningful, this is not the case with the Digit Symbol Coding subtest, as only modest practice effects would be expected across serial assessments (Lezak et al., 2004; McCaffrey et al., 2000). These results contradict Grove at al.'s (2003) findings which indicate that the inhibition of protein kinase leads to impaired synaptic efficiency. However as mentioned previously, it is difficult to generalise these findings to humans as imatinib was injected directly into the CNS of these animals, and therefore would be expected to have greater adverse effects.

Executive Function

Verbal Fluency Subtest (Letter and Category Fluency Conditions) (D-KEFS)

A review of the central trends within the data revealed no significant change in the letter fluency condition of the Verbal Fluency subtest by the twelve month assessment. Levine, Miller, Becker, Selnes and Cohen (2004) and others (Dikmen, Heaton, Grant, & Temkin, 1999) indicated that whilst some improvement in verbal fluency is expected with practice, the magnitude of this difference is often small (3.08 increase in raw score) and therefore potentially non-significant.

Trails B (Trail-making Test)

The repeated measures ANOVA revealed no significant change in the samples performance on the Trails B component of the Trail-making test over time. The literature about the benefits of practice on the Trails B component of the Trail-making test is inconsistent (Basso, Bornstein, & Lang, 1999; Bornstein, Baker, & Douglas, 1987; Durvasuka et al., 1996); therefore it is again difficult to establish whether the lack of improvement is of clinical importance.

Sorting Test (D-KEFS)

The repeated measures ANOVA revealed a non-significant trend towards improved performance on the free sort condition of the Sorting Test at the twelve month review. The absence of significant change across assessments is curious as Dikmen et al. (1999) indicated that tests involving problem solving and strategy, such as the Sorting Test, tend to have the largest practice effects. This is likely to be associated with the notion of test-wiseness mentioned above; as participants become familiar with the task, they refine and more readily employ strategies for successful problem solving (Lezak et al., 2004).

Findings from the Sorting Test should be interpreted with some caution, as the psychometric qualities of a number of measures in the D-KEFS have been criticised. Schmidt (2003) claimed that the reliability values in the D-KEFS were generally below the minimum accepted standard, and could not be recommended for clinical use. Whilst Shunk, Davis, and Dean (2006) also raised concerns about the measures' psychometric properties but indicated that the test's strength was associated with its ability to provide rich qualitative information. In contrast, Homack, Lee, and Riccio (2005) described the D-KEFS as a promising clinical and research tool. Further to this, early research undertaken by De Renzi Faglioni, Savoiardo and Vignolo, 1966 and others (McFie & Piercy, 1952; Newcombe, 1969) on the use of card sort tests (as cited in Lezak et al., 2004) claimed that the test was insensitive, as it failed to differentiate healthy individuals from brain injured patients.

In summary, the pattern was one of stable cognitive function over time, with some areas of non-significant improvement in processing speed and executive function.

4.4 DEMOGRAPHICS, AFFECT, FATIGUE, AND COGNITION

The third aim of the current study was to examine whether changes in verbal learning and verbal memory, and other cognitive measures were related to mood and affect, demographics (i.e., FSIQ, SES, educational attainment), and fatigue. Demographic variables were recorded at the baseline assessment, whilst mood, affect, and fatigue were examined on all three occasions. Correlations were performed to identify whether

significant changes in cognitive function were associated with the above-mentioned variables at the baseline, six month, and twelve month assessments.

4.4.1 Verbal Learning and Memory

4.4.1.1 Mood, Affect, and Verbal Memory

Mood and Verbal Memory

A highly significant correlation was found between mood and recall on the Logical Memory subtest at the baseline assessment. Participants who reported more depressive symptoms on the BDI-II tended to recall less prose both immediately after the information was presented and following a delay. All of the participants had been informed of their diagnosis in the days or weeks prior to the baseline assessment. Whilst a number of the participants stated that they had adjusted to the diagnosis, others described significant levels of mood disturbance. It is not unreasonable to expect that these depressive symptoms would impact verbal memory function, particularly given the variety of mood-related cognitive deficits described in various studies (Castaneda et al., 2008; Liotto & Mayberg, 2001; Veiel, 1997; Zakzanis et al., 1998) and Zakzanis et al.'s (1998) claim that episodic memory is usually most affected. In support of this, there was a changing relationship between mood and verbal memory throughout the course of the research. Most participants undertaking the six and twelve month reviews had seen some improvement in their blood counts over time, and were now reporting less mood disturbance. As per the results, mood was no longer associated with verbal memory function by the final review.

This highlights an issue that was previously discussed regarding the impact of mood on the assessment of baseline functioning (See Introduction Section 1.6.1: Transplant Therapies). Ahles (2004) and van Dam et al. (1998) contend that the distress associated with receiving the diagnosis may affect participants' performance during the initial cognitive assessment. Therefore the baseline assessment may not be a true indication of the participant's pre-morbid ability. In the current study, the majority of participants reported minimal depressive symptoms on the BDI-II at baseline. Only one participant described moderate depressive symptoms, and one reported depressive symptoms in the severe range. This argues against the possibility that participant's overall baseline

performances were significantly lowered by mood.

Further to this, mood was not significantly related to verbal learning and memory function on the RAVLT. This finding is in clear contrast to the current literature, which suggests that depressed individuals demonstrate impaired immediate recall on the RAVLT, as they struggle to generate strategies to aid their learning (Payne, 2000). Interestingly, in the case study presented earlier (See 3.9.3: Case Study 3), Jane's total learning on the RAVLT improved considerably as her mood lifted. An inspection of the individual data shows there was considerable variability.

Verbal Memory and Affect

State anxiety was not significantly related to verbal learning and memory function at any stage of the assessment process. In spite of this, participants consistently reported a sense of dread as they approached the verbal memory tasks and described these as the most confronting and difficult tests. Although it was surprising that state anxiety was not significantly associated with verbal memory performances, the present finding is consistent with Hoffman and Al'Absi (2004), conclusions that acute mental stress has no measurable effect on performance on the RAVLT and Logical Memory tests.

4.4.1.2 Fatigue and Verbal Memory

Fatigue was not significantly associated with the immediate or delayed recall of meaningful verbal information on the Logical Memory subtest. This was in spite of consistent reports of fatigue at the baseline assessment, which lessened over the course of the year.

In contrast, there was a relationship between levels of fatigue and total verbal learning on the RAVLT at the baseline assessment. Grants and Adams (1996) indicated that learning the unstructured and poorly organised material in the RAVLT demands more cognitive resources than learning well-organised verbal information. For example, the Logical Memory subtest provides contextual cues and an inherent structure that aids learning and recall, whilst one must rely more heavily on their own abilities to organise information to enhance learning on the RAVLT (Brooks, Weaver, & Scialfa, 2006). Given that this requires more effortful processing, it is anticipated that high levels of fatigue would have greater influence on participants' performance on the RAVLT as

opposed to the Logical Memory subtest. This finding is consistent with Buck-Gengler and Healey (2001) and others (Healey & Bourne, 1995) who report that task complexity mediates the impact of fatigue.

4.4.1.3 FSIQ and Verbal Memory

A further aim of the present study was to investigate the relationship between verbal memory and demographic variables. According to the analysis, participants' FSIQ was highly correlated with their performance on most measures of verbal memory. Participants with higher IQs tended to recall more prose on the Logical Memory subtest; a trend which was evident at the baseline assessment and twelve month review, and applied to both the immediate and delayed recall conditions. This finding is consistent with the current literature, which indicates that memory and intellectual capacity are highly correlated (Vakil, Shelef-Reshef, & Levi-Schiff, 1997). However these results are also in line with the theory of cognitive reserve, which contends that individuals' with greater intellectual ability have a larger reserve of capacity to buffer them against the full impact of brain insult (Banich, 2004; Prigatano, 1998; Satz, 1993). Furthermore, intelligent individuals may be more able to learn and develop strategies to compensate for any changes in their cognitive function (Banich, 2004). Given this, participants with higher FSIQs would be expected to continue to perform better than others participants by the final review.

The relationship between participants' immediate verbal recall on the RAVLT and FSIQ was approaching significance. This trend was present at the twelve month review but not the initial baseline assessment. This was consistent with Vakil et al.'s (1997) study, which indicated that individuals with higher FSIQs tend to recall more information on the RAVLT. Given that this trend emerged by the twelve month assessment after repeated exposure to the measure, this may reflect the effect of practice over time. This finding supports Rapport et al.'s (1997) assertion that brighter individuals tend to benefit more from repeated administrations of tests. With this in mind, we might expect to see that brighter individuals have improved more than their peers at one year.

4.4.1.4 Demographics and Verbal Memory

Socio-economic Status

Socio-economic status was also positively related to some measures of verbal learning and memory but not others. Participants with a higher SES immediately recalled more prose during the Logical Memory subtest at the six month review. This relationship was again approaching significance at the final assessment. There was also a tendency for participants from higher socio-economic backgrounds to perform better on the delayed recall component of the Logical Memory subtest at six months, and the RAVLT at one year.

This is consistent with Turell et al. (2002) and others (Bouchard & Segal, 1981) finding that individuals with a higher SES tend to demonstrate better overall cognitive function, as expressed by higher FSIQs. According to Weitan (1992), this relationship between SES and FSIQ is associated with the types of learning opportunities available to individuals. That is, individuals from higher socio-economic backgrounds tend to enjoy a more enriched environment, which enables them to reach their full potential cognitively. Furthermore, higher levels of SES have also been associated with increased cognitive reserve, as demonstrated by slower rates of cognitive decline in normal ageing (Turell et al., 2002) and Alzheimer's disease (Barco, López, Ribal, Pérez, & Pérez, 2008*;* Bracco et al., 2007). This greater cognitive reserve might limit the expression of any neurotoxic changes.

Educational Attainment (Years of Education)

A further objective of the current research was to investigate the relationship between years of education and memory in CML patients. Participants' performance on the Logical memory subtest and Trial 6 of the RAVLT were not significantly associated with their educational attainment by the final assessment. This finding contrasts with the body of literature which claims that the challenges associated with education enhance one's reserve of cognitive ability by contributing to increased neural connectivity (Jacobs, Schall & Scheibel, 1993). However it supports findings reported by Anderson and Lajoie (1996) that indicate that educational attainment is not consistently associated with performances on the RAVLT. It should be noted that the range of "Years of Education" in the current study was quite restricted, with most

participants reporting between 9-11 years of schooling. A repeat sample with a wider range of educational attainment might show a significant correlation.

4.4.2 Other Cognitive Functions

Participants failed to demonstrate any significant change on other cognitive measures (i.e., not verbal learning and memory) over time. Therefore no further investigations were undertaken to examine the relationship between these cognitive measures and other demographics and mood-related variables.

4.5 DOSE AND COGNITION

Another aim of the current study was to investigate the relationship between dose and cognitive function. As per the previous analysis, this was sub-divided into verbal learning and memory, and other measures of cognitive function. The relationship between cognition and dose was examined at the six and twelve month reviews, as patients were not taking imatinib during the baseline assessment. Medication was prescribed in 400mg, and 600mg, and 800mg doses.

4.5.1 Verbal Learning and Memory

There was no relationship between dose and performance on the Logical Memory subtest and immediate recall on the RAVLT. Given the small sample size and the fact that the sample was further subdivided according to dosage, these findings must be viewed with some caution.

Regardless of this, the current finding is somewhat counter-intuitive, as one would expect that higher dose was associated with greater levels of neurotoxicity and therefore poorer memory performances. However this finding may provide further evidence of the agent's low CNS permeability. Interestingly, 'Marie's' performance declined in the final assessment, as her dosage increased from 400mg to 800mg before the twelve month review (See Section 3.9.1: Case Study 1). However there was also a subtle increase in her state anxiety over this time. Qualitatively, Marie reported significant anticipatory anxiety as she approached the later assessments.

A further examination of individual performances revealed that two of the three participants receiving the highest dose had FSIQs in the superior range, whilst both participants taking 600mg recorded high average to superior FSIQs at the baseline assessment. Thus, we might expect that these participants had a larger cognitive reserve which could modulate any potential neurotoxic effects. A further review of these findings indicated that, in general, younger participants received the highest dose of imatinib, and by chance these subjects also recorded better overall FSIQs.

4.5.2 Other Cognitive Measures

The relationship between imatinib dose and performance on other measures of cognitive function was not investigated, as there was no significant change in participants' performance on these cognitive measures over time.

4.6 EMOTIONAL FUNCTIONING

The majority of patients reported minimal to mild symptoms of depression on the BDI-II at the baseline assessment. Only one patient described moderate symptoms, whilst another reported depressive symptoms within the severe range. This was surprising given that all of the participants had just received news of the diagnosis. In general, most participants stated that they had come to terms with the diagnosis, and were 'determined to make the most of the time (they) had left'. One might assume that such a rapid adjustment to the diagnosis is more a function of denial rather than genuine adjustment. If this was indeed the case then increasing mood symptoms should have emerged over the course of the year. In contrast, there was a subtle improvement in mood by the six month assessment, a result which was maintained by the one year review. By six months, none of the participants described themselves as severely depressed, whilst a higher proportion of the sample reported minimal depressive symptoms.

This pattern of improved mood contrasts with reports about the mood-related consequences of other transplant and non-transplant treatments. According to Syrjala et al. (2005), mood disturbance is commonly observed after ASCT, and anti-depressant and anti-anxiolytic use remains high even 10 years after transplantation. Significant

affective and psychiatric disturbances have also been associated with interferon alpha, with rates of depression reported to be as high as 48% in some patients (Malek-Ahmadi & Hilsabeck, 2007). The risk of mood disturbance increases the longer patients continue treatment with this agent (Hensley et al., 2000; Poynard et al., 1996; Valentine et al., 1998). Unlike imatinib, interferon alpha use is also commonly associated with adverse physical consequences (Hahn et al., 2003; Homewood et al., 2003). It is possible that the high incidence of such effects may contribute to difficulties with adjustment and emotional disturbance.

4.7 QUALITY OF LIFE

Participants reported decreases in fatigue and subtle improvements in quality of life on the FACT-Leu questionnaire by the six and twelve month reviews. Qualitatively, most people described heightened fatigue and a general reduction in their level of function in the weeks or months prior to their diagnosis. By the six and twelve month assessment, participants were reporting a decrease in their level of fatigue, and most stated that they were slowly resuming their pre-morbid sporting, work, and social activities. Improved quality of life has been reported in the literature, as the drug can be self-administered on an outpatient basis (Deininger & Druker, 2003). Furthermore, other studies have described significantly better quality of life, physical functioning, and well being when compared to interferon alpha plus cytarabine ($p= 0.001$) (Hahn et al., 2003). Homewood et al. (2003) indicated that the toxic effects of interferon alpha compromised patients' social functioning and quality of life, as most patients experienced heightened pain, worsening fatigue, nausea, and vomiting.

Mixed findings have been reported regarding quality of life and transplant therapies for CML. Reduced social function and poorer quality of life is described in transplant patients with lowered mood (Ahles et al., 1996). However these factors were reportedly associated with the intensity and toxicity of preparatory regimes, prolonged hospitalisations and recovery, and risk of mortality. In contrast, Andrykowski et al. (2005) indicated that patients described improved interpersonal relationships, greater self-esteem, a renewed and enhanced appreciation of life, and a heightened spirituality following ASCT. A thorough comparison of the quality of life and emotional outcomes of ASCT and imatinib patients, whilst interesting, is beyond the scope of this thesis.

4.8 LIMITATIONS AND FUTURE DIRECTIONS

There were a number of limitations in the current study, which need to be considered in the overall findings. Many of these limitations have been presented earlier but will be briefly summarised again here.

It is likely that the current results were inflated by practice, given that participants were assessed every six months. Chelune (2002) contends that practice effects may still be apparent one to two years after the initial assessment session. Although attempts were made to minimise these effects by using alternate forms, improvements in performance are likely as participants become increasingly familiar with the testing process (Uchimaya et al., 1995). In later assessments, participants' may recall details of the test process, which could change their approach to the task. In spite of this, the apparent practice effects in the current study suggest that participants were retaining information over time; a finding which argues against learning and memory impairments in CML patients receiving imatinib treatment.

Future research efforts might consider using the practice adjusted reliable change index (RCI) measure (Chelune, Naugle, Lüders, Sedlak & Awad, 1993). This method enables the researcher to establish statistically significant change in cognitive performance (Vardy et al., 2008), whilst controlling for the psychometric properties of the test and practice effects. A constant value is inserted into the RCI formula to adjust for practice effects over time. There has been considerable research activity to derive accurate constants to adjust for practice (Chelune et al., 1993, Temkin, Heaton, Grant & Dikmen, 1999). Unfortunately, the RCI formula cannot currently be used for most individual subtest scores, as constants are available for index scores on the WAIS-III and WMS-III but very few subtest measures (Chelune et al., 1993). This means that the RCI formula will enable the researcher to control for practice but it will increase the assessment burden on participants, as further testing will be required to obtain index scores. Issues of study design will need to be counter-balanced with the needs of the participant.

Fischer (1999) proposed a different solution to counter practice effects, which may be useful in future research. Given that practice effects are reported to be most apparent

between the first and second assessment, it may prove beneficial to complete two baseline assessments prior to the commencement of treatment (Benedict & Zgaljardic, 1998; Fischer, 1999). This possibility has merit from an experimental perspective. However it may not be practical from a clinical viewpoint, as the commencement of treatment would need to be delayed. It may be more appropriate to reduce the number of assessments, and undertake an initial baseline assessment followed by a twelve month review. Although practice effects may still be apparent, participants would have less opportunity to learn the material and the magnitude of these effects should diminish over time. Initially, a six month review was included in the current study to investigation the possible cumulative effects of imatinib. Based on findings from the current study, there appears to be little evidence of a cumulative effect over time. Therefore it may not be necessary to undertake a six month review in future research.

A further limitation of the current study was the lack of control group. As mentioned earlier, significant attempts were made to recruit a useful comparator in order to control for the effects of practice, and the effects of the disease process itself. Choosing an appropriate control group was challenging. A group of CML participants not requiring imatinib treatment would serve as the perfect comparator, however this was not practical as imatinib is the first line treatment for CML. Although a range of options were discussed, it was agreed that the most appropriate control group would comprise patients with CLL and NHL. These diseases were chosen as they were considered comparable haematological conditions not requiring chemotherapy. Unfortunately, in spite of significant attempts, only one person was enrolled in the study after twelve months of recruitment. The few other patients who ultimately declined reported concerns about the time commitment required to participate. The assessment itself required up to twelve hours of participants time over the year. The first assessment could take up to four hours to complete. In future it may prove to be more practical to reduce the amount of assessment by decreasing the number of assessments (i.e., a baseline assessment and one year review), and limiting the number of assessment tasks. Recruiting control participants may have been more achievable if the time commitment was less onerous. Certainly a number of CML participants raised concerns about the length of the assessment process by the final review. Further to this, control group participants were not offered any remuneration. Most patients were employed and therefore needed to take leave from work in order to participate. Part of this issue

would be addressed by reducing the amount of assessment, however remuneration may aid recruitment in the future.

Given the relationship between mood and verbal memory function in the current study, future research may also consider utilising a control group of depressed but otherwise healthy participants. This might enable researchers to differentiate the impact of mood on cognition, from the impact of the treatment.

A further consideration in the study was the limited sample size. Initially it was anticipated that 15 CML participants would be recruited within a year. Although the initial recruitment period was extended by over six months, only thirteen people were enrolled in the study (with twelve completing the full protocol). This highlights the rarity of the condition, particularly given that the sample includes most of the newly diagnosed CML patients from four of the main cancer centres within Victoria over that time. This highlights a number of challenges for research in this area. Firstly, it is anticipated that further research would need to incorporate cancer centres from across Australia in order to increase the size of the sample. Secondly, the issue of sample size has implications for research design and data analysis. As mentioned previously the ICCTF recommends the assessment of a broad range of cognitive domains (Vardy et al., 2008). However, each additional dependent variable will require a larger sample size to ensure that inferential statistical tests will have sufficient power to detect a real difference. In the current study, effect size was used to assess the magnitude of any changes in cognitive performance over time. In addition, limiting the number of dependent variables assessed in the future may also minimise the potential impact of a small sample size.

In addition to this, a quarter of the participants spoke English as their second language. Whilst this might be a reasonably representative sample of the population, it also raises concerns about the reliability of neuropsychological tests when assessing individuals from different cultures. Most of our current instruments have been produced in highly developed westernised societies and as such, tend to reflect the knowledge and experiences of the dominant culture within those societies (Anastasi & Urbina, 1997). Shuttleworth-Edwards et al. (2004) claimed that culture provides individuals with a

framework for thinking, feeling, and acting and it is these influences that mediate the development of language, factual knowledge, procedural skills, and 'test-wiseness'. Shuttleworth et al. (2004) suggested that this latter skill, which includes such things as familiarity with test-taking situations and previous experience using pencils, is a powerful moderator of test performance. Thus, an individual from an ethnic minority with limited education may demonstrate impairment that has more to do with their level of 'test-wiseness' or the cultural bias of the tests than brain pathology (Ogden, 2001).

Artiola i Fortuny and Mullaney (1998) argued that cross-cultural bias could be reduced if clinicians endeavoured to learn more about the patient's cultural background. Further to this, the clinician should, where possible, utilise tests developed on the population of interest or use well-constructed tests with less emphasis on culturally specific knowledge (e.g., tests tapping fluid intelligence).

The other potential limitation associated with the current research was the use of the D-KEFS. This measure has come under increasing scrutiny of late, as critics claim that its reliability is below the minimum accepted level (Schmidt, 2003). Some authors state that the D-KEFS may provide useful qualitative information (Shunk et al., 2006), whilst others (Schmidt, 1998) deem it unsuitable for clinical use. More specifically, there are very few studies involving the Sorting Test from the D-KEFS and no information about the relative contribution of pre-morbid capacity and demographics. The use of sorting tests in general is questionable as De Renzi et al. (1966) and others (McFie et al., 1952; Newcombe, 1969) claimed that the test was insensitive, as it failed to differentiate healthy individuals from brain injured patients (as cited in Lezak et al., 2004). However the letter fluency condition of the Verbal Fluency test has not received the same degree of criticism. This measure, originally developed from the controlled word association test (COWAT), is highly reliable and well-regarded (Dikmen et al., 1999), and continues to be a useful measure for research in the area.

Future research efforts should also focus on the impact of newer tyrosine kinase inhibitors on cognition in CML. Recent clinical trials have indicated that agents, such as Dasatinib, have greater CNS permeability (Porkka et al., 2008). Whilst this agent is regarded as an effective treatment for CML patients with CNS involvement, it also risks greater CNS toxicities. Thus, findings from previously mentioned animal studies about

the impact kinase inhibitors on learning and memory might be more relevant to this population.

4.9 CONCLUSIONS

The current study investigated the impact of imatinib on cognitive function in a representative sample of adult patients with newly diagnosed CML. Recent studies identified subtle adverse effects to the immunological, respiratory, endocrine, and reproductive systems (Seymour et al., 2004). Prior to the current study there had been no systematic prospective investigation of the neuropsychological sequelae of chronic imatinib use. However there was growing evidence about the agent's potential neurotoxic effects (Grove et al., 2004; Moresco et al., 2003). Therefore the current study is not only significant for the CML population but also other patients prescribed imatinib for conditions such as GIST. The present study was conducted to see whether there were neurotoxic effects to ensure that patients could be fully informed about any adverse consequences of treatment.

The results of this study suggest that imatinib does not negatively impact verbal learning and verbal memory, attention and working memory, motor and processing speed, and executive function. Previous findings about the impact of imatinib on neurological function may be attributed to the experimental methods employed by the researchers, as imatinib was directly injected into the brain or the kinase was deleted from the hippocampus. In clinical practice the agent has low CNS penetration, thus one would expect far less impact on the brain.

In fact there was a general trend toward improved function over time on specific measures of verbal learning and verbal memory, motor and processing speed, and executive function. There was limited evidence in the literature to suggest that improvements in cognitive function (i.e., beyond baseline levels) were in any way associated with imatinib use. However there was some indication that imatinib could slow the progression of neurodegenerative disease (Alvarez et al., 2004). It is anticipated that the trend towards improved function may be an artefact of improving mood, lowered fatigue, practice effects, and potentially the small sample size.

Furthermore, participants' with greater levels of mood disturbance and heightened fatigue tended to perform more poorly on measures of verbal memory, whilst state anxiety was not significantly associated with performance on verbal memory tasks. Participants' with higher FSIQ and SES also tended to perform better on these tasks, whilst educational attainment was not consistently related to verbal memory. The relationship between FSIQ, SES, and verbal memory was attributed to cognitive reserve but may also be related to one's ability to benefit from practice effects. Higher dose was not associated with participants' performance on verbal memory tasks.

In conclusion, there is no evidence to suggest that imatinib negatively impacts cognition in CML patients over time. However there was some indication of improvement in function by six and twelve months. This is encouraging given the cognitive and emotional sequelae associated with earlier treatments for CML (Hensley et al., 2000; Malek-Ahmadi & Hilsabeck, 2007; Meyers et al., 1991; Poynard et al., 1996; Syrjala et al., 2005; Valentine et al., 1998; Valentine et al., 2004). This new therapy not only offers patients a significant survival advantage (Hochaus et al., 2007) and improved prognosis but generally allows patients a better quality of life, together with less emotional disturbance and cognitive impairment. Although the current findings are encouraging, newer kinase inhibitors with greater CNS penetration are soon to be released into the market (Porkka et al., 2008). Thus further research will be needed to elucidate the neuropsychological sequelae of these therapies to ensure that patients are informed about the potential consequences of such treatment.

5. REFERENCES

Ahles, T.A. (2004). Cognitive side effects of myeloblative allogeneic hematopoietic cell transplantation. *Blood*, 104 (10), 3003-3004.

Ahles, T.A., & Saykin, A.J. (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *National Review of Cancer*, 7, 192-201.

Ahles, T.A., Saykin, A.J., Furstenberg, C.T., Cole, B., Mott, L.A., & Skalla, M.B., et al. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *Journal of Clinical Oncology*, 20 (2), 485-493.

Ahles, T.A., Saykin, A.J., Noll, W.W., Furstenberg, C.T., Guerin, S., & Cole, B., et al. (2003). The relationship between the APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncology*, 12, 612-619.

Ahles, T.A., Tope, D.M., Furstenberg, C., Hann, D., & Mills, L. (1996). Psychologic and neuropsychologic impact of autologous bone marrow transplantation. *Journal of Clinical Oncology*, 14 (5), 1457-1462.

Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. *Journal of Psychiatric Research*, 39, 207-214.

Alvarez, A.R., Sandoval, P.C., Leal, N.R., Castro, P.U., & Kosik, K.S. (2004). Activation of the neuronal c-Abl tyrosine kinase by amyloid-beta-peptide and reaction oxygen species. *Neurobiology of Disease*, 17 (2), 326-336.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition – Text Revision (DSM-IV-TR)*. Washington: American Psychiatric Association.

Amodio, P., De Toni, E., Cavalletto, L., Mapelli, D., Bernardinello, E., & Del Piccolo, F., et al. (2005). Mood, cognition and EEG changes during interferon α (alpha-IFN) treatment for chronic hepatitis C. *Journal of Affective Disorders*, 84 (1): 93-98.

Anastasi, A., & Urbina, S. (1997). *Psychological Testing.* New-Jersey: Prentice Hall International.

Anderson, V.A., & Lajoie, G. (1996). Development of memory and learning skills in school-aged children: A neuropsychological perspective. *Applied Neuropsychology*, 3/4, 128-139.

Anderson, V., & Moore, C. (1995). Age at injury as a predictor of outcome following paediatric head injury. *Child Neuropsychology*, 1, 187-202.

Andrykowski, M.A., Bishop, M.M., Hahn, E.A., Cella, D.F., Beaumont, J.L., & Brady, M.J., et al. (2005). Long-term health-related quality of life, growth, and spiritual well-being after hematopoietic stem-cell transplantation. *Journal of Clinical Oncology*, 23 (3), 599-608.

Andrykowski, M.A., Brady, M.J., & Henslee-Downey, P.J. (1994). Psychosocial factors predicitive of survival after allogeneic bone marrow transplantation for leukemia. *Psychosomatic Medicine*, 56, 432-439.

Andrykowski, M.A., Schmitt, F.A., Gregg, M.E., Brady, M.J., Lamb, D.G., & Heslee-Downey, P.J. (1992). Neuropsychologic impairment in adult bone marrow transplant candidates. *Cancer*, 70, 2288-2297.

Antigenics Inc. (2008). The Philadelphia Chromosome (Figure). Retrieved May 3, 2008, from http://www.antigenics.com.au/diseases/cml.html

Antony, M.M. & Rowa, K. (2005). Evidence-based assessment of anxiety disorders in adults. *Psychological Assessment*, 17, 256-266.

Arango-Lasprilla, J.C., Rosenthal, M., Deluca, J., Komaroff, E., Sherer, M., & Cifu, D., et al. (2007). Traumatic brain injury and functional outcomes: Does minority status matter? *Brain Injury*, 21(7), 701-708.

Arbuthnott, K., & Frank, J. (2000). Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. *Journal of Clinical and Experimental Neuropsychology*, 22 (4), 518-528.

Artiola i Fortuny, L., & Mullaney, H. (1998). Assessing patients whose language you do not know: can the absurb be ethical? *The Clinical Neuropsychologist*, 19, 615-623.

Ashcraft, M.H. (2002). Maths anxiety: Personal, educational and cognitive consequences. *Current Directions in Psychological Science*, 11, 181-185.

Australian Institute of Health and Welfare & Australasian Association of Cancer Registries (2004). Cancer in Australia, 2001, AIHW Cat. No. CAN 23, AIHW, Canberra.

Australian Institute of Heath and Welfare. (2005, August 25). Cancer Incidence Projections for Australia 2002 – 2011. Retrieved August 19, 2008, from http://www.aihw.gov.au/publications/index.cfm/title/10164

Australian Medicines Handbook. (2005). *Australian Medicines Handbook*. Adelaide: Australian Medicines Handbook Pty Ltd.

Baker, K.S., Gurney, J.G., Ness, K.K., Bhatia, R., Forman, S.J., & Francisco, L., et al. (2004). Late effects in survivor of chronic myeloid leukemia treated with hematopoietic cell transplantation: results from the bone marrow transplant survivor study. *Blood*, 104 (6), 1898-1906.

Baldo, J.V., & Shimamura, A.P., Delis, D.C., Kramer, J., & Kaplan, E. (2001). Verbal and design fluency in patients with frontal lobe lesions. *Journal of the International*

Neuropsychological Society, 7, 585-596.

Banich, M.T. (2004). *Cognitive Neuroscience and Neuropsychology* (2nd ed.). Boston: Houghton Mifflin Company.

Baron, I.S. (2004). *Neuropsychological evaluation of the child*. New York: Oxford University Press.

Barco, N., López, S., Ribal, B., Pérez, O., & Pérez, M.A. (2008). Cognitive impairment in the early phase of multiple sclerosis and its relationship with mood, demographic and clinical variables [Abstract]. *Psicothema*, 20(4), 538.

Basso, M.R., Bornstein,R.A., & Lang, J.M. (1999). Practice effects of commonly used measures of executive function across twelve months. *The Clinical Neuropsychologist*, 13, 283-292.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Beck depression inventory-II*. San Antonio: The Psychological Corporation.

Beck, A.T., Steer, R.A., & Garbin, M.G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, 8, 77-100.

Beelen, D.W., Graeven, U., & Elmaagacli. (1995). Prolonged administration of interferon-α in patients with chronic-phase Philadelphia chromosome-positive chronic myelogenous leukemia before allogeneic bone marrow transplantation may adversely affect transplant outcome. *Blood*, 85, 2981-2990.

Benedict, R.H.B., & Zgaljardic, D.J. (1998). Practice effects during the repeated administrations of memory tests with and without alternate forms. *Journal of Clinical & Experimental Neuropsychology*, 20, 339-352.

Bhati, R., & Verfaillie, C.M. (1998). Leukaemia. *Lymphoma*, 28, 241-254.

Biggs, J.C., Szer, J., Crilley, P., Atkinson, K., Downs, K., & Dodds, A., et al. (1992). Treatment of chronic myeloid leukemia with allogeneic bone marrow transplantation after preparation with BuCy2. *Blood*, 77, 1660-1665.

Bigler, E.D. (1995). Brain morphology and intelligence. *Developmental Neuropsychology*, 11, 377-403.

Bjorkman, I.K., Fastbom, J., Schmidt, I.K., & Bersten, C.B. (2002). Drug-drug interactions in the elderly. *Annals of Pharmacotherapy*, 36, 1675-1681.

Bolin, R.W., Robinson, W.A., Sutherland, J., & Hamman, R.F. (1982). Bulsulfan versus Hydroxyurea in long-term therapy of chronic myelogenous leukemia. *Cancer*, 50, 1683-1686.

Boone, K.B. (1999). Neuropsychological assessment of executive functions: Impact of age, education, gender, intellectual level, and vascular status on executive test scores. In B.L. Miller & J.L. Cummings (Ed.), *The Human Frontal Lobes: Functions and Disorders*. New York: Guilford Press.

Bornhauser, M., Kiehl, M., Siegert, W., Schetelig, J., Hertenstein, B., & Martin, H., et al. (2001). Dose-reduced conditioning for allografting in 44 patients with chronic myeloid leukaemia: A retrospective analysis. *British Journal of Haematology*, 115, 119-124.

Bornstein, R.A., Baker, G.B., & Douglas, A.B. (1987). Short-term retest reliability of the Halstead-Reitan Battery in a normal sample. *Journal of Nervous & Mental Disease*, 175, 229-232.

Bracco, L., Piccini, A., Baccini, M., Bessi, V., Biancucci, F., & Nacmias, B., et al. (2007). Pattern and progression of cognitive decline in Alzheimer's disease: Role of premorbid intelligence and ApoE genotype. *Dementia and Geriatric Cognitive Disorders*, 24, 483-491.

Brooks, D.N., & McKinley, W. (1987). Return to work within the first seven years of

head injury. *Brain Injury*, 1, 5-15.

Brooks, B.L., Weaver, L.E., & Scialfa, C.T. (2006). Does impaired executive functioning differentially impact verbal memory measures in older adults with suspected dementia? *The Clinical Neuropsychologist*, 20, 230-242.

Buchdunger, E., Zimmermann, J., Mett, H., Meyer, T., Muller, M., & Druker, B.J. et al. (1996). Inhibition of Abl protein tyrosine-kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. *Cancer Research*, 56, 100-104.

Buckelew, S.P., & Hannay, H.J. (1986). Relationship among anxiety, defensiveness, sex, task difficult, and performance on various neuropsychological tasks. *Perceptual and Motor Skills*, 63, 711-718.

Buck-Gengler, L.J., & Healey, A.F. (2001). Process underlying long-term repetition priming in data-entry. *Journal of Experimental Psychology: Learning, Memory and Cognition*, 27, 879-888.

Cancino, G.I., Toledo, E.M., Leal, N.R., Hernandez, D.E., Yévenes, L.F., & Inestrosa, N.C., et al. (2008). STI571 prevent apoptosis, tau phosphorylation and behavioural impairments induced by Alzheimer's β-amyloid deposits. *Brain*, 131, 2424-2442.

Caraceni, A., Gangeri, L., Martini, C., Filiberto, B., Brunelli, C., & Baldini, M., et al. (1998). Neurotoxicity of interferon-alpha in melanoma therapy: results from a randomised controlled trial. *Cancer*, 83, 482-89.

Carella, A.M., Frassoni, F., Melo, J., Sawyers, C., Eaves, C., & Eaves, A., et al. (1997). New insights in biology and current therapeutic options for patients with chronic myelogenous leukemia. *Haematologica*: 82, 478-495.

Carpiniello, B., Orru, M.G., Baita, A., Pariante, C.M., & Farci, G. (1998). Mania induced by withdrawal of treatment with interferon alpha (letter). *Archives of General Psychiatry*, 55, 88-89.

Castaneda, A.E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., & Lönnqvist, J. (2008). A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *Journal of Affective Disorder*, 106, 1-27.

Chelune, G.J. (2002) Assessing reliable neuropsychological change. In R.D. Franklin (Ed.), *Prediction in Forensic and Neuropsychology: Sound Statistical Practices* (pp. 115-137). Hoboken: Psychology Press.

Chelune, G.J., Naugle, R.I., Lüders, H., Sedlak, J., & Awad, I.A. (1993). Individual change after epilepsy surgery: Practice effects and base-rate information. *Neuropsychology*, 7, 41-52.

Chronic Myeloid Leukemia Trialists' Collaborative Group. (1997). Interferon alpha versus chemotherapy for chronic myeloid leukemia: A meta-analysis of seven randomised trials. *Journal of the National Cancer Institute*, 89 (21), 1616-1620.

CML Treatment Options. (2006). The Glivec International Site. Retrieved May 26, 2006, from http://www.glivec.com/content/target_cml/treatment_cml.jsp

Cohen, J. (1988). *Statistical Power for the Behavioural Sciences*. Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Cornelissen, J.J., Ploemacher, R.E., Wognum, B.W., Borsboom, A., Kluin-Nelemans, H.C., & Hagemeijer, A., et al. (1998). An in vitro model for cytogenetic conversion in CML: Interferon (alpha) preferentially inhibits the outgrowth of malignant stem cells preserved in long-term culture. *The Journal of Clinical Investigation*, 102, 976-983.

Correa, D.D., DeAnglis, L.M., Shi, W., Thaler, H., Glass, A., & Abrey, L.E. (2004). Cognitive functions in survivors of primary central nervous system lymphoma. *Neurology*, 62 (4), 548-555.

Corso, A., Lazzarino, M., Morra, M., Merante, S., Astori, C., & Bernasconi, P., et al.

(1995). Chronic myelogenous leukemia and exposure to ionising radiation – a retrospective study of 443 patients. *Annals of Hematology*, 70, 79-82.

Crowe, S.F., Hale, M., Dean, S., El Hadj, D., Macdonell, G., & Sarkissian, G., et al. (2001). The effect of heightened levels of physiological arousal on neuropsychological measures of attention in a nonclinical sample. *Australian Psychologist*, 36 (3), 239 - 243

Curt, G.A., Breitbart, W., Cella, D., Groopman, J.E., Herning, S.J., & Itri, L.M., et al. (2000). Impact of cancer-related fatigue on the lives of patients: New findings from the fatigue coalition. *The Oncologist*, 5, 353-360

Dawes, R.M., Faust, D., & Meehl, P.E. (1989). Clinical versus actuarial judgement. *Science*, 243, 1668-1673.

Deininger, M.W.N., & Druker, B.J. (2003). Specific targeted therapy of chronic myelogenous leukemia with imatinib. *Pharmacological Reviews*, 55, 401-423.

Deininger, M., Goldman, J.M., Lydon, N.B., & Melo, J.V. (1997). The tyrosine kinase inhibitor CGP57148B directly inhibits the growth of BCR-ABL positive cells. *Blood*, 90, 3691-3698.

Delano-Wood, L., Abeles, N., Sacco, J.M., Wierenga, C.E., Horne, N.R., & Bozoki, A. (2008). Regional white matter pathology in mild cognitive impairment: differential influence of lesion type on neuropsychological functioning. *Stroke: A Journal of Cerebral Circulation*, 39 (1), 794-749.

Delis, D., Kaplan, E., & Kramer, J. (2001). *Delis-Kaplan Executive Function Scale*. San Antonia: The Psychological Corporation.

Delis, D.C., Squires, L.R., Birhle, A., & Massman, P. (1992). Componential analysis of problem-solving ability: Performance in patients with frontal lobe damage and amnestic patients on a new sorting test. *Neuropsychologica*, 30, 636-697.

Demetri, G. (2007). Structural reengineering of imatinib to decrease cardiac risk in cancer therapy. *The Journal of Clinical Investigation*, 117 (12), 3650-3653.

de Witte, T., Pikkemaat, F., Hermans, J., van Biezen, A., Mackinnan, S., & Cornelissen, J., et al. (2001). Genotypically nonidentical related donors for transplantation of patients with myelodysplastic syndromes: comparison with unrelated donor transplantation and autologous stem cell transplantation. *Journal of Leukemia*, 15 (12), 1878-1884.

Diagnosing CML for Healthcare Professionals. (2006). The Glivec International Site. Retrieved May 26, 2006, from http://www.glivec.com/content/target_cml/diagnosis_cml.jsp

Dikmen, S., Heaton, R., Grant, I., & Temkin, N. (1999). Test-retest reliability and practice effects of Expanded Halstead-Reitan Neuropsychological Test Battery. *Journal of the International Neuropsychological Society*, 5, 346-447.

Dimitrov, M., Grafman, J., Soares, A.H.R., & Clarke, K. (1999). Concept formation and concept shifting in frontal lesions and Parkinson's disease patients assessed with the California card sorting test. *Neuropsychology*, 13 (1), 135-143.

Druker, B.J., Guilhot, F., O'Brien, S.G., Gathmann, I., Kantarjian, H., & Gattermann, N., et al. (2006). Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. *New England Journal of Medicine*, 355(23), 2408-2417.

Druker, B.J., Tamura, S., Buchdunger, E., Ohno, S., Segal, G.M., & Fanning, S., et al. (1996). Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nature Medicine*, 2, 561-566.

Durvasula, R.S., Satz, P., Hinkin, C.H., Uchiyama, C., Morgenstern, H., & Miller,

E.N., et al (1996). Does practice make perfect?: Results of a six year longitudinal study with semi-annual testing. *Archives of Clinical Neuropsychology*, 11, 386.

Ebnoether, M., Stentoft, J., Ford, J., Buhl, L., & Gratwohl, A. (2002). Cerebral oedema as a possible complication of treatment with imatinib. *Lancet*, 359 (9319), 1751-1752.

Erlandsson, A., Larsson, J., & Forsberg-Nilsson, K. (2004). Stem cell factor is a chemoattractant and a survival factor for CMS stem cells. *Experimental Cell Research*, 10, 301 (2), 201-210.

Eson, M.E., Yen, J.K., & Bourke, R.S. (1978). *Assessment of recovery from serious head injury*. Journal of Neurology, Neurosurgery, and Psychiatry, 41, 1036-1042.

Etienne, G., Cony-Makhoul, P., & Mahon, F.X. (2002). Imatinib mesylate and grey hair. *New England Journal of Medicine*, 347, 446.

Faderl, S., Talpaz, M., Estrov, Z., O'Brien, S., Kurzrock, R., & Kantarjian, H.M. (1999). The Biology of Chronic Myeloid Leukemia. *New England Journal of Medicine*, 341, 164-172.

Fattovich, G., Giustina, G., Favarato, S., & Ruol, A. (1996). Investigators of the Italian association for the study of the liver: a survey of adverse events in 11 241 patients with chronic viral hepatitis treated with alfa interferon. *Journal of Hepatology*, 24, 38-47.

Field, A. (2005). *Discovering Statistics Using SPSS* (2nd ed.). London: Sage Publications.

Francis, G. (2007). *Introduction to SPSS for Windows Version: Version 15 and 14 with Notes for Studentware* (5th ed.). Frenchs Forest, NSW: Pearson Education Australia.

Freeman, J.R., & Broshek, D.K. (2002). Assessing cognitive dysfunction in breast cancer: What are the tools? *Clinical Breast Cancer*, 3 (3): S91-99.

Fruttiger, M., Karlsson, L., Hall, A.C., Abramsson, A., Calver, A.R., & Boström, H., et al. (1999). Defective oligodendrocyte development and severe hypomyelination in PDGF-A knockout mice. *Development*, 126, 457-467.

Gale, R.P., Hehlmann, R., Zhang, M.J., Hasford, J., Goldman, J.M., & Heimpel, H., et al. (1998). Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. *Blood*, 91 (5). 1810-1819.

Gass, C.S. (2002). Personality assessment of neurologically impaired patients. In: Butcher, J.N. (2nd Eds,.). *Clinical personality assessment: Practical approaches.* New York: University Press. pp 208-224.

Geary, C.F. (2000). Historical review: the story of chronic myeloid leukaemia. *British Journal of Haematology*, 110, 2-11.

Geffen, G.M., Butterworth, P., Forrester, G.M., & Geffen, L.B. (1994). Auditory verbal learning test components as measures of the severity of closed-head injury. *Brain Injury*, 8 (5), 405-411.

Geffen, G.M., Butterworth, P., & Geffen, L.B. (1994). Test-retest reliability of a new form of the Auditory Verbal Learning Test (AVLT). *Archives of Clinical Neuropsychology*, 9, 303-316.

Geffen, G.M., Moar, K.J., O'Hanlan, A.P., Clark, C.R., & Geffen, L.B. (1990). Performances measures of 16 to 86 year old males and females on the auditory verbal learning test. *The Clinical Neuropsychologist*, 4, 45-63.

Ghanei, M., & Vosoghi, A.A. (2002). An epidemiologic study to screen for chronic myelocytic leukemia in war victims exposed to mustard gas. *Environmental Health Perspectives,* 110 (5), 519-521.

Goldman, J.M., & Melo, J.V. (2003). Mechanisms of disease: Chronic myeloid

leukemia - advances in biology and new approaches to treatment. *New England Journal of Medicine*, 349 (15), 1451-1464.

Goldstein, G., & Watson, J.R. (1989). Test-retest reliability of the Halstein-Reitan neuropsychological battery and the WAIS in the neuropsychiatric population. *The Clinical Neuropsychologist*, 3, 265-273.

Gordon, M.Y., Marley, S.B., Lewis, J.L., Davidson, R.J., Nguyen, D.X., & Grand, F.H., et al. (1998). Treatment with interferon (alpha) preferentially reduces the capacity for amplification of granulocytes-macrophage progenitors (CFU-GM) from patients with chronic myeloid leukemia but spares normal CFU-GM. *The Journal of Clinical Investigation*, 102, 710-715.

Gorre, M.E., Mohammed, M., Ellwood, K., Hsu, N., Paquette, R., & Rao, P.N., et al. (2001). Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science*, 293, 86-880.

Grant, I., & Adams, K.M. (1996). *Neuropsychological Assessment of Neuropsychiatric Disorders.* New York: Oxford University Press.

Grant, S.G.N., O'Dell, T.J., Karl, K.A., Stein, P.L., Soriano, P., & Kandel, E.R. (1992). Impaired long-term potentiation, spatial learning, and hippocampal development in fyn mutant mice. *Science*, 258, 1903-1910.

Gratwohl, A., Hermans, J., Goldman, J.M., Arcese, W., Carreras, E., & Devergie, A., et al. (1998). Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. *The Lancet*, 352, 1087-1092.

Gratwohl, A., Hermans, J., Nederwieser, D., Frassoni, F., Arcese, W., & Gahrton, G., et al. (1993). Bone marrow transplantation for chronic myeloid leukemia: long-term results. *Bone Marrow Transplant*, 12, 509-516.

Gratwohl, A., Hermans, J., Niederwieser, D., van Biezen, A., van Houwelingen, H.C.,

& Apperley, J. (2001). Female donors influence transplant-related mortality and relapse incidence in male recipients of sibling blood and marrow transplantations. *Journal of Hematology*, 2 (6), 363-371.

Groopman, J.E. (1998). Fatigue in cancer and HIV/AIDS. *Oncology*, 12, 335-344.

Grove, M., Demyanenoko, G., Echarri, A., Zipfel, P.A., Quiroz, M.E., & Rodriguiz, R.M., et al. (2004). AB12-deficient mice exhibit defective cell migration, aberrant dendritic spine morphogenesis, and deficits in learning and memory. *Molecular and Cellular Biology*, 24 (24), 10905-10922.

Guilhot, F., Chastang, C., Michallet, M., Guerci, A., Harousseau, J.L., & Maloisel, F., et al. (1997). Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. *North England Journal of Medicine*, 337, 223.

Haddow, A., & Timmis, G.M. (1953). Myleran in chronic myeloid leukaemia: chemical constitution and biological action. *Lancet*, 1, 207-208.

Hahn, E.A., Glendenning, G.A., Sorensen, M.V., Hudgens, S.A., Druker, B.J., & Guilhot, F., et al. (2003). Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low dose cytabarine: Results from the IRIS study. *Journal of Clinical Oncology*, 21 (11), 2138-2146.

Hasford, J., Pfirrmann, M., Hehlmann, R., Allan, N.C., Baccarani, M., & Kluin-Nelemans, J.C., et al. (1998). A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alpha. *Journal of the National Cancer Institute*, 90: 850-858.

Healey, A.F., & Bourne, L.E. Jr. (1995). *Learning and memory of knowledge and skills*. Thousand Oaks, C.A: Sage Publications.

Hehlmann, R., Ansari, H., Hasford, J., Heimpel, H., Hossfeld, K., & Kolb, H.J., et al.

(1997). Comparative analysis of the impact of risk profile and of drug therapy on survival in CML using Sokal's index and new score. *British Journal of Haematology*, 97, 76.

Hehlmann, R., Heimpel, H., Hasford, J., Kolb, H.J., Pralle, H., & Hossfeld, D.K., et al. (1993). Randomised comparison of bulsulfan and hydroxyurea in chronic myelogenous leukemia: Prolongation of survival by hydroxyurea. *Blood*, 82 (2), 398-407.

Hensley, M.L., Peterson, B., Silver, R.T., Larson, R.A., Schiffer, C.A., & Szatrowski, T.P. (2000). Risk factors for severe neuropsychiatric toxicity in patients receiving interferon alfa-2b and low-dose cytarabine for chronic myelogeneous leukemia: Analysis of cancer and leukemia group b 9013. *Journal of Oncology*, 18 (6), 1301-1308.

Hochhaus, A., Druker B.J., Larson, R.A., O'Brien, S.G., Gathmann, I., & Guilhot, F. (2007). IRIS 6-year follow-up: Sustained survival and declining annual rate of transformation in patients with newly diagnosed chronic myeloid leukemia in the chronic phase (CML-CP) treated with imatinib. *Blood*, 110 (11), 15a.

Hoffbrand, A.V., Pettit, J.E., & Moss, P.A.H. (2005). *Essential Haematology*. Oxford: Blackwell Science.

Hoffman, M., Ryan, J.L., Figueroa-Moseley, C.D., Jean-Pierre, P., & Morrow, G.R. (2007). Cancer-related fatigue: The scale of the problem. *The Oncologist*, 12 (1), 4-10.

Hoffman, R., & al'Absi, M. (2004). The effect of acute stress on subsequent neuropsycholoical test performance. *Archives of Clinical Neuropsychology*, 19 (4), 497-506.

Homack, S., Lee, D., & Riccio, C.A. (2005). Test-review: Delis-Kaplan Executive Function System. *Journal of Clinical and Experimental Neuropsychology*, 27, 599-609.

Homewood, J., Watson, M., Richards, S.M., Halsey, J., & Shepherd, P.C.A. (2003). Treatment of CML using IFN-∝: Impact on quality of life. *The Hematology Journal*, 4, 253-262.

Horowitz, M.M., Rowlings, P.A., & Passweg, J.R. (1996). Allogeneic bone marrow transplantation for CML: a report from the international bone marrow transplant registry. *Bone Marrow Transplant*, 17, 5-6.

Howard, M.R., & Hamilton, P.J. (2002). *Haematology: An illustrated colour text*. (2nd Ed.), Great Britain: Churchill Livingstone.

Inagaki, M., Yoshikawa, E., Matsuoka, Y., Sugawara, Y., Nakano, T., & Akechi, T. et al. (2007). Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer*, 109, 146-156.

Iop, A., Manfredi, A.M., & Bonura, S. (2004). Fatigue in cancer patients receiving chemotherapy: an analysis of published studies. *Annals of Oncology*, 15, 712-720.

Jacobs, B., Schall, M., & Scheibel, A.B. (1993). A quantitative dendritic analysis of Wernicke's area: II. Gender, hemispheric, and environmental factors. *Journal of Comparative Neurology*, 23, 97-111.

Jacobson, P.B., Hann, D.M., Azzarello, L.M., Horton, J., Balducci, L., & Lyman, G.H. (1999). Fatigue in women receiving adjuvant chemotherapy for breast cancer: Characteristics, course, and correlates. *Journal of Pain and Symptom Management*, 18, 233-242.

James, C.W., & Savini, C.J. (2001). Homicidal ideation secondary to interferon. *Annals of Pharmacotherapy*, 35, 962-963.

Janssen, H.L., Brouwer, J.T., van der Mast, R.C., & Schalm, S.W. (1994). Suicide associated with alpha-interferon therapy for chronic viral hepatitis. *Journal of Hepatology*, 21, 241-243.

Joiner Jr., T.E., Walker, R.L., Pettit, J.W., & Perez, M. (2005). Evidence-based assessment of depression in adults. *Psychological Assessment*, 17, 267-277.

Johnson, M.K. (1990). Functional forms of human memory. In J.L. McGaugh's, N. M. Weinberger, and G. Lynch's (Eds.), *Brain organization and memory. Cells, systems, and circuits*. New York: Oxford University Press.

Jones, F.L., & McMillan, J. (2001). Scoring occupational categories for social research: A review of current practice, with Australian examples. *Work, Employment & Society*, 15 (3), 539-563.

Kantarjian, H.M., Giles, F.J., O'Brien, S.M., & Talpaz, M. (1998). Clinical course and therapy of chronic myelogenous with interferon alpha and chemotherapy. *Hematology/Oncology Clinics of North America*, 12, 31-80.

Kantarjian, H.M., O'Brien, S., Smith, T.L., Rios, M.B., Cortes, J., & Beran, M., et al. (1999). Treatment of Philadelphia chromosome-positive early chronic phase chronic myelogenous leukemia with daily doses of interferon alpha and low-dose cytarabine. *Journal of Clinical Oncology*, 17 (1), 284-92.

Kantarjian, H.M., Sawyers, C., Hochaus, A., Guilhot, F., Schiffer, C., & Gambacorti-Passerini, C. (2002). *North England Journal of Medicine*, 346, 646-652.

Kantarjian, H.M., Talpaz, M., O'Brien, S., Giles, F., Faderl, S., & Verstovsek, S. (2005). Survival benefits with imatinib mesylate therapy in patients with accelerated-phase chronic myelogenous leukemia-comparison with historic experience. *Cancer*, 103 (10): 2099-2108.

Katafuchi, K.T., Li, A., Hirota, S., Kitamura, Y., Hori, T. (2000). Impairment of spatial learning and hippocampal synaptic potentiation in c-kit mutant rats. *Learning & Memory*, 7 (6), 383-392.

Keinan, G., & Friedland, N. (1984). Dilemmas concerning the training of individual

for task performance under stress. *Journal of Human Stress*, 10, 185-190.

Keinan, G., Friedland, N., Kahneman, D., & Roth, D. (1999). The effect of stress on the suppression of erroneous competing response. *Anxiety, Stress & Coping: An International Journal*, 12, 455-476.

Keith, J.R., Puente, A.E., Malcolmson, K.L., Tartt, S., Coleman, A.E., & Marks, H.F. (2002). Assessing postoperative cognitive change after cardiopulmonary bypass surgery. *Neuropsychology*, 16 (3): 411-421.

Kerkelä, R., Grazette, L., Yacobi, R., Iliescu, C., Patten, R., & Beahm, C., et al. (2006). Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nature Medicine*, 12, 908–916.

Kortte, K.B., Horner, M.D., Johnson, R.H. & Windham, W.K. (2002). The trail making test, Part B: Cognitive flexibility or ability to maintain set? *Applied Neuropsychology*, 9 (2), 106-109.

Kongsley, D. (1999). Interferon-alpha induced 'tertiary mania'. *Hospital Medicine*, 60, 381-382.

Kramer, S. (1968). The hazards of therapeutic irradiation of the central nervous system. *Clinical Neurosurgery*, 15, 301-318.

Laack, N.N., & Brown, P.D. (2004). Cognitive sequelae of brain radiation in adults. *Seminars in Oncology*, 31 (5), 702-713.

Langer, T., Martus, P., Ottensmeier, H., Hertzberg, H., Beck, J.D., & Meier, W. (2002). CNS late-effects after ALL therapy in childhood. Part II: neuropsychological performance in long-term survivors of childhood ALL: impairments in concentration, attention, and memory. *Medical and Pediatric Oncology,* 38 (5), 320-328.

Le Coutre, P., Mologni, L., Cleris, L., Marchesi, E., Buchdunger, E., & Giardini, R.,

et al. (1999). In vivo eradication of human BCR/ABL-positive leukemia cells with an ABL kinase inhibitor. *Journal of the National Cancer Institute*, 91, 163-168.

Leukaemia Foundation. (2005). Fact Sheet Leukaemia. Retrieved April 17, 2008, from www.leukaemia.org.au/web/aboutdiseases/leukaemias_index.php

Levine, A.J., Miller, E.N., Becker, J.T., Selnes, O.A., & Cohen, B.A. (2004). Normative data for determining significance of test-retest differences on eight common neuropsychological instruments. *The Clinical Neuropsychologist*, 18, 373-384.

Levine, M.N., Gent, M., & Hirsh, J. (1988). The thrombogenic effect of anticancer therapy in women with stage II breast cancer. *New England Journal of Medicine*, 318, 404-407.

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

Licino, J., Kling, M.A., & Hauser, P. (1998). Cytokines and brain function: relevance to interferon-α–induced mood and cognitive changes. *Seminars in Oncology*, 30-38.

Lindahl, P., Johansson, B.R., Leveen, P., & Betscholtz, C. (1997). Pericyte loss and microanaurysm formation in PDGF-B- deficient mice. *Science*, 277, 242-245.

Liotto, M., & Mayberg, H.S. (2001). The role of functional neuroimaging in the neuropsychology of depression. *Journal of Clinical and Experimental Neuropsychology*, 23 (1), 121-136.

Loberiza, F.R., Rizzo, J.D., Bredeson, C.N., Antin, J.H., Horowitz, M.M., & Weeks, J.C., et al. (2002). Association of depressive syndrome and early deaths among patients after stem-cell transplantation for malignant diseases. *Journal of Clinical Oncology*, 20 (8), 2118-2126.

Malek-Ahmadi, P., & Hilsabeck, R.C. (2007). Neuropsychiatric complications of

interferons: Classification, neurochemical bases, and management. *Annals of Clinical Psychiatry*, 19 (2), 113-123.

Marieb, E.N. (1989). *Human anatomy and physiology*. California: Benjamin Cummings Publishing Company.

Martin, R., Sawrie, S., Gilliam, F., Mackay, M., Fraught, E., & Knowlton, R., et al. (2002). Determining reliable cognitive change after epilepsy surgery: Development of reliable change indices and standardised regression-based change norms for the WMS-III and WAIS-III. *Epilepsia*, 43 (12), 1551-1558.

Matarazzo, J.D., & Hermann, D.O. (1984). Base rate data for the WAIS-R: test-retest stability and VIQ-PIQ differences. *Journal of Clinical Neuropsychology*, 6, 351-366.

Maunder, R.G., Hunter, J.J., & Feinman, S.V. (1998). Interferon treatment of hepatitis C associated with symptoms of PTSD. *Psychosomatic*, 39, 461-464.

McAllister, T.W., Ahles, T.A., Saykin, A.J., Ferguson, R.J., McDonald, B.C., & Lewis, L.D., et al. (2004). Cognitive effects of cytotoxic cancer chemotherapy: predisposing risk factors and potential treatments. *Current Psychiatry Reports*, 6 (5), 364-371.

McCaffrey, R.J., Duff, K., & Westervelt, H.J. (2000). *Practitioner's guide to evaluating change with intellectual instruments*. New York: Kluwer Academic/Plenum Press.

McGlave, P., Bartsch, G., Anasetti, C., Ash, R., Beatty, P., & Gajewski, J., et al. (1993). Unrelated donor marrow transplantation therapy for chronic myelogenous leukemia: initial experience of the National Marrow Donor Program. *Blood*, 81, 543-550.

McGlave, P., Kollman, C., & Shu, X.O. (1996). The first 1000 unrelated donor

transplants for CML: Lessons from the national marrow donor program (NMDP) experience. *Blood*, 88 (1), 483.

Meador, K.J. (1998). Cognitive side effects of medications: *Neurologic Clinics*, 16, 141-155.

Medical Research Council's Working Party for Therapeutic Trials in Leukemia. (1968). Chronic granulocyctic leukemia: Comparison of radiotherapy and bulsulfan therapy. *British Medical Journal of Clinical Research*, 1, 201.

Merx, K., Muller, M.C., Kreil, S., Lahaye, T., Paschka, P., & Schoch, C. (2002). Early reduction of BCR-ABL mRNA transcript levels predicts cytogenetic responses in chronic phase CML patients treated with imatinib after failure of interferon alpha. *Leukemia*, 16, 1579.

Meyers, C. (2000). Neurocognitive dysfunction in cancer patients. *Oncology*, 14, 75-78.

Meyers, C.A., Scheibel, R.S., & Forman, A.D. (1991). Persistent neurotoxicity of systematically administered interferon-alpha. *Neurology*, 41, 672-676.

Michiels, V., de Grucht, V., Cluydts, R., & Fischler, B. (1997). Attention and information processing in patients with chronic fatigue syndrome. *Journal of Clinical and Experimental Neuropsychology*, 21 (5), 709-729.

Milner, B. (1964). Some effects of frontal lobectomy in man. In J.M. Warren and K. Ackert's (Ed.), *The Frontal Granular Cortex and Behaviour* (pp. 313-334). New York: McGraw-Hill.

Moen, M.D., McKeage, K., Plosker, G.L., & Siddiqui, M.A.A. (2007). Imatinib: A review of its use in chronic myeloid leukaemia. *Drugs*, 67(2), 299-320.

Moore, A.R., & O'Keefe, S.T. (1999). Drug-induced cognitive impairment in the elderly. *Drugs & Aging*, 15 (1), 15-28.

Moresco, E.M., Scheetz, A.J., Bornmann, W.G., Koleske, A.J., & Fitzsimonds, R.M. (2003). Abl family nonreceptor tyrosine kinases modulate short-term synaptic plasticity. *Journal of Neurophysiology,* 89 (3), 1678-1687.

Moretti, R., Torre, P., Antonello, R., Cattaruzza, T., Cazzato, G., & Bava, J., et al. (2005). Neuropsychological evaluation of late-onset post-radiotherapy encephalopathy: A comparison with vascular dementia. *Journal of the Neurological Sciences*, 229-230, 195-200.

Moulignier, A., Allo, S., Zittoun, R., & Gout, O. (2002). Recombinant interferon-{alpha}-induced chorea and frontal cortical dementia. *Neurology*, 58 (2), 328-330.

O'Brien, S.G. (1997). Autografting for chronic myeloid leukaemia. *Bailléres Clinical Haematology*, 10, 369-388.

O'Brien, S.G., Guilhot, F., Larson, R.A., Gathmann, I., Baccarani, M., & Cervantes & F., et al. (2003). Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *New England Journal of Medicine*, 348, 994-1004.

Ogden, J.A. (2001). First do no harm. Culturally-appropriate neuropsychological assessment for indigenous people: a position paper. *Brain Impairment*, 2 (7), 1-10.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., & McFadden, E.T., et al. (1982). Toxicity and response criteria of the eastern cooperative oncology group. *American Journal of Clinical Oncology*, 5:649-655

Ottowitz, W.E., Dougherty, D., & Savage, C.R. (2002). The neural network basis for abnormalities of attention and executive function in major depressive disorder: Implications for application of the medical disease model to psychiatric disorders. *Harvard Review of Psychiatry*, 10, 86-99.

Parth, P., Dunlap, W.P., Kennedy, R.S., Lane, N.E., & Ordy, J.M. (1989). Motor and

cognitive testing of bone marrow transplant patients after chemoradiotherapy. *Perceptual and Motor Skills*, 68, 1227-1241.

Pavol, M.A., Meyers, C.A., Rexer, J.L., Valentine, A.D., Mattis, P.J., & Talpaz, M. (1995). Pattern of neurobehavioural deficits associated with interferon alfa therapy for leukemia. *Neurology*, 45, 947-950.

Payne, H.C. (2000). Traumatic brain injury, depression and cannabis use – assessing their effects on a cognitive performance. *Brain Injury*, 14 (5), 479-489.

Pedersen, A.D., Rossen, P., Mehlsen, M.Y., Pedersen, C.G., Zachariae, R., & Von Der Maase, H. (2009). Long-term cognitive function following chemotherapy in patients with testicular cancer. *Journal of the International Neuropsychological Society*, 1-6.

Peper, M., Steinvorth, S., Schraube, P., Fruehauf, S., Hass, R., & Kimmig, B.N., et al. (2000). Neurobehavioural toxicity of total body irradiation: A follow-up in long-term survivors. *International Journal of Radiation Oncology, Biology, and Physics*, 46 (2), 303-311.

Ponsford, J. (2004). *Cognitive and Behavioural Rehabilitation: From Neurobiology to Clinical Practice.* New York: The Guilford Press.

Porkka, K., Koskenvesa, P., Lundan, T., Rimpilalnen, J., Mustjoki, S., & Smykla, R., et al. (2008). Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood*, 112 (4), 1005-112.

Poynard, T., Leroy, V., Cohard, M., Thevenot, T., Mathurin, P., & Opolon, P., et al. (1996). Meta analysis of interferon randomised trials in the treatment of viral hepatitis C: Effects of dose and duration, *Hepatology*, 24, 778-789.

Prigatano, G.P. (1998). *Principles of Neuropsychological Rehabilitation*. New York: Oxford University Press.

Psychological Corporation (The) (1997). *WAIS-III and WMS-III technical Manual*. San Antonia, TX: The Psychological Corporation.

Putman, K., De Wit, L., Schoonacker, M., Baert, I., Beyens, H., & Brinkmann, N., et al. (2007). Effects of socio-economic status on functional and motor recovery after stroke: A European multicentre study. *Journal of Neurology, Neurosurgery & Psychiatry*, 78 (6), 593-599.

Rapport, L.J., Brines, D.B., Axelrod, B.N., & Theisen, M.E. (1997). Full scale as a mediatory of practice effects: The rich get richer. *The Clinical Neuropsychologist*, 11, 375-380.

Ransom, M.T. (2008). Executive function differences in medicated depressed, non-medicated depressed, and non-medicated non-depressed individuals [Abstract]. *Dissertation Abstracts International: Section B: The Sciences and Engineering*, 68 (12-B), 8409.

Reiffers, J., Goldman, J., Meloni, G., Cahn, J.Y., & Gratwohl, A. (1994). Autologous stem cell transplantation in chronic myelogenous leukemia: A retrospective analysis of the European group for bone marrow transplantation. *Bone Marrow Transplantation*, 14, 407-410.

Reitan, R.M., & Wolfson, D. (1995). Category test and trail making test as measures of frontal lobe functions. *Clinical Neurologist*, 9, 50-56.

Reitan, R.M., & Wolfson, D. (2004). Trail making test as an initial screening procedure for neuropsychological impairment in older children. *Archives of Clinical Neuropsychology*, 19, 281-288.

Ren, R. (2002). The molecular mechanism of chronic myelogenous leukemia and its therapeutic implications: studies in a murine model. *Oncogene*, 21, 8629-8642.

Rieckman, P. (2008). Imatinib buys time for brain after stroke. *Nature Medicine*, 14 (7), 712-713.

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of the evidence for threshold theory. *Neuropsychology*, 7, 273-295.

Savage, D.G., Szydlo, R.M., & Goldman, J.M. (1997). Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. *British Journal of Haematology*, 96 (1), 111-116.

Sawyers, C.L. (1999). Medical progress: Chronic myeloid leukemia. *The New England Journal of Medicine*, 342 (17), 1330-1340.

Sawyers, C.L., Hochhaus, A., Feldman, E., Goldman, J.M., Miller, C.B., & Ottman, O.G. (2002). Imatinib induces haematological and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: Results of a phase II study. *Blood*, 99, 3530-3539.

Saykin, A.J., Ahles, T.A., & McDonald, B.C. (2003). Mechanisms of chemotherapy-induced cognitive disorders. Neuropsychological, pathophysiological, and neuroimaging perspectives. *Seminars in Clinical Neuropsychiatry*, 8, 201-216.

Saykin, A.J., Ahles, T.A., & Schoenfeld, D. (2003). Gray matter reduction on voxel-based morphometry in chemotherapy-treated cancer survivors. *Journal of the International Neuropsychological Society*, 9, 246.

Schagen, S.B., Muller, M.J., Boogerd, W., Mellenbergh, G.J., & van Dam, F. (2006). Change in cognitive function after chemotherapy: A prospective longitudinal study in breast cancer patients. *Journal of the National Cancer Institute*, 98, 1742- 1745.

Schagen, S.B., Muller, M.J., Boogerd, W., Rosenbrand, R. M., van Rhijn, D., & Rodenhuis, L., et al. (2002). Late effects of adjuvant chemotherapy on cognitive function: A follow-up study in breast cancer patients. *Annals of Oncology*, 13, 1387-1397.

Schear, J.M., & Sato, S.D. (1989). Effects of visual acuity and visual motor speed and dexterity on cognitive test performance. *Archives of Clinical Neuropsychology*, 4, 25-32.

Scheibel, R.S., Valentine, A.D., O'Brien, S.O., & Meyers, C.A. (2004). Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. *Journal of Neuropsychiatry and Clinical Neurosciences*, 16 (2), 185-191.

Scherwath, A., Mehnert, A., Schleimer, B., Schirmer, L., Fehlauer, F., & Kreienberg, R., et al. (2006). Neuropsychological function in high risk breast cancer survivors after stem-cell supported high-dose chemotherapy versus standard-dose chemotherapy: Evaluation of long-term treatment effects. *Annals of Oncology*, 17, 415-423.

Schmidt, M. (2003). Hit or miss? Insight into executive functions. *Journal of the International Neuropsychological Society*, 9, 962-964.

Schiffer, C.A., Hehlmann, R., & Larson, R. (2003). Perspectives on the treatment of chronic phase and advanced phase CML and Philadelphia chromosome positive ALL. *Leukemia*, 17, 691-699.

Schultheiss, T.E., Kun, L.E., Ang, K.K. & Stephens, L.C. (1995). Radiation response of the central nervous system. *International Journal of Radiation Oncology, Biology and Physics*, 31, 1093-1112.

Schwartzberg, P.L., Stall, A.M., Hardin, J.D., Bowdish, K.S., Humaran, T., & Boast, S., et al. (1991). Mice homozygous for the abl mutation show poor viability and depletion of selected B and T cell populations. *Cell*, 65, 1165-1175.

Seymour, J.F., Grigg, A.P., Reynolds, J., Matthews, J., Schwarer, A.P., & Herrmann, R., et al. (2004). Imatinib's potential effects on fertility, immunity and pulmonary function: a prospective study in patients with previously untreated CML [Abstract). *Blood,* 104, 292a.

Sheline, G.E., Warra, W.M., & Smith, V. (1980). Therapeutic irradiation and brain injury. *International Journal of Radiation Oncology, Biology and Physics*, 6, 1215-1228.

Shum, D.H.K., McFarland, K.A., & Bain, J.D. (1990). Construct validity of eight tests of attention: Comparison of normal and closed head injured samples. *The Clinical Neuropsychologist*, 4, 151-162.

Shunk, A.W., Davis, A.S., & Dean, R.S. (2006). Test review of the Delis-Kaplan Executive Function System. *Applied Neuropsychology*, 13, 275-279.

Shuttleworth-Edwards, A.B., Kemp, R.D., Rust, A.L., Muirhead, J.G.L., Hartman, & Radloff, S.E. (2004). Cross-cultural effects on IQ test performance: A review and preliminary normative indications on WAIS-III test performance. *Journal of Clinical and Experimental Neuropsychology,* 26 (7), 903-920.

Silver, R.T., Woolf, S.H., Hehlmann, R., Appelbaum, F.R., Anderson, J., & Bennett, C., et al. (1999). An evidence-based analysis of the effects of bulsulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: Developed for the American Society of Hematology. *Blood*, 94 (5), 1517-1536.

Silverman, D.H., Castellon, S.A., & Abraham, L. (2003). Abnormal regional brain metabolism in breast cancer survivors after adjuvant chemotherapy is associated with cognitive changes. *Proceedings of the American Society for Clinical Oncology*, 22, 12.

Sohlberg, M.M., & Mateer, C.A. (2001). *Cognitive rehabilitation: An Integrative Neuropsychological Approach*. New York: The Guilford Press.

Sokal, J.E., Cox, E.B., & Baccarani, M. (1984). Prognostic discrimination in "good-risk" chronic granulocyctic leukemia. *Blood*, 63: 789-799.

Souhami, R., & Tobias, J. (2005). *Cancer and its management.* (5th ed.). Oxford: Blackwell Publishing.

Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., Vagg, P.R., & Jacobs, G.A. (1983). *Manual for the state-trait anxiety inventory,* Palo Alto: Consulting Psychologists Press.

Starr, J.M., & Lonie, J. (2008). Estimated pre-morbid IQ effects of cognitive and functional outcomes in Alzheimer disease: A longitudinal study in a treated cohort. *BMC Psychiatric*, 8, 27.

Stein, R.A., & Strickland, T.L. (1998). A review of the neuropsychological effects of commonly used prescription medications. *Archives of Clinical Neuropsychology*, 13, 259-284.

Stemmer, S.M., Stears, J.C., Burton, B.S., Jones, R.B., & Simon, J.H. (1994). White matters changes in patients with breast cancer treated with high-dose chemotherapy and autologous bone marrow support. *American Journal of Neuroradiology*, 15, 1267-1273.

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*. Oxford: Oxford University Press.

Sun, L., Lee, J., & Fine, H.A. (2004). Neuronally expressed stem cell factor induces neural stem cell migration to areas of brain injury. *The Journal of Clinical Investigation,* 113 (9), 1364-1374.

Syrjala, K.L., Dikman, S., Langer, S.L., Roth-Roerner, S., & Abrams, J.R. (2004). Neuropsychologic changes from before transplantation to 1 year in patients receiving myeloblative allogenic hematopoietic cell transplant. *Blood*, 104 (10), 3386-3392.

Syrjala, K.L., Langer, S.L., Abrams, J.R., Storer, B.E., & Martin, P.I. (2005). Late

effects of hematopoietic cell transplantation among 10-year adult survivors compared with case-matched controls. *Journal of Clinical Oncology*, 23 (27), 6596-6606.

Talpaz, M., Kantarjian, H., Kurzrock, R., Trujillo, J.M., & Gutterman, J.U. (1991). Interferon alpha produced sustained cytogenetic responses in chronic myelogenous leukemia. Philadelphia chromosome positive patients. *Annals of Internal Medicine*, 114, 532.

Talpaz, M., Kantarjian, H., Liang, J., Calvert, L., Hamer, J., & Tibbits, P., et al. (1995). Percentage of Philadelphia chromosome (Ph)-negative and Ph-positive cells found after autologous stem cell transplantation for chronic myelogeneous leukemia depends on the diploid cells induced by conventional dose chemotherapy before collection of autologous cells. *Blood*, 85, 3257-3263.

Talpaz, M., McCredie, K.B., Mavligit, G.M., & Gutterman, J. (1983). Leucocyte interferon-induced myeloid cyto-reduction in chronic myeloid leukemia. *Blood*, 62, 1052-1056.

Talpaz, M., Silver, R.T., Druker, B.J., Goldman, J.M., Gambacorti-Passerini, C., & Guilhot, F. (2002). Imatinib induces durable haematological and cytogenetic responses in patients with chronic myelogenous leukemia: Results of a phase II study. *Blood*, 99, 1982-1937.

Taylor, H.G., Schatschneider, C., & Rich, D. (1992). Sequelae of haemophilius influenzae meningitis: Implications for the study of brain disease and development. In M. Tramontana & S. Hooper (Eds.), *Advances in child neuropsychology*. New York: Springer-Verlag.

Temkin, N.R., Heaton, R.K., Grant, I., & Dikmen, S.S. (1999). Detecting significant change in neuropsychological test performance. A comparison of four models. *Journal of the International Neuropsychological Society*, 5, 357-369.

Tiersky, L., Johnson, S. K., Lange, G., Natelson, B. H., & DeLuca, J. (1997). The

neuropsychology of chronic fatigue syndrome: A critical review. *A Journal of Clinical and Experimental Neuropsychology*, 19, 560-586.

Toren, P., Sadeh, M., Wolmer, L., Eldar, S., Koren, S & Weizman, R., et al. (2000). Neurocognitive correlates of anxiety disorders in children: A preliminary report. *Journal of Anxiety Disorder*, 14 (3), 239-247.

Turrell, G., Lynch, J.W., Kaplan, G.A., Everson, S.A., & Helkala, E.L. (2002). Socioeconomic position across the lifecourse and cognitive function in late middle age. *Journal of Gerontology. Series B, Psychological Sciences and Social Sciences*, 57 (1), S43-51.

Tybulewicz, V.L., Crawford, C.E., Jackson, P.K., Bronson, R.T., & Mulligan, R.C. (1991). Neonatal lethality and lymphopenia in mice with a homozygous disruption of the c-abl proto-oncogene. *Cell,* 65, 1153-1163.

Tzingounis, A.V., & Nicoli, R.A. (2006). Arc/Arg3.1: Linking gene expression to synaptic plasticity and memory. *Neuron*, 52, 403-407.

Uchimaya, C.L., D'Elia, L.F., Dellinger, A.M., & Becker, J.T. (1995). Alternate forms of the Auditory-Verbal Learning Test: Issues of test comparability, longitudinal reliability, and moderating demographic variables. *Archives of Clinical Neuropsychology*, 10, 133-145.

Vakil, E., Shelef-Reshef, E., & Levi-Schiff, R. (1997). Procedural and declarative memory processes: Individuals with and without mental retardation. *American Journal on Mental Retardation*, 102, 147-160.

Valentine, A.D., Meyers, C.A., Kling, M.A., Richelson, E., & Hauser, P. (1998). Mood and cognitive side effects of interferon-α therapy. *Seminars in Oncology*, 25 (1), 39-47.

Vallar, G., & Baddeley, A. (1984). Fractionation of working memory: neuropsychological evidence for a phonological short-term store. *Journal of Verbal Learning and Verbal Behaviour*, 23, 151-161.

van Dam, F.S., Schagen, S.B., Muller, M.J., Boogerd, W., Wall, E., & Droogleever, M.E., et al. (1998). Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard dose chemotherapy. *Journal of the National Cancer Institute*, 90, 210-218.

van der Kogel, A.J. (1986). Radiation-induced damage in the central nervous system: An interpretation of target cell responses. *British Journal of Cancer*, 7, 207-217.

Van Rhee, F., Szydlo, R.M., Hermans, J., Devergie, A., Frassoni, F., & Arcese, W. (1997). Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: A report from the Chronic Leukemia working party of the European group for blood and marrow transplantation. *Bone Marrow Transplant*, 20, 553-560.

Vardy, J., Wefel, J.S., Ahles, T., Tannock, I.F., & Schagen, S.B. (2008). Cancer and cancer-therapy related cognitive dysfunction: An international perspective from the Venice cognitive workshop. *Annals of Oncology*, 19, 623-629.

Veiel, H.O.F. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology*, 19 (4), 587-603.

Vial, T., & Descotes, J. (1994). Clinical toxicity of the interferons. *Drug Safety*, 10, 115.

Webster, K., Chivington, K., Shonk, C., Evemenco, S., Yount, S., & Hahn, E., et al. (2002). Measuring quality of life (QOL) among patients with Leukemia: The functional assessment of cancer therapy – Leukemia (Fact-Leu). *Quality of Life Research*, 11(7), 678.

Wechsler, D. (1981). *The Wechsler adult intelligence scale – revised (WAIS-R) Manual*. New York: The Psychological Corporation.

Wechsler, D. (1997a). *The Wechsler adult intelligence scale – III (WAIS-III).* San Antonia: The Psychological Corporation.

Wechsler, D. (1997b). *The Wechsler memory scale-III (WMS-III)*. San Antonia: The Psychological Corporation.

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

Wefel, J.S., Witgert, M.E., & Meyers, C.A. (2009). Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. *Neuropsychological Review*, 18:121-131.

Weiten, W. (1992). *Psychology: Themes and Variations.* California: Pacific/Cole.

Widiger, T.A., & Samuel, D.B. (2005). Evidence-based assessment of personality disorders. *Psychological Assessment.* 17, 278-287.

Wolff, N.C., Richardson, J.A., Egorin, M., & Ilaria, R.L. (2003). The CNS is a sanctuary for leukemic cells in mice receiving imatinib mesylate for Bcr/Abl-induced leukemia. *Blood*, 15, 101 (12), 5010-5013.

Woodard, J.L., Goldstein, F.C., Roberts, V.J., & McGuire, C. (1999). Convergent and discriminate validity of the CVLT. *Journal of Clinical and Experimental Neuropsychology*, 21, 553-558.

Woodliff, H.J., & Hermann, R.P. (1976). *Concise Haematology.* London: Edward Arnold Ltd.

Yan, J., Wang, Y., & Cui, Y. (2007). Executive function in obsessive-compulsive disorder [Abstract]. *Chinese Mental Health Journal*, 21 (7), 492.

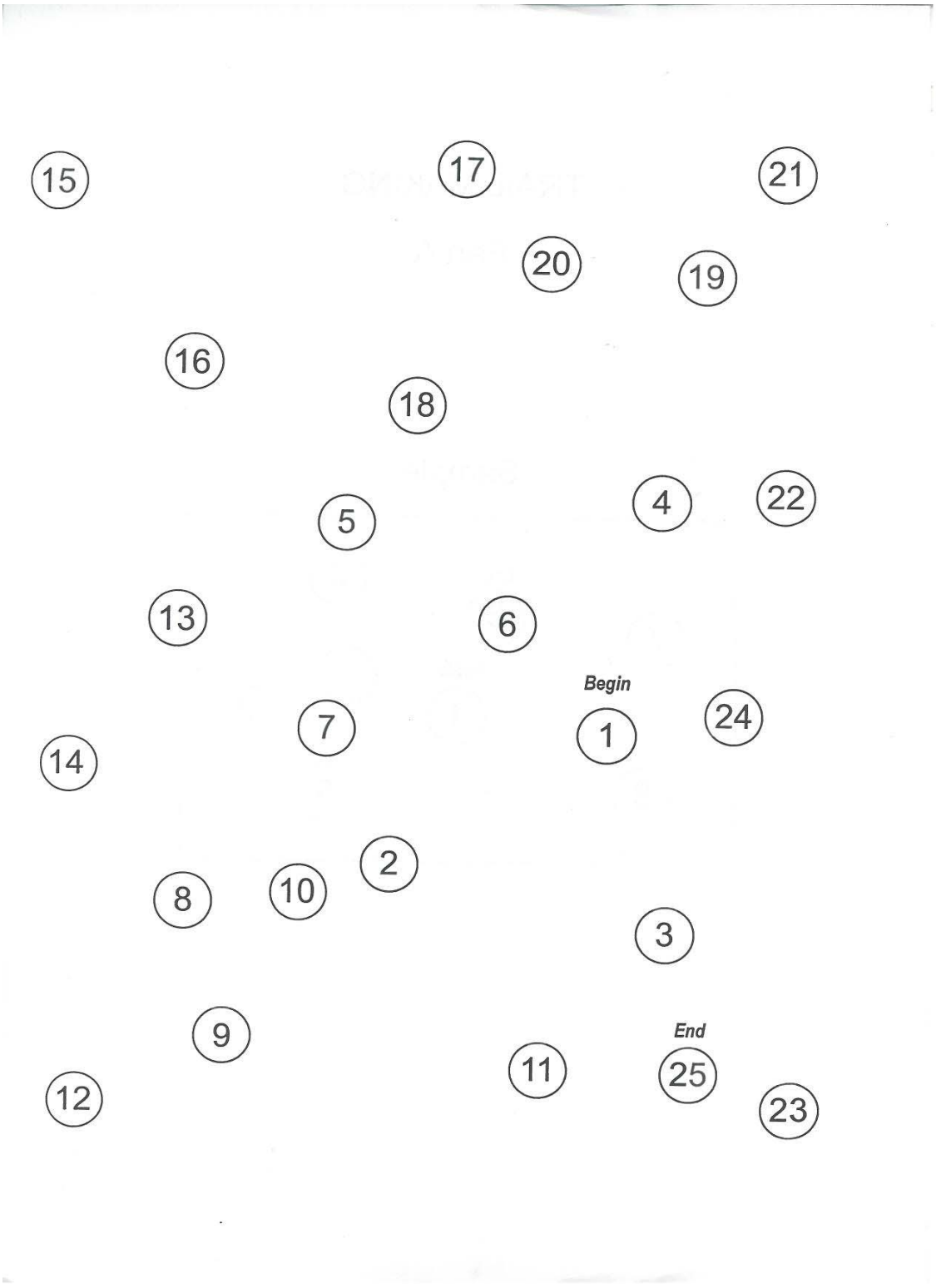
Yun-fei, Z. (2005). A preliminary study of cognitive dysfunction in obsessive-compulsive disorder. *Chinese Journal of Clinical Psychology* [Abstract], 13 (3), 337.

Zakzanis, K.K., Leach, L., & Kaplan, E. (1998). On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry, Neuropsychology, and Behavioural Neurology*, 11(3), 111-119.

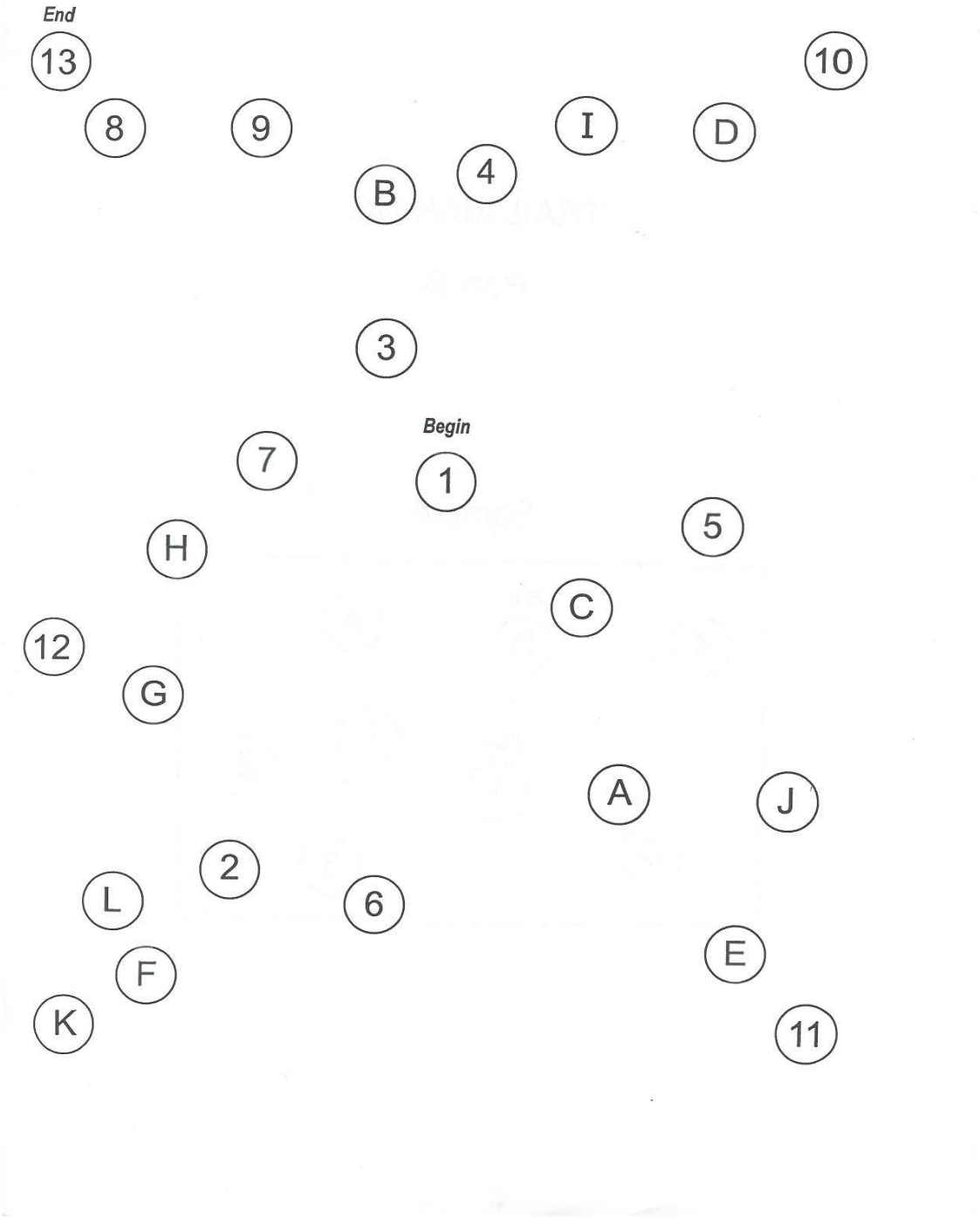
6. APPENDICES

Appendix A: Trail-making Test (including Trails A and B)

Trails A



Trails B



Appendix B: Rey Auditory Verbal Learning Test (Form 1)

RAVLT Sample Scoring Sheet

Name: _____

Date: _____

Examiner: _____

_____

(Note: Do not re-read list A for Recall Trail A6 and A7)

	Recall Trials						Recall Trials			
List A	A1	A2	A3	A4	A5	List B	B1	A6	A7	
Drum						Desk				Drum
Curtain						Ranger				Curtain
Bell						Bird				Bell
Coffee						Shoe				Coffee
School						Stove				School
Parent						Mountain				Parent
Moon						Glasses				Moon
Garden						Towel				Garden
Hat						Cloud				Hat
Farmer						Bota				Farmer
Nose						Lamb				Nose
Turkey						Gun				Turkey
Color						Pencil				Color
House						Church				House
River						Fish				River
#correct										

Total A1 to A5 = _____

Trial A6 – A5 = _____

Recognition # targets correctly identified _____

distractors correctly identified _____

Word List for Testing RAVLT Recognition

Bell (A)	Home (SA)	Towel (B)	Boat (B)	Glasses (B)
Window (SA)	Fish (B)	Curtain (A)	Hot (PA)	Stocking (SB)
Hat (A)	Moon (A)	Flower (SA)	Parent (A)	Shoe (B)
Barn (SA)	Tree (PA)	Color (A)	Water (SA)	Teacher (SA)
Ranger (B)	Balloon (PA)	Desk (B)	Farmer (A)	Stove (B)
Nose (A)	Bird (B)	Gun (B)	Rose (SPA)	Nest (SPB)
Weather (SB)	Mountain (B)	Crayon (SA)	Cloud (B)	Children (SA)
School (A)	Coffee (A)	Church (B)	House (A)	Drum (A)
Hand (PA)	Mouse (PA)	Turkey (A)	Stranger (PB)	Toffee (PA)
Pencil (B)	River (A)	Fountain (PB)	Garden (A)	Lamb (B)

Appendix C – Auditory Verbal Learning Test (Alternate Version)

AVLT- Alternate form

Name: _____

Date: _____

Examiner: _____

_____

(Note: Do not re-read list A for Recall Trail A6 and A7)

	Recall Trials						Recall Trials			
List A	A1	A2	A3	A4	A5	List B	B1	A6	A7	
Pipe						Bench				Pipe
Wall						Officer				Wall
Alarm						Cage				Alarm
Sugar						Sock				Sugar
Student						Fridge				Student
Mother						Cliff				Mother
Star						Bottle				Star
Painting						Soap				Painting
Bag						Sky				Bag
Wheat						Ship				Wheat
Mouth						Goat				Mouth
Chicken						Bullet				Chicken
Sound						Paper				Sound
Door						Chapel				Door
Stream						Crab				Stream
#correct										

Total A1 to A5 = _____
Trial A6 – A5 = _____
Recognition # targets correctly identified _____
distractors correctly identified _____

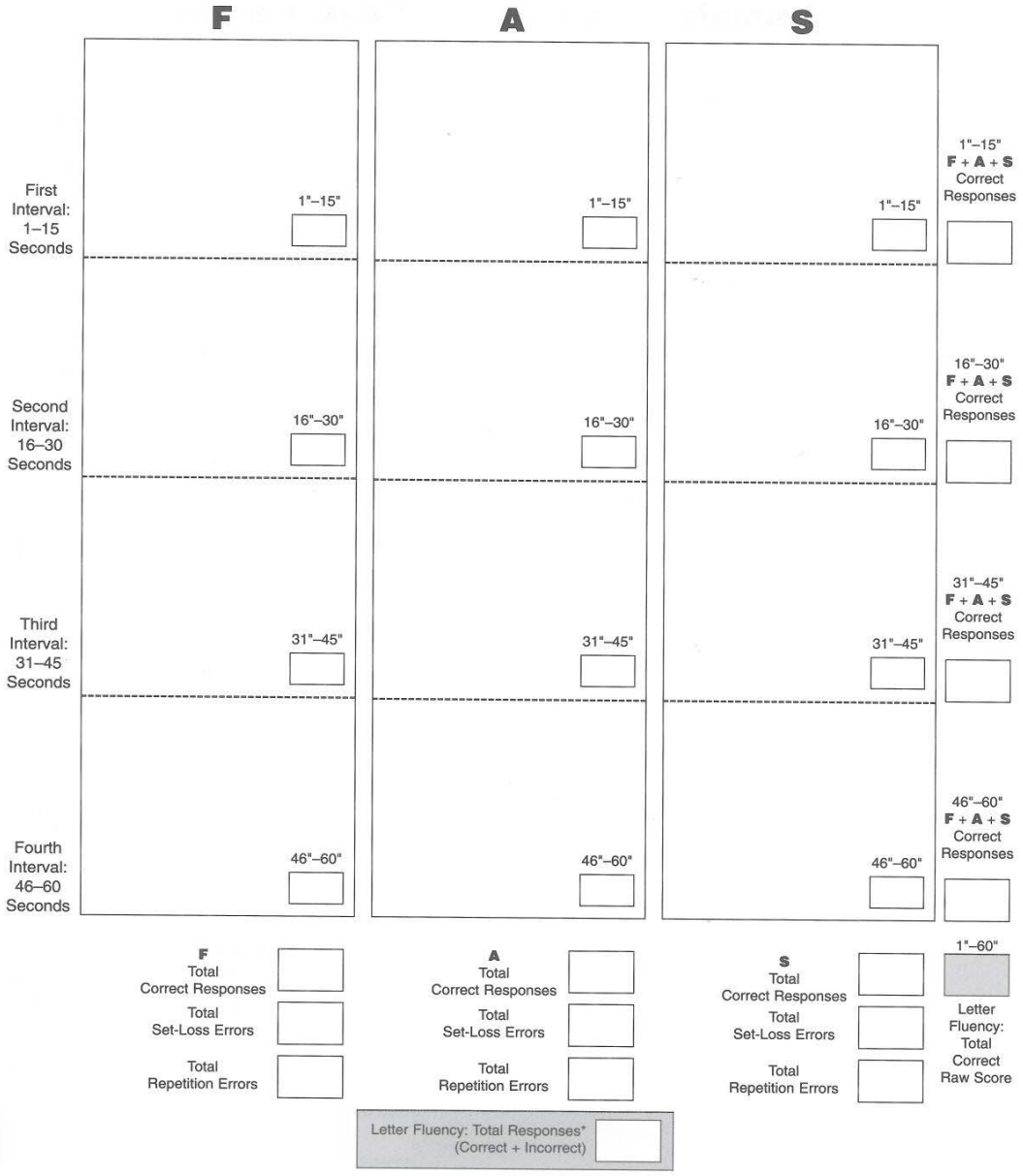
Word List for Testing AVLT Recognition

Alarm (A)	Eye (SA)	Soap (B)	Ship (B)	Bottle (B)
Aunt (SA)	Crab (B)	Wall (A)	Car (PA)	Seat (SB)
Bag (A)	Star (A)	Clock (SA)	Mother (A)	Sock (B)
Creek (SA)	Rag (PA)	Sound (A)	Duck (SA)	Tone (SA)
Officer (B)	Bun (PA)	Bench (B)	Wheat (A)	Fridge (B)
Mouth (A)	Cage (B)	Bullet (B)	Floor (SPA)	Rock (SPB)
Arrow (SB)	Cliff (B)	Night (SA)	Sky (B)	Bread (SA)
Student (A)	Sugar (A)	Chapel (B)	Door (A)	Pipe (A)
Hail (PA)	Cream (PA)	Chicken (A)	Bridge (PB)	Ball (PA)
Paper (B)	Stream (A)	Coat (PB)	Painting (A)	Goat (B)

Appendix D: Delis-Kaplan Executive Functioning System - Verbal fluency (Standard Form) – letter fluency condition

D-KEFS Verbal Fluency Test

Condition 1: Letter Fluency

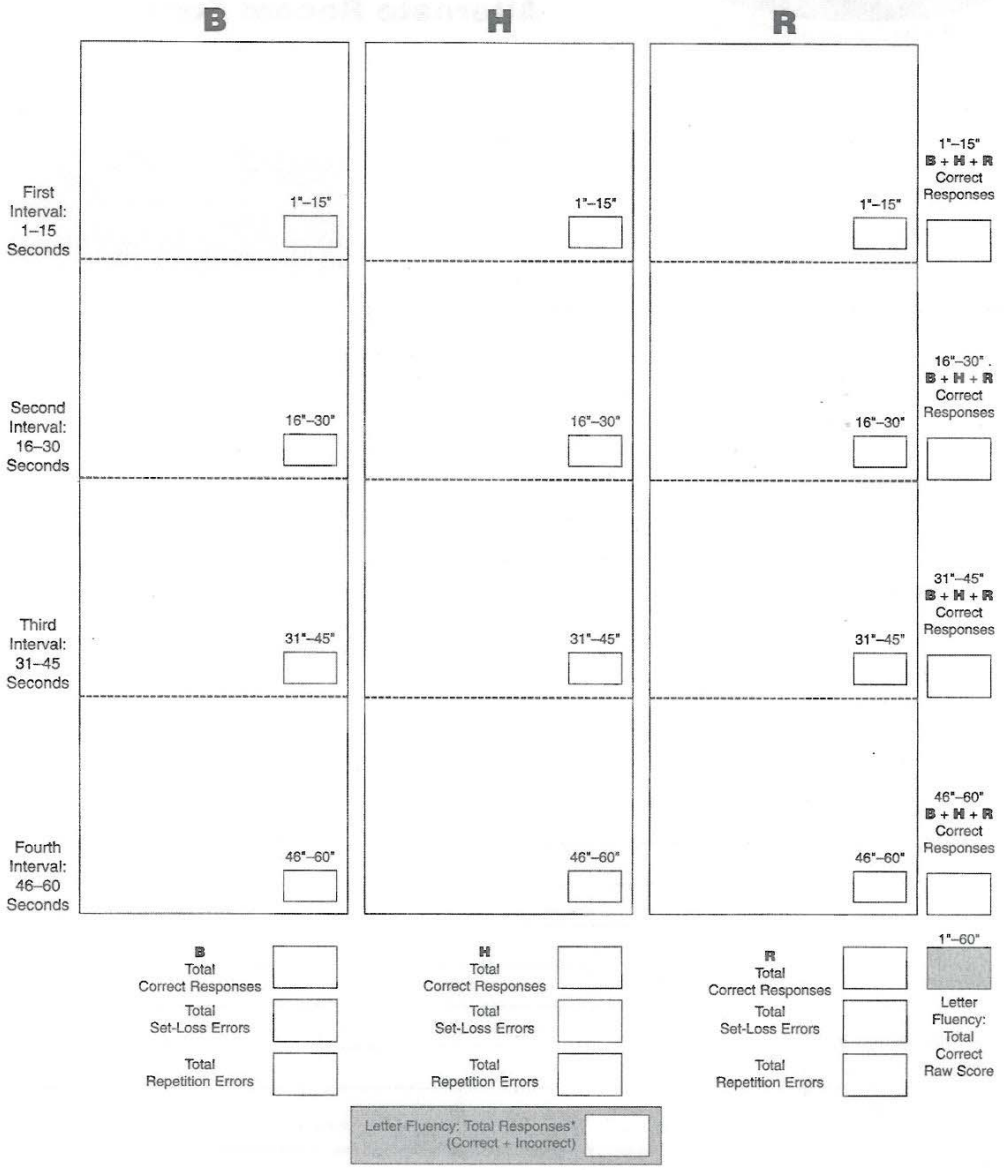


* *Note*: Some repetition errors are coded also as set-loss errors; each double-coded error counts as only one response for the total responses measure.

Appendix E: Delis-Kaplan Executive Functioning System - Verbal fluency (Alternate Form) –letter fluency condition

D-KEFS Verbal Fluency Test

Condition 1: Letter Fluency



* *Note*: Some repetition errors are coded also as set-loss errors; each double-coded error counts as only one response for the total responses measure.

Appendix F: Delis-Kaplan Executive Functioning System - Sorting Test (Standard form) – free sort condition

D-KEFS Sorting Test

Screening Pretest

Words Incorrectly Read: _____ Raw Score: _____

Words Not Understood: _____ Raw Score: _____

Condition 1–Free Sorting: Card Set 1

Discontinue administration of Card Set 1 after either (a) the examinee indicates that he or she cannot identify any more sorts, even after receiving the single prompt to keep trying; (b) 240 seconds (4 minutes) of cumulative ***sorting*** time have elapsed; or (c) the examinee has completed 10 attempted sorts.

First Sort

Description:

Sorting Time (Seconds) ☐

Sort:

Animals	Air	1 Syllable
Transportation	Land	2 Syllables

Verbal Sorts

Large	Curved	Uppercase	Blue	White
Small	Straight	Lowercase	Yellow	Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Second Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Animals	Air	1 Syllable
Transportation	Land	2 Syllables

Verbal Sorts

Large	Curved	Uppercase	Blue	White
Small	Straight	Lowercase	Yellow	Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Third Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Animals	Air	1 Syllable
Transportation	Land	2 Syllables

Verbal Sorts

Large	Curved	Uppercase	Blue	White
Small	Straight	Lowercase	Yellow	Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 1 *(continued)*

Fourth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Animals / Transportation	Air / Land	1 Syllable / 2 Syllables	Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Fifth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Animals / Transportation	Air / Land	1 Syllable / 2 Syllables	Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Sixth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Animals / Transportation	Air / Land	1 Syllable / 2 Syllables	Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Seventh Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Animals / Transportation	Air / Land	1 Syllable / 2 Syllables	Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 1 *(continued)*

Eighth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Animals / Transportation	Air / Land	1 Syllable / 2 Syllables

Verbal Sorts

Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Ninth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Animals / Transportation	Air / Land	1 Syllable / 2 Syllables

Verbal Sorts

Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Tenth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Animals / Transportation	Air / Land	1 Syllable / 2 Syllables

Verbal Sorts

Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 1

	Raw Score
Total Description Score	☐
Number of Confirmed Correct Sorts	☐

Appendix G: Delis-Kaplan Executive Functioning System - Sorting Test (Alternate form) – free sort condition

D-KEFS Sorting Test

Screening Pretest

Words Incorrectly Read: _____ Raw Score: _____

Words Not Understood: _____ Raw Score: _____

Condition 1–Free Sorting: Card Set 3

Discontinue administration of Card Set 3 after either (a) the examinee indicates that he or she cannot identify any more sorts, even after receiving the single prompt to keep trying; (b) 240 seconds (4 minutes) of cumulative ***sorting*** time have elapsed; or (c) the examinee has completed 10 attempted sorts.

First Sort

Description:

Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Foods / Nature	Liquids / Solids	R Words / S Words	Dashed / Solid	Shapes Match / Shapes Different	Words 1 Color / Words Multicolor	3 Sides / 4 Sides	Tall Letters / Short Letters
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Second Sort

Description:

Cumulative Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Foods / Nature	Liquids / Solids	R Words / S Words	Dashed / Solid	Shapes Match / Shapes Different	Words 1 Color / Words Multicolor	3 Sides / 4 Sides	Tall Letters / Short Letters
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Third Sort

Description:

Cumulative Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Foods / Nature	Liquids / Solids	R Words / S Words	Dashed / Solid	Shapes Match / Shapes Different	Words 1 Color / Words Multicolor	3 Sides / 4 Sides	Tall Letters / Short Letters
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 3 *(continued)*

Fourth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Foods Nature	Liquids Solids	R Words S Words	Dashed Solid	Shapes Match Shapes Different	Words 1 Color Words Multicolor	3 Sides 4 Sides	Tall Letters Short Letters
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Fifth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Foods Nature	Liquids Solids	R Words S Words	Dashed Solid	Shapes Match Shapes Different	Words 1 Color Words Multicolor	3 Sides 4 Sides	Tall Letters Short Letters
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Sixth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Foods Nature	Liquids Solids	R Words S Words	Dashed Solid	Shapes Match Shapes Different	Words 1 Color Words Multicolor	3 Sides 4 Sides	Tall Letters Short Letters
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Seventh Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Foods Nature	Liquids Solids	R Words S Words	Dashed Solid	Shapes Match Shapes Different	Words 1 Color Words Multicolor	3 Sides 4 Sides	Tall Letters Short Letters
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 3 *(continued)*

Eighth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Verbal Sorts			Perceptual Sorts				
Foods / Nature	Liquids / Solids	R Words / S Words	Dashed / Solid	Shapes Match / Shapes Different	Words 1 Color / Words Multicolor	3 Sides / 4 Sides	Tall Letters / Short Letters

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Ninth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Verbal Sorts			Perceptual Sorts				
Foods / Nature	Liquids / Solids	R Words / S Words	Dashed / Solid	Shapes Match / Shapes Different	Words 1 Color / Words Multicolor	3 Sides / 4 Sides	Tall Letters / Short Letters

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Tenth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Verbal Sorts			Perceptual Sorts				
Foods / Nature	Liquids / Solids	R Words / S Words	Dashed / Solid	Shapes Match / Shapes Different	Words 1 Color / Words Multicolor	3 Sides / 4 Sides	Tall Letters / Short Letters

For an ***incorrect*** sort, mark the cards of one group: Rice River Rocks Sandwich Sea Soup

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 3

Raw Score

Total Description Score ☐

Number of Confirmed Correct Sorts ☐

Appendix H: Functional Assessment of Cancer Therapy – Leukaemia module

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Leu (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Leu (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BRM1 3	I am bothered by fevers	0	1	2	3	4
P2	I have certain parts of my body where I experience significant pain	0	1	2	3	4
BRM1 2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU 1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
BMT 6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU 5	I feel uncertain about my future health	0	1	2	3	4
LEU 6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM1 9	I have emotional ups and downs	0	1	2	3	4
LEU 7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

Appendix I: Case Report Form

CST1571K2301

Adverse Experience Log

Subject number ______________ Subject initials ________________

Adverse Event	SAE? (Y/N)	Grade 1-4 (CTCAE)*	Relationship to trial drug 0 = not suspected 1= suspected	Start date	End date	Action taken** (see codes below)	Investigator signature	Mark if continuing at final exam
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			
				___/___/___ day/month/year	___/___/___ day/month/year			

* NIH/NCI-Common Terminology Criteria for Adverse Events Version 3.

** Codes for Action Taken: 0 = no action taken, 1 = study drug dose adjusted or temporarily interrupted, 2 = study drug permanently discontinued due to adverse experience, 3=concomitant medication taken, 4 = non drug therapy given, 5 = hospitalisation, prolonged hospitalisation

ConmedAELogSTI2301 17 May05

Appendix J: NIH/NCI Common Terminology Criteria for Adverse Events

ADVERSE EVENT	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD					
Haemoglobin (Hgb)	WNL	<LLN - 10.0 g/dL <LLN - 100 g/L <LLN - 6.2 mmol/L	8.0 - <10. 0g/dL 80 - <100 g/L 4.9 - <6.2 mmol/L	6.5 - <8.0 g/dL 65 - <80 g/L 4.0 - <4.9 mmol/L	<6.5 g/dL <65 g/L <4.0 mmol/L
Leukocytes (total WBC)	WNL	<LLN - 3.0 x 10^9/L <LLN - 3000/mm^3	≥2.0 - <3.0 x 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9/L ≥1000 - <2000/mm^3	<1.0 x 10^9/L <1000/mm^3
Lymphopenia	WNL	<LLN - 1.0 x 10^9/L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3	-
Neutrophils/ Granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9/L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 - x 10^9/L <500/mm^3
Platelets	WNL	<LLN - 75.0 x 10^9/L <LLN - 75,000/mm^3	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥10.0 - <50.0 x 10^9/L ≥10,000 - <50,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
CARDIOVASCULAR					
Cardio-ischemia/ infarction	None	Non-specific T-wave flattening or changes	Asymptomatic, ST- and T-wave changes suggesting ischemia	Angina without evidence of infarction	Acute myocardial infarction
Cardiac left ventricular function	None	Asymptomatic, decline of resting ejection fraction of ≥10% but <20% of baseline value; shortening fraction ≥24% but <30%	Asymptomatic but resting ejection fraction below LLN or decline of resting ejection fraction of ≥20% of baseline value; 24% shortening fraction	CHF responsive to treatment	Severe of refractory CHF or requiring intubation
Hypertension	None	Asymptomatic, transient increase by >20mm Hg (diastolic) or to >150/ 100 if previously WNL; not requiring treatment	Recurrent or persistent or symptomatic increase by >20mm Hg (diastolic) or to >150/ 100 if previously WNL; not requiring treatment	Requiring therapy or more intensive therapy than previously	Hypertensive crisis
Hypotension	None	Changes, but not requiring therapy (including transient orthostatic hypotension)	Requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	Requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	Shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Nodal/junctional ar/dysrhythmia	None	Asymptomatic, not requiring treatment	Symptomatic, but not requiring treatment	Symptomatic and requiring treatment	Life-threatening (eg. Arryhythmia associated with HCF, hypotension, syncope, shock)
Pericardial effusion/ pericarditis	None	Asymptomatic effusion, not requiring treatment	Pericarditis (rub, ECG changes, and/or chest pain)	With physiologic consequences	Tamponade (drainage of pericardial window required)
COAGULATION					
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Partial thromboplastin time (PTT)	WNL	> ULN - ≤1.5 x LLN	>1.5 - ≤2.0 x ULN	>2 x ULN	-
Prothrombin time (PT)	WNL	> ULN - ≤1.5 x LLN	>1.5 - ≤2.0 x ULN	>2 x ULN	-

ADVERSE EVENT	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4

GASTROINTESTINAL

Constipation	None	Requiring stool softener or dietary modification	Requiring laxatives	Constipation requiring manual evacuation or enema	Obstruction or toxic megacolon
Diarrhoea patients without colostomy	None	Increase of <4 stools/day over pre-treatment	Increase of 4-6 stools/day, or nocturnal stools	Increase of ≥7 stools/day, or incontinence, or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; or haemodynamic collapse
Diarrhoea patients with colostomy	None	Mild increase in loose, watery colostomy output compared with pre-treatment	Moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	Severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	Physiologic consequences requiring intensive care; or haemodynamic collapse
GIT (from AMLM7, not NCI scale)	None	Mild abdominal pain & diarrhoea	Moderately severe pain, distension, diarrhoea	Severe pain, ileus	Life-threatening GIT bleeding, diarrhoea, perforation
Nausea	None	Able to eat	Oral intake significantly decreased	No significant intake, requiring IV fluids	-
Stomatitis/ pharyngitis (oral/pharyngeal mucositis)	None	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful erythema, edema, or ulcers, but can eat or swallow	Painful erythema, edema, or ulcers, requiring IV hydration	Severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
Vomiting	None	1 episode in 24 hours over pre-treatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; or haemodynamic collapse

HEMORRHAGE

Haematuria (in the absence of vaginal bleeding)	None	Microscopic only	Intermittent gross bleeding, no clots	Persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	Open surgery or necrosis or deep bladder ulceration
Hemorrhage - other (specify site, _____)	None	Mild, without transfusion	-	Requiring transfusion	Catastrophic bleeding, requiring major or non-elective intervention

HEPATIC

Alkaline phosphatase	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin	WNL	>ULN - 2.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 20.0 x ULN	>10.0 x ULN
Liver dysfunction/ failure (clinical)	Normal	-	-	Asterixis	Encephalopathy or coma
SGOT (AST)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
SGPT (ALT)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Gamma GT (?GT)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
LDH	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

METABOLIC

Amylase	WNL	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>1.5 - 2.0 x ULN	>5.0 x ULN
Hypercalcemia	WNL	>ULN - 11.5 mg/L >ULN - 2.9 mmol/L	>11.5 - 12.5 mg/L >2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/L >3.1 - 3.4 mmol/L	>13.5 mg/L >3.4 mmol/L
Hyperglycemia	WNL	>ULN - 160 mg/L >ULN - 8.9 mmol/L	>160 - 250 mg/L >8.9 - 13.9 mmol/L	>250 - 500 mg/L >13.9 - 27.8 mmol/L	>500 mg/L >27.8 mmol/L or acidosis
Hypocalcemia	WNL	>ULN - 8.0 mg/L >ULN - 2.0	7.0 - <8.0 mg/L 1.75 - <2.0	6.0 - <7.0 mg/L 1.5 - <1.75 mmol/L	<6.0 mg/L <1.5 mmol/L

		mmol/L	mmol/L		
Hypoglycemia	WNL	>ULN - 55 mg/L >ULN - 3.0 mmol/L	40 - <55 mg/L 2.2 - <3.0 mmol/L	30 - <40 mg/L 1.7 - <2.2 mmol/L	<30 mg/L <1.7 mmol/L
Hypomagnesemia	WNL	>ULN - 1.2 mg/L >ULN - 0.5 mmol/L	0.9 - <1.2 mg/L 0.4 - <0.5 mmol/L	0.7 - <0.9 mg/L 0.3 - <0.4 mmol/L	<0.7 mg/L <0.3 mmol/L

NEUROLOGY

Depressed level of consciousness	Normal	Somnolence or sedation not interfering with function	Somnolence or sedation interfering with function, but not interfering with activities of daily living	Obtundation or stupor; difficult to arouse; interfering with activities of daily living	Coma
Mood alteration - depression	Normal	Mild mood alteration that interferes with function	Moderate mood alteration interfering with function, but not interfering with activities of daily living	Severe mood alteration interfering with activities of daily living	Suicidal ideation or danger to self
Neuropathy - motor	Normal	Subjective weakness; no objective findings	Mild objective weakness interfering with function but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis
Neuropathy - sensory	Normal	Loss of deep tendon reflexes or parasthesia (including tingling) but not interfering with function	Objective sensory loss or parasthesia (including tingling) interfering with function, but not interfering with activities of daily living	Sensory loss or parasthesia interfering with activities of daily living	Permanent sensory loss that interferes with function

RENAL

Creatinine	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Proteinuria	Normal or <0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ or 3+ 1.0 - 3.5 g/24 hours	4+ or >3.5 g/24 hours	Nephritic syndrome

ADVERSE EVENT	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
OTHER (General)					
Allergic reaction / hypersensitivity (including drug fever)	None	Transient rash, drug fever <38^{0}C (<100.4^{0}F)	Urticaria, drug fever ≥38^{0}C (≥100.4^{0}F), and/or asymptomatic bronchospasm	Symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema / angioedema	Anaphylaxis
Alopecia	Normal	Mild hair loss	Pronounced hair loss	-	-
Dyspnea (shortness of breath)	Normal	-	Dyspnea on exertion		
Fatigue (lethargy, malaise, asthenia)	None	Increased fatigue over baseline, but not altering normal activities	Moderate (*eg*.decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	Severe (*eg*.decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	Bedridden or disabling
Fever (in the absence of neutropenia, where	None	38.0 - 39.0^{0}C (100.4 - 102.2^{0}F)	39.1 - 40.0^{0}C (102.3 - 104.0^{0}F)	>40.0^{0}C (104.0) for >24 hours	>40.0^{0}C (104.0) for >24 hours

neutropenia is defined as AGC <1.0 x 10^9/L)					
Headache	None	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	Severe pain: pain or analgesics severely interfering with activities of daily living	Disabling
Infection / Febrile neutropenia - other (specify, _____)	None	Mild	Moderate	Severe	Disabling
Injection site reaction	None	Pain or itching or erythema	Pain or swelling with inflammation or phlebitis	Ulceration or necrosis that is severe or prolonged, or requiring surgery	Life-threatening or disabling
Inner ear / Hearing	Normal	Hearing loss on audiometry only	Tinnitus or hearing loss, not requiring hearing aid or treatment	Tinnitus or hearing loss correctable with hearing aid or treatment	Severe unilateral or bilateral loss (deafness) not correctable
Ocular / visual	Normal	Mild	Moderate	Severe	Unilateral or bilateral loss of vision (blindness)
Rash / desquamation	None	Macular or popular eruption or erythema without associated symptoms	Macular or popular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	Generalized symptomatic erythroderma or macular, popular, or vesicular eruption or desquamation covering ≥50% of body surface area	Generalized exfoliative dermatitis or ulcerative dermatitis
Weight gain / loss	<5.0%	5.0 - <10.0%	10.0 - <20.0%	≥20.0%	-

Adapted from National Cancer Institute (NCI) Common Toxicity Criteria (CTC) - Version 2.0

Appendix K: Ethics Approval Form

VICTORIA UNIVERSITY | A NEW SCHOOL OF THOUGHT

MEMO

TO	Dr Denise Charman Acting Chair University Human Research Ethics Committee	DATE	12 September 2007
FROM	Dr Alan Tucker School of Psychology		
CC	Dr Amy Scholes, Royal Melbourne Hospital Ms Kerrie Shiell, D Psych-Clin Neuropsych candidate		
SUBJECT	Ethics Approval - HRETH 06/42		

Dear Denise,

RE: **HRETH:06/42: Sequential Neuropsychologic Assessment of Patients on a Protein-kinase Inhibitor**

As you will be aware, following the resignation of Dr Ada Kritikos from the University, I have now taken over the supervision of Victoria University aspects of Ms Kerrie Shiell's Doctor of Psychology-Clinical Neuropsychology thesis. Dr Amy Scholes continues as supervisor, based at the Royal Melbourne Hospital.

I note that the Committee last year gave provisional approval , subject to **certain matters** being addressed. I trust that the following and accompanying documents meets the Committee's requirements.

Revise collection dates

- The collection dates documented on page 1 of the original application have been changed to, 27/09/2007 – 27/09/2009.

The Plain Language Statement (Q.7) should be simplified

- A simplified version of the plain language statement is included on page four and five.

Revise collection dates (page 9)

- The commencement date on page 9 has been changed to 27/09/2007

Page 10. item 13: Check the box indicating that payment will be made to subjects and payment included in information to participants.

- The above-mentioned item has been checked

The treating doctor not to recruit participants but rather the student researcher do so.

- The student will now recruit patients following liaison with the primary hospital clinician (see question 12).

Page 13, item 18 (b): The student cannot be responsible for the security of the data; it is the responsibility of the principal researcher.

- Dr Amelia Scholes, principal researcher and Royal Melbourne Hospital staff member, to maintain the security of the data.

The Participant Information and Consent form should include a complaints box.

- Complaints box added to the Participant Information and Consent form (see Appendix B)

As it would be difficult to detect whether changes were due to the influence of the drug or the disease, the Committee queried the design and strongly recommended a control or comparison group, say of patients who are not on the drug.

- A control group has been added to the study design. The specifics of this group are outlined in the amended application (see page 6). The control group will comprise 15 adult patients with newly diagnosed CLL or low grade NHL not currently requiring chemotherapy (this will increase the numbers from 15 to 30 patients). Although this is not a 'perfect' comparator, patients in the two groups will be matched as closely as possible for age and sex, the only major identifiable difference treatment with imatinib in the CML cohort. The control group will be reviewed after 10 patients and further patients may be selectively recruited if there are any discrepancies in the age/sex match to the target group.

We have included a copy of the amended application with track changes and a clean copy for your consideration.

Yours sincerely,

Dr Alan Tucker
Clinical Neuropsychologist
Senior Lecturer, School of Psychology

The Human Research Ethics Committee operates in accordance with the *NHMRC National Statement of Ethical Conduct in Research Involving Humans, 1999*

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ABN 73 802 706 972

MELBOURNE HEALTH

RESEARCH DIRECTORATE

Research Directorate - Human Ethics Committee Approval Form

Telephone: 9342 8530 Facsimile: 9342 8548

This is to certify that

HREC Project No: 2005.228 Approval date: 15/03/2006 Expiry date: 15/03/2009

Project Title: Sequential neuropsychologic assessment of patients on a protein-kinase inhibitor.

Principal Investigator: A/Prof. Andrew Grigg
Clinical Haematology and Medical Oncology
The Royal Melbourne Hospital
C/- The Post Office
PARKVILLE VIC 3050

Sponsored by:

Protocol No: Version: 4 Dated: 22/11/2005

Participant Information and Consent Form: Version 2 dated 27th January 2006

Investigator Brochure:

Other enclosures:(please describe eg advertisement etc.)

Conducted at: Royal Melbourne Hospital **has been approved**

It is now your responsibility to ensure that all people conducting this research project are made aware of which documents have been approved.

This approval is subject to ongoing, current and valid insurance coverage throughout the duration of the conduct of the study.

You are required to notify the Secretary of the Human Research Ethics Committee of

- Any change in the protocol and the reason for that change together with an indication of ethical implications (if any) by submitting an amendment to the study.
- Serious adverse effects on subjects and the action taken to manage them, including amended Plain Language Statement and Consent Form where appropriate.
- Any unforseen events.
- Your inability to continue as Principal Investigator, or any other change in research personnel involved in the study
- A delay of more than 12 months in the commencement of the project.
- The actual date of commencement of the study.

You are required to submit to the Human Research Ethics Committee

- An Annual Report every twelve months for the duration of the project.
- A detailed Final Report at the conclusion of the project.

The Human Research Ethics Committee may conduct an audit at any time.

An extension of the project beyond the stated conclusion date should be sought from the Human Research Ethics Committee.

Signed: [redacted]
Dr. Angela Watt
Manager – Human Research Ethics Committee

Appendix L: Results of Repeated Measures ANOVA

Digit Span

Descriptive Statistics

	Mean	Std. Deviation	N
Att1DSpan	10.42	3.315	12
Att2DSpan	10.83	3.186	12
Att3DSpan	10.67	3.339	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
Time	Pillai's Trace	.092	.507[a]	2.000	10.000	.617
	Wilks' Lambda	.908	.507[a]	2.000	10.000	.617
	Hotelling's Trace	.101	.507[a]	2.000	10.000	.617
	Roy's Largest Root	.101	.507[a]	2.000	10.000	.617

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.949	.520	2	.771	.952	1.000	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	1.056	2	.528	.554	.582
	Greenhouse-Geisser	1.056	1.904	.555	.554	.574
	Huynh-Feldt	1.056	2.000	.528	.554	.582
	Lower-bound	1.056	1.000	1.056	.554	.472
Error(Time)	Sphericity Assumed	20.944	22	.952		
	Greenhouse-Geisser	20.944	20.939	1.000		
	Huynh-Feldt	20.944	22.000	.952		
	Lower-bound	20.944	11.000	1.904		

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Level 2 vs. Level 1	2.083	1	2.083	1.000	.339
	Level 3 vs. Level 1	.750	1	.750	.508	.491
Error(Time)	Level 2 vs. Level 1	22.917	11	2.083		
	Level 3 vs. Level 1	16.250	11	1.477		

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	1358.231	1	1358.231	134.074	.000
Error	111.435	11	10.130		

Digit Symbol Coding

Descriptive Statistics

	Mean	Std. Deviation	N
PS1CD	11.08	4.252	12
PS2CD	11.58	4.078	12
PS3CD	12.00	4.023	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
time	Pillai's Trace	.439	3.913[a]	2.000	10.000	.056	.439
	Wilks' Lambda	.561	3.913[a]	2.000	10.000	.056	.439
	Hotelling's Trace	.783	3.913[a]	2.000	10.000	.056	.439
	Roy's Largest Root	.783	3.913[a]	2.000	10.000	.056	.439

Mauchly's Test of Sphericity[b]

Measure:CD

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
time	.955	.456	2	.796	.957	1.000	.500

Tests of Within-Subjects Effects

Measure:CD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
time	Sphericity Assumed	5.056	2	2.528	5.081	.015	.316
	Greenhouse-Geisser	5.056	1.915	2.640	5.081	.017	.316
	Huynh-Feldt	5.056	2.000	2.528	5.081	.015	.316
	Lower-bound	5.056	1.000	5.056	5.081	.046	.316
Error(time)	Sphericity Assumed	10.944	22	.497			
	Greenhouse-Geisser	10.944	21.062	.520			
	Huynh-Feldt	10.944	22.000	.497			
	Lower-bound	10.944	11.000	.995			

Tests of Within-Subjects Contrasts

Measure:CD

Source	time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
time	Level 2 vs. Level 1	3.000	1	3.000	3.000	.111	.214
	Level 3 vs. Level 1	10.083	1	10.083	8.587	.014	.438
Error(time)	Level 2 vs. Level 1	11.000	11	1.000			
	Level 3 vs. Level 1	12.917	11	1.174			

Tests of Between-Subjects Effects

Measure:CD
Transformed Variable:Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1602.370	1	1602.370	96.337	.000	.898
Error	182.963	11	16.633			

Logical Memory I

Descriptive Statistics

	Mean	Std. Deviation	N
M1LMI	10.67	3.055	12
M2LMI	11.25	3.019	12
M3LMI	12.42	3.579	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.597	7.413[a]	2.000	10.000	.011	.597
	Wilks' Lambda	.403	7.413[a]	2.000	10.000	.011	.597
	Hotelling's Trace	1.483	7.413[a]	2.000	10.000	.011	.597
	Roy's Largest Root	1.483	7.413[a]	2.000	10.000	.011	.597

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.909	.955	2	.620	.917	1.000	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	19.056	2	9.528	8.403	.002	.433
	Greenhouse-Geisser	19.056	1.833	10.396	8.403	.003	.433
	Huynh-Feldt	19.056	2.000	9.528	8.403	.002	.433
	Lower-bound	19.056	1.000	19.056	8.403	.014	.433
Error(Time)	Sphericity Assumed	24.944	22	1.134			
	Greenhouse-Geisser	24.944	20.164	1.237			
	Huynh-Feldt	24.944	22.000	1.134			
	Lower-bound	24.944	11.000	2.268			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	4.083	1	4.083	1.669	.223	.132
	Level 3 vs. Level 1	36.750	1	36.750	13.364	.004	.549
Error(Time)	Level 2 vs. Level 1	26.917	11	2.447			
	Level 3 vs. Level 1	30.250	11	2.750			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1571.704	1	1571.704	162.647	.000	.937
Error	106.296	11	9.663			

Logical Memory II

Descriptive Statistics

	Mean	Std. Deviation	N
M1LMII	10.67	2.640	12
M2LMII	12.42	3.370	12
M3LMII	12.92	3.554	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.568	6.568[a]	2.000	10.000	.015	.568
	Wilks' Lambda	.432	6.568[a]	2.000	10.000	.015	.568
	Hotelling's Trace	1.314	6.568[a]	2.000	10.000	.015	.568
	Roy's Largest Root	1.314	6.568[a]	2.000	10.000	.015	.568

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	Df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.769	2.625	2	.269	.812	.933	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	33.500	2	16.750	10.096	.001	.479
	Greenhouse-Geisser	33.500	1.625	20.617	10.096	.002	.479
	Huynh-Feldt	33.500	1.866	17.948	10.096	.001	.479
	Lower-bound	33.500	1.000	33.500	10.096	.009	.479
Error(Time)	Sphericity Assumed	36.500	22	1.659			
	Greenhouse-Geisser	36.500	17.873	2.042			
	Huynh-Feldt	36.500	20.531	1.778			
	Lower-bound	36.500	11.000	3.318			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	36.750	1	36.750	9.136	.012	.454
	Level 3 vs. Level 1	60.750	1	60.750	14.449	.003	.568
Error(Time)	Level 2 vs. Level 1	44.250	11	4.023			
	Level 3 vs. Level 1	46.250	11	4.205			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1728.000	1	1728.000	187.579	.000	.945
Error	101.333	11	9.212			

WordList A6

Descriptive Statistics

	Mean	Std. Deviation	N
M1WLa6	.5175	.99187	12
M2WLa6	.1683	.96254	12
M3WLa6	1.1000	.77831	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.532	5.686[a]	2.000	10.000	.022	.532
	Wilks' Lambda	.468	5.686[a]	2.000	10.000	.022	.532
	Hotelling's Trace	1.137	5.686[a]	2.000	10.000	.022	.532
	Roy's Largest Root	1.137	5.686[a]	2.000	10.000	.022	.532

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.990	.097	2	.953	.990	1.000	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	5.317	2	2.658	6.731	.005	.380
	Greenhouse-Geisser	5.317	1.981	2.684	6.731	.005	.380
	Huynh-Feldt	5.317	2.000	2.658	6.731	.005	.380
	Lower-bound	5.317	1.000	5.317	6.731	.025	.380
Error(Time)	Sphericity Assumed	8.689	22	.395			
	Greenhouse-Geisser	8.689	21.790	.399			
	Huynh-Feldt	8.689	22.000	.395			
	Lower-bound	8.689	11.000	.790			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	1.463	1	1.463	1.887	.197	.146
	Level 3 vs. Level 1	4.072	1	4.072	5.568	.038	.336
Error(Time)	Level 2 vs. Level 1	8.529	11	.775			
	Level 3 vs. Level 1	8.044	11	.731			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	4.252	1	4.252	7.391	.020	.402
Error	6.329	11	.575			

WordList Recognition

Descriptive Statistics

	Mean	Std. Deviation	N
M1RecogA	.8633	.42737	12
M2RecogA	-.4775	1.77295	12
M3RecogA	.7992	.45811	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.420	3.623[a]	2.000	10.000	.066	.420
	Wilks' Lambda	.580	3.623[a]	2.000	10.000	.066	.420
	Hotelling's Trace	.725	3.623[a]	2.000	10.000	.066	.420
	Roy's Largest Root	.725	3.623[a]	2.000	10.000	.066	.420

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.370	9.931	2	.007	.614	.651	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	13.727	2	6.864	6.288	.007	.364
	Greenhouse-Geisser	13.727	1.227	11.185	6.288	.021	.364
	Huynh-Feldt	13.727	1.302	10.540	6.288	.019	.364
	Lower-bound	13.727	1.000	13.727	6.288	.029	.364
Error(Time)	Sphericity Assumed	24.012	22	1.091			
	Greenhouse-Geisser	24.012	13.501	1.779			
	Huynh-Feldt	24.012	14.326	1.676			
	Lower-bound	24.012	11.000	2.183			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	21.574	1	21.574	6.140	.031	.358
	Level 3 vs. Level 1	.049	1	.049	.089	.771	.008
Error(Time)	Level 2 vs. Level 1	38.647	11	3.513			
	Level 3 vs. Level 1	6.130	11	.557			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1.872	1	1.872	4.152	.066	.274
Error	4.961	11	.451			

WordList Total

Descriptive Statistics

	Mean	Std. Deviation	N
M1WLtot	.7250	.93752	12
M2WLtot	.1932	1.38588	12
M3WLtot	1.3050	.83174	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.723	13.057[a]	2.000	10.000	.002	.723
	Wilks' Lambda	.277	13.057[a]	2.000	10.000	.002	.723
	Hotelling's Trace	2.611	13.057[a]	2.000	10.000	.002	.723
	Roy's Largest Root	2.611	13.057[a]	2.000	10.000	.002	.723

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.466	7.633	2	.022	.652	.704	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	7.422	2	3.711	6.630	.006	.376
	Greenhouse-Geisser	7.422	1.304	5.692	6.630	.016	.376
	Huynh-Feldt	7.422	1.407	5.273	6.630	.014	.376
	Lower-bound	7.422	1.000	7.422	6.630	.026	.376
Error(Time)	Sphericity Assumed	12.313	22	.560			
	Greenhouse-Geisser	12.313	14.343	.859			
	Huynh-Feldt	12.313	15.482	.795			
	Lower-bound	12.313	11.000	1.119			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	3.394	1	3.394	1.873	.198	.145
	Level 3 vs. Level 1	4.037	1	4.037	10.179	.009	.481
Error(Time)	Level 2 vs. Level 1	19.935	11	1.812			
	Level 3 vs. Level 1	4.362	11	.397			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	6.590	1	6.590	8.335	.015	.431
Error	8.697	11	.791			

Letter Fluency

Descriptive Statistics

	Mean	Std. Deviation	N
EF1LetFl	8.92	3.872	12
EF2LetFl	9.17	3.538	12
EF3LetFl	9.92	3.476	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.277	1.917[a]	2.000	10.000	.197	.277
	Wilks' Lambda	.723	1.917[a]	2.000	10.000	.197	.277
	Hotelling's Trace	.383	1.917[a]	2.000	10.000	.197	.277
	Roy's Largest Root	.383	1.917[a]	2.000	10.000	.197	.277

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound

Time	.902	1.026	2	.599	.911	1.000	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	6.500	2	3.250	1.873	.177	.146
	Greenhouse-Geisser	6.500	1.822	3.567	1.873	.182	.146
	Huynh-Feldt	6.500	2.000	3.250	1.873	.177	.146
	Lower-bound	6.500	1.000	6.500	1.873	.198	.146
Error(Time)	Sphericity Assumed	38.167	22	1.735			
	Greenhouse-Geisser	38.167	20.046	1.904			
	Huynh-Feldt	38.167	22.000	1.735			
	Lower-bound	38.167	11.000	3.470			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	.750	1	.750	.186	.674	.017
	Level 3 vs. Level 1	12.000	1	12.000	3.000	.111	.214
Error(Time)	Level 2 vs. Level 1	44.250	11	4.023			
	Level 3 vs. Level 1	44.000	11	4.000			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1045.333	1	1045.333	86.819	.000	.888
Error	132.444	11	12.040			

Free Sorts

Descriptive Statistics

	Mean	Std. Deviation	N
EF1FrSort	9.83	4.549	12
EF2FrSort	11.08	2.575	12
EF3FrSort	12.08	3.175	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.383	3.102[a]	2.000	10.000	.089	.383
	Wilks' Lambda	.617	3.102[a]	2.000	10.000	.089	.383
	Hotelling's Trace	.620	3.102[a]	2.000	10.000	.089	.383
	Roy's Largest Root	.620	3.102[a]	2.000	10.000	.089	.383

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.905	.995	2	.608	.913	1.000	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	30.500	2	15.250	4.050	.032	.269

	Greenhouse-Geisser	30.500	1.827	16.695	4.050	.036	.269
	Huynh-Feldt	30.500	2.000	15.250	4.050	.032	.269
	Lower-bound	30.500	1.000	30.500	4.050	.069	.269
Error(Time)	Sphericity Assumed	82.833	22	3.765			
	Greenhouse-Geisser	82.833	20.096	4.122			
	Huynh-Feldt	82.833	22.000	3.765			
	Lower-bound	82.833	11.000	7.530			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	18.750	1	18.750	2.285	.159	.172
	Level 3 vs. Level 1	60.750	1	60.750	6.666	.026	.377
Error(Time)	Level 2 vs. Level 1	90.250	11	8.205			
	Level 3 vs. Level 1	100.250	11	9.114			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1452.000	1	1452.000	145.789	.000	.930
Error	109.556	11	9.960			

Trails B

Descriptive Statistics

	Mean	Std. Deviation	N
EF1TrailsB	-.4892	1.56958	12
EF2TrailsB	-.2375	1.66027	12
EF3TrailsB	.0303	1.60934	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.334	2.508[a]	2.000	10.000	.131	.334
	Wilks' Lambda	.666	2.508[a]	2.000	10.000	.131	.334
	Hotelling's Trace	.502	2.508[a]	2.000	10.000	.131	.334
	Roy's Largest Root	.502	2.508[a]	2.000	10.000	.131	.334

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.627	4.660	2	.097	.729	.811	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	1.619	2	.810	2.370	.117	.177

	Greenhouse-Geisser	1.619	1.457	1.111	2.370	.136	.177
	Huynh-Feldt	1.619	1.623	.998	2.370	.130	.177
	Lower-bound	1.619	1.000	1.619	2.370	.152	.177
Error(Time)	Sphericity Assumed	7.515	22	.342			
	Greenhouse-Geisser	7.515	16.029	.469			
	Huynh-Feldt	7.515	17.851	.421			
	Lower-bound	7.515	11.000	.683			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	.760	1	.760	.842	.378	.071
	Level 3 vs. Level 1	3.238	1	3.238	3.676	.082	.250
Error(Time)	Level 2 vs. Level 1	9.926	11	.902			
	Level 3 vs. Level 1	9.688	11	.881			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	.647	1	.647	.272	.612	.024
Error	26.132	11	2.376			

State Anxiety

Descriptive Statistics

	Mean	Std. Deviation	N
StAnxiety1	58.25	17.147	12
StAnxiety2	49.83	11.328	12
StAnxiety3	44.50	20.305	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
time	Pillai's Trace	.327	2.426[a]	2.000	10.000	.138
	Wilks' Lambda	.673	2.426[a]	2.000	10.000	.138
	Hotelling's Trace	.485	2.426[a]	2.000	10.000	.138
	Roy's Largest Root	.485	2.426[a]	2.000	10.000	.138

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
time	.996	.041	2	.980	.996	1.000	.5

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	1153.389	2	576.694	2.838	.080

	Greenhouse-Geisser	1153.389	1.992	579.057	2.838	.080
	Huynh-Feldt	1153.389	2.000	576.694	2.838	.080
	Lower-bound	1153.389	1.000	1153.389	2.838	.120
Error(time)	Sphericity Assumed	4469.944	22	203.179		
	Greenhouse-Geisser	4469.944	21.910	204.012		
	Huynh-Feldt	4469.944	22.000	203.179		
	Lower-bound	4469.944	11.000	406.359		

Tests of Within-Subjects Contrasts

Source	time	Type III Sum of Squares	df	Mean Square	F	Sig.
time	Level 2 vs. Level 1	850.083	1	850.083	2.140	.171
	Level 3 vs. Level 1	2268.750	1	2268.750	5.251	.043
Error(time)	Level 2 vs. Level 1	4368.917	11	397.174		
	Level 3 vs. Level 1	4752.250	11	432.023		

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	31042.231	1	31042.231	217.448	.000
Error	1570.324	11	142.757		

Mood

Descriptive Statistics

	Mean	Std. Deviation	N
MoodInt1	11.17	10.008	12
MoodInt2	7.58	5.992	12
MoodInt3	7.58	6.680	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
time	Pillai's Trace	.220	1.412[a]	2.000	10.000	.288
	Wilks' Lambda	.780	1.412[a]	2.000	10.000	.288
	Hotelling's Trace	.282	1.412[a]	2.000	10.000	.288
	Roy's Largest Root	.282	1.412[a]	2.000	10.000	.288

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
time	.200	16.087	2	.000	.556	.573	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
time	Sphericity Assumed	102.722	2	51.361	2.045	.153

	Greenhouse-Geisser	102.722	1.111	92.442	2.045	.178
	Huynh-Feldt	102.722	1.146	89.621	2.045	.177
	Lower-bound	102.722	1.000	102.722	2.045	.181
Error(time)	Sphericity Assumed	552.611	22	25.119		
	Greenhouse-Geisser	552.611	12.223	45.210		
	Huynh-Feldt	552.611	12.608	43.830		
	Lower-bound	552.611	11.000	50.237		

Tests of Within-Subjects Contrasts

Source	time	Type III Sum of Squares	df	Mean Square	F	Sig.
time	Level 2 vs. Level 1	154.083	1	154.083	1.836	.203
	Level 3 vs. Level 1	154.083	1	154.083	2.604	.135
Error(time)	Level 2 vs. Level 1	922.917	11	83.902		
	Level 3 vs. Level 1	650.917	11	59.174		

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	924.593	1	924.593	21.264	.001
Error	478.296	11	43.481		

FACT-Leu

Descriptive Statistics

	Mean	Std. Deviation	N
FACTleu1	124.967	36.9178	12
FACTleu2	135.217	25.1804	12
FACTleu3	132.10	26.183	12

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.342	2.602[a]	2.000	10.000	.123	.342
	Wilks' Lambda	.658	2.602[a]	2.000	10.000	.123	.342
	Hotelling's Trace	.520	2.602[a]	2.000	10.000	.123	.342
	Roy's Largest Root	.520	2.602[a]	2.000	10.000	.123	.342

Mauchly's Test of Sphericity[b]

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.525	6.444	2	.040	.678	.740	.500

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	662.642	2	331.321	1.334	.284	.108

	Greenhouse-Geisser	662.642	1.356	488.703	1.334	.280	.108
	Huynh-Feldt	662.642	1.480	447.800	1.334	.282	.108
	Lower-bound	662.642	1.000	662.642	1.334	.273	.108
Error(Time)	Sphericity Assumed	5464.664	22	248.394			
	Greenhouse-Geisser	5464.664	14.915	366.384			
	Huynh-Feldt	5464.664	16.277	335.719			
	Lower-bound	5464.664	11.000	496.788			

Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Level 2 vs. Level 1	1260.750	1	1260.750	4.272	.063	.280
	Level 3 vs. Level 1	610.613	1	610.613	.729	.411	.062
Error(Time)	Level 2 vs. Level 1	3246.570	11	295.143			
	Level 3 vs. Level 1	9209.787	11	837.253			

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	205181.618	1	205181.618	281.620	.000	.962
Error	8014.333	11	728.576			

Appendix M: Recall and Recognition Scores on the Standard and Alternate forms of the Auditory Verbal Learning Test (Geffen et al., 1994).

	Session 1	Session 2	Pearson's r
Trial 1	6.67 (1.29)	6.98 (1.71)	.34*
Trial 2	9.08 (1.96)	9.18 (2.03)	.45**

Trial 3	10.82 (2.09)	10.86 (1.85)	.43**
Trial 4	11.59 (1.99)	11.49 (2.18)	.68**
Trial 5	12.10 (1.85)	12.37 (2.07)	.74**
List B	5.86 (1.60)	5.84 (1.82)	.28*
Trial 6	10.65 (2.67)	10.88 (2.94)	.70**
Trial 7	10.76 (2.81)	10.39 (3.02)	.67**
Total	50.25 (7.08)	50.88 (8.02)	.77**
Recognition	13.84 (1.50)	13.51 (1.57)	.38**