# Working Memory in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia

Pauline Richards, M.A.

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

Department of Psychology
Carleton University
Ottawa, Ontario
Canada

*Your file Votre référence*
*ISBN: 978-0-494-18234-5*
*Our file Notre référence*
*ISBN: 978-0-494-18234-5*

ABSTRACT

The purpose of this thesis was to investigate working memory in a sample of long-term survivors of ALL. Three studies were completed. The mean age of participants was 14 years. In Study One, measures of IQ and Verbal and Visual Memory were administered to 16 long-term survivors of ALL and two control groups: 11 siblings of the ALL survivors, and 16 long-term survivors of Wilms' tumor. Although mean IQ scores were within one standard deviation of the normative mean, long-term survivors of ALL performed below control groups on Full Scale IQ, Verbal IQ, and Performance IQ. Long-term survivors of ALL scored below the survivors of Wilms' tumor on the General Memory Index. Siblings did not differ from either treatment group on any memory measure. There were no significant group differences on tests of immediate and delayed verbal and visual memory or delayed recognition.

Study Two investigated the prevalence of leukoencephalopathy in 15 of the 16 survivors of ALL using MRI and CT scans. The structural integrity of their brains were rated on a scale from 0 (no abnormality) to 4 (severe leukoencephalopathy). Forty percent of the group had a score greater than 0 on MRI, and 33% had a score greater than 0 on CT. There was no association between MRI/CT scores and measures of IQ and memory.

Study Three specifically examined working memory. The three groups were administered the Petrides Self-Ordered Pointing Test, an experimental task shown to reflect functioning in the mid-dorsolateral prefrontal cortex, which has been consistently linked to the maintenance/monitoring phase of working memory in humans. No significant group differences were found on this test once age was covaried. ALL

survivors were significantly lower on the Finger Windows subtest and the Working Memory Indices of the CMS/WMS-III and Behavior Rating Inventory of Executive Function questionnaire. These results do not implicate self-ordered pointing and the corresponding brain regions measured by this test as being impacted by treatment in this population. However, subtle implications remain that suggest working memory is indeed affected in this population. Further research involving Baddeley's central executive component of working memory is suggested.

Acknowledgements

First, I would like to say a special thank you to all of the long-term survivors of ALL, their siblings, the long-term survivors of Wilms' tumor and the parents for supporting this thesis and for making it possible by their participation.

Thank you to my thesis advisors, Dr. Shelley Parlow and Dr. Sally Kuehn, for your support, patience, understanding, multiple read throughs and meetings during which I benefited you're your constructive criticism and expertise. I wish to thank my thesis committee members, Dr. Dan McIntyre and Dr. Jo-Anne LeFevre, for their time and valued input into the proposal and the final product.

Thank you to my External Advisor, Dr. Marcia Barnes, for the time you put into reading the manuscript and for your comprehensive review. Thank you also for traveling from Guelph to be at the defense! I appreciated your positive perspective, expertise, and your thoughtfulness during the defense. Thank you to my Internal Advisor, Dr. Ann Laubstein, for your time and excellent comments on the manuscript. I really enjoyed your enthusiasm and your insight. It is always interesting to receive input from someone outside the field of psychology, which brings such a unique perspective to the topic.

Thank you to the Children's Hospital of Eastern Ontario Research Institute for the student bursary that supported this project. This thesis would not have been possible without the input and support of Dr. Elizabeth Shu and the Oncology Department at CHEO. Thank you to Donna Grimard who organized and arranged all of the participants and appointments. It would have taken a lot longer to collect the data without your help! Special thanks to Dr. Mary-Ann Matzinger for scoring all of the CTs and MRIs.

Thank you to Carol Bentivoglio for your time and for sharing your wealth of psychometric experience! Thank you to Amanda George for your time, expertise and training, all that double scoring (yikes!), and for the use of your office for so many years! Thank you both for your friendship and for all the great memories I have of CHEO (especially Looney Tunes)!!! I really miss you guys! Thank you to Dr. Isabelle Montour-Proulx for the time you invested on my behalf by testing all of the French-speaking participants. It was much appreciated!

To my parents and brother for their love and support. Everything good that I am is a reflection of the three of you. To my dear friends, thank you for your love and support (in alphabetical order): Allison, Amanda, Bekim, Bernie, Bobby, Bonnie, Carole, Christine, Janice, Jennifer, John, Johnny, Lisa, Lynn, Nadiney Bean, Renata, Rob, and Scott. I don't know what I would do without you all!

To Dr. M. A. Persinger, thank you for inspiring me in this direction and for your example of reaching for the highest standard while keeping your feet on the ground and still hunting for Easter eggs! ☺ You're the best!

To Dr. Tom Boniferro for seeing in me what I had forgotten and for giving me a chance to find it again, thank you. To Dr. Janice Kurita for your support, encouragement, and friendship, thank you. I'm so grateful for you both!

And thank you most especially to Yves, for standing by me these past 16 years through all of the hardship and the good times, for your support emotionally and financially, for your unwavering commitment to our relationship, for always believing in me, and for making me a better person by knowing and being loved by you.

TABLE OF CONTENTS

List of Tables

List of Figures

Chapter 1



Chapter 3

# CHAPTER ONE

## INTRODUCTION

Malignancy in children is relatively rare. Economic advantages in most industrialized nations have resulted in greater control of infectious disease and reduced congenital abnormalities; consequently, cancer has become the leading cause of death from disease in children (Steinherz & Simone, 1998). Of the cancers, leukemia is the most common form in children (Neglia & Robison, 1988; Steinherz & Simone, 1998). One subcategory, acute lymphoblastic leukemia (ALL), comprises 80% of child leukemia cases (Diamond & Matthay, 1988). In the 1940s, children diagnosed with ALL could expect a median survival of only three months; but in the past 50 years, there have been dramatic advances in treatment. Since the 1980s, 95% of all children treated for ALL achieve a complete remission, and more than 55% will be in continuous remission (no relapse) five years after diagnosis (Diamond & Matthay, 1988; Hoffman Marymont, 2000). The major breakthrough in the treatment of ALL, achieved in the early 1970s, was the addition to the therapeutic regimen of central nervous system prophylaxis (preventative) treatment (Pui, 1997). The central nervous system had been the most common site of relapse after the leukemia had gone into remission. By effectively preventing recurrence of the disease in the central nervous system, central nervous system prophylaxis greatly enhanced the likelihood of long-term, disease-free survival.

Unfortunately, there is a caveat to this success: some children who survive childhood leukemia and its treatment experience permanent cognitive deficits caused by the same therapy that has enabled them to live. It has long been recognized that the intensive therapies used in treatment of ALL carry an unavoidable burden of toxicity to

the central nervous system, referred to as "neurotoxicity" (e.g., Soni, Marten, Pitner, Duenas, & Powazek, 1975). Adverse sequelae include endocrine abnormalities and associated growth problems (Katz, Pollock, Jacaruso, & Morad, 1993); secondary malignancies (Neglia & Robison, 1988); and, most frequently, neuropsychological changes that may result in learning problems (Cousens, Waters, Said, & Stevens, 1988; Frankel, Stock, Byrd, & Bloomfield, 2001). Parents of the survivors of ALL initially observed the latter in their children whose learning difficulties seemed more serious than might be expected given school absence or pre-morbid functioning (Eiser & Tillman, 2001). Among the first complaints of parents were that their child appeared to have mastered the material the night before a test but remembered little the next morning, and that increasing amounts of time were spent at home finishing work not completed at school (Pui, 2000). A number of studies were subsequently published to try to establish whether or not these learning difficulties were an inevitable consequence of central nervous system prophylaxis (e.g., Goff, Anderson, & Cooper, 1980). During the past 30 years of this research, it has become clear that a percentage of long-term survivors of ALL demonstrate impaired cognitive skills, associated specifically with central nervous system prophylaxis, that impedes their academic achievement (e.g., Mulhern, Fairclough, & Ochs, 1991; Waber & Mullenix, 2000). In addition, imaging studies have suggested a frequency of structural brain abnormalities (e.g., cerebral atrophy, intracerebral calcifications) as high as 41% to 53% in long-term survivors of ALL (e.g., Hertzberg et al., 1997; Riccardi, Brouwers, Di Chiro, & Poplack, 1985). The relationship between reported cognitive impairment and these structural brain abnormalities in the ALL population remains a source of debate. This issue is addressed in Chapter Four.

The sources of neurotoxicity from central nervous system prophylaxis are chemotherapy (specifically, a drug called methotrexate) and cranial radiation therapy (Pui, 2000). These will be discussed in detail in Chapter Two. The most commonly used psychological index of neurotoxicity has been the Intelligent Quotient (IQ) score (Pui, 2000). Early studies reported that although the mean IQ scores for the long-term survivors of ALL were within one standard deviation of the mean (85 to 115), there were clinically significant differences in IQ between the survivors and control groups that included: their siblings, healthy age-matched controls, and non-central nervous system treated cancer control groups. Studies that have reported significant decreases in IQ as a result of central nervous system prophylaxis have also shown decreases in tests of academic achievement (e.g., Mulhern et al., 1991; Ochs et al., 1991). The question of whether IQ declines could be secondary to one or more central processing deficits involving short-term and/or working memory, has been, and continues to be, investigated (e.g., Mulhern, Wasserman, Fairclough & Ochs, 1988).

Research by Lesnik, Ciesielski and their colleagues has revealed evidence that later developing brain structures are more at risk to damage from neurotoxicity. Their research has demonstrated altered development of the dorsolateral prefrontal cortices and posterior vermis of the cerebellum in long-term survivors of ALL, both of which develop later in ontogeny. This together with Petrides' extensive research implicating the dorsolateral prefrontal cortices in working memory is the basis for suspicion that working memory is relatively impaired in these children.

This thesis consisted of three studies. The first study investigated cognitive functioning in a sample of 16 long-term survivors of ALL and two control groups: 11 of

their siblings and 16 long-term survivors of Wilms' tumor (see Appendix A for a description of Wilms' tumor). Long-term survival is defined as being in remission for three or more years. Standardized measures of intelligence and memory were administered to replicate studies of intelligence already conducted with the ALL population and determine the comparability of the current sample to those in the literature. Memory is of interest in this population based on parental reports of learning difficulties in this population. Wilms' tumor was considered the best non-central nervous system treated cancer control group and comparative disease because, next to ALL, it is the largest population of long-term survivors of childhood cancer with a modal age at diagnosis similar to ALL. In addition, the treatment for Wilms' tumor, which occurs in the kidneys, includes aggressive chemotherapy and/or radiation therapy but not to the central nervous system (Waber et al., 1990).

The literature has been inconsistent in its reports of the correlation between neuroradiological anomalies and cognitive sequelae in this population. The second study examined the neuroanatomical integrity of the brain in long-term survivors of ALL only. Cranial Tomography (CT) and Magnetic Resonance Imaging (MRI) scans were obtained and the neuroradiological findings were compared with the results of Study One to investigate the correlation between noted cognitive impairments and structural brain abnormalities.

The third study built on the first study by investigating working memory processes in the three groups. Working memory was assessed using the Self-Ordered Pointing Test (Petrides & Milner, 1982). Although this test is experimental and, as such, has not been normed, it has been validated on monkeys (Petrides, 1994b), adult humans

(Petrides, 1996), and children (Archibald & Kerns, 1999). This measure is based on Petrides' model of working memory (Petrides, 2000b) and was chosen because neuroimaging studies have demonstrated a relationship between this test and mid-dorsolateral prefrontal cortex. Research by Lesnik, Ciesielski, Hart, Benzel, & Sanders (1998) and Ciesielski, Lesnik, Benzel, Hart, & Sanders (1999) demonstrated that later developing brain structures, including the vermis of the cerebellum and the prefrontal cortices, are more at risk to damage from central nervous system prophylaxis. Based on neuroimaging studies that show that neural systems including the cerebellum and dorsolateral prefrontal cortex are involved in cognitive reasoning tasks, it is plausible to suspect that abnormal development of these structures may contribute to the cognitive difficulties reported in long-term survivors of ALL. Given the extensive research linking the dorsolateral prefrontal cortex to working memory, it is reasonable to assess this ability in this population, something that has not been done previously. Chapter Two will discuss the unique problems and sequelae of treatment associated with ALL.

# CHAPTER TWO

## ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

The term 'neoplasm' refers to any new growth of body tissue that is uncontrollable and progressive (Dorland, 1988). Neoplasms can be malignant (i.e., having properties of invasion and metastasis), or they can be benign (i.e., encapsulated; not invasive); the latter being more favorable for recovery (Dorland, 1988). Malignant neoplasms (cancer) are the leading cause of death by disease in children under 15 years of age (Steinherz & Simone, 1998). They rank second only to accidental death in mortality rates for this age group (Neglia & Robison, 1988; Picard & Rourke, 1995). The causative agent for neoplastic growth in the majority of children (and adults) remains unknown (Steinherz & Simone, 1998). The current understanding is that no single agent causes cancer, but it is due to a complex interaction of host, environmental and genetic factors (Mulhern, Phipps, & White, 2004; Steinherz & Simone, 1998).

The leukemias are a subgroup of malignant neoplasms that arise primarily from the hematopoietic (blood-forming) system (McKenna & Baehner, 1991). The acute leukemias are among the most frequent types of neoplasms observed in children (Picard & Rourke, 1995). Of the acute leukemias, which include acute lymphoblastic, acute nonlymphoblastic, and acute myelogenous leukemias, ALL has the highest incidence occurring during childhood, accounting for 70-90% of all acute leukemia cases (Neglia & Robison, 1988). ALL also has the most favorable survival outcome of the acute leukemias and is therefore the most prone to long-term cognitive sequelae (Brown & Madan-Swain, 1993; Frankel, et al., 2001; Hoffman Marymont, 2000; McKenna & Baehner, 1991; Mulhern, Hancock & Fairclough, 1992).

ALL is a disease of both children and adults. The age, sex, and demographic characteristics of ALL reveal a peak incidence in the preschool (2-5 years) age range (Frankel, et al., 2001; Hoffman Marymont, 2000; Neglia & Robison, 1988; Steinherz & Simone, 1998). After the age of five, diagnosis of ALL declines but subsequently begins to rise again in the third decade of life (Brown & Madan-Swain, 1993; Neglia & Robison, 1988). Early signs of ALL may be similar to those of the flu or other common diseases, such as fever that will not go away, feeling weak or tired all the time, aching bones or joints, or swollen lymph nodes. As reported by Pui (2000), common presenting symptoms include: pale skin and weakness (due to anemia), excessive bruising and nosebleeds (due to low blood platelet count), fever and persistent infections (due to low white blood cell count), fatigue, weight loss, bone pain, abdominal pain, and possibly enlargement of the lymph nodes, liver, and spleen. Diagnosis is made on the basis of blood cell counts following an initial blood test. A bone marrow aspiration and biopsy may also be done. Prognosis is dependent on several variables: gender, socioeconomic status (SES), age at diagnosis, initial white blood cell count, and response to treatment. Whereas, all of these variables are associated with survival outcome, only gender, SES, and age at diagnosis have been shown to contribute to the prognosis of long-term cognitive sequelae, and these will be addressed later in this chapter.

Historical Development of Treatment Protocols

Prior to 1948, life expectancy after a diagnosis of ALL was 3 to 6 months. In 1948, Farber, Diamond, Mercer, Sylvester, and Wolff reported that administration of the folic acid antagonist, aminopterin (a chemotherapeutic drug with anticancer cell properties), resulted in remission in approximately 30% (5 out of 16) of their sample of children treated for ALL. Although the remissions induced were temporary, this modest success inspired further research on chemotherapeutic agents. Over the next decade, the beneficial effects of a number of drugs were demonstrated. However, significant improvements in survival rates were not realized until combinations of drugs were implemented in treatment protocols. By the early 1960s, the treatment of ALL involved combining drugs in such a way as to kill the maximum number of leukemic cells while minimizing the suppression of cell proliferation in normal bone marrow (Picard & Rourke, 1995).

With the higher rate of remission induced by treatment, the migration of leukemic blast cells to the central nervous system, specifically the leptomeninges which are a combination of pia and arachnoid layers that cover the brain and spinal cord (Dorland, 1988), had not been anticipated and had gone undetected. This progression of leukemic cells into the central nervous system suggested that the leukemic cells were able to cross the blood brain barrier and find sanctuary there because the chemotherapeutic drugs were not adequately crossing the blood-brain barrier to be able to destroy them (Haaxma-Reiche, 2003). Consequently, over 50% of children experienced their first relapse in the central nervous system approximately four weeks after diagnosis. This relapse signaled the impending onset of a full systemic relapse. Ninety-five percent of the children who

relapsed died (Picard & Rourke, 1995). The proliferation of leukemic blast cells in the leptomeninges therefore emerged as a major limiting factor for disease control because of the high mortality rate associated with central nervous system relapse. To achieve greater survival rates, the addition to the treatment regimen of a form of central nervous system prophylaxis treatment was necessary.

Central nervous system prophylaxis follows specific protocols, which are carefully designed modes of therapy for each specific type of cancer, constructed by medical oncology experts (Waber & Mullenix, 2000). Each protocol is evaluated for safety and effectiveness in achieving long-term remissions or cures. National cooperative studies involving many institutions have led to substantial breakthroughs in treatment development and evaluation (Ferguson Noyes, 1986). Generally, protocols incorporate chemotherapeutic drugs administered orally, intravenously (directly into the blood stream), or intrathecally (via lumbar puncture directly into the fluid surrounding the brain and spinal cord), with or without 1800 to 2400 rads of cranial radiation therapy (Waber & Mullenix, 2000).

The first successful treatment protocols were standardized and did not vary among children. In order to maximize effectiveness, current protocols are more individualized, involving careful assignment of children to leukemic risk groups based on age and leukocyte (white blood cell) count. The National Cancer Institute and the Cancer Therapy Evaluation Program's consensus categorizes children 1 to 9 years of age with a leukocyte count less than 50 x $10^9$/liter of blood as "standard-risk" (Waber & Mullenix, 2000). The standard-risk category is comprised of nearly two-thirds of children with ALL. Adolescents, infants under one year, and children with a high leukocyte count or

certain genetic markers, are considered "high risk". Children classified as high-risk receive more intensive treatment (Eiser & Tillman, 2001). The present project focuses on long-term survivors of ALL treated under the Dana-Farber Cancer Institute/Children's Hospital Consortium Protocols. Unfortunately, information regarding their disease risk level was unobtainable. Details of their treatment protocol are outlined in Appendix B.

Treatment protocols are continually being developed and modified according to effectiveness and toxicity. The ultimate goal of protocol development is to maximize treatment efficacy while minimizing toxicity (Waber & Mullenix, 2000). As oncologists evaluate risks and benefits associated with specific treatment protocols, they need to know how outcomes are affected by variations in intensity and components of treatment. Many years of follow-up are required to answer these questions. Extended follow-up periods are needed because of the long-term evolution of actual neurotoxic effects as well as the possibility that some sequelae may emerge only later in response to developmentally relevant challenges, such as the increased complexity of information processing and abstract reasoning demanded of older children (Waber & Mullenix, 2000). Because of the learning problems frequently found in this population, psychologists are important contributors to this follow-up and to the development and evaluation of ALL treatment programs.

Stages of Treatment

The treatment of ALL today is aimed at survival by total eradication of the disease (no relapse or metastases). A child diagnosed with ALL now has a 95% chance of achieving remission, and in excess of a 50% chance of remaining in complete continuous remission for at least 5 years (Hoffman Marymont, 2000; Picard & Rourke, 1995). ALL is unique among the leukemias in that it requires prolonged continuation treatment to sustain remission. Studies have indicated that a minimum treatment time of 24 months is required to sustain remission, with no further benefit apparent when treatment is extended beyond 3 years (Picard & Rourke, 1995). Therefore, the average length of treatment for ALL is 36 months (Pui & Crist, 1995).

Approaches to the treatment of ALL may vary somewhat between treatment centers, but all modern treatment protocols consistently emphasize remission induction followed by consolidation (sometimes called intensification) therapy to eliminate any remaining leukemic cells. These phases of treatment are followed by a maintenance phase to ensure continuation of remission (Picard & Rourke, 1995; Pui & Crist, 1995). Central nervous system prophylaxis is typically started after remission induction (at 4 weeks after diagnosis) and continues throughout consolidation and maintenance therapy. These three phases of treatment will be discussed in more detail in the following section. Central nervous system prophylaxis will be discussed last due to its particular relevance to this thesis.

*Remission Induction*

Remission induction begins immediately after diagnosis and lasts until continuous complete remission is achieved. Thus, the goal of remission induction is to rapidly

induce a complete remission, generally defined as the restoration of normal bone marrow, by directly destroying cancer cells (Pui & Crist, 1995). This stage of treatment typically includes administration of a glucocorticoid (dexamethasone or prednisone) and vincristine. Since 1963, the administration of vincristine and prednisone to induce remission has been the standard against which the effects of all other chemotherapeutic agents are compared (Picard & Rourke, 1995). The attainment of complete remission, following the administration of this combination of drugs, occurs in 97 to 99% of children. The glucocorticoids are used in treating ALL because they have a direct cytolytic effect (cell destroying) against cancerous cells, particularly when combined with an alkaloid such as vincristine, which binds to tubulin and prevents microtubule formation, thereby arresting cells in metaphase (Wen, 2003). Other active chemotherapeutic drugs are often added to the remission induction regimen to further improve the remission rate. The children in the current study received prednisone, vincristine, L-asparaginase, and daunorubicin. L-asparaginase inhibits protein synthesis in cancerous cells dependent on the essential amino acid, asparagine (Wen, 2003). Daunorubicin is an antibiotic also used to destroy cancer cells (Dorland, 1988; Wen, 2003).

When induction fails it is usually due to primary drug resistance or toxicity. A higher rate of relapse, and potentially shorter survival, is correlated with an increase in time necessary to induce remission and with treatment resistance (Pui et al., 1992). Those patients who do not go into remission at the end of the usual induction period (4 weeks) are offered the option of bone marrow (allogeneic hematopoietic stem cell) transplantation at the end of an extended remission induction period of approximately 2-4

weeks (Pui & Crist, 1995). Notably, remission does not mean complete eradication of the leukemic blast cells, rather it means that the small number of cells remaining cannot be detected by modern day instruments (Picard & Rourke, 1995).

*Intensification/Consolidation and ReInduction Therapy*

When complete remission is achieved, patients still harbor as many as $1 \times 10^{10}$ leukemic cells in their body (Pui & Crist, 1995). Therefore, most protocols include an early consolidation (sometimes called intensification) phase to further ensure remission. Intensive chemotherapy is reintroduced, using the same drugs from the remission induction, to further reduce the number of leukemic cells (Frankel et al., 2001). This phase of treatment is typically administered from the $16^{th}$ to the $20^{th}$ week after beginning therapy (Pui & Crist, 1995). Children in the current study were administered the same four drugs as used during the remission induction phase.

*Continuation/Maintenance Treatment*

It has been well established that continued therapy prolongs the period of remission (Picard & Rourke, 1995). In order to ensure continuation of remission, the child receives 6-mercaptopurine and weekly administration of systemic methotrexate (Frankel, et al., 2001). These drugs are said to have fewer side effects, making them more suitable for the long-term use required during this phase of treatment (Picard & Rourke, 1995). Continuation treatment typically lasts from the end of consolidation up to 36 months post-diagnosis (Pui & Crist, 1995). Children in the current study were given prednisone, vincristine, oral methotrexate, and 6-mercaptopurine during maintenance treatment. 6-mercaptopurine is a purine derivative that is used for its anticancer cell

properties (Dorland, 1988). Methotrexate will be discussed in the next section due to its particular relevance to this thesis.

*Central Nervous System Prophylaxis*

Of the medical innovations responsible for increased survival of children treated for ALL, it is widely agreed that the addition of central nervous system prophylaxis to treatment has had the greatest impact on remission and long-term survival (Picard & Rourke, 1995). To reiterate, central nervous system prophylaxis refers to treatment given for the sole purpose of preventing the development of a secondary cancer in the central nervous system. One of the earliest regimens used for central nervous system prophylaxis consisted of 2400 rads of cranial radiation administered concurrently with five 12mg/m$^2$ doses of lumbar intrathecal injections of methotrexate soon after patients entered remission. This regimen was shown to reduce the incidence of central nervous system relapse from approximately 90% to 10% (Aur, Simone, Hustu & Verzosa, 1972) and this combination and dosage remained the "gold standard" for some time (Haaxma-Reiche, 2003). However, reports of neurotoxicity from radiation in the developing brain created controversy. Consequently, some centers reduced the dose of cranial radiation therapy from 2400 rads to 1800 rads (Eiser & Tillman, 2001). In some cases (e.g., Bleyer, 1988) cranial radiation therapy was completely removed from standard-risk protocols due to reports that the synergistic effect of cranial radiation combined with chemotherapy (specifically methotrexate) was even more neurotoxic. This was due to the possibility that the methotrexate enhanced the effect of the cranial radiation (Waber & Mullenix, 2000).

*Cranial Radiation Therapy.* The term "radiation" refers to the process of emitting radiant energy in the form of waves or particles. The unit of radiation (or "dose") is called the rad or centiGray (cGy). One rad equals one cGy (Halperin, 1986). Radiation oncologists use high-energy electromagnetic radiation or high-speed particles, generated by machine, to injure cells (Greenberg, 1998). When radiation interacts with living tissue, direct action of the radiation on critical sites in targeted cells, i.e., the cell's chromosomes, membrane, or intracellular organelles, is probable. This direct action ionizes (raises to an excited state) the cell and sets off a chain of reactions that may lead to biologic change (Halperin, 1986). Radiation most commonly acts indirectly through its action on water. By its interaction with a water molecule, radiation produces highly reactive free radicals that damage the DNA double helix producing biologic changes. These biologic changes include single strand chromosome breaks, double strand chromosome breaks, and damage to the pyrimidine bases of the DNA. These events result in cell death and the inability for a cell to reproduce (Greenberg, 1998; Halperin, 1986).

The goal of cranial radiation therapy is to target cancerous cells and stop them from reproducing. However, a caveat to this is that healthy cells are also destroyed and the physician must strike a balance between killing cancerous cells while destroying the least amount of healthy cells possible. The dose of radiation tolerated by an organ or structure cannot be characterized as an absolute number but is associated with a certain probability of a radiation-induced complication. This concept is referred to as the minimal tissue tolerance dose, which is that dose of radiation associated with a 5% rate of complications (e.g., cognitive late effects) occurring within 5 years of treatment. The

tissue tolerance dose for the brain is reported to be between 5000 and 6000 rads, cumulatively (Halperin, 1986). The standard cranial radiation dose in ALL therapy is 1800 to 2400 rads.

*Chemotherapy*. The modern age of cancer chemotherapy began during the 1940s when patients with prostate cancer benefited from the administration of estrogens (Ferguson Noyes, 1986). Numerous other effective chemotherapeutic agents were discovered in the 1950s. Chemotherapeutic drugs, developed and researched by pharmaceutical companies and affiliated universities and/or research institutes, are commonly classified by their cell cycle activity and presumed mechanism of action (Knobf, Fasacreta, Valentine, & McCorkle, 1998). The life cycle of a proliferating cell is divided into four phases: the mitotic (cell division) phase, gap 1, the DNA synthetic phase, and gap 2. During the DNA synthetic phase, the cell grows by synthesizing proteins. During the mitotic phase, the cell divides to make two cells. Gaps 1 and 2 are considered to be resting states of the cell (Ferguson Noyes, 1986). The main difference between normal cells and cancer cells is that cancer cells have fewer restraints on their growth (Ferguson Noyes, 1986). Chemotherapy for ALL typically consists of methotrexate, administered intrathecally (directly into the spinal canal via lumbar puncture) and/or intravenously, alone or in combination with cytosine arabinoside, hydrocortisone, and systemic steroids (Moleski, 2000). Methotrexate is used in the treatment of a wide range of cancers, including ALL. It is a dihydrofolate reductase inhibitor. It acts during the DNA synthetic phase of the cell cycle by preventing the conversion of folic acid to tetrahydrofolate, required for purine and thymidine (two types of amino acids) synthesis (Wen, 2003). Early clinical trials established that methotrexate

was the single most effective agent in continuation therapy compared to other chemotherapeutic agents (Ochs, Parvey & Mulhern, 1986). Although it crosses the blood brain barrier relatively poorly, significant central nervous system concentrations can be achieved when the drug is administered intrathecally or when high intravenous doses are used. The clinical expression of its neurotoxicity is determined by the dosage, its route of administration, and the use of other therapeutic modalities with overlapping neurotoxicities such as cranial radiation therapy (Wen, 2003). Lower dosage, intravenous administration, and no concurrent cranial radiation therapy results in fewer short- and long-term sequelae.

*Cranial Radiation Therapy and Chemotherapy Combined Treatment.* The term "radiosensitization" refers to the application of an agent that, when given concomitantly with ionizing radiation, increases the lethal effects of ionizing radiation. Oxygen was one of the first agents to be identified as producing this effect when combined with radiation (Bonner, 2000). Subsequently, many oxygen mimetics evolved into chemotherapeutic agents. In the early days of ALL treatment, chemotherapy was added to cranial radiation therapy with the intention of enhancing the oxidizing capacity of radiation, which would led to cell death. Considerable investigations were carried out to develop pharmacologic agents (such as methotrexate) that might mimic the radiosensitizing properties of oxygen while displaying a better diffusion capacity into potentially anoxic tissue compared with the diffusion of oxygen (Bonner, 2000).

There is a synergistic interaction of cranial radiation therapy with intrathecal methotrexate that may result in greater deficits in those children who received both as compared with those who received only one or the other (Bleyer, 1988). The interaction

of cranial radiation therapy and chemotherapeutic agents is still being investigated to discover those that may be more lethal to cancer cells, but still have an acceptable level of toxicity with respect to normal cells (Bonner, 2000).

## Late-Delayed Complications of Cranial Radiation and Chemotherapy

Physicians categorize sequelae according to the date of onset after administration: acute complications occur within days to weeks; early-delayed complications occur within about 1-6 months; and, late-delayed complications follow prophylaxis by more than 6 months but can be delayed by many years after successful completion of medical therapy (Behin & Delattre, 2003). While the acute and early-delayed effects are transient, the late-delayed effects are generally chronic, if not progressive (Pui, 2000), and are the focus of this thesis. A detailed review of the late effects literature is presented in Chapter Three. There is no literature indicating that the transient acute and early-delayed effects contribute to the nature of the late-delayed effects.

### *Leukoencephalopathy*

Common to both cranial radiation therapy and chemotherapy, leukoencephalopathy is the most frequently reported medical complication associated with central nervous system prophylaxis in long-term survivors of ALL. Leukoencephalopathy affects the white matter in both hemispheres of the brain as well as the areas of the cerebrum that surround the ventricles. It is believed to represent myelin degeneration (Stehbens et al., 1991).

Several predisposing factors put some children at greater risk for leukoencephalopathy, including younger age at cranial radiation, higher radiation dose,

greater radiation volume, and combined treatment with chemotherapy (Behin & Delattre, 2003). The leukoencephalopathy usually occurs following repeated administration of intrathecal methotrexate or high-dose intravenous methotrexate, but has also been described after standard-dose intravenous methotrexate. Although this syndrome may be produced by methotrexate alone, it is exacerbated by cranial radiation therapy, especially if it is administered before or during methotrexate therapy. It is possible that cranial radiation therapy either potentiates the toxic effects of methotrexate or disrupts the blood-brain barrier, allowing higher concentrations of methotrexate to reach the brain (Wen, 2003).

As stated previously, the characteristic sign of leukoencephalopathy is the gradual development of cognitive impairment months into treatment or years after treatment. Deficits range from mild learning disabilities to severe progressive cognitive decline, together with somnolence, seizures, ataxia, and hemiparesis (Wen, 2003). Some children treated with intrathecal methotrexate and cranial radiation therapies, or intermediate and high-dose methotrexate alone, have shown a deterioration of IQ more than 15 points (Montour-Proulx et al., 2004). Leukoencephalopathy on neuroradiological scans presents as cerebral atrophy and diffuse white matter lesions. Cerebral spinal fluid may show increased myelin basic protein concentration as a result of myelin breakdown (Wen, 2003). Pathologic lesions at autopsy range from loss of oligodendrocytes and gliosis to a necrotizing leukoencephalopathy (Price & Jamieson, 1975). There is demyelination, axonal swelling, dystrophic mineralization of axonal debris, and fibrinoid necrosis of small blood vessels. Occasionally, children may have a mineralizing microangiopathy, characterized by calcification of capillaries and venules, especially in the basal ganglia.

The clinical course is variable. Many patients stabilize, but the course is progressive in some patients and leads to death. No effective treatment is available. The cause of leukoencephalopathy is unknown. Possibilities include injury to cerebral vascular endothelium increasing blood brain barrier permeability, depletion of reduced folates in the brain, inhibition of cerebral glucose or protein metabolism, inhibition of catecholamine synthesis, or disturbance of myelin metabolism (Wen, 2003).

*Mineralizing Microangiopathy*

Primarily a result of cranial radiation therapy, mineralizing microangiopathy is characterized by the presence of focal central nervous system calcifications of the blood vessels in the gray matter, originating in the putamen (basal ganglia) and later in the anastomotic border zones of the cortex (Price & Birdwell, 1978). Mineralizing microangiopathy involves the degeneration of the microvasculature, along with dystrophic calcifications of adjacent areas. These lesions may not manifest for several months to years following radiation (Stehbens et al., 1991). Clinical findings reported most often include memory deficits, learning disorders, declines in IQ scores, and behavioural difficulties. Children younger than 10 years of age at the time of diagnosis are especially susceptible, as well as children treated for relapses that receive additional cranial radiation therapy and systemic chemotherapy (Stehbens et al., 1991).

In summary, the treatment of ALL involves the administration of multiple drugs that adversely affect the central nervous system. Radiation and intrathecal methotrexate have both been implicated as major causes of chronic central nervous system damage among these children. The possibility that methotrexate administered intravenously and/or the chemotherapeutic administration of steroids during remission induction may

contribute in some way to the observed damage to the central nervous system has also been reported (Waber et al., 2000; Waber & Mullenix, 2000).

In the next chapter, literature is reviewed that reports on how this damage is manifested in the cognitive domains of intelligence, academics, and memory.

# CHAPTER THREE

## Study One

## Global Intelligence and Memory in Long-term Survivors of ALL

## INTRODUCTION

Nine review papers have been found, since 1985, summarizing adverse cognitive effects associated with treatment protocols for ALL (e.g. Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Gamis & Nesbit, 1991; Johnston, 1985; Madan-Swain & Brown, 1991; Montour-Proulx, et al., 2004; Picard & Rourke, 1995; Robaey et al., 2000; Williams & Davis, 1986). The nature and severity of these cognitive sequelae, and whether or not they may be associated with exposure to cranial radiation therapy, intrathecal methotrexate, or a combination of the two, remain a source of debate. Mulhern et al. (1992), in his review of methodological issues impacting research in this area, cites several issues that could contribute to the discrepancies in the literature. These will be outlined first, beginning with choice of sample participants.

### Methodological Issues in Research on Late Effects of Central Nervous System Prophylaxis

Sources of error can limit the generalizability of experimental findings. Mulhern et al. (1992) reported that design issues that were difficult to control or whose impact was not yet realized, plagued many of the earlier studies investigating cognitive development in survivors of ALL. The single most important source of error, common to all clinical studies, is sampling bias due to the participant selection criteria (Mulhern et al., 1992;

Waber & Mullenix, 2000). Ideally, in this research, the preferred method is to enroll the entire eligible cohort or to randomly select from eligible patients. The selection of study participants is further influenced by the nature of the clinical study. For example, most studies can be roughly divided into those that formally evaluate a treatment protocol as part of a prospective research program and those that prospectively or retrospectively evaluate a group of leukemic patients as part of their ongoing clinical treatment (Mulhern et al., 1992). The prospective research programs use consecutive admissions or random samples of consecutive admissions. This is the preferred method, whereas, the latter studies collect their test data from children who are available for assessment or from clinical records of leukemic children who had been previously referred to the psychology service for clinical evaluation. Children chosen by this method are often select groupings who are examined because they are having learning or behaviour problems. Consequently, children with significant problems may be overrepresented among those referred or volunteering for participation (Mulhern et al., 1992; Williams & Davis, 1986). Conversely, most cognitive studies of childhood ALL to date have focussed on children in continuous complete remission. As a result, more severe forms of ALL may be underrepresented in most samples (Waber & Mullenix, 2000; Williams & Davis, 1986). Reviews of the literature should note these procedures to better address any result biases created by the method and criteria of sample selection.

Documenting the reasons that otherwise eligible patients did not participate is necessary so that exclusionary criteria can be compared between studies (Mulhern et al., 1992). Mulhern and his colleagues recommended the exclusion of the following patients from studies of long-term survivors of ALL: patients with premorbid or congenital

neurodevelopmental disorders; patients with central nervous system leukemia at the time of diagnosis; and patients with any form of relapse. Premorbid conditions and central nervous system leukemia directly impact the brain independent of prophylactic treatment. Relapse results in the need for much more intensive treatment that greatly increases the probability of neurotoxicity and subsequent long-term cognitive sequelae. While these children can be studied in and of themselves, combining them with children who do not have these complications creates much greater variability within a group and may result in a loss of statistical power. Furthermore, it is a violation of the fundamental assumption in cross-sectional studies, that the treatment group was equivalent to the control groups prior to therapy (Mulhern et al., 1992).

Another important design issue is whether or not external controls or comparison groups are needed, and if so, what their composition should be. Certainly, leaving one group of children with ALL untreated is not ethical. Control for the debilitating effects of prolonged, aversive treatment for life-threatening illness can be achieved using non-central nervous system cancer control groups, e.g., solid tumors such as Wilms' tumor, Ewing's sarcoma, and Hodgkin's lymphoma. None of these groups receive central nervous system treatment of any kind. Most receive systemic chemotherapy, surgery, and/or radiation (Williams & Davis, 1986). Alternatively, patients may also serve as their own controls in longitudinal studies that provide for serial evaluations over time. If the tests are corrected for normally expected improvements in performance with increasing age, as are standardized IQ tests (i.e., Wechsler scales), this provides a powerful method for evaluating neuropsychological changes. The most frequently used control subjects comprise nonclinical comparison groups, such as siblings or age and SES

matched schoolmates. The investigator usually assumes that the study group patients were not generally different from peers or siblings prior to treatment. Observed neuropsychological differences between groups suggest that the study group has changed from premorbid status, assuming that the untreated comparison group remains stable over time and undergoes normal development (Mulhern et al., 1992).

One of the strongest experimental designs used in the literature involves comparing long-term survivors to children who are newly diagnosed with ALL, using standardized cognitive tests. This design has revealed that compromised neuropsychological functioning may not be evident within the first few years of treatment, but can emerge years later (Brown et al., 1992a; Brown et al., 1992b; Copeland et al., 1988; Goff et al., 1980; Jannoun & Chessells, 1987; Moss, Nannis, & Poplack, 1981; Stehbens & Kisker, 1984). Alternatively, researchers have also used a longitudinal design to compare children when they are first diagnosed to when they have been off treatment for three or more years. For example, two studies published by Ochs et al. (1991), and Ochs and Mulhern (1992), compared children with ALL at the beginning of treatment and again three or more years after treatment. There were two treatment groups. One received 1800 rads of cranial radiation therapy plus intrathecal methotrexate. The other group received intrathecal methotrexate only. No differences were observed between the two treatment groups. However, when scores were compared from the beginning of treatment to three or more years post-treatment, decreases in IQ were observed in both groups. Both Full Scale IQ and Verbal IQ (but not Performance IQ) decreased significantly between these two time points. Five children in each group (22% and 19%, respectively) had decreases in Full Scale IQ greater than or equal to 15

points (1 standard deviation). This is a clinically significant decline. Despite the decrease, the mean IQ score was in the Average range. Nevertheless, this result is highly relevant to those studies that do not reveal between-group differences because it suggests that deterioration may have still occurred over time.

In summary, it is important, when reviewing the literature, to understand how the participants were selected, what the study design is and how it influenced that selection, what the participant exclusionary criteria were, and the composition of the control groups. Consecutive admissions or random samples of consecutive admissions are the preferred method of participant selection.

## Prognostic Variables in Long-Term Cognitive Sequelae

As mentioned previously, age at diagnosis, gender, and SES can influence the cognitive outcome of ALL treatment in the long term. These are three of several prognostic variables that have been demonstrated to influence the cognitive outcome of treatment in the ALL population. Only more recently have researchers begun to control for these and other variables that should be considered in determining the effects of treatment, ultimately for the prevention of neurotoxicity. These variables include, in addition to age at diagnosis, gender, and socioeconomic status: school absenteeism and time since treatment completion.

*Gender.* The importance of gender as a prognostic variable both in terms of survival and long-term cognitive sequelae has been frequently demonstrated (e.g., Robison et al., 1984; Schlieper, Esseltine, & Tarshis, 1989; Waber et al., 1990). While there is a predominance of ALL in males that is consistent across racial and geographic

boundaries, females are more susceptible to the cognitive deficits of treatment (Bleyer, 1995; Brown & Madan-Swain, 1993; Gaynon, Trigg & Uckin, 2000; Neglia & Robison, 1988; Picard & Rourke, 1995; Sather, Miller, Nesbit, Heyn, & Hammond, 1981; Waber & Mullenix, 2000). Although Waber et al. suggest a biological etiology, the mechanisms behind these gender differences are not yet clear and no formal theories have been advanced (Pui, 2000).

Waber and her colleagues have published several studies reporting on the significant gender differences of cognitive sequelae two or more years after treatment for ALL. Research reporting on the late effects of three separate treatment protocols involving children treated at the Dana-Farber Institute between 1973 and 1991, revealed that females exhibit greater vulnerability with respect to global cognitive functioning compared to males. This is based on the results of a test battery comprised of the Wechsler Intelligence Tests and standardized tests of academic achievement administered to long-term survivors across 10 institutions in North America. Waber et al. (2000) reported that a global deficit of this type is consistent with damage to white matter. Further, this global deficit results from a synergistic interaction of methotrexate and cranial radiation therapy, which affects females disproportionately. That is to say, the females in the sample are more likely to have lower global intelligence scores compared to males due to their differential vulnerability to the synergistic effects of cranial radiation and methotrexate treatment. Waber and Mullenix hypothesized that an increase in the dose of either agent will potentiate the toxicity of the combination. Consequently, the male to female ratio in a given sample must be considered when analyzing and interpreting the data.

*Socioeconomic Status (SES).* In their epidemiological report of childhood ALL, Neglia and Robison (1988) noted that SES could reflect both environmental and genetic influences, including factors such as race, maternal age, parental education, and occupational exposures to toxic substances. This makes it difficult to directly assess a single SES factor. They further reported that a higher SES was associated with increased risk of ALL in children. Although not consistent, this result has proven to be reproducible. In fact, ALL (moreso than other cancers) has been referred to as a disease of the middle and upper middle classes. It is not certain why this is the case. Despite this uncertainty, SES should be controlled for in studies of ALL due to the genetic and environmental factors that can independently effect cognitive development.

*Age at Diagnosis.* Age at diagnosis is a critical variable in predicting long-term cognitive sequelae of ALL. Research on ALL since the 1970s has indicated that complications of central nervous system prophylaxis are most pronounced under three conditions (Picard & Rourke, 1995): 1) when prophylaxis involves the administration of high doses of cranial radiation therapy and intrathecal methotrexate; 2) when radiation is directed toward the entire craniospinal axis (note that radiation is rarely directed toward the entire craniospinal axis in children with ALL); and, 3) when cranial radiation therapy is administered at younger ages (before age 4 to 5 years).

Younger age at diagnosis has been consistently linked with lower IQ scores. Balsom et al. (1987) reported an approximate 20 point mean IQ difference between groups when survivors who were 4-years-old or younger at treatment were compared to survivors older than 4 years. Ochs and Mulhern (1992) also reported that treatment with intrathecal methotrexate when less than four years of age was associated with decreased

Full Scale IQ. This finding is supported by studies that do not report significantly lower IQ scores when only children diagnosed after the age of five are assessed (e.g., Schuler et al., 1990). However, this is not always demonstrated (e.g., Ochs, Berg, Ch'ien, Coburn, & Parvey, 1982). In such cases, the gender distribution of the clinical sample, as well as the presence of structural abnormalities on neuroradiological scans, may influence the findings.

*School Absenteeism.* Given the high number of days missed in school due to their illness, it is possible that healthy siblings perform better on standardized tests simply because their learning has been uninterrupted. This question can be addressed in two ways. First, the number of school days missed by each participant with ALL can be added to the analysis as a control variable. Second, employing a non-central nervous system cancer comparison group with a comparable age at diagnosis controls for this possible confound because their attendance will also have been interrupted by illness and treatment. However, studies that compared long-term survivors of ALL with long-term survivors of non-central nervous system cancer have consistently demonstrated lower IQ scores in the long-term survivors of ALL, suggesting that factors other than school absenteeism are contributing to lowered IQ.

*Time Since Treatment.* An important factor that needs to be controlled for, as well as systematically studied for poor cognitive outcome following central nervous system prophylaxis, is the amount of time elapsed since completion of central nervous system treatment (Mulhern, et al., 1992). The importance of time since treatment as an independent variable was recognized as early on as the 1970s. An early, and frequently cited, publication is Soni et al. (1975). This protocol driven study addressed the question

of whether children whose central nervous system treatment included cranial radiation therapy experience more intellectual impairment than those who did not receive cranial radiation therapy do. They reported two studies in this paper: a prospective study and a retrospective study. Each used a different sample. In the prospective study, 14 children with ALL were randomly assigned to one of two groups that received either 2400 rads of cranial radiation therapy alone or in combination with intrathecal methotrexate. They were compared to 19 children who had received radiation therapy to parts of the body other than the central nervous system (Wilms' tumor, Ewing's sarcoma, and Hodgkin's disease). A test of general intelligence was administered and repeated at four points in time: during induction (pre-cranial radiation therapy baseline), immediately after cranial radiation therapy (2.5 weeks for children receiving cranial radiation therapy and intrathecal methotrexate; 4 weeks for children receiving cranial radiation therapy alone), 6 months post-cranial radiation therapy and 18 months post-cranial radiation therapy. No significant differences in IQ scores were found between the children with ALL and the controls at any point in time. Furthermore, there were no significant changes over time in the IQ scores for either group. Based on this prospective work, we would conclude that there were no adverse effects of central nervous system prophylaxis. Furthermore, cranial radiation therapy did not appear to produce any ill effects.

In the retrospective study, 11 children with ALL, who had received 2400 cGy of cranial radiation therapy (without chemotherapy), were compared to a group of children with an unspecified form of cancer who had received no central nervous system treatment, but similar systemic chemotherapy. The ALL children had been off treatment for an average of 2 years at the time of the initial testing. Intelligence was again assessed

and re-tested 6 and 18 months after initial testing. As with the prospective study, no significant differences were found between the two groups, and there were no significant changes in IQ over time. This again suggested no adverse effects could be attributed to central nervous system prophylaxis, even when it included cranial radiation therapy. It was not known at the time that the effects of cranial radiation therapy on cognitive functioning are often delayed and generally become apparent only 3-5 years after treatment has been terminated. Even without this knowledge, Soni and her colleagues cautioned that not enough time may have passed since the end of treatment to really measure the long-term effects of treatment (Packer, Meadows, Rorke, Goldwein & D'Angio, 1987). Thus, the time since treatment interval was not long enough to detect late effects.

In a follow-up study Goff et al. (1980) re-evaluated Soni et al.'s (1975) subjects 3-6 years after treatment termination and compared them to a group of children with newly diagnosed, yet untreated, ALL. The long-term survivors achieved significantly lower IQ scores than the newly diagnosed children. Notably, the samples in this study included children who had relapsed and had complications due to treatment, such as seizures. Modern day studies would exclude these children. Nevertheless, these results suggested that there could be a decline in cognitive level in a group of children 3-6 years post-treatment who had not shown any deficits on the same intellectual measure at 18 months post-treatment.

This issue is far from being closed. However, the illness and its complications often preclude the consistent timing of assessment resulting in children being tested at widely different points in their treatment and recovery. This makes comparison difficult.

Studies conducted in the 1980s often did not consider this variable and used a criterion for continuous complete remission periods that ranged from months to years post diagnosis or treatment (Williams & Davis, 1986). Therefore, it should come as no surprise that studies in which the samples of patients were assessed at different points after central nervous system treatment are divided with respect to their conclusions. For example, Lansky et al. (1984), Taylor, Albo, Phebus, Sachs, & Bierl (1987), and Said, Waters, Cousens, & Stevens (1989) all employed longitudinal designs and reported adverse effects associated with central nervous system therapy. However, Harten et al. (1984), and Trautman et al. (1988) reported no adverse effects. Times since treatment in these studies ranged from as little as nine months post central nervous system therapy to as much as thirteen years post-therapy.

Late Effects of Central Nervous System Prophylaxis: Review of the Literature

Cognitive manifestations of neurotoxicity may not be expressed until years after the completion of treatment (Packer et al., 1987). These delayed manifestations (late effects) are generally of more practical and long-term significance for survivors than are the immediate and often transient effects (Moore, Packer, Karl, & Bleyer, 1994). Despite variance in methodology, studies have accumulated (Ochs et al., 1991; Ochs & Mulhern, 1992; Waber et al., 2001; Waber et al., 1995) that provide convincing evidence that many long-term survivors of ALL experience persistent cognitive deficits in a number of domains. What remain to be resolved are the precise characteristics of the prophylactic treatment and the extent to which each treatment results in neurotoxicity. Researchers

continue to investigate and determine the treatment protocol that will result in a high survival rate with a low neurotoxicity rate.

The present review will focus on intellectual, academic, and memory skills in long-term survivors of ALL who are at minimum, two years post-treatment. Although most researchers define long-term survival as being off treatment for three or more years, a recent study (Mulhern et al., 2004) suggested that the effects of intrathecal methotrexate can manifest sooner. Therefore, to be conservative, a cut-off of two years off treatment was used in the present review.

*Global Intelligence*

Early investigations into the cognitive outcome of long-term survivors of ALL relied primarily on measures of intelligence. Measures of intelligence were chosen because of their long history of determining a child's potential for success in the classroom (Eiser & Tillman, 2001). A critique of the concept of intelligence, and a review of how it develops in children, is beyond the scope of this thesis. Readers are referred to Flanagan and Ortiz (2001) for an excellent review of current theories.

The most commonly used measures of intelligence are the Wechsler Intelligence Scales. The Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III; Wechsler, 1996) was designed for use with children 6 to 16 years of age. Children aged 2 years 6 months to 7 years 3 months are administered the Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III; Wechsler, 2002). The Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III; Wechsler, 1997a) is designed for use with individuals 16 years of age or older.

Most studies in the literature use the Wechsler scales of intelligence. Therefore, for consistency, the literature review on intelligence in survivors of ALL will focus on those studies that used the Wechsler scales. The Wechsler IQ tests typically yield one overall composite score, the Full Scale IQ. This is typically derived from two overall scores: the Verbal IQ and the Performance (Nonverbal) IQ. Scores between 90 and 109 are classified in the Average range. Scores between 80 and 89 are classified Low Average, and scores between 110 and 119 are classified High Average. The Wechsler tests have been standardized so that the mean score is 100 with a standard deviation of 15. Scores within one standard deviation of the mean (i.e., 85 to 115) are achieved by 68% of the normal population, and are considered as statistically average.

As a group, long-term survivors of ALL typically have mean Full Scale IQ, Verbal IQ, and Performance IQ scores that are within one standard deviation of the normative Average, which falls between 85 and 115, inclusive (e.g., Bakke, Fossen & Storm-Mathiesen, 1993; Brown et al., 1998; Giralt et al., 1992; Goff et al., 1980; Kingma et al., 2001; Langer et al., 2002; Moore, Kramer, Wara, Halberg, & Ablin, 1991; Ochs, Berg, Ch'ien, Coburn, & Parvey, 1982; Ochs & Mulhern, 1992; Pfefferbaum-Levine et al., 1984; Precourt et al., 2002; Schuler et al., 1990). Further, the distributions of IQ scores in such samples are normal, indicating that outliers are not driving the mean. These findings have been reported across varying treatment protocols. However, when the long-term survivors of ALL are compared to their pre-disease levels, to their healthy siblings, and to long-term survivors of cancer in which neither the disease nor the treatment involved the central nervous system, it becomes clear that many of them either decline over time in their cognitive abilities or stagnate and fail to progress with their

peers (e.g., Eiser, 1980; Meadows et al., 1981; Mulhern et al., 1991; Ochs & Mulhern, 1992; Ochs et al., 1991; Taylor et al., 1987). Regardless, the means are not accurately describing this population of children. That is to say, when the range of scores is examined, it is clear that more ALL children fall significantly below the normative mean than do children in control groups.

Researchers have sought to determine the factors that may contribute to this cognitive decline. The role of cranial radiation therapy was the first factor to be investigated, once it was generally accepted that the children were adversely affected. A meta-analysis by Cousens et al. (1988) concluded that an average IQ decrement of about two-thirds of a standard deviation (i.e., about 10 points) from pre-disease level follows central nervous system prophylaxis. The probability for adverse effects was greater in children whose treatment protocol included cranial radiation therapy.

Cranial radiation therapy was then compared to intrathecal methotrexate. Researchers have consistently reported that children who received 2400 rads of cranial radiation therapy combined with intrathecal methotrexate achieved significantly lower IQ scores compared to control groups and compared to groups who received only intrathecal methotrexate. This was the case even when, as is typical, group means were within one standard deviation of the normative mean (e.g., Pavlovsky et al., 1983; Pfefferbaum-Levine et al., 1984; Schuler et al., 1990; Waber et al., 1990). In response to these reports, physicians reduced the dosage of cranial radiation therapy from 2400 to 1800 rads. Therefore, researchers began investigating the cognitive late effects of central nervous system prophylaxis that included 2400 versus 1800 rads of cranial radiation therapy. Most studies reported that survivors of ALL receiving 2400 rads had lower IQ scores

compared to those who received 1800 rads of cranial radiation therapy. Children who received 1800 rads did not differ significantly from control groups (e.g., Wilms' tumor, siblings, or age and SES matched peers) or from those ALL children who received only intrathecal methotrexate (e.g., Cousens, Ungerer, Crawford & Stevens, 1991; Halberg et al., 1991; Moore et al., 1991). This suggested that the adverse cognitive effects of prophylactic treatment could be accounted for by the cranial radiation therapy. It can be further suggested that IQ decreases as radiation therapy intensity increases.

Not all researchers agreed with this finding, however. Some (e.g., Mulhern et al., 1991) have not found significant differences between children who received 2400 rads versus 1800 rads versus intrathecal methotrexate on measures of intelligence. A closer look at most of these studies indicates that the lack of group differences can be accounted for by confounds in methodology, which are sometimes difficult to control for in clinical research. For example, in Mulhern et al.'s study, 77 long-term survivors of ALL were selected consecutively and randomly assigned to receive one of three prophylactic regimens: 2400 rads of cranial radiation therapy combined with intrathecal methotrexate, 1800 rads of cranial radiation therapy combined with intrathecal methotrexate, and intrathecal methotrexate combined with a high-dose oral methotrexate. Participant selection was appropriate and groups were matched on SES. However, the intrathecal methotrexate group was significantly younger at diagnosis and had less off-treatment time (although a minimum of 2 years had elapsed since treatment in both groups) compared to the other two groups. Also, gender ratios were not reported. Furthermore, the intrathecal methotrexate-only group received additional high-dose oral and parenteral methotrexate.

Halberg et al. (1991) also reported no difference between groups of ALL survivors who had received 2400 rads versus 1800 rads of cranial radiation. In their study, the gender ratio was 1:1 and the groups were equivalent concerning age at diagnosis and time off treatment. However, Halberg et al. reported that, in addition to the different prophylactic regimens, children in the study received differing chemotherapy drugs and doses. The differences were not specified but could certainly have added to the variance between groups.

These two studies reveal some of the complications that make it difficult to discern whether the lack of group differences implied that the treatment did not negatively impact the patients, or whether the lack of group differences were the result of a confound in the methodology, e.g., age at diagnosis and time since treatment, which are critical variables in any study with this population. Also, gender ratio was not reported in Mulhern et al.'s (1991) study. If there were significantly more males than females in Mulhern et al.'s study, this could also account for the lack of group differences because females are reported to be more vulnerable to cognitive late effects of prophylaxis. Furthermore, Halberg et al.'s (1991) study demonstrated that systemic chemotherapy should also be considered when including chemotherapy-only groups as it can also contribute to cognitive late effects. In both of Ochs' studies, the chemotherapy only group received extra methotrexate, administered orally or intravenously, to compensate for not receiving cranial radiation therapy and to ensure survival. Other studies reported no performance differences between treatment groups once the absence of cranial radiation therapy was compensated for by either increased (high-dose) intrathecal methotrexate or the addition of another chemotherapeutic drug to the regimen (e.g., Giralt

et al., 1992). However, it is uncertain whether this is because cranial radiation therapy is the source of cognitive late effects, or whether higher-dose methotrexate results in the same sequelae.

In contrast, two recent studies reported significant group differences in survivors who had received 1800 rads combined with chemotherapy versus chemotherapy-only (Kingma et al., 2001; Langer et al., 2002). In Kingma et al.'s study, three children received a higher dosage of cranial radiation therapy (2500 rads) out of 28 in the group, which could have lowered the overall group mean compared to the chemotherapy only controls. In Langer et al.'s study, group differences could have been accounted for by differences in a variety of disease-related clinical measures (i.e., blood counts). This again illustrates how sensitive the research is to treatment-related variables and how difficult it is to eliminate sources of error variance to uncover unbiased answers to its questions.

Following the observation that high-dose intrathecal methotrexate may result in cognitive deficits that are equivalent to those associated with cranial radiation therapy, researchers began to assess the effect of methotrexate more systematically. Waber et al. (1995) investigated the synergistic effects of cranial radiation therapy combined with intrathecal methotrexate versus a higher dose of intrathecal methotrexate and no cranial radiation in children assigned for treatment based on risk group. Standard-risk was defined as: children between 2 and 9 years of age with a presenting leukocyte count of less than 20,000/$mm^3$, absence of T-cell immunologic markers, no radiologic evidence of a mediastinal mass, no evidence of biphenotypic leukemia, absence of the Philadelphia chromosome [t (9;22)], and no clinical signs or cytologic evidence of CNS leukemia. All

other participants were considered high-risk. Standard-risk children did not receive cranial radiation therapy in this study, whereas high-risk children received 1800 rads (no one received 2400 rads). Children were then randomly assigned to receive high-dose or conventional-dose methotrexate. The WISC-III was administered to all the children. This revealed a Full Scale IQ deficit in females who had received the high-dose methotrexate combined with cranial radiation therapy. Their scores were lower than females, but not males, which had received either dosage or methotrexate without cranial radiation therapy. For the first time, a study reported that it is the synergistic effect of these two treatments that resulted in a decline in IQ and not necessarily just the high dose methotrexate in and of itself.

The selective vulnerability of females to the synergistic effects of cranial radiation therapy and intrathecal methotrexate may explain the finding of Kingma et al. (2001). They reported that children treated with cranial radiation therapy and intrathecal methotrexate performed more poorly on measures of IQ compared to those that did not receive cranial radiation therapy but received high-dose methotrexate. However, there were significantly more females in the group that received cranial radiation therapy, increasing the probability of finding a significant group difference based on gender differences alone.

Thus, the current research suggests that the combination of cranial radiation therapy and intrathecal methotrexate has a synergistic effect resulting in more adverse cognitive sequelae than either treatment alone. The sequence of cranial radiation therapy and intrathecal methotrexate administration may also be important. Balsom et al. (1987) observed mean IQ scores in the Low Average range in a sample of long-term survivors

treated with intrathecal methotrexate and 2400 rads of cranial radiation therapy. There were 53 children assessed 3 to 11 years post-treatment. Twenty-three of the children received intrathecal methotrexate before cranial radiation therapy, and 30 received the intrathecal methotrexate simultaneously with cranial radiation therapy. Those who had received the intrathecal methotrexate before cranial radiation therapy had significantly higher Full Scale IQ, Verbal IQ, and Performance IQ scores post-treatment. Their scores were in the Average range, whereas those who received these two treatments simultaneously had a mean IQ score in the Low Average range. Given that most studies previously reported IQ scores in the Average range, this raises the question of whether most ALL samples received cranial radiation before intrathecal methotrexate. Furthermore, the possibility that the common report of mean group IQ scores in the Average range is in fact a result of the sequence of prophylactic agents and not necessarily representative of the outcome of ALL survivors in general, has significant repercussions.

In summary, a review of this body of research suggests that intelligence typically declines to a mild degree in long-term survivors of ALL. To what extent the effects of systemic chemotherapy and the substitution of high-dose methotrexate for cranial radiation therapy contribute to this decline and whether any of the decline is due to the disease itself continues to be addressed in the literature. However, it is generally accepted at this time that the decline is more likely due to adverse effects of treatment, particularly methotrexate and cranial radiation. The effects appear to be worse when higher doses of cranial radiation and/or methotrexate are administered, and possibly when cranial radiation and methotrexate are administered at the same point in time. Sampling

bias and order of administration of prophylactic agents may also be important but are not often reported in the past or current literature. Age at treatment, gender, SES, and time since treatment are clearly critical variables that should be controlled between groups to increase power so that legitimate differences can be revealed consistently.

*Academic Achievement*

In this section, studies documenting academic achievement in survivors of ALL off treatment for a minimum of 2 years will be reported. Kaplan, Smith, and Grobstein (1974) were the first to document learning difficulties in this population. They observed a pattern of slow learning and decrements in academic achievement. Many subsequent studies reported that approximately 40% of their sample of long-term survivors of ALL required special education services at some point in their academic careers (e.g., Kingma et al., 2001; Kingma, Rammeloo, vander Does-van den Berg, Rekers-Mombarg, & Postma, 2000; Meadows et al., 1981).

Researchers have estimated academic achievement by: standardized testing, by tallying the number of survivors requiring special education services, or by obtaining an estimate of the child's academic achievement either from their school grades or from teacher and/or parent reports via standardized questionnaires. Unfortunately, most studies have not considered school absences and their impact on academic achievement. In some cases, the participants had finished all treatment before beginning kindergarten. However, in many studies this issue was not addressed at all, limiting the generalizability of the study results such that below average academic achievement may not be due solely to prophylaxis but may also result from an unavailability to learn during illness and treatment.

Consistent with reports that the mean intelligence scores for ALL samples fall within one standard deviation of the mean, mean academic achievement scores also fall within this range. It should be noted that wide variability is evident across studies.

Studies that have obtained information about long-term survivors academic achievement through parent and/or teacher standardized questionnaires have all reported significantly lower achievement in this population (Mulhern et al., 1988; Noll et al., 1997; Shelby, Nagle, Barnett-Queen, Quattlebaum, & Wuori, 1998; Williams et al., 1991). Williams et al. constructed a 112-item survey asking parents to rate their child's ability in 8 areas: memory, language, higher cognitive abilities, apraxia, hyperactivity/impulse control, learning behaviour, and academic skills (e.g., math ability). School absences were also obtained. A 5-point likert scale ranging from "(1) not at all like this child" to "(5) extremely like this child" was used to rate the items. The ALL survivors had received 1800 rads of CRT plus IT MTX or chemotherapy-only prophylaxis. The ALL survivors were compared to age, sex, race, and SES matched healthy controls, and to a third group of children who had been diagnosed with a learning disability (average intelligence with a significant weakness in at least one academic skill area).

Results of the survey indicated that significantly more ALL survivors had repeated a grade compared to the control groups. Williams et al. (1991) also reported that survivors of ALL had missed significantly more days of school compared to both control groups. The survivors grade point average (C+ range) was higher than that of the learning disabled group but lower than the healthy controls, albeit it was not indicated as to whether this was a significant difference. With regard to the 8 areas surveyed, the

survivors of ALL rated significantly worse than the healthy controls only on the Academic Skills subscale. Also, they were rated significantly higher than the learning disabled group on all subscales except Academic Skills, on which they did not differ significantly from the learning disabled children. The two ALL treatment groups did not differ significantly in any area. Group profiles revealed wide variability between areas for both the learning disabled and ALL groups, whereas the healthy controls had very little variability among the areas surveyed. These results are consistent with the wide variability of scores revealed by academic testing in the ALL survivor population. More importantly, they indicate that, overall, parents of these survivors do report significant academic difficulties compared to healthy controls.

Williams et al. (1991) were one of the first groups to compare long-term survivors of ALL to children with diagnosed learning disabilities. The most salient result of their study was the similarity of the ALL survivors to the learning disabled children in the areas of Academic Skills. On all other aspects of function surveyed, parents rated their long-term survivor of ALL as similar to controls, but with regard to Academic Skills, they were rated as similar to learning disabled students. Notably, parent-rating biases could not be ruled out as influencing the findings. Nevertheless, Williams et al. interpreted this to indicate that leukemic children have specific deficits in academic skills, while other everyday cognitive abilities are largely intact.

Studies that have used the Child Behavior Checklist (Achenbach, 1991) to survey parents (Hill et al., 1998; Mulhern et al., 1988; Noll et al., 1997; Ochs & Mulhern, 1992; Shelby et al., 1998) have found similar results to Williams et al. (1991). The Child Behavior Checklist is a standardized inventory designed to identify deficits in social

competence and excessive behaviour problems in children and adolescents 4 to 18 years of age. School performance is measured by comparing the child's grades to other children their age (worse, average, or better) for each subject, i.e., math, English, science, social studies, etc., as well as noting whether or not the child receives special education services (yes or no). Each study reported that a significant percentage of the ALL survivor sample had school competence scores that fell in the borderline to clinically significant range compared to normative values. Only one study (Shelby et al., 1998) reported additional elevations on the behavioural scales. This suggests that the academic difficulties do not necessarily occur in the context of psychosocial problems, albeit Hill et al. (1998) report on the impact of academic difficulties on the survivors psychological state and vocational adjustment. None of the studies reported any significant effects of treatment (CRT versus no CRT) or age at diagnosis. Unfortunately, school absences were not reported in these studies. All studies reported the limitations of using parent feedback as a measure of school abilities. Also, the questionnaire yields only an overall school performance score and does not break down this performance into different subject areas.

Standardized tests of academic achievement have been used to directly compare long-term survivors acquired knowledge in the areas of reading, spelling, math, and writing compared to same-aged peers. The most common standardized test of academic achievement used in the survivor of ALL literature is the Wide Range Achievement Test (WRAT). Studies before 1993 used the revised edition, the WRAT-R, and those after 1993 typically used the more recent 3rd Edition, the WRAT-III (Wechsler, 1993). The

WRAT yields standard scores, with a mean of 100 and a standard deviation of 15, on measures of reading decoding, math calculation, and spelling dictation.

Only one study included both parent reports of school performance together with academic testing of the long-term survivors of ALL. Ochs and Mulhern (1992) compared children with ALL at the beginning of treatment and again three or more years after treatment. There were two treatment groups. One received 1800 rads of cranial radiation therapy plus intrathecal methotrexate. The other group received intrathecal methotrexate only. Subjects were administered the Wechsler intelligence battery and the WRAT-R test of academic achievement. Parents completed the Child Behavior Checklist. No differences were observed between the two treatment groups with respect to reading decoding, spelling dictation, or math calculation. However, within each of the treatment groups, 24 to 27 percent of the sample had significant decreases in arithmetic scores between the beginning of treatment and three or more years post-treatment. Reading decoding scores were decreased in 27% of the children who received CRT, compared to only 8% of those who received chemotherapy-only for prophylaxis. Spelling was the least affected, overall, with 12 to 16 percent of children obtaining significantly decreased scores three or more years post-treatment. Notably, school absences were not reported. These results were consistent with the results of the Child Behavior Checklist completed by the parents. Only the school performance subscale was significantly low. Seventy-seven percent of the total sample had repeated one or more grades and 46 percent of the children had received special educational assistance. There were no significant differences between treatment groups. Although the overall mean math calculation

scores for each group were more than one standard deviation below the mean, the reading decoding and spelling dictation mean scores were within the Average range.

Difficulties with mathematics are the most consistently demonstrated, compared to achievement in other academic areas (Ghelani et al., 2000; Mulhern et al., 1991; Ochs & Mulhern 1992; Ochs et al., 1991; Pfefferbaum-Levine et al., 1984; Raymond-Speden et al., 2000). This may be because the cumulative learning required for math is easily disrupted by school absences. Furthermore, there are several different types of math, and so the risk of a decline in math is greater than in reading or spelling.

In one of the more extensive studies of academic achievement in this population, Peckham, Meadows, Bartel, and Marrero (1988) documented actual school performance of long-term survivors of ALL whose pre- and post-treatment IQ scores were known. Eighteen survivors were followed for educational progress 8 to 10 years after treatment with 2400 rads of cranial radiation therapy. Visits were made to each child's school to review the child's cumulative school record for attendance, grades, standardized test scores, and anecdotal data. Each child's teacher(s) were interviewed about learning strengths and weaknesses. Parents were also visited and interviewed to obtain a longitudinal view of their child's learning history. When possible, the child was observed in class and interviewed as well. Using pre-treatment IQ levels, the survivors, as a group, achieved a mean of –2.7 years below expected levels in both reading and mathematics. Using post-treatment IQ levels, the survivors still achieved –2.1 to –2.2 years below expected reading and mathematics levels, respectively. Neither gender nor pre-treatment IQ scores were significantly associated with academic achievement in this study. Thirty-nine percent of the sample was in a special education classroom. Of those

in regular classrooms, several had been retained one grade and/or had received tutoring. Parents mentioned mathematics most frequently as an area of difficulty.

Comparisons between prophylactic regimens on standardized measures of academic achievement suggest that academic achievement may be differentially affected compared to intellectual functioning. That is, children receiving cranial radiation therapy have not been shown to differ, by either parent report or achievement tests, from those who received chemotherapy-only for prophylaxis (Ochs & Mulhern, 1992; Pfefferbaum-Levine et al., 1984; Precourt et al., 2002).

In summary, research has demonstrated that long-term survivors of ALL are more likely than their siblings to enter a special education or learning disabled program (Haupt et al., 1994). Survivors also achieve lower than their expected levels (given premorbid IQ) on tests of reading and mathematical skills (Peckham, et al., 1988). However, IQ and achievement scores appear not to be associated in this population (Peckham, et al., 1988; Ochs & Mulhern, 1992). Psychoeducational tests typically reveal a pattern consistent with a specific learning disability in math and reading rather than a global cognitive deficit (Peckham et al., 1988). This suggests that, whereas overall mean IQ scores remain in the Average range, scores on standardized achievement tests are significantly below the normative level, and below what would be predicted from their IQ scores. With intelligence being relatively unaffected, this raises the question of what cognitive process is disrupted to result in learning difficulties.

*Memory*

Studies relying exclusively on intelligence tests are limited in their ability to clarify more specific cognitive impairments because they rely heavily on previously

acquired information (Eiser & Tillman, 2001). Standardized tests of memory, however, are not reliant on previously acquired information. As such, some researchers argue that they are more sensitive indicators of learning aptitude than IQ and academic achievement tests (Mulhern et al., 1988). Memory deficits could account for parent reports of difficulties retaining information learned the day before. Alternatively, the deficits could be caused by a slowing in the rate of acquisition of new skills and information. A brief review of how memory has been conceptualized over the years is presented next. This is followed by a review of memory studies completed with long-term survivors of ALL.

*Memory Taxonomies.* Memory is an umbrella term that covers a variety of different forms of acquisition, retention, and use of habits, skills, knowledge, and experiences (Tulving, 1992). It is now well documented that memory is not a single entity but comprises several systems mediated by distinct brain regions (Schacter & Tulving, 1994; Squire, 2002; 2004). Schacter and Tulving state that memory systems are not forms of memory or memory processes or memory tasks or expressions of memory, although these terms are related to the concept of a memory system. Forms of memory can include verbal memory, recognition memory, or visual memory, whereas memory processes refers to a specific operation carried out in the service of memory performance, i.e., encoding, rehearsal, retrieval. Schacter and Tulving state that a memory system is defined in terms of its brain mechanisms, the kind of information it processes, and the principles of its operation. Memory systems can be distinguished in terms of the kinds of information they process and the principles by which they operate.

The important principle, that the ability to acquire new memories is a distinct brain function, separable from intelligence, was established by the famous case of H.M.

(Scoville & Milner, 1957). This case further indicated that the medial temporal lobes were important for a specific type of memory function, known as declarative memory (Squire, 2002). Subsequent memory research focused heavily on cases of amnesia. The study of amnesia has provided strong evidence for distinguishing between a capacity-limited immediate memory (short-term memory), which is intact in amnesia, and more long-lasting memory (long-term memory), which is impaired in amnesia (Squire, 1986).

In addition to a distinction between short-term and long-term memory functions, recent findings suggest a further distinction within the domain of long-term memory. Studies demonstrated that amnesic patients had preserved learning and memory skills in the perceptual-motor domain (Squire, 1982). Case H.M., for example, exhibited progressive learning of a mirror-tracing task across three days of testing, despite reporting on each day that he had no memory of having performed the task before (Milner, 1962). This finding suggested a distinction between information that is based on rules or procedures and information that is based on specific facts or events (Squire, 1982). Traditionally, this dichotomy has been defined under the two umbrella terms: declarative and nondeclarative memory.

Declarative memory is the kind of memory that is meant when the term "memory" is used in everyday language. It refers to the capacity for conscious recollection about facts and events and is the kind of memory that is impaired in amnesia. Declarative memory allows remembered material to be compared and contrasted. It supports the encoding of memories in terms of relationships among multiple items and events. Characteristics of declarative memory easily lend themselves to animal experimentation. The stored representations are flexible and can guide performance

under a wide range of test conditions. Declarative memory is representational. It provides a way to model the external world, and as a model of the world it is either true or false (Squire, 2004). In contrast, nondeclarative memory is expressed through performance rather than recollection. It is neither true nor false. It does not store representations of external states of the world, it operates on an automatic rather than a consciously controlled level, and its output is noncognitive. The memories are revealed through reactivation of the systems within which the learning originally occurred (Schacter & Tulving, 1994; Squire, 2004).

The distinction between declarative and nondeclarative memory was fundamental, because it was subsequently confirmed that these different kinds of memory are supported by different brain systems. Research with rodents, monkeys, and amnesic humans (see Zola-Morgan & Squire, 1990) demonstrated that declarative memory depends on the integrity of the medial temporal lobe and diencephalic brain structures, whereas the nondeclarative memory system functions independently of these brain structures (Schacter & Tulving, 1994; Squire, 1982; 2002). In the 1950s, Scoville and Milner (1957) described the severe amnesia that followed bilateral surgical removal of the medial temporal lobe in patient H.M. Subsequently, surgical lesions of the medial temporal lobe in monkeys, which approximated the damage sustained by H.M., were shown to reproduce many features of human amnesia. In particular, both monkeys and humans were impaired on tasks of declarative memory, but fully intact at skill and habit learning and other tasks of nondeclarative memory (Zola-Morgan & Squire, 1993).

In the mid-80s, based on research that implicated various brain structures with apparently different forms of memory and learning, the perspective shifted from a simple

dichotomy to a framework that accommodated multiple memory systems based on a biological framework. Squire's (2004) most recent taxonomy begins with the dichotomy of declarative versus nondeclarative memory. Declarative memory is further divided into memory for facts (semantic memory) and memory for events (episodic memory). Semantic memory makes possible the acquisition and retention of factual information about the world in the broadest sense; knowledge and beliefs about the world that people gain, access, and use, both general and specific, concrete and abstract. Episodic memory enables individuals to remember happenings they have witnessed in their own personal past, that is, to consciously recollect experienced events as embedded in a matrix of other happenings in subjective time (Schacter & Tulving, 1994).

Work with monkeys and humans with amnesia identified the structures in the medial temporal lobe and midline diencephalon that are important for declarative memory. The relevant medial temporal lobe structures are the hippocampus (including the dentate gyrus and subicular complex) and adjacent cortical areas that are anatomically related to the hippocampus, especially the entorhinal, perirhinal, and parahippocampal cortices. The important structures in the diencephalon appear to be the anterior thalamic nucleus, the mediodorsal nucleus, and connections to and from the medial thalamus within the internal medullary lamina (Squire & Zola-Morgan, 1991). Damage to the midline diencephalon has been linked with severe amnesia (Markowitsch, 1988). The two structures most frequently implicated have been the mammillary nuclei and the mediodorsal thalamic nucleus. Neuropathological findings from Korsakoff's syndrome have led to the view that damage to the mammillary nucleus itself is critical, either alone

or in combination with damage to the mediodorsal thalamic nucleus (Zola-Morgan & Squire, 1993).

One important target of the diencephalic and medial temporal lobe structures is the frontal lobe, especially the ventromedial frontal cortex. The role of the medial temporal lobe and medial thalamic system is only temporary. As time passes after learning, memory stored in the neocortex gradually becomes independent of medial temporal lobe structures (Squire & Zola-Morgan, 1991). This conclusion rests partly on the finding that remote memory is often fully intact in amnesic patients and on the finding of temporally graded retrograde amnesia in prospective studies of monkeys and rats with lesions (Squire, Haist, & Shimamura, 1989; Zola-Morgan & Squire, 1990). Thus, medial temporal lobe and medial thalamic structures are not the repository for permanent memory. This system is required at the time of learning and during a lengthy period thereafter, while a slow developing, more permanent memory is established in the neocortex (Squire, 2004).

Nondeclarative memory is further divided into procedural (skills and habits), priming and perceptual learning, simple classical conditioning, and nonassociative learning. Procedural memory has been shown to rely on the integrity of the striatum, while priming and perceptual learning relies on the integrity of the neocortex. Simple classical conditioning can be further subdivided into emotional responses and skeletal responses, which involve the amygdala and cerebellum, respectively. Nonassociative learning relies on reflex pathways (Squire, 2004). Schacter and Tulving (1994) describe procedural memory as characterized by gradual, incremental learning. It operates at an automatic rather than consciously controlled level and its output is noncognitive. It

appears to be especially well suited for picking up and dealing with invariance in the environment over time.

In the ALL literature, the types of memory most often investigated are short-term verbal and nonverbal (visual and spatial) memory (e.g., Brouwers & Poplack, 1990; Waber et al., 1995). Long-term memory has been examined only in the context of delayed recall, due to a lack of standardized measures. Although the findings are not consistent across all studies, most studies report some form of memory deficit in children treated for ALL as compared to control groups.

*Review of Memory Studies in ALL.* Memory test batteries for children were unavailable until the 1990s. Prior to this, memory was assessed in children using a variety of individual standardized memory tests that measured: 1) story memory; 2) rote verbal memory; 3) verbal multitrial learning; 4) visual and spatial memory; and, 5) visual learning. Story memory measures a child's ability to recall verbal information presented within a context. For example, the child is read a 5 to 6 sentence story and is asked to recall it immediately. A delayed trial is usually administered by asking the child to recall the story again approximately 30 minutes after initial recall. Rote verbal memory is usually assessed by the Digit Span subtest of the Wechsler intelligence scales. The first half of the Digit Span subtest requires the child to immediately repeat a string of digits read to them. Historically, this has been interpreted as auditory short-term memory. The second half requires the child to repeat what they hear backwards, this is argued to further require working memory abilities, as the child must manipulate the remembered information. The true nature of this test, and whether it reflects memory or attention or

both, is an ongoing debate in the literature (see D'Esposito & Postle, 1999). However, digit span and other span tests continue to frequent studies of memory.

The Rey Auditory-Verbal Learning or California Verbal Learning Tests assesses verbal multitrial learning. These tests demonstrate a child's ability to learn an unrelated list of words over repeated trials. A variation of this is the Selective Reminding Test, Verbal and Nonverbal formats (Buschke & Fuld, 1974). In the verbal form, the child is read a list of 10 words and asked to recall as many as possible. The child is reminded only of those words that have not been recalled on the previous trial. There are eight trials. This test permits separate estimates of short-term recall, including words they were reminded of, and continuous long-term retrieval, which is the number of words recalled without reminding. The two forms differ only in the nature of the material to be remembered: verbal vs. nonverbal (spatial). However, nonverbal (visuospatial) memory is most frequently assessed using the Rey-Osterreith Complex Figure. This test examines a child's ability to reproduce, immediately and after approximately 20 minutes, a complex figure previously copied. Finally, visual learning is often measured by pencil and paper maze tests that require the child to find their way out of a maze as quickly as possible.

Administrations of story memory tests, rote verbal and nonverbal (span) memory tests, tests of list learning (with and without reminding), the Rey complex figure immediate recall, and maze tests have yielded inconsistent results in the ALL literature. As before, control of prognostic variables and treatment regimens is essential for comparison across studies. However, unlike intelligence assessments that generally use the same test battery, memory tests are much more diverse. Consequently, results can

vary depending on the requirements of the memory test used. For example, the Rey-Osterreith complex figure requires organizational and motor skills, as well as memory capability. As such, it cannot be considered a pure memory measure. Consideration of the tests used therefore becomes important. Unfortunately, consistent uses of specific memory tests across studies are rare and even fewer studies have used the same memory tests in survivors off treatment for two or more years. Only three studies met this criterion. Consequently, the effects of cranial radiation versus chemotherapy on memory abilities remain unclear.

Brouwers and Poplack (1990) conducted a study of memory in 23 long-term survivors of ALL, off all treatment a minimum of four years, and who received both 2400 rads of cranial radiation therapy and intrathecal methotrexate for central nervous system prophylaxis. Survivors were divided into three groups based on results of their CT scans: five with intracerebral calcifications (indicative of mineralizing microangiopathy), eight with cortical atrophy (indicative of leukoencephalopathy), and 10 with normal CT scans. Measures of verbal and nonverbal memory were administered. Results revealed significant differences on the Wechsler Memory Scale story memory subtest and the Rey-Auditory Verbal Learning Test. Specifically, children with intracerebral calcifications achieved significantly lower scores on these tests compared to those with cortical atrophy and those with normal CT scans. Children with cortical atrophy were significantly below those with normal scans only on story memory but not on the verbal (list) learning test. There were no significant differences between groups on measures of nonverbal memory and learning (measured by the Rey-Osterreith Complex Figure and the Stylus Mazes tests, respectively).

Giralt et al. (1992) examined verbal and nonverbal memory, as well as the ability to learn new verbal and nonverbal information, in two groups of ALL survivors who received 2400 rads of cranial radiation therapy combined with either intrathecal methotrexate, or with intrathecal methotrexate and cytosine arabosine. The two treatment groups did not differ significantly on any measure. However, in contrast to Brouwers and Poplack's (1990) study, both groups performed poorly when compared to the normative mean on nonverbal memory and learning tests (Rey-Osterreith Complex Figure Test and the Porteus Mazes Test, respectively). Specific difficulty on the Rey-Osterreith Complex Figure Test has been frequently and consistently demonstrated in long-term survivors of ALL treated with varying protocols once they are compared to the normative mean (e.g., Waber et al., 2001). Waber and her colleagues reported that the child's ability to recall the figure, rather than draw the figure, resulted in the lower scores. They also noted that providing cues for recall helped the children perform better. In another study by Waber et al. (2000), children who received one of two different corticosteroids as part of their central nervous system treatment achieved lower scores on the Rey-Osterreith Complex Figure Test. Waber and her colleagues surmised that such an effect would be consistent with the theorized role of the hippocampus in cognitive development. However, Hill, Ciesielski, Hart, and Jung (2004) were unable to demonstrate any associations between MRI morphometric measures of the right and left hippocampi and measures of memory in 10 long-term survivors of ALL. This study is discussed in detail in Chapter 5.

The literature reporting on memory abilities in long-term survivors of ALL, off treatment for a minimum of 2 years, is somewhat variable, but not without suggesting mechanisms for the impairments. All studies do report some disruptions of memory.

Since memory encompasses such a wide range of skills, each aspect would need to be investigated before coming to any conclusions. Hill et al.'s (2004) study would seem to suggest that the hippocampus is not directly impacted by central nervous system treatment. As such, disruptions in memory abilities may be a secondary result to disruptions in the ability to organize information optimally for retrieval or to slower information processing, both associated with frontal lobe functions.

The current study investigates intelligence and memory in 16 long-term survivors of ALL, 10 of their siblings, and 16 long-term survivors of Wilms' tumour. This study was designed to describe the sample in terms of intelligence level and to examine aspects of short-term and delayed recall.

Hypotheses

1. Independently replicated studies have demonstrated lower mean intelligence scores in long-term survivors of ALL compared to their siblings and non-central nervous system treated cancer groups. Therefore, it was expected that the long term survivors of ALL would have lower Full Scale IQ scores as well as Verbal and Performance IQ scores compared to their healthy siblings and long-term survivors of Wilms' tumor.
2. Although findings of memory impairments are less consistent in the literature, it was hypothesized that long-term survivors of ALL would have a mean General Memory Index score that was below that of their healthy siblings and long-term survivors of Wilms' tumor.

3. Given that no study has reported impairments on measures of face recognition, picture memory, or spatial location memory, it was not expected that the long-term survivors of ALL would have mean scores below the control groups on Visual Immediate and Delayed Memory.
4. Given the frequent reports of story memory impairment in the literature, it was hypothesized that the long-term survivors of ALL would have mean scores on the Verbal Immediate and Delayed Memory Indices that were below both control groups.
5. There are no reports in the literature that state impairments with memory recognition tests. Therefore, group differences on the Delayed Recognition Index were not expected.
6. Given the consistent reports in the literature of age as an important prognostic variable, it was hypothesized that age at diagnosis would be positively associated with intellectual and memory scores.
7. Given that all of the long-term survivors of ALL in this study were at least 3 years post-treatment, a significant correlation between time since treatment and the intelligence and memory scores was not expected.

# METHOD

## Participants

A total of 43 sets of parents gave informed consent for their children to participate in this study. To obtain this sample, the total population of survivors of ALL and Wilms' tumor treated consecutively at the Children's Hospital of Eastern Ontario between 1983 and 1991 were identified by the pediatric oncologist and invited, by letter, to participate in this study. This comprised twenty-four long-term survivors of ALL diagnosed and treated according to the Boston protocol [see Appendix B] at the Children's Hospital of Eastern Ontario, and twenty-two survivors of Wilms' tumor (a cancer group who did not receive any treatment to the central nervous system and who were diagnosed and treated at the Children's Hospital of Eastern Ontario). If the long-term survivor had siblings (who were no more than 5 years older or younger than the ALL survivor), the one closest in age was also asked to participate. Long-term survival for ALL and Wilms' tumor was defined as a state of continuous complete remission that had lasted a minimum of three years beyond the completion of treatment. Long-term survivors of ALL were not eligible to participate if they had experienced any form of relapse or any serious injury or illness since the end of treatment. The studies were approved by the Research Ethics Boards at the Children's Hospital of Eastern Ontario and the Department of Psychology at Carleton University. Informed written consent was obtained for each participant from the parents, or from the participant themselves if they were 16 years or older.

Sixteen of the 24 long-term survivors of ALL agreed to participate in the study and were scheduled for testing. Two survivors could not be reached and were lost to follow-up. Six survivors refused to participate in the study for personal reasons. Of the

16 survivors of ALL, 11 had at least one sibling who was eligible and agreed to participate (having a eligible sibling, however, was not a requirement to participate in the study. Only one sibling per survivor of ALL was tested). Two survivors did not have any siblings and three siblings refused to participate for personal reasons. Sixteen of the 22 survivors of Wilms' tumor agreed to participate. Two refused to participate for personal reasons, one could not participate because she lived too far away, one agreed to participate but could not be scheduled due to conflicting timetables, one refused due to unwillingness to come to the hospital, and one had suffered further medical problems (specifics not made available) making her ineligible for this study.

Demographic statistics (SES, age at diagnosis, time off treatment, length of treatment, age at testing) of the final sample are presented in Table 1. Socioeconomic status was estimated using the highest grade completed by the parent with the most education (each grade was its own score, e.g., grade 13 = a score of 13; college, university, Masters' level, and Ph.D, were scored as 14, 15, 16, and 17, respectively). The frequency distribution of gender, handedness, and, language of testing, for each group: survivors of ALL, siblings of ALL, and survivors of Wilms' tumor, are shown in Table 2. Handedness was recorded as the hand with which the child wrote (each child was asked whether or not they were ambidextrous; none were). Language of testing was determined by the language in which the child was being schooled and by asking their language preference. A test of frequency distributions using the Chi-Square statistic indicated that the proportion of gender, handedness, and language did not differ between the three groups. However, there is clearly a disproportionate number of males compared to females in the survivors of ALL group (13 vs. 3, respectively). This distribution is

consistent with expectations as ALL is more prevalent in males, but it is likely that this difference did not reach significance due to the overall small sample size. Furthermore, since there were so few females available for this study, it was not possible to verify the gender effects reported in the literature.

Of the 16 ALL survivors, only one had finished treatment before starting school. Of the remaining 15, school absences were obtainable for nine. Each participant was requested to bring in report cards for all grades completed so that days absent could be copied down. When this was not possible, permission was obtained from the parent to contact the school for this information. Where obtainable, the school was faxed a form and asked to fill in the number of school absences and fax it back to the examiner. School absences were obtainable for 6 of the 11 siblings. Of the 16 Wilms' tumor survivors, all but two had completed treatment before starting school. School absences obtained indicated that one Wilms' tumor survivor had missed an entire school year (Junior Kindergarten), and the other missed a total of 45 days during Junior and Senior Kindergarten. For the school years spent in treatment, the days absent for each survivor of ALL and their sibling (if available) are presented in Table 3. The mean days absent for the nine survivors of ALL was 38.2±4.7, whereas for the six siblings it was 12.9±5.9.

Table 1.

*Group Means and Standard Deviations for Parental Education (used to estimate SES), Age at Diagnosis, Time Off Treatment, Length of Treatment, and Age at Testing.*

| Variable | ALL *n*=16<br>Mean (SD)<br>Range | Siblings of ALL *n*=11<br>Mean (SD)<br>Range | Wilms' Tumor *n*=16<br>Mean (SD)<br>Range |
|---|---|---|---|
| Parental Education* | 14.5±2.6<br>8.0 | 14.2±2.4<br>6 | 14.1±2.7<br>9 |
| Age at Diagnosis (years) | 3.3±1.6<br>6.3 | N/A | 2.5±1.7<br>6 |
| Time Off Treatment (years) | 9.7±2.7<br>7.9 | N/A | 7.9±2.8<br>12.5 |
| Length Of Treatment (years)[a] | 2.6±0.5<br>2.1 | N/A | 0.9±0.5<br>1.6 |
| Age at Testing (years) | 15.7±3.1<br>9.8 | 14.7±4.2<br>11.8 | 13.1±4.0<br>13.2 |

*Level of parent education: numbers up to 13 equal grade equivalent; 14=college; 15=university; 16=Masters' degree; 17=Ph.D

[a]$p<0.001$

Table 2.

*Group Distributions of Gender, Handedness, and Language of Testing*

| Variable | ALL $n$=16 | Siblings of ALL $n$=11 | Wilms' tumor $n$=16 |
|---|---|---|---|
| Gender | | | |
| Males | 13 | 6 | 9 |
| Females | 3 | 5 | 7 |
| Handedness | | | |
| Right | 15 | 11 | 13 |
| Left | 1 | 0 | 3 |
| Language of Testing | | | |
| English | 13 | 10 | 13 |
| French | 3 | 1 | 3 |

In each case, treatment of the children with ALL with the Boston protocol that consisted of four phases: induction; central nervous system prophylaxis; consolidation; and, maintenance, continued over a period of approximately 3 years. Children diagnosed with ALL were allocated to receive central nervous system prophylaxis by one of three regimens: 2400 rads of cranial radiation therapy combined with intrathecal methotrexate; 1800 rads of cranial radiation therapy combined with intrathecal methotrexate; or intrathecal methotrexate alone. Of the sixteen participants, four received 2400 rads of cranial radiation therapy in addition to chemotherapy, three received 1800 rads of cranial radiation therapy in addition to chemotherapy, and nine received chemotherapy only. Unfortunately, information regarding whether or not those children who did not receive cranial radiation therapy received high-dose methotrexate could not be obtained from the records.

Measures and Procedures

Standardized measures of intelligence and memory functioning were administered to all participants. The Wechsler Intelligence Scale for Children, 3rd Edition was used to assess intellectual functioning in children aged 6 to 15 years, and the Wechsler Adult Intelligence Scale, 3rd Edition was used for participants aged 16 and older (Wechsler, 1996; 1997a). The Children's Memory Scale (Cohen, 1997) was used to assess memory functioning in children 5 to 15 years of age, whereas, the Wechsler Memory Scale-Third Edition (Wechsler, 1997b) was used for individuals aged 16 and older. Specific

Table 3.

*Days Absent During Each School Year in Treatment for Long-Term Survivors of ALL and Their Siblings. (JK=Junior Kindergarten; SK=Senior Kindergarten)*

| Group | Grades attended during treatment | Total days absent during grades | Average days absent during treatment |
|---|---|---|---|
| ALL | JK | 29 | 29 |
| ALL | JK,SK,1 | 187 | 62.3 |
| ALL | JK | 32 | 32 |
| ALL | JK | 54 | 54 |
| ALL<br>Sibling | JK,SK,1 | 69<br>17 | 23<br>5.7 |
| ALL<br>Sibling | JK | 29<br>0 | 29<br>0 |
| ALL<br>Sibling | SK (did not attend JK) | 38<br>9.5 | 38<br>9.5 |
| ALL<br>Sibling | 2,3,4,5 | 99.5<br>38 | 24.9<br>9.5 |
| ALL<br>Sibling | JK,SK | 103<br>82 | 51.5<br>41 |

information regarding the materials, task demands, time requirements, and psychometric properties of each measure is available in Appendix C. In order to ensure accuracy, the intelligence and memory protocols were scored initially by the examiner, and then again by an independent psychometrist. A psychologist with provincial registration who provided verbal feedback of the results privately to each family of the ALL survivors supervised the assessments.

The study was conducted at the Children's Hospital of Eastern Ontario in a small office that was quiet and without distraction. Each participant underwent approximately four hours of psychometric testing in one session. The principal investigator carried out most of the assessments. Seven participants required administration of the tests in the French language. A bilingual psychologist performed these evaluations. The principal investigator was blind to the medical history (group) of the child at the time of assessment. The highest level of education achieved by the child's parents (the higher of the two) determined SES.

## Statistical Analyses

Raw scores on the standardized measures of intelligence and memory were totaled and converted to standard scores using the normative data provided from each respective test as per each task's test manual. The IQ tests yielded the following composite scores: Full Scale IQ, Verbal IQ, and Performance IQ. The memory tests yielded the following measures: General Memory Index, Verbal Immediate Memory and Verbal Delayed Memory Indices, Visual Immediate and Visual Delayed Memory Indices, and Delayed Recognition Memory Index.

The data were screened for outliers, floor or ceiling effects, distribution, and satisfaction of statistical assumptions. In order to test for group differences, a series of Multivariate Analyses of Variance (MANOVA) were run on the composite scores listed above. Group differences were assessed for Full Scale IQ and the General Memory Index simultaneously because these two scores were the total composite scores of IQ and memory, respectively. If the MANOVA was significant for either or both Full Scale IQ and the General Memory Index, separate MANOVA analyses were run to examine group differences on Verbal IQ and Performance IQ simultaneously, and Verbal Immediate, Visual Immediate, Verbal Delayed, Visual Delayed, and Delayed Recognition Memory simultaneously. Verbal IQ and Performance IQ were grouped together because they both comprise Full Scale IQ. Verbal Immediate, Visual Immediate, Verbal Delayed, Visual Delayed, and Delayed Recognition Memory were grouped together because they comprise the General Memory Index. These groupings were also intended to minimize Type 1 error due to the small sample size.

In analyses that yielded a significant multivariate F statistic, univariate Analyses of Variance (ANOVA) were used to determine which of the dependent measures had group differences. The Tukey test ($p < 0.05$) was used, which is a conservative measure, for posthoc pairwise comparisons between groups (Tabachnik & Fiddell, 2001).

Several independent variables in this sample may account for any group differences revealed by MANOVA: SES, the average number of days absent from school prior to the completion of treatment, age at diagnosis, length of time off all treatment, participant's age at the time of testing for this thesis, and whether or not the child had required special education services. First, a One-Way Analysis of Variance was used to

test for group differences for each variable. Second, a Pearson Product Moment correlation was used to investigate the relationships between these variables and the IQ and memory index scores.

The analyses up to this point were run on the pooled sample of ALL survivors regardless of whether or not they received cranial radiation therapy and at what dose. The final analysis tested the effect of cranial radiation therapy and its dosage on IQ and Memory Index scores for the survivors of ALL only. MANOVAs were used to test the differences on all IQ and Memory Index scores between those survivors of ALL who had received cranial radiation therapy as part of their treatment and those who had received chemotherapy only. MANOVAs were then used to test for differences between those survivors of ALL who had received 1800 rads of cranial radiation therapy and those who had received 2400 rads of cranial radiation therapy.

# RESULTS

Table 4 shows the means and standard deviations for IQ and Memory Indices for the ALL group as a whole and for the ALL group males and females separately. In the general population, the mean IQ is 100 with a standard deviation of 15. The memory indices also have a population mean of 100 with a standard deviation of 15. As shown in Table 4, the means for the total group and for females were within one standard deviation of the expected normative mean for all indices. While most indices for the males were within one standard deviation of the normative mean, the mean Full Scale IQ and Performance IQ scores for males fell just below one standard deviation from the normative mean.

The distributions for the IQ indices and Memory Indices are shown in Figures 1, 2, and 3. All participants with scores under 85 were considered to be below average in intelligence. There were no siblings, and only one Wilms' tumor survivor, who had Full Scale IQ, Verbal IQ or Performance IQ scores in this range. However, five (31%) participants in the ALL group had both Full Scale IQ and Performance IQ scores below 85, and seven (44%) had Verbal IQ scores below 85.

A similar pattern of scores was found for the Memory Indices. Seven (44%) of the survivors of ALL had General Memory Index scores below 85. In contrast, only one sibling and one Wilms' tumor survivor had a General Memory Index score below 85. When the Visual and Verbal memory indices were examined, the results were similar. Five (31.3%) of the survivors of ALL had Visual and Verbal Immediate, and Visual and

Table 4.

*Means (Standard Deviations) of IQ and Memory Indices in long-term survivors of ALL*

| Test Index (X=100, SD=15) | Total (*n*=16) | Male (*n*=13) | Female (*n*=3) |
|---|---|---|---|
| Full Scale IQ | 86.4 (19.7) | 84.4 (21.4) | 95.3 (4.9) |
| Verbal IQ | 87.8 (18.2) | 86.7 (20.0) | 92.7 (7.6) |
| Performance IQ | 87.7 (19.4) | 84.9 (20.5) | 99.7 (4.2) |
| General Memory Index | 89.3 (19.9) | 85.6 (20.2) | 105.3 (6.1) |
| Visual Immediate Memory Index | 91.4 (16.6) | 90.5 (18.2) | 95.0 (6.2) |
| Visual Delayed Memory Index | 92.2 (14.8) | 90.6 (16.0) | 99.0 (4.6) |
| Verbal Immediate Memory Index | 91.4 (16.9) | 88.3 (17.0) | 105.0 (7.9) |
| Verbal Delayed Memory Index | 92.3 (17.3) | 88.9 (17.5) | 107.0 (1.7) |
| Delayed Recognition Memory Index | 92.6 (16.4) | 88.9 (14.4) | 108.3 (17.6) |

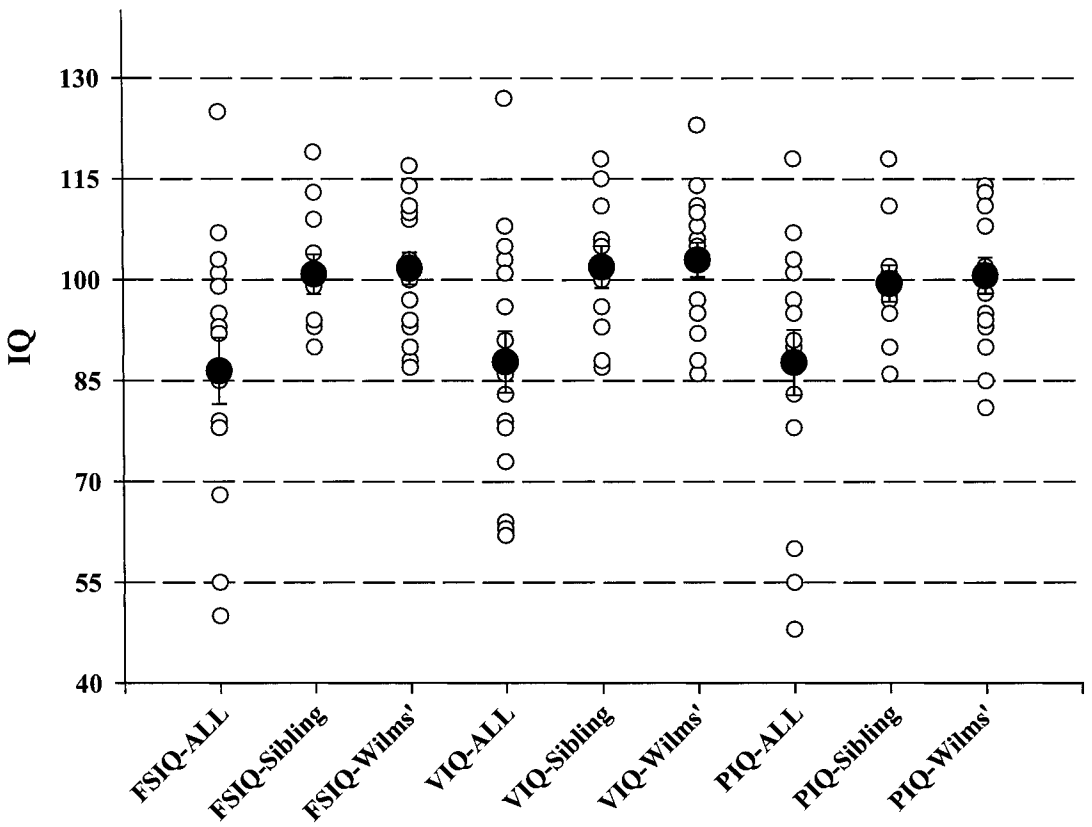



Figure 1. Distribution, mean and Standard Error of the Mean of Full Scale (FSIQ), Verbal (VIQ) and Performance (PIQ) Intelligence Quotients by group.

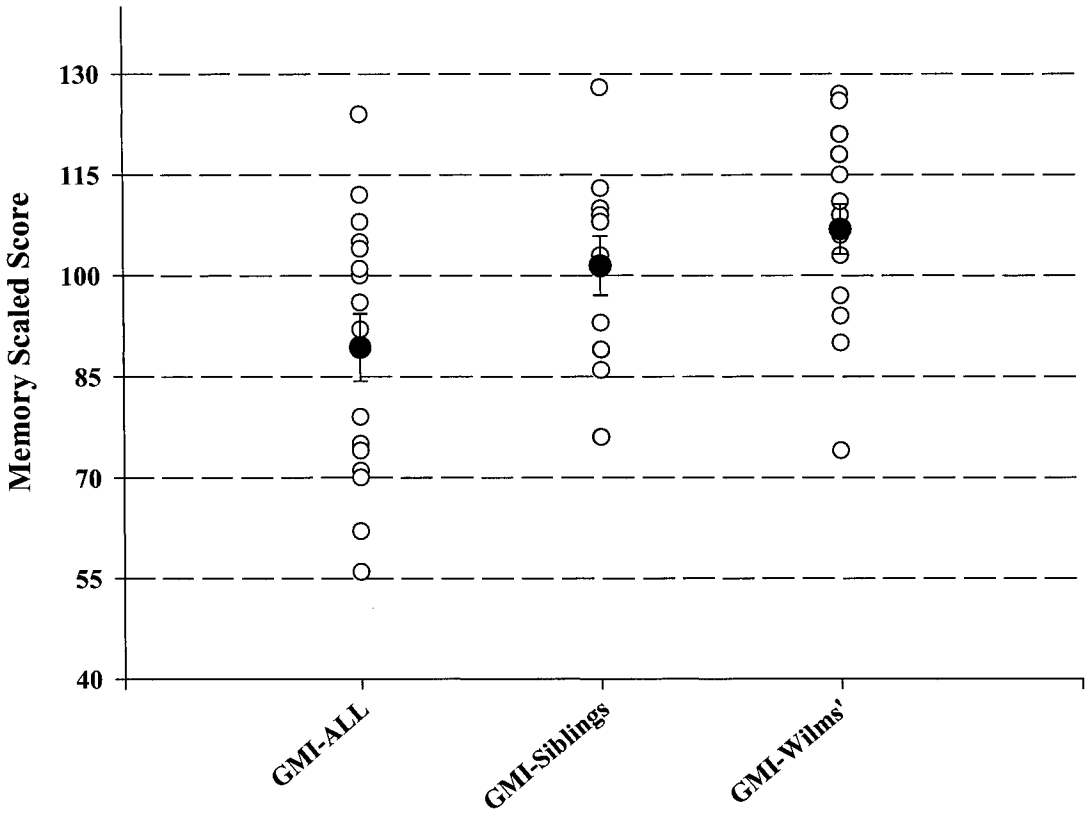



Figure 2. Distribution, mean and SEM of General Memory Index (GMI) by group.

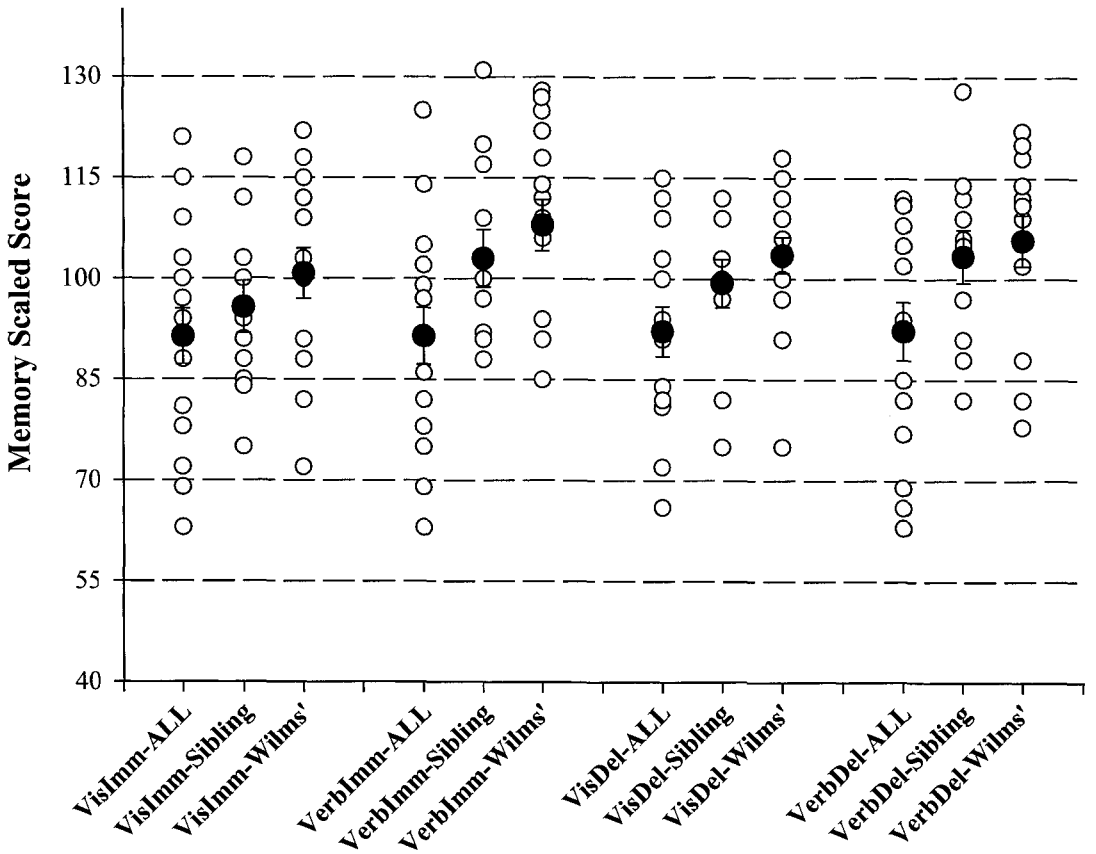



Figure 3. Distribution, mean and Standard Error of the Mean for Visual and Verbal Immediate Memory and Visual and Verbal Delayed Memory by group.

Verbal Delayed Memory Indices below 85. However, there were no siblings or Wilms' tumor survivors with verbal immediate memory scores below 85, and only one to two in each control group had scores below 85 on visual immediate and delayed memory, and verbal delayed memory.

The means and standard deviations for Verbal, Performance, and Full Scale IQ scores are shown for the three groups in Table 5. The means and standard deviations for the General Memory Index, the Visual Immediate and Visual Delayed Indices, the Verbal Immediate and the Verbal Delayed Indices, and the Delayed Recognition Index are presented, for the three groups, in Table 6.

A MANOVA was performed with Full Scale IQ and the General Memory Index which showed a significant group difference, $F(4,76) = 2.90$, $p < 0.05$, $p.eta^2=0.13$, $power=0.76$. Subsequent univariate ANOVAs showed significant differences between groups on both DVs: Full Scale IQ, $F(2,39) = 5.31$, $p < 0.01$, $p.eta^2=0.21$, $power=0.81$, and the General Memory Index, $F(2,39) = 4.46$, $p < 0.05$, $p.eta^2=0.19$, $power=0.73$. Post-hoc Tukey tests (Tabachnick & Fidell, 2001) showed that the survivors of ALL achieved a lower mean Full Scale IQ score compared to their siblings and survivors of Wilms' tumor. However, concerning the General Memory Index, the survivors of ALL achieved a lower mean score compared to the survivors of Wilms' tumor but not compared to their siblings. The two control groups did not differ significantly from each other on either score.

A separate MANOVA conducted on Verbal IQ and Performance IQ scores revealed a significant difference between groups, $F(4,78) = 2.71$, $p < 0.05$, $p.eta^2=0.12$,

Table 5.

*Groups Means and Standard Deviations for the WISC-III and WAIS-III.*

| Measure | ALL $n$=16 | Siblings of ALL $n$=11 | Wilms' Tumor $n$=16 |
|---|---|---|---|
| Full Scale IQ[a] | 86.4 (19.7) | 100.8 (9.8) | 101.7 (9.5) |
| Verbal IQ[a] | 87.8 (18.2) | 101.9 (10.4) | 102.9 (10.3) |
| Performance IQ[b] | 87.7 (19.4) | 99.5 (9.0) | 100.6 (10.8) |

[a] ALL < controls, $p < 0.01$

[b] ALL < controls, $p < 0.05$

Table 6.

*Group Means and Standard Deviations for the Memory Indices.*

| Measure | ALL $n$=16 | Siblings of ALL $n$=11 | Wilms' Tumor $n$=16 |
|---|---|---|---|
| General Memory Index[a] | 89.3 (19.9) | 101.5 (14.6) | 106.9 (14.3) |
| Visual Immediate Memory Index | 91.4 (16.6) | 95.7 (12.9) | 100.8 (15.0) |
| Visual Delayed Memory Index | 92.2 (14.8) | 99.4 (12.0) | 103.5 (10.5) |
| Verbal Immediate Memory Index[b] | 91.4 (16.9) | 103.0 (14.2) | 107.9 (15.3) |
| Verbal Delayed Memory Index[b] | 92.3 (17.3) | 103.4 (13.1) | 105.7 (14.7) |
| Delayed Recognition | 92.6 (16.4) | 103.6 (15.2) | 103.7 (14.4) |

[a] ALL < Wilms', $p$< 0.05

[b] not significant after Bonferroni correction

*power*=0.73. Consequently, an ANOVA was conducted separately on each dependent variable and indicated that groups differed on both Verbal IQ, $F(2,40) = 5.68, p < 0.01$, $p.eta^2$=0.22, *power*=0.84, and Performance IQ, $F(2,40) = 3.84, p < 0.05$, $p.eta^2$=0.16, *power*=0.66. Tukey post-hoc test showed that the survivors of ALL achieved lower scores on Verbal and Performance IQ compared to both control groups, who were not different from each other.

Due to the disproportionate number of males to females in the survivors of leukemia group, these analyses were repeated selecting for males only. The results were not different from the above analyses (results not shown).

A MANOVA was performed on the Visual and Verbal Immediate and Delayed Indices, and the Delayed Recognition Index to determine any group differences. This analysis did not reveal any significant differences between groups (*power* = 0.51). However, due to the significant findings of the MANOVA on the General Memory Index, separate ANOVAs were conducted on the memory indices contributing to this index. A Bonferroni procedure for experimenter-wise type-one error was performed. None of the variables reached statistical significance under the calculated critical alpha value ($p \leq 0.01$). However, the Verbal Immediate, $F(2,40) = 4.45, p < 0.05$, $p.eta^2$=0.19, *power*=0.73, and Verbal Delayed, $F(2,39) = 3.29, p < 0.05$, $p.eta^2$=0.14, *power*=0.59, Memory Indices approached significance.

The means and standard deviations for dependent variables: SES, age at diagnosis, time off treatment, length of treatment, and age at testing, were shown for all groups in Table 1. The number of days absent from school, prior to the end of treatment, in those children who started school before finishing treatment were shown in Table 3. A

one-way Analysis of Variance on each dependent variable indicated a significant difference between the long-term survivors of ALL and their siblings on days absent during treatment, $F(1,14)=11.2, p < 0.01$. There was no discernible difference between survivors of ALL and Wilms' tumor because only two of the Wilms' tumor survivors had started school before ending treatment. The analyses further indicated that the survivors of leukemia were in treatment significantly longer than the survivors of Wilms' tumor, $F(1,31)=86.7, p<0.001$. There were no significant differences between the groups on any of the remaining variables. A Pearson Product Moment correlation did not reveal any relationships between these variables (including school absences) and the IQ and memory index scores in any of the groups.

The means and standard deviations for IQ and Memory Index scores of those survivors of ALL who received cranial radiation therapy versus those who did not are presented in Table 7. Of the survivors of ALL who received cranial radiation therapy, the means and standard deviations for IQ and Memory Index scores of those who received 1800 rads versus 2400 rads are shown in Table 8. A MANOVA was conducted on the IQ and Memory Index scores between those survivors of ALL whom received cranial radiation therapy ($n$=7) and those who did not ($n$=9), as well as between those who received 1800 rads ($n$=3) and 2400 rads ($n$=4) of cranial radiation therapy. However, there was insufficient power (power $\leq 0.6$ for all analyses) to detect group differences due to the very small number of participants in these treatment groups.

Table 7.

*Group Means and Standard Deviations for IQ and Memory Indices of survivors of ALL who received versus did not receive cranial radiation therapy (CRT).*

| Measure | CRT *n*=7 | No CRT *n*=9 |
|---|---|---|
| Full Scale IQ | 76.6 (15.8) | 94.1 (19.7) |
| Verbal IQ | 79.4 (15.0) | 94.3 (18.6) |
| Performance IQ | 77.9 (17.4) | 95.3 (18.0) |
| General Memory Index | 82.3 (21.6) | 94.8 (17.8) |
| Visual Immediate Memory Index | 87.4 (22.0) | 94.4 (11.3) |
| Visual Delayed Memory Index | 88.9 (16.4) | 94.8 (13.9) |
| Verbal Immediate Memory Index | 87.3 (13.9) | 94.7 (19.1) |
| Verbal Delayed Memory Index | 88.4 (16.1) | 95.3 (18.5) |
| Delayed Recognition Memory Index | 86.6 (16.9) | 97.2 (15.3) |

Table 8.

*Group Means and Standard Deviations for IQ and Memory Indices of survivors of ALL who received 1800 rads of cranial radiation therapy versus 2400 rads CRT.*

| Measure | 1800 rads *n*=3 | 2400 rads *n*=4 |
|---|---|---|
| Full Scale IQ | 65.3 (14.2) | 85.0 (12.1) |
| Verbal IQ | 66.0 (6.1) | 89.5 (10.5) |
| Performance IQ | 72.0 (21.6) | 82.3 (15.3) |
| General Memory Index | 80.0 (24.6) | 84.0 (22.8) |
| Visual Immediate Memory Index | 85.3 (31.2) | 89.0 (17.6) |
| Visual Delayed Memory Index | 89.7 (22.5) | 88.3 (14.1) |
| Verbal Immediate Memory Index | 84.0 (13.1) | 89.8 (16.0) |
| Verbal Delayed Memory Index | 89.7 (10.8) | 87.5 (21.0) |
| Delayed Recognition Memory Index | 77.3 (19.9) | 93.5 (12.5) |

# DISCUSSION

This prospective study explored the intellectual abilities and short-term and delayed verbal and visual memory skills of 16 survivors of ALL from the entire cohort of 24 children treated on the Boston protocol at the Children's Hospital of Eastern Ontario. Despite the limitations of a small sample size, this study of long-term survivors of ALL, their siblings, and a non-central nervous system treated cancer group with comparable modal age at diagnosis, addressed several hypotheses. The first hypothesis, that long-term survivors of ALL, as a group, would have a significantly lower mean Full Scale IQ, was supported. The second hypothesis, that the survivors of ALL, as a group, would have lower mean Verbal and Performance IQ scores compared to their siblings and to survivors of Wilms' tumor, was also supported. Furthermore, as expected, the mean IQ scores for ALL children were within one standard deviation of the mean. This is in agreement with the studies that investigate IQ in survivors that have been off treatment for two or more years (e.g., Bakke et al., 1993; Precourt et al., 2002). The agreement between the literature and this study supports that our ALL sample is comparable to the ALL samples in most other studies.

Until 1990, there had been a paucity of standardized memory measures normed on children. The current study is one of the first to test long-term survivors of ALL on a memory battery standardized for children. The survivors of ALL had a significantly lower General Memory Index score compared to the Wilms' survivor group, as predicted by Hypothesis Three. However, the difference between the survivors and their siblings, did not reach significance. There are several possible reasons for this outcome. First, it should be ruled out that the stress of having a sibling go through lengthy treatment of a

life-threatening disease might have impacted the siblings' development in some way. Second, it could be that their comparably weaker memory scores are genetically based. A comparison of the eleven pairs of scores (comparing each sibling with their ALL brother or sister) did not reveal striking similarities between scores of the survivor and their sibling across the 11 pairs. Third, it may be that the number of siblings was insufficient to reveal group differences compared to the number of ALL and Wilms' tumor survivors in this study.

The fourth and sixth hypotheses, which predicted that the ALL survivors would not have lower mean Visual Immediate and Delayed Memory and Delayed Recognition Index scores, respectively, compared to both control groups, was supported. The fifth hypothesis stating that ALL survivors would differ from controls on the mean Verbal Immediate and Delayed Memory Index scores was not supported after a Bonferroni correction for multiple tests.

The seventh hypothesis predicted an association between age at diagnosis and the intelligence and memory index scores. This was not supported. However, all but two survivors of ALL in this study were diagnosed before age five, and the literature has consistently reported that children younger at diagnosis fare worse cognitively two or more years following prophylaxis (Cousens et al., 1988).

The eighth hypothesis, which predicted that time since treatment would not be associated with impairment in this study, was supported. This was expected despite consistent reports in the literature that time since treatment is an important prognostic variable, because all participants were five or more years off all treatment.

Unfortunately, due to the small male to female (13:3) ratio in the survivors of ALL sample, this study was not able to test for the reported gender effect in Waber and Mullenix's (2000) Dual-Cognitive-Process Model. Visual inspection of the scores did not reveal any potential patterns that would suggest the three females performed more poorly than the 13 males.

The long-term survivors of ALL in this study included children who did not receive cranial radiation therapy, those who received 2400 rads, and those who received 1800 rads. Aside from this difference, chemotherapy during each stage of treatment was reportedly the same for each child. However, due to insufficient power to detect true differences, it could not be determined whether the group differences were due to the scores of those children who received cranial radiation therapy. An examination of the individual scores did indicate a trend in that direction.

A significant amount of effort in experimentally controlling for confounding variables was made, minimizing erroneous statements from the analysis. First, the entire cohort was approached for participation and 67% were enrolled in the study. Reasons for nonparticipation were documented and no child refused to participate for health reasons or due to medical history, minimizing biases in this study. Medical history was documented and no child had suffered extraneous medical problems such as head injury, seizures, or illness involving the central nervous system. Long-term survivors of ALL received equivalent chemotherapy and differed only in whether or not they received cranial radiation therapy. The lack of randomization to central nervous system prophylaxis groups and a small sample size were two uncontrollable study limitations. However, this is the norm throughout the literature on this population. Power analyses

were conducted in order to determine the probability of achieving significance under the same conditions, and effect size ($eta^2$) was indicated since it was not dependent on sample size. It should be noted that for almost all reported significant findings, power was at 0.75 or greater. Effect size was also reported and showed that 15 or more percent of the variance could be explained by group membership, which is within expectations for a clinical study of this type. It is also important to note that all subjects were relatively intact other than the difficulties revealed by the testing. Thus, the effect sizes shown would be commensurate with subtle changes due to treatment.

The results of this study contribute to a growing of literature that reports adverse effects of central nervous system prophylaxis on the intellectual abilities of long-term survivors of ALL compared to control groups. Tests of verbal and visual immediate and delayed recall failed to reveal memory deficits in this sample of survivors of ALL. However, the group difference between the survivors of ALL and Wilms' tumor on the Verbal Immediate and Delayed Memory Index scores approached significance. In this instance, verbal and delayed verbal memory was assessed by the Story Memory and Word Pair Associations subtests. Greater power would be necessary to determine if a memory weakness, as measured by these tasks, was indeed evident in this sample.

The results of this study do not rule out a working memory difficulty. The subtests that comprised the verbal and visual immediate and delayed memory indices required maintenance of information but did not require monitoring or manipulation of that information. Working memory is addressed in Study 3.

# CHAPTER FOUR

## Study Two

## Neuroimaging of Brain Strucures in Long-term Survivors of ALL

## INTRODUCTION

Neuroimaging, or neurological scans, are non-invasive methods for early detection of brain injury from either a primary source (disease), or from a secondary source (treatment of that disease). Neuroimaging is now a valid expense for ALL patients because autopsy reports (Price & Jamieson, 1975) indicated that distinct neurotoxic treatment effects were associated with central nervous system prophylaxis. The two effects most frequently reported by Price were leukoencephalopathy and mineralizing microangiopathy (intracerebral calcifications).

Neuroimaging also allows us to monitor the progress of brain development post-treatment to ensure that the children treated for ALL remain in remission. A secondary benefit of this monitoring is that a record of brain changes can be obtained for post-hoc analysis of treatment-related effects over time. These images, usually from Cranial Computerized Tomography (CT) scan and the Magnetic Resonance Imaging (MRI) scans, are also used to correlate neuropsychological findings with the observed brain changes (Wilson et al., 1991).

In the 1980s, CT scans were the most widely used neuroradiological method to detect structural changes in the brains of children with ALL. Reported frequencies of abnormal changes on CT scans in the brains of children who had been treated with cranial radiation therapy combined with intrathecal methotrexate ranged from 1% to 53% (Esseltine et al., 1981; Ochs et al., 1983; Peylan-Ramu, Poplack, Pizzo, Adornato, & Di

Chiro, 1978; Riccardi et al., 1985). These observations are from studies that varied with respect to treatment protocols, time off treatment, and schedule of CT scans, making consistent conclusions difficult. As this thesis addresses the late effects of treatment, studies in which CT scans were conducted a minimum of 2 years post-treatment are most relevant. Five studies met this criterion. Riccardi et al. (1985) and Hertzberg et al. (1997) addressed the effects of cranial radiation therapy versus chemotherapy only. Hertzberg et al. further investigated the correlation between impairment on cognitive tests and neuroradiological evidence of brain changes. Schuler et al. (1990) compared those survivors of ALL with abnormal CT scans to healthy controls, and then examined the correlation between test scores and scan abnormalities. Finally, in two studies, Brouwer, Riccardi, Fedio and Poplack (1985) and Brouwer and Poplack (1990) report on the ability of neuropsychological test scores to discriminate between groups categorized by type of CT scan abnormality.

Riccardi et al. (1985) re-examined 24 of a sample of 32 (75%) leukemics 7 years or more after the initiation of central nervous system prophylaxis (therefore a minimum of 4 years post-treatment). Children treated for ALL in this study had received 2400 rads of cranial radiation therapy and were randomly allocated to receive either intrathecal methotrexate or intrathecal cytosine arabinoside (a drug similar to methotrexate). Initial CT scans were obtained for all participants 2 years after starting central nervous system treatment (see Peylan-Ramu et al., 1978). At that time, 12 of the 24 (50%) showed evidence of brain abnormalities on CT: four (33.3%) had ventricular dilatation, five (41.7%) had subarachnoid space dilatation, one (8.3%) displayed a decreased attenuation coefficient (thought to represent demyelination), and two (16.7%) had a combination of

two of these abnormalities. No participants showed any evidence of intracerebral calcifications. However, four years post-treatment, three (25%) of the participants whose CT scans were previously normal, now had intracerebral calcifications. Ten of the 12 children who previously had CT abnormalities showed these same anomalies on MRI, and two children (one with subarachnoid space dilatation, and one with ventricular dilatation) had also developed intracerebral calcifications in the interim. The other two children (the other child with subarachnoid space dilatation and the one with decreased attenuation coefficient) now had normal CT scans, indicating that their abnormalities had resolved or could no longer be detected with this technique. Riccardi and his colleagues reported no association between the type of intrathecal drug used (methotrexate versus cytosine arabinoside) and the presence or types of CT scan abnormality. This finding was interpreted as suggesting that cranial radiation therapy, common to both groups, was the source of the abnormalities that developed. Indeed, radiation has been implicated in the development of intracerebral calcifications when used to treat other diseases involving the central nervous system (e.g., Harwood-Nash & Reilly, 1970). Riccardi et al. further interpreted their findings as support that children who survive treatment for ALL do not necessarily go on to be free of the sequelae induced by this treatment when abnormalities are not observed early on, stressing the importance of time since treatment as a prognostic variable.

Hertzberg et al. (1997) compared the CT and MRI neuroradiological results of long-term survivors of ALL off all treatment for a minimum of 4.5 years. The gender ratio was 50:50. Participants received one of three central nervous system prophylaxis regimens: intrathecal and systemic medium-high dose methotrexate; 1200 to 1800 rads

of cranial radiation therapy administered after intrathecal and systemic medium-high dose methotrexate; 1200 to 1800 rads of cranial radiation therapy administered during or after intrathecal methotrexate (no systemic methotrexate). Abnormal scans were found in 61 of 118 (52%) children. There were no group differences between chemotherapy regimens. However, low density areas on CT scan (indicative of white matter changes possibly associated with leukoencephalopathy) combined with cerebral atrophy, the most common brain alteration, occurred significantly more in children who had received cranial radiation therapy.

Hertzberg et al. (1997) further examined the association between scan results and cognitive abilities as measured by the Wechsler intelligence tests, the Recurring Figures memory test (Kimura, 1963), and the d2-Concentration Test for attention (Brickenkamp, 1981). Only the d2-Concentration Test scores were significantly lower in the 52% of children with abnormal scans when compared to the children with normal scans. However, correlations were observed between the appearance of specific brain alterations and several of the psychological test scores. That is, children with areas of low density (white matter changes possibly due to leukoencephalopathy) had lower scores on the d2-Concentration Test and the Freedom from Distractibility Index of the WISC-R. The detection of intracerebral calcifications (in four children) was significantly correlated with lower scores on the d2-Concentration Test and the Recurring Figures Memory Test. This study was one of the few to demonstrate a significant correlation between scan abnormalities and standardized cognitive tests.

Schuler et al. (1990) found abnormal CT scan results in 17 out of 33 (45%) long-term survivors of ALL, off all treatment for a minimum of 10 years. They also

demonstrated more errors on measures of short-term memory and attention, as well as visual-bimanual motor coordination between the survivors, who had been treated with 2400 rads of cranial radiation therapy combined with intrathecal methotrexate, and 25 healthy age-matched controls. However, performance on the psychological tests did not correlate significantly with the occurrence of noted scan abnormalities: cerebral atrophy and intracranial calcification. Notably, areas of low density were not reported as in Hertzberg et al.'s (1997) study.

The use of memory tests in distinguishing between children with and without structural brain abnormalities on CT scans was reported by Brouwers et al. (1985) and Brouwers and Poplack (1990). They studied twenty-three long-term survivors of ALL, off treatment for a minimum of 3 years. Survivors received 2400 rads of cranial radiation therapy and were randomized to receive either cytosine arabinoside or intrathecal methotrexate during the period of cranial radiation. On the basis of CT scan results, long-term survivors of ALL were divided into three groups: 10 with normal CT findings, five with intracerebral calcifications, and eight with cortical atrophy. Measures of verbal memory, nonverbal memory, verbal learning, nonverbal learning, concept formation and shifting, verbal fluency, and switching of attention were administered. Cognitive testing and CT scans were conducted on the same day. Discriminant analysis results reliably predicted CT scan findings on the basis of a child's cognitive test results with an 87% overall accuracy. Measures of verbal memory, concept formation and shifting, verbal fluency, and switching of attention were the most powerful in discriminating between the CT groups. Comparisons on the verbal and nonverbal memory and learning tests indicated that children with intracerebral calcifications performed worse than the other

two CT groups on tests of verbal memory and verbal learning as opposed to the nonverbal performance tests.

These five studies indicate greater impairment when prophylaxis includes cranial radiation therapy. In addition, the sensitivity of standardized memory tests to brain scan abnormalities is suggested in Hertzberg et al.'s (1997) study. However, further research needs to be done to confirm this finding, as many more studies do not demonstrate significant correlations between memory scores and brain scan abnormalities.

By the 1990s, advances in neuroradiological technology allowed researchers to expand on the CT scan findings by utilizing MRI technology (Bakke et al., 1993; Cetingul et al., 1999; Ciesielski et al., 1999; Harila-Saari, Paakko, Vainionpaa, Pyhtinen, & Lanning, 1998; Kingma, Mooyaart, Kamps, Nieuwenhuizen, & Wilmink, 1993; Lesnik et al., 1998; Paakko, Vainionpaa, Lanning, Laitinen, & Pyhtinen, 1992). Whereas the CT scan is best suited to detect intracerebral calcifications, the MRI technology is more sensitive to demyelination of white matter. Consequently, studies using MRI technology have revealed treatment-related central nervous system damage not demonstrable by other imaging techniques (Bleyer, 1995; Paakko, et al., 1992). For these reasons, the use of MRI with long-term survivors of ALL has been an invaluable tool to demonstrate the presence of acquired brain abnormalities (Asato et al., 1992; Wilson et al., 1991). Again, studies reviewed were limited to those who report on long-term survivors of ALL, i.e., 2 years or more off all treatment. Two studies met this criterion.

Kingma et al. (1993) studied 35 long-term survivors of ALL who had been off treatment for an average of 5.3 years (range 2 to 8.6 years). All participants had received central nervous system prophylaxis consisting of cranial radiation therapy combined with

intrathecal methotrexate. The cranial radiation dosage ranged from 1500 to 2500 rads depending on the child's age at treatment, with younger children receiving lower dosages. MRI scans revealed that 18 of the 35 participants (51%) had a definite brain abnormality and 6 of the 35 (17%) had probable abnormalities. White matter damage was the most frequent abnormality and this was found in seven of the scans with definite abnormalities and four of the scans with probable abnormalities. The white matter changes were located in the centrum semiovale and in subcortical areas. Other abnormalities were: enlarged sulci or ventricles, suggestive of cortical atrophy; and calcifications.

Harila-Saari et al. (1998) studied 32 long-term survivors who had been off treatment for 5 years. Fifteen of the children received intrathecal methotrexate and 17 received cranial radiation therapy combined with intrathecal methotrexate (the radiation dose was 1800 rads for five children, 2200 rads for one child, 2400 rads for ten children, and 3000 rads for one child). Abnormalities were found in eight of the 32 children (25%). Four of the 8 survivors showed white matter changes. Signs of cortical atrophy were observed in five patients. There were no significant differences between treatment groups concerning the number of abnormalities detected. The survivors were also administered a Wechsler intelligence test and the NEPSY (Korkman, 1988) neuropsychological test battery for children that measures various aspects of attention, language, motor and sensory functions, visuospatial functions, and memory. Fifty percent of the children displayed impairment on tests of memory and visuospatial functions. However, the children with abnormal MRI findings did not differ significantly in their performance on the cognitive tests from the patients with normal MRI findings.

In summary, only one study of long-term survivors reported a significant correlation between CT scan results and tests of attention and memory. No significant correlations between results of MRI scan and cognitive testing have been reported previously. However, studies consistently report CT and MRI abnormalities in a large percentage of their survivors of ALL sample, as well as on tests of intellectual, memory, and attention.

The current study conducted CT and MRI scans on the survivors of ALL to determine the severity of leukoencephalopathy for each participant. The association between the IQ and Memory Indices obtained in Study One and the severity of leukoencephalopathy was also addressed.

Hypotheses

1. Previous research has demonstrated a higher rate of leukoencephalopathy, characterized by white matter damage, calcifications, and cerebral atrophy, in long-term survivors of ALL. Therefore, it was expected that the majority of participants in this study would have leukoencephalopathy scores greater than zero, as indicated by the Common Toxicity Criteria scale.
2. Most studies have not reported significant correlations between MRI or CT results and standardized measures of intelligence and memory. Therefore, it was expected that higher MRI or CT leukoencephalopathy scores (based on a 5-point likert scale, with higher number indicating greater abnormality) would not be associated with IQ and memory scores.

# METHOD

## Participants

Of the sixteen long-term survivors of ALL (diagnosed and treated on the Boston protocol at the Children's Hospital of Eastern Ontario between 1983 and 1991), who participated in Study One, all were invited to participate in Study Two. Fifteen agreed and were scheduled for both CT and MRI scans at the Children's Hospital of Eastern Ontario. A registered pediatric neuroradiologist read and interpreted the scans. One survivor declined participation because she was pregnant.

## Measures and Procedures

### *Cranial Computerized Tomography (CT)*

A CT scan was obtained for each participant. CT scanning of the head was performed with a fourth generation Toshiba Xpress GX. (Toshiba Corporation, Japan.) Axial slices were obtained at 10 mm slice intervals without intravenous contrast enhancement.

The CT scans were reviewed for evidence of brain abnormalities consistent with neurotoxicity. The presence or absence of leukoencephalopathy was graded using the Common Toxicity Criteria (Version 2) 5-point scale (National Institutes of Health, National Cancer Institute).

### *Magnetic Resonance Imaging (MRI)*

An MRI scan was obtained for each participant. MRI was performed with a 1.5-tesla unit (Signa, GE Medical Systems, Milwaukee, WI). Sagittal and axial T1 weighted images were generated with a spin echo pulse sequence. Sequence parameters were as

follows: repetition time (TR) = 500 milliseconds, echo time (TE) = 14 milliseconds, slice thickness 5.0 mm, slice separation 2.5 mm, matrix: 256 x 192. Axial FSE T2 weighted images were obtained with the following parameters: TR = 4000 milliseconds, TE = 98 milliseconds, with the other parameters similar to the T1 weighted images. Axial fluid attenuating inversion recovery (FLAIR) images were obtained with the following parameters: TR = 9002 milliseconds, TE = 138 milliseconds, inversion time (TI) = 2200 milliseconds, with the other parameters similar to the T1 weighted pulse sequence.

The MRI scan was reviewed for evidence of brain abnormalities consistent with neurotoxicity. There are rules for coding severity of leukoencephalopathy ranging from 1 to 5 as appears on the Common Toxicity Criteria (Version 2) 5-point scale (National Institutes of Health, National Cancer Institute), which is shown in Table 1.

Statistical Analyses

The number of participants with a grade 1 level of leukoencephalopathy or higher was determined and the frequency was converted to a percentage. Each of the fifteen participants was scored as either 0 (no leukoencephalopathy) or 1 (at least mild presence of leukoencephalopathy). Given the ordinal nature of the data, a nonparametric test was used for the analysis. Specifically, a Spearman Rho correlation was run between this dichotomous score and the IQ and Memory Index scores, as well as age at diagnosis, age at time of scan, and time off treatment.

# RESULTS

The grade of leukoencephalopathy for each survivor of ALL for both CT and MRI scans are presented in Table 2. A grade of 0 indicated a normal scan; a grade of 1 to 4 indicates some form of abnormality. The criterion for the grading is shown in Table 1.

Six out of 15 survivors (40%) had a score greater than 0 on their MRI and 5 out of 15 (33%) had a score greater than 0 on their CT. Of seven who received cranial radiation therapy in addition to chemotherapy, four (57%) showed some form of abnormality on their MRI and/or CT. Two of the four had received 1800 rads and the remaining two had received 2400 rads. Thus, within this small sample, there was no pattern of results that would suggest an association between administration and dosage of cranial radiation therapy and CT or MRI results. Two participants who did not receive cranial radiation therapy showed abnormalities on their scans.

The Full Scale IQ and General Memory Index are also shown. Spearman Rho correlations were not significant between grade of leukoencephalopathy and: IQ and Memory indices, age at diagnosis, age at time of scan, and time off treatment. However, a qualitative examination of the data did reveal that the only child with severe bilateral abnormalities also had the lowest scores on both measures.

Table 1.

*Common Toxicity Criteria (Version 2) 5-Point Likert Scale.*

| Leukoencephalopathy Rating | Description |
|---|---|
| 0 | None |
| 1 | Mild increase in subarachnoid space; and/or<br>Mild ventriculomegaly; and/or<br>Small (±multiple) focal T2 hyperintensities involving periventricular white matter or , 1/3 of susceptible areas of the cerebrum |
| 2 | Moderate increase in subarachnoid space; and/or<br>Moderate ventriculomegaly; and/or<br>Focal T2 hyperintensities extending into the centrum semiovale or involving 1/3 to 2/3 of susceptible area of the cerebrum |
| 3 | Severe increase in subarachnoid space;<br>Severe ventriculomegaly;<br>Near total white matter T2 hyperintensities or diffuse low attenuation (CT);<br>Focal white matter necrosis (cystic) |
| 4 | Severe increase in subarachnoid space;<br>Severe ventriculomegaly;<br>a. Diffuse low attenuation with calcification (CT);<br>b. Diffuse white matter necrosis (MRI) |

Table 2.

*Grade of Leukoencephalopathy for Fifteen Survivors of A.L.L.*

| Gender | Received Cranial Radiation Therapy? | Age at Diagnosis (yrs) | Age at Scan (yrs) | Time Off Treatment (yrs) | CT Scan Grade | MRI Scan Grade | Full Scale IQ X=100 SD=15 | General Memory Index X=100 SD=15 |
|---|---|---|---|---|---|---|---|---|
| Female | Yes[b] | 2.8 | 18.3 | 12.4 | 1 | 1 | 92 | 100 |
| Male | Yes[b] | 2.7 | 18.8 | 13.2 | 0 | 1 | 95 | 105 |
| Male | Yes[b] | 3.1 | 15.3 | 8.8 | 0 | 0 | 68 | 56 |
| Male | Yes[b] | 4.9 | 20.7 | 11.9 | 1 | 1 | 85 | 75 |
| Male | Yes[a] | 2.5 | 11.1 | 5.8 | 4a | 3 | 50 | 62 |
| Male | Yes[a] | 4.9 | 15.3 | 7.0 | 0 | 0 | 68 | 70 |
| Male | Yes[a] | 6.6 | 20.4 | 9.3 | 0 | 0 | 78 | 108 |
| Female | No | 2.5 | 16.8 | 11.7 | 4a | 1 | 101 | 112 |
| Male | No | 0.3 | 16.5 | 13.7 | 0 | 0 | 55 | 74 |
| Male | No | 2.0 | 10.6 | 5.8 | 0 | 0 | 79 | 79 |
| Male | No | 2.6 | 13.4 | 8.0 | 0 | 0 | 103 | 71 |
| Male | No | 2.7 | 18.9 | 13.5 | 0 | 0 | 107 | 101 |
| Male | No | 3.0 | 13.7 | 7.5 | 1 | 1 | 85 | 92 |
| Male | No | 3.2 | 16.1 | 10.1 | 0 | 0 | 99 | 96 |
| Male | No | 3.4 | 13.9 | 7.0 | 0 | 0 | 125 | 124 |

[a] 1800 rads

[b] 2400 rads

# DISCUSSION

This study reported the findings of two scans conducted on 15 of the 16 long-term survivors of ALL from Study One. One participant did not undergo the scans because she was pregnant. Both CT and MRI scans were used because of their sensitivity to different structural changes. CT scan is more sensitive to intracerebral calcifications while the MRI scan is more sensitive to white matter abnormalities. The CT scan results indicated mild abnormalities in 50 percent and severe abnormalities in 13 percent of the survivors of ALL. MRI scans, rated by a pediatric neuroradiologist using the Common Toxicities Criteria, revealed mild abnormalities in 30 percent and severe abnormalities in 7 percent of the survivors of ALL. These results support the first hypothesis. Because the long-term survivors of ALL received equivalent chemotherapy and differed only in whether or not they received cranial radiation therapy, and at what dosage, these changes are likely due to treatment received during CNS prophylaxis.

Results of the current study revealed no significant correlation between the scores on the Common Toxicity Criteria scale and the standardized intelligence and memory scores obtained in Study One, which supports the second hypothesis. However, given that brain changes were indicated by the scans, this does not necessarily indicate an absence of brain impairment that would contribute to the lower IQ and Memory Index scores. MRI and CT scans may not be sensitive enough to detect the type of damage incurred in this population. MRI and CT technology are limited to identifying gross pathologies in the brain. Subtle changes in the brain, with respect to neuroconnections and neurochemistry, may go undetected. For example, studies that have used evoked response potential have reported that a positive 300 millisecond spike, related to stimulus

recognition, appears approximately 100 milliseconds later in ALL survivors compared to control groups, suggesting problems with auditory discrimination in this population (e.g., Lahteenmaki et al., 2001). These results can be caused by changes in the brain due to central nervous system treatment that the current study did not investigate. Kingma et al. (2001) state that poor relationships between structure and function are not surprising, considering that the developing brain has normal but significant variations.

Technology may not have been the only limitation to detecting subtle effects. It should be noted that the restricted range of scores of leukoencephalopathy (0 to 4) may not have allowed for a fair analysis of the relationship between scan scores and IQ and memory scores. Depending on feasibility, future studies could incorporate a Likert scale with a wider range. A more powerful procedure would be to use volumetric measurements (e.g., Ciesielski et al., 1998). This would yield parametric data that could be analyzed with more powerful tools than are available with nonparametric statistics. Furthermore, it would allow the researcher to measure specific brain regions more precisely and would remove the qualitative aspect of scoring. Ideally, the quantitative and qualitative could be combined to benefit from the eye of a trained observer. Kingma et al. (2001) state that imaging techniques, such as functional MRI, positron emission tomography, single photon emission tomography, and magnetic resonance spectroscopy, may also provide new opportunities to understand late changes in brain functioning in ALL survivors.

The lack of randomization to central nervous system prophylaxis group and the small sample size, as well as the absence of neuroradiological measures for the control groups, were study limitations. Subsequently, power was indicated to show the

probability of observing a significant effect if the study were to be replicated. One other limitation of this study was that specific brain regions were not looked at. Therefore, localization of the structural changes was limited and structures important in memory, such as the prefrontal lobes and the hippocampus, could not be rated. Furthermore, damage to the cerebellum has also been reported in this population (Lesnik et al., 1998). Not frequently discussed is that in addition to the cortical and subcortical structures, the literature shows that the cerebellum is involved in cognition with neural pathways to the prefrontal regions directly involved in working memory (Fiez et al., 1996). The scan results did not allow for information about localized regions, therefore definitive statements about these brain regions and the cognitive test scores were not possible. Despite these limitations, this study supported evidence in the literature that neuroradiological scans alone are insufficient to indicate long-term cognitive sequelae in survivors of ALL.

# CHAPTER FIVE

## Study Three

## Working Memory in Long-Term Survivors of Childhood ALL

## INTRODUCTION

It is now well established that long-term survivors of childhood ALL have a higher probability of underachieving in school, particularly in mathematics (Kingma et al., 2001; Meadows et al., 1981; Mulhern et al., 1988; Noll et al., 1997; Shelby, Nagle, Barnett-Queen, Quattlebaum, & Wuori, 1998; Williams et al., 1991). Results from studies assessing memory in survivors of ALL raise the possibility that these difficulties are, in part, secondary to memory impairments (Brouwers and Poplack, 1990; Giralt et al., 1992; Waber et al., 2000; 2001). However, it has not yet been consistently demonstrated which memory systems are specifically impaired in these survivors. This chapter will review three theories of working memory, and proposes that this is one of the aspects of functioning adversely affected in this population. Research implicating the prefrontal lobes as an area of vulnerability, due to their protracted rate of development, will also be presented. The development of the prefrontal lobes, and the implications for working memory in children will then be discussed.

### Working Memory

"Within cognitive psychology and neuropsychology, the term 'working memory' refers to a system that has evolved for the short-term maintenance and manipulation of information necessary for the performance of such complex tasks as learning,

comprehension, and reasoning" (Baddeley, 1998; Schacter & Tulving, 1994). Typically, the amount of information kept active, or "on-line", ranges between 1-10 items (Smith & Jonides, 1998), whereas the duration of holding that information on-line is reported to be between 20 (Goldman-Rakic, 1996) and 60 seconds (Smith & Jonides, 1998).

There are several points of agreement among researchers of working memory: 1) the prefrontal cortex plays a major role in the most complex aspects of human thought, such as reasoning and planning; 2) a set of elemental processes, including the maintenance, manipulation, and utilization of mental representations, constitutes an operational working memory system, which greatly contributes to these higher cognitive functions; 3) working memory involves both a short-term storage capacity for maintaining mental representations in an active state and a capacity for processing or manipulating information held in the working memory buffer, often referred to as the central executive; and, 4) the working memory system is divided into components that require different cognitive operations, including: a pure storage component, whose contents decay rapidly; a rehearsal component that can reactivate the rapidly decaying contents of the storage component; and, an 'executive' component that regulates the processing of the contents of working memory (Baddeley, 1986; Levy & Goldman-Rakic, 2000; Petrides, 2000b; Smith & Jonides, 1998). Situations that require people just to maintain information for a brief time require only the storage and rehearsal components, whereas, situations that require manipulation of information that is being kept active in working memory further involve the executive component (Petrides, 2000b; Smith & Jonides, 1998).

The neuroanatomical correlates of these components have been elucidated by studies with animals with surgically induced lesions, patients with frontal lobe excisions, and functional neuroimaging on humans. Studies recording the activity of single neurons in monkeys performing various delayed-response tasks have demonstrated that neurons in the lateral prefrontal cortex continue to discharge during the delay period, suggesting that they serve to maintain temporarily the processed information. This work established the existence of sustained neuronal activity during a delay period and lent credence to the idea of a separate maintenance function in working memory (see Petrides, 2000a). Further animal single-cell studies have identified different populations of neurons that display distinctive responses during different phases of a working memory task, perhaps indicating neural dissociations between storage, maintenance and executive processes in working memory (see Goldman-Rakic, 1995; 1996).

Three prominent theories of working memory, namely those of: Baddeley, Petrides, and Goldman-Rakic, are presented in the next sections. It is generally agreed that Miller, Galanter, and Pribram (1960) first proposed the term "working memory", which was adopted by Baddeley and Hitch (1974) as they introduced the first working memory model.

## The Baddeley Theoretical Framework of Working Memory

The Baddeley and Hitch (1974) model of working memory comprises a central 'attentional control' system supplemented by two principal slave systems: the 'phonological loop' and the 'visuospatial sketchpad'. More recently, Baddeley (2000) has proposed the addition of the 'episodic buffer'.

*The Central Executive*

The working memory system has complex relations with long-term memory systems via the 'central executive', a theoretical construct proposed to interface between long-term memory and other systems and to bring working memory into conscious awareness (Baddeley, 1998; Schacter & Tulving, 1994). The central executive is assumed to be responsible for the selection and execution of strategies, and for maintaining and switching attention as the need arises. The capacities to focus, divide, and switch attention were postulated to be critical components of the central executive (Baddeley, 2003). Damage to the frontal lobes produces what has been termed the 'dysexecutive' or 'frontal lobe' syndrome. The central executive is also assumed to be responsible for coordinating information that we take in and process via the two slave systems (Baddeley, 1998).

*The Episodic Buffer*

The episodic buffer comprises a limited capacity system that provides temporary storage of information and which is capable of integrating information from a variety of sources into a unitary episodic representation. The central executive is assumed to be in control of the buffer, which is capable of retrieving information, reflecting on that information, and where necessary, manipulating and modifying it (Baddeley, 2000).

The buffer is episodic in the sense that it holds episodes whereby information is integrated across space and potentially extended across time. Baddeley (2000) compares it, in that respect, to Tulving's concept of episodic memory. It differs, however, in that it is assumed to be a temporary store that can be preserved in densely amnesic patients with grossly impaired episodic long-term memory. This component is a buffer in that it serves

as an interface between a range of systems, each involving a different set of codes, by using a common multi-dimensional code. The buffer is assumed to be limited in capacity because of the computational demand of providing simultaneous access to the necessarily wide range of different codes (Baddeley, 2000).

The central executive, through the medium of conscious awareness, can access the episodic buffer. It can influence the content of the buffer by attending to a given source of information, whether perceptual, from other components of working memory, or from long-term memory, providing a mechanism for modeling the environment and for creating new cognitive representations, which in turn might facilitate problem solving (Baddeley, 2000).

*The Phonological Loop*

Research of Baddeley's model has largely focussed on the phonological loop, making it the best-developed component of the working memory model. The phonological loop (Baddeley, 2003) comprises a passive phonological store, which is accessed directly by auditory information and which can hold memory traces for a few seconds before they fade unless revived by the second component, an active articulatory loop that facilitates the maintenance of verbal information on-line by subvocal rehearsal. The articulatory control process can also translate visually presented information into a phonological code by means of subvocal naming (Baddeley, 2000.

The phonological loop is assumed to have developed on the basis of processes initially evolved for speech perception (the phonological store) and production (the articulatory rehearsal component). Therefore, Baddeley et al. (1998) have proposed that the phonological loop evolved to facilitate the acquisition of language. Support for this

hypothesis came initially from a case study of an adult patient with a pure phonological loop deficit who failed to acquire the vocabulary of a new language (Baddeley et al., 1998). Furthermore, factors shown to disrupt the phonological loop, i.e., articulatory suppression, phonological similarity, and word length (see Baddeley, 2003), also disrupt the acquisition of foreign vocabulary, but not learned association of unrelated word pairs, which is based on semantic coding (Papagno, Valentine, & Baddeley, 1991; Papagno & Vallar, 1992). The loop is particularly suited to the retention of sequential information, and its function is reflected most clearly in the memory span task, whereby a sequence of items such as digits, must be repeated back immediately in the order of presentation. Digit span, the maximum number of digits that can be retained perfectly 50 percent of the time is assumed to be determined jointly by the durability of the memory trace, and the time required to refresh the trace by subvocal rehearsal (Baddeley, 2000).

*The Visuospatial Sketchpad*

The 'visuospatial sketchpad' is proposed to be a subsystem that can hold and manipulate material of a visual or spatial nature. Research has supported the need to distinguish between visual and spatial memory. Spatial span is typically measured by asking the participant to imitate a sequence tapped out by the experimenter on either an array of blocks (presented horizontally) or holes in a board (presented vertically), with sequence length increasing until performance breaks down. Pattern span is the visual (nonspatial) counterpart of this task, in which the participant is shown matrices of cells of which a random 50% are filled. The matrix is then removed and the subject attempts to recall which cells were filled, with matrix size increasing (beginning with a 2 X 2 matrix) until performance breaks down. Visual interference has been shown to disrupt pattern

span, but not spatial span, and vice versa (e.g., Della Sala, Gray, Baddeley, Allamano, & Wilson, 1999). Other distinctions have been proposed, such as spatial and object coding (Smith, Leonard, Crane, & Milner, 1995), dynamic (spatial) and static (pattern) coding (Pickering, 2001), as well as a kinesthetic or motor dimension of coding (Smyth & Pendleton, 1990). Baddeley (2003) reported that visuospatial working memory is an "active but poorly integrated area of research" at this time and, therefore, this is the least well-developed component of the model.

*Anatomical Localization*

Research based on location of lesions in patients and neuroimaging in normal participants indicates that Baddeley's components of working memory are localized in different brain regions. The phonological loop is the most clear-cut, for which lesion studies have indicated the involvement of the left temporoparietal region (Vallar & Papagno, 2002; Paulesu, Frith & Frackowiak, 1993). Neuroimaging studies have supported this conclusion, identifying Brodman's Area 40 as the locus of the storage component, and Broca's area as being involved in the rehearsal component.

A direct comparison of phonological and visuospatial working memory identified visuospatial working memory as primarily localized in the right hemisphere, in agreement with earlier lesion studies. The right inferior parietal cortex, right premotor cortex, and right inferior frontal cortex have also been implicated (Baddeley, 2003).

Although not specifically reported, the central executive and the episodic buffer are assumed to be associated with frontal lobe function (Baddeley, 2000). Lesion studies and functional neuroimaging have provided extensive evidence for an association between executive functioning and the frontal lobes. It has reportedly been challenging

to associate different executive processes with specific anatomical locations (D'Esposito et al., 1995; Duncan & Owen, 2000; Klingberg, Kawashima, & Roland, 1996). Baddeley (2003) has indicated that there remains a clear need to relate the central executive to the extensive work that exists on executive control, which is mostly concerned with the analysis of frontal lobe function.

## The Role of the Prefrontal Cortex in Working Memory

Experimental studies in both monkeys and humans have clearly demonstrated the critical role of the prefrontal cortex in the neural network subserving working memory (Goldman-Rakic, 1987; Smith & Jonides, 1999). Virtually all working memory studies involving neuroimaging have reported activation in the lateral frontal cortex, and have provided evidence that this region plays a critical role in working memory (Goldman-Rakic, 1995, 1996; Petrides, 1994a, 1994b, 1995; Petrides, Alivisatos, & Evans, 1995; Petrides, Alivisatos, Evans, & Meyer, 1993a, 1993b). The lateral cortex is comprised of regions that are anatomically and cytoarchitectonically distinct in both human and nonhuman primates. In the human brain, the ventrolateral frontal cortex largely occupies the inferior frontal gyrus and comprises architectonic areas 47/12 and 45. The dorsolateral areas 9 and 46 occupy the middle part of the superior and middle frontal gyri, with a considerable proportion of this cortex lying within the depths of the middle frontal sulcus.

There is strong consensus regarding the association between prefrontal mechanisms and working memory capacity. However, there is less agreement about how working memory is organized within the prefrontal cortex. Petrides and his colleagues

have proposed a *process oriented* theoretical framework. This model proposes that segregation within the prefrontal cortex is based on the nature of processing within working memory (Petrides, 1995). The ventrolateral prefrontal cortex is proposed to be involved with the active organization of sequences of responses based on conscious, explicit retrieval of information from posterior association systems and active comparison of stimuli held in short-term memory. In contrast, the dorsolateral frontal regions subserve a secondary level of executive processing and are recruited only when active manipulation and monitoring of information within working memory are required. As such, both visual-spatial and visual nonspatial stimuli held in working memory may be processed within the ventrolateral and/or dorsolateral frontal cortex, depending upon the particular demands of the task being performed (Owen, 1997; Petrides et al., 1993a, 1993b, 1994a, 1994b). This model is supported, mostly, by neuroimaging studies on human participants.

Goldman-Rakic proposes an alternate model whereby the functional organization of the prefrontal cortex, with respect to working memory operations, is "domain-specific". Goldman-Rakic (1987) postulates that working memory is organized within the prefrontal cortex based on the sensory nature of the information being processed in working memory, regardless of the level of processing. Accordingly, the mid-dorsolateral cortex is specialized for visual-spatial processing, whereas the ventrolateral cortex is involved in nonspatial visual (e.g., object/face) processing. Levy and Goldman-Rakic (2000) report that "domain-specific" does not mean "modality-specific". Several sensory modalities feed into the mechanisms related to the different domains from which working memory operates.

*Goldman-Rakic's Theoretical Framework of Working Memory*

Levy and Goldman-Rakic (2000) report that the extrinsic connections of the prefrontal cortex are consistent with a "domain-specific" model. The dorsolateral prefrontal cortex, proposed to be involved in visuospatial working memory, receives dense projections from the inferior parietal association cortex, which is a region involved in visuospatial processing (Friedman & Goldman-Rakic, 1994; Petrides & Pandya, 1994). The ventrolateral prefrontal cortex, proposed to be involved with nonspatial visual (object/face) working memory, is networked with the inferotemporal association cortex, which is a region involved with the representation of visual objects (Fuster, 1990; Seltzer & Pandya, 1989). Given that the dorsolateral and ventrolateral prefrontal cortices are the recipients of differential projections from areas that are themselves specialized visual processing areas (spatial versus feature), Levy & Goldman-Rakic (2000) argue that this is highly suggestive of a parallel organization of domain-specific modules within the prefrontal cortex.

Single cell recording and lesion studies with nonhuman primates have offered support for the domain-specific model. The delayed-response tasks have been a primary instrument for assessing working memory capacity in monkeys. Their main feature is that they require monkeys to maintain a mental representation during a delay period and then use this representation to guide the choice of response at the end of the delay. The delayed-response tasks can be formatted to examine different modalities of working memory, i.e., visual, spatial, tactile, object/feature (see Goldman-Rakic, 1987). This research has associated lesions of the dorsolateral prefrontal cortex with impairment on spatial delayed-response tasks (Funahashi, Bruce & Goldman-Rakic, 1993; Goldman-

Rakic, 1987) and on haptic (touch) and visual delayed matching-to-sample tasks (Shindy, Posley & Fuster, 1994). Single cell recording studies are consistent with these results and report a greater number of activated neurons in the dorsolateral prefrontal cortex when the monkey is maintaining spatial information in short-term memory (see Funahashi, Chafee & Goldman-Rakic, 1993).

Monkeys with lesions of the dorsolateral prefrontal cortex were unimpaired on nonspatial delayed-response tasks in which they had to remember physical features (patterns, shapes, or colours) of objects over a short delay period. Lesions of the ventromedial prefrontal cortex, and to a lesser extent of the ventrolateral prefrontal cortex, produced impairment on these tasks (see Mishkin & Manning, 1978). Again, results of single-cell recordings are consistent with these studies in that very few of the neurons in the dorsolateral prefrontal region were tuned specifically to the identity or features of objects, whereas neurons in the ventrolateral prefrontal cortex were related to object features (see Wilson, O'Scalaidhe & Goldman-Rakic, 1994).

*Petrides' Theoretical Framework of Working Memory*

Petrides (1995; 1991) proposes a two-level hypothesis of the involvement of the lateral frontal cortex in working memory. According to this hypothesis, the "ventrolateral frontal cortical areas, including the principal sulcus of the dorsolateral frontal cortex, are the initial recipients of information from posterior association areas and are the locus of the initial interaction of executive processing within short-term memory for modality-specific and multimodal information. The dorsolateral frontal cortex that lies above the principal sulcus, on the other hand, constitutes a second-level

interaction with short-term memory when planning and organization, i.e. monitoring within working memory, are required" (Petrides, 1994b).

Petrides (1990; 1991; 1994a; 1994b; 1995; 1996; 2000a; 2000b) has published extensively on the role of the dorsolateral prefrontal cortex. Petrides' work with adult patients has indicated that the dorsolateral prefrontal cortex is critical in working memory (Petrides & Milner, 1982). In the human brain, the superior and middle frontal gyri comprise the dorsolateral prefrontal cortex. It is divided into three regions: anterior, mid-, and posterior dorsolateral prefrontal cortex. Studies of monkeys with surgically induced precise lesions implicated the mid-dorsolateral prefrontal cortex as a specialized area in which information could be held on-line for monitoring and manipulation (Petrides, 1991, 1995 & 1996). This is in contrast to the ventrolateral frontal lobe region that has been implicated in sequential organization of information retrieved from posterior association regions. Inferring from Ciesielski et al.'s (1999) developmental chronometry hypothesis, and Lesnik et al.'s (1998) study, long-term survivors of ALL might be at risk for impairments resulting from damage to the later developing dorsolateral prefrontal region. Lesnik et al. also found abnormal development of the prefrontal cortices and the posterior vermis of the cerebellum in a sample of childhood ALL survivors. Although the posterior cerebellar vermis does not feed directly into the prefrontal lobes, it has strong connections with the dentate nucleus of the cerebellum. The dentate nucleus feeds directly into the mid-dorsolateral prefrontal lobes. Therefore, based on the observed deficits, reviewed in study one, it is reasonable to suggest that this region is specifically susceptible to the neurotoxic effects of central nervous system prophylaxis.

Owen (1997) reviewed the results of recent functional neuroimaging studies, conducted with humans, in order to examine how the lateral frontal cortex processes visual-spatial and visual nonspatial material. He reported that there was evidence to support the activation of the mid-dorsolateral and/or mid-ventrolateral frontal cortices in spatial and visual nonspatial working memory tasks. Whether one or both of these areas is activated seems to depend on the precise cognitive processes that were required on the particular task being performed. For example, the mid-ventrolateral frontal regions were activated when the participant was required to maintain only one or a few locations in memory for the duration of each trial, thereby emphasizing the short-term retention of visual-spatial information within working memory. The mid-dorsolateral frontal region became involved when the task required that the participant constantly monitor and manipulate an ongoing series of visual-spatial locations within working memory, and make comparisons between each new stimulus and stimuli presented earlier in the sequence.

In attempting to characterize the specific contribution of the human mid-dorsolateral prefrontal cortex to working memory, Petrides and Milner (1982) developed a series of working memory tasks, which could be used with both monkeys and humans, called the self-ordered and externally ordered tasks. The important aspect of these working memory tasks was that successful performance was based not only on the maintenance of information in short-term memory, but also on the monitoring of this information. In the self-ordered working memory task, the participants are presented with different arrangements of the same set of stimuli and, on each trial, they have to select a different stimulus until all have been selected once. The relative position of the

stimuli changes from trial to trial to ensure that the subject is guided by memory of the objects and not their locations. Successful performance, therefore, requires that the subjects keep track of which stimuli that they have already selected and which remain to be selected. Thus, previous choices must be held in mind for monitoring purposes. The test generally consists of three trials for each of four sets of stimuli. Therefore, the participant has to remember not only which stimuli they have already selected in previous trials, but which ones they have selected in the current trial. In the externally ordered working memory task, the participant is asked to observe the random presentation of stimuli from a known set, in order to determine which ones have not been presented. The random selection (self-ordered) or random presentation (externally ordered) of the stimuli is a simple experimental means of assuring close monitoring of the information by the participant. In other words, in these tasks, short-term memory is coupled with the executive process of monitoring that information (Petrides 1996).

In nonhuman primates, mid-dorsolateral prefrontal lesions give rise to severe and long-lasting impairments on the self-ordered and externally ordered working memory tasks. Notably, it has been reported by Petrides (1996; 2000a) that the impairment on these monitoring working memory tasks after mid-dorsolateral prefrontal lesions occurs in individuals for whom basic memory processes are intact. Monkeys with mid-dorsolateral lesions are able to perform normally on basic memory recognition tasks in which they have to discriminate novel from familiar stimuli. In addition, they perform well on delayed matching-to-sample tasks in which they have to recognize which of two recurrent stimuli was most recently presented. As well, they perform well on the delayed object-alternation task in which they have to alternate their response from one stimulus to

the other after each delay period. In other words, it has been demonstrated that memory judgements, based on the relative recency of stimuli and the simple maintenance of information during the delay, have been preserved despite mid-dorsolateral prefrontal damage. This basic memory processing, however, is inadequate to support accurate performance on the self-ordered and externally ordered working memory tasks that are designed to place demands on the ability to monitor the information within working memory. That is, the performance of these animals was severely impaired when the task demands exceeded those supported basic memory processes (e.g., familiarity, primacy, or recency judgements).

*The Petrides Self-Ordered Pointing Test.* The Petrides Self-Ordered Pointing Test is theoretically based, but has been well validated as a measure of working memory in adults (Petrides et al., 1993b, 1994a, 1994b). It has also been validated as a test of working memory in children (Archibald & Kerns, 1999). It purportedly assesses an individual's capacity to initiate a sequence of responses, to retain the responses, and to monitor the results of a response. The utility of this task as a measure of working memory in children has been supported by studies of children with disorders hypothesized to be associated with frontal lobe pathology (Diamond, Prevor, Callender, & Druin, 1997). The Self-Ordered Pointing Test requires only a simple pointing response. Having this relatively simple task response requirement is thought to reduce some of the confounding effects of other "nonexecutive" cognitive processes. The level of difficulty of this measure is developmentally appropriate across a range of ages. A strong age-related increment of performance has been shown, consistent with

documented patterns of frontal lobe development across childhood (Archibald and Kerns, 1999).

This study investigated working memory skills in the participants from Study One. The children's ability to monitor information within working memory was assessed by the Petrides' Self-Ordered Pointing test. Parental observations of behaviours associated with impaired working memory were obtained via a standardized questionnaire, the Behaviour Rating Inventory of Executive Function (Gioia, Isquith, Guy, & Kenworthy, 2000).

## Development of the Prefrontal Lobes

The prefrontal cortex undergoes one of the longest periods of development of any brain region, taking over two decades to reach full maturity in humans (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). Even during the first year of life, significant maturational changes occur in the prefrontal cortex that helps to make possible important cognitive advances (Diamond, 2002). The acquisition of cognitive functions that depend on the prefrontal cortex have been measured by numerous experimental tasks. These gains in cognitive functions have paralleled confirmed physical changes in the prefrontal cortex from 1 to 3 years old, 3 to 7 years old, and 7 years old to early adulthood.

*Development during the first year of life.* Piaget introduced the A-not-B task over 50 years ago and it has since been used worldwide to study infant cognitive development (Piaget, 1954). An almost identical task, the delayed response task, has been widely used to study prefrontal lobe development, specifically in the dorsolateral region, in monkeys.

As described by Diamond (2002), "in the A-not-B/Delayed Response task, a participant watches as a desired object is hidden in one of two hiding places that differ only in left-right location. A few seconds later the participant is encouraged to find the hidden object. He or she must hold in mind over those few seconds where the object was hidden. Over trials, the participant must keep this mental record to reflect where the reward was hidden most recently. The participant is rewarded for reaching correctly by being allowed to retrieve the hidden object, thus reinforcing the behaviour of reaching to that location. Hence the tendency to emit that response is strengthened. When the reward is hidden at the other location, the participant must inhibit the tendency to repeat the rewarded response and instead respond accordingly to the representation held in mind of where the reward was hidden most recently. This task thus requires an aspect of working memory (holding information in mind), resistance to proactive interference, and inhibition of a prepotent action tendency (the tendency to repeat a positively reinforced response)."

By approximately 7.5 to 8 months old, infants reach correctly at the first hiding location with 2 to 3 second long delays. However, when the reward is hidden at the other location, infants err by reaching back to the first location. There is a marked improvement in their performance between 7.5 to 12 months of age. Each month they can withstand delays approximately 2 seconds longer, so that by 12 months of age they can succeed at this task with delays of almost 10 seconds (Diamond, 1985; Diamond & Doar, 1989). There is a period of marked growth of the dendritic branches in the dorsolateral prefrontal cortex from 7.5 to 12 months (Koenderink, Uylings, & Mrzljak, 1994). The level of glucose metabolism in this brain region also increases during this

period reaching adult levels by one year of age (Chugani & Phelps, 1986). Diamond (2002) has proposed that the gains in the A-not-B/Delayed Response task are firmly linked to the functioning of the dorsolateral prefrontal cortex.

Object retrieval tasks have also been used to chart development in the ability to inhibit a prepotent response. For example, a toy is placed in a clear box, open on one side. The infant can see the toy through one of the closed sides of the box and must integrate seeing the toy through one side of the box with reaching to a different side. There is a strong pull to try to reach straight for the toy; that prepotent response must be inhibited when another side of the box is open. Infants aged 6 to 8 months reach only at the side through which they are looking. They must look through the opening and continue to do so to reach in and retrieve the toy. Infants 8 to 10 months old can look through the opening and reach in while looking through a closed side. By 11 to 12 months old, infants do not need to look along the line of reach at all (Diamond, 1990).

Human infants improve on both the A-not-B/delayed response and object retrieval tasks during the same age period. In humans, developmental improvements on both the A-not-B/delayed response and object retrieval tasks are related to changes in the pattern of electrical activity detected by EEG over the frontal and parietal cortex (Fox & Bell, 1990). Lesions of the dorsolateral prefrontal cortex in monkeys also disrupt performance on the object retrieval tasks (Diamond, 1990). In summary, prefrontal lobe development is actively taking place before 1 year of age and continues for two decades thereafter. Infants demonstrate gains in abilities associated with this brain region, which involve inhibition of a previously rewarded response with delays up to 10 seconds. This is a rudimentary skill necessary for working memory.

*Development at 1 to 3 years of age.* This growth period is relevant to survivors of ALL as most are diagnosed and begin treatment by the age of 3. Continued improvements in the ability to inhibit prepotent responses have been documented by several researchers. Koslowski and Bruner (1972) charted the developmental progression between the ages of 12 and 24 months in the ability to use a lazy Susan to bring a toy within reach (an object retrieval task). This task requires relating the lazy Susan and its movement to the toy and its movement. It also requires that the child inhibit reaching on a direct line of sight and that they inhibit the tendency to push the lazy Susan in the direction one wants the toy to go (the child must push left to make the toy go right). The ability to inhibit a prepotent response in order to perform a modulated or different response improved markedly from 22 to 33 months of age.

*Development at 3 to 7 years of age.* This period is also relevant to children treated for ALL because treatment is usually still taking place during this time. Substantial neuronal changes are taking place. The density of neurons in the dorsolateral prefrontal cortex is highest at birth and declines thereafter. At 2 years of age, the density is 55% above the adult mean, but by age 7 it is only 10% above adult levels (Huttenlocher, 1990). Thus, there is a dramatic change in neuronal density in this brain region between 2 and 7 years of age. The synaptic density increases after birth and reaches its maximum at about 1 year of age; by 7 years of age the decrease in synaptic density is significant, though not yet down to adult levels (Huttenlocher, 1979).

Paralleling these neurological developments, the period of 3 to 7 years of age, especially 3 to 5 years, is a time of marked improvements on many cognitive tasks that require holding information in mind while inhibiting a prepotent response. The

development of the ability to hold information in mind about the same situation and inhibit the impulse to give one answer over another (prepotent response) has been demonstrated with numerous conditional discrimination tasks. The day-night task (Diamond, Kirkham, & Amso, 2002) and Luria's tapping test (Luria, 1966) are two such highly correlated tests. In the day-night task, the child must say "night" when shown a white card with a picture of the sun, and say "day" when shown a black card with the moon and stars. Children 3.5 to 4.5 years old find this very difficult. Improvements in accuracy are observed from 3.5 to 7 years of age, with improvement in speed of responding occurring primarily from 3.5 to 4.5 years. The difficulty young children experience with this task is based on the semantic relationship between what they are supposed to say and not say. For example, if shown two different pictures of an abstract design and asked to say "day" to one and "night" to the other, 3 year olds have no trouble. This suggests that the need to learn and remember two rule sets is not in itself sufficient to account for the poorer performance of 3-year-old children, and inhibition of the prepotent response is only difficult when a change in semantics is necessary. This suggests that children aged 3 can perform relatively complex tasks but fail when asked to do the task in a different way. This is because they have to actively inhibit the old way of performing in order to switch set. This ability to switch set has been associated with the dorsolateral prefrontal cortex in both children and adults.

Luria's tapping task also requires remembering two rules and inhibiting a prepotent response to switch set and make the opposite response instead. In this task, the child is told to "tap once when the experimenter taps twice, and tap twice when the experimenter taps once". The greatest improvement in accuracy on this task occurred

between 3.5 and 4 years of age, while the greatest improvement in speed of responding occurred between 4.5 and 5 years of age (Diamond, 2002). Performing this task has been shown to increase activation in the dorsolateral prefrontal cortex in normal adults, in comparison with mimicking the experimenter's tapping response (Brass, Zysset, & von Cramon, 2001). The tapping task is positively correlated with the day-night task. Children with phenylketonuria, who are thought to have reduced dopamine in the prefrontal cortex, are impaired in their performance of both tasks (Diamond, 2001).

Card sorting tasks have also been used to demonstrate the development of the ability to switch set. Zelazo et al.'s (1995) card sorting task is considered the simplest of these measures. The child must sort cards correctly by the first criterion (e.g., colour). They must then switch to sorting cards by a second criterion (e.g., shape). Children 3 years of age fail when they must switch to a new sorting criterion, similar to prefrontally lesioned adults. However, they can correctly state the new criterion. By 4 years of age, most children can succeed with 2-dimensions and 1-switch. By age 5, all can succeed on this simple switching task.

Kirkham, Cruess, & Diamond (2003) reported that errors occur on the card sorting task because of difficulty in inhibiting or overcoming what they termed *attentional inertia*, the tendency to continue to focus on what had been initially relevant. Even when informed of alternatives, 3-year-old children remain stuck in their initial way of perceiving, and cannot reverse their initial response. There is a pull to focus on the previously relevant dimension and to respond on that basis, which must be inhibited before the correct response can be made. This is noted even when it is clear that the child knows the correct response. By 5 years of age, most children can reverse their initial

response. Diamond (2002) noted that this tendency to focus on a previously relevant dimension never really goes away, and traces of it can be measured even in healthy young adults. Increasing the perceptual salience of the previous dimension further impairs performance in both children and adults. However, decreasing the perceptual salience, for example, by sorting the cards face down, improves performance for 4-year-olds on the Zelazo's card task. Redirecting attention to the currently relevant dimensions also improves performance. For example, if the experimenter asks the child to label, aloud, the card to be sorted, the performance of most 3-year-olds improves. The dorsolateral prefrontal lobes were only required when participants needed to refocus their attention (i.e., overcome attentional inertia) and switch to a different dimension (Meyer et al., 1998; Pollmann, 2001).

In summary, the developmental course of the prefrontal lobes leaves this brain region vulnerable to the effects of the neurotoxic, albeit necessary, prophylactic treatment administered to children diagnosed with ALL. Memory involves many regions of the brain and certain regions of the brain are much more important for some types of memory than for others. Although the results of few studies support the view that circumscribed prefrontal lobe lesions are sufficient to produce classical amnesic syndromes, there are specific aspects of memory functioning mediated by the anterior cerebral structures, such as working memory (Romine & Reynolds, 2004).

### Vulnerability of Later Developing Brain Structures

Ciesielski, Lesnik, and their colleagues investigated how the rate at which brain structures develop, from conception onwards, determines which areas are the most

vulnerable to early neurotoxicity. Lesnik et al. (1998) and Ciesielski et al. (1999) proposed the *developmental chronometry* hypothesis that predicts later developing brain structures are more affected by the toxic effects of central nervous system prophylaxis than earlier maturing brain structures. The studies about to be presented show reduced volumes in specific brain areas that are still developing and are consequently most at risk to neurotoxicity. Specifically, the prefrontal lobes are among the last brain regions to mature. These studies suggest that abilities dependent on the normal development of the prefrontal lobes are those most likely to be affected in this population.

Lesnik et al. (1998) investigated the neocerebellar-frontal subsystem, which has a slow rate of maturation and may have particular prolonged vulnerability to damage during central nervous system prophylaxis. They hypothesized that the later developing neocortical posterior vermis of the cerebellum would be more affected by neurotoxicity than the earlier maturing anterior vermis of the cerebellum, in the context of Average whole brain volume. Their hypothesis was tested in ALL survivors whose central nervous system prophylaxis included only chemotherapy (intrathecal methotrexate), and who were off treatment for at least 3 years, and on healthy controls matched for age, sex, handedness, and SES. MRI imaging scans confirmed their hypothesis. Specifically, the ALL survivors had significantly smaller volume of the neocortical posterior vermis of the cerebellum compared to controls. The cerebellum is known to project via the thalamus to multiple motor areas of the cerebral cortex (Middleton & Strick, 2001). However, research has also reported on the role of the cerebellum in cognitive (nonmotor) functioning via the neocerebellar-prefrontal (closed) loop (Fiez et al., 1996). In nonhuman primates, it has been observed that the dorsolateral prefrontal cortex

(Brodmann's area lateral 9 and dorsal 46) receives input from the cerebellum (Middleton & Strick, 2001), and that the dorsolateral prefrontal cortex is critical to working memory (Petrides et al., 1982; 1990; 1991; 1994; 1995; 1996; 1999). Therefore, Lesnik et al. had hypothesized that if the later developing posterior neocerebellum was found to be abnormal, there would be a corresponding abnormality in the later developing prefrontal cortices. This was examined using morphometric measures of the right and left prefrontal lobes (as was done with the cerebellum), as well as by neuropsychological measures. Results of the morphometric analyses indicated that the ALL survivors had significantly smaller cortex volume in both the right and left prefrontal lobes compared to controls.

To determine whether these volumetric differences were associated with a functional difference, Lesnik et al. (1998) administered five neuropsychological tests: the Trail Making Test, parts A and B (Army Individual Test Battery, 1944), the Complex Figure Test, copy and immediate recall (Osterreith, 1944), and the Coding subtest from the WISC-III (Wechsler, 1996). The Trail Making Test part A requires the child to connect consecutively numbered circles, while part B requires the child to consecutively connect numbered and lettered circles (1-A-2-B). The Trail Making Test has been reported to assess visual-spatial attention, search and sequencing, visuomotor coordination, and cognitive flexibility – abilities associated with the prefrontal lobes. Part B is particularly associated with prefrontal regions given its requirement that the child switch between sets of stimuli by inhibiting irrelevant set and attending to the alternative set. The Complex Figure Test requires the child to copy a detailed, multi-element geometric design and then immediately reproduce it from short-term memory.

The Coding subtest from the WISC-III requires the child to copy from a legend at the top of the page. The legend is a row of numbers, 1 to 9, and each number has its own symbol. The child must fill in blank spaces beneath rows of numbers according to the legend, as quickly as possible, for 120 seconds. This task requires visual-motor integration.

Results revealed significant group differences on the Trail Making Test part B, the Complex Figure Test Immediate Recall, and the WISC-III Coding subtest. Lesnik et al. (1998) concluded that these results supported the hypothesis that children treated for ALL before five years of age, with chemotherapy, demonstrated cognitive impairment that implicated cerebellar-frontal regions.

More recently, Hill et al. (2004) investigated the functioning and integrity of the hippocampus, an earlier developing component of the cortico-limbo-diencephalic system. The hippocampus has efferent connections to the mammillary bodies and reciprocal connections to prefrontal cortex. Hill and her colleagues speculated that deficits in memory skills would accompany volumetric reductions in right and left hippocampi. They tested this in a sample of ten long-term survivors of ALL whose central nervous system prophylaxis involved only chemotherapy (intrathecal methotrexate) administered before the age of five years. Ten control children, matched for age, SES, and gender ratio were also scanned and tested. Results did not support Hill et al.'s hypothesis. No significant differences were found between the groups on measures of delayed verbal list learning, story memory, and visual-spatial learning (intervals of approximately 30 minutes from immediate recall). Furthermore, no significant differences were found between the groups on whole brain volumes, right or left hippocampal volumes, nor

hippocampal asymmetry. There were no significant associations in either group between hippocampal volume, asymmetry, and any delayed memory measure. Therefore, Hill et al. suggested that the macrostructure of the hippocampus is relatively resistant to the deleterious effects of the chemotherapy. However, they also stated that these results should be taken with caution due to the small sample size. These results support Ciesielski et al.'s (1999) and Lesnik et al.'s (1998) developmental chronometry hypothesis. Importantly, this study suggests that memory impairments observed in this population may not be due to damage in the limbic system, but, other brain regions known to contribute to memory, including the prefrontal cortex.

Given the evidence from Ciesielski et al.'s (1998) and Lesnik et al.'s (1999) findings that long-term survivors of ALL demonstrate impairments associated with an abnormality in the later developing neocerebellar-frontal subsystem, working memory may also be vulnerable to central nervous system prophylaxis in this population due to its reliance on the prefrontal regions.

Hypotheses

1. Given the vulnerability of later developing regions of the brain (e.g., mid-dorsolateral prefrontal cortex) to damage from treatment, it was predicted that long-term survivors of ALL would make significantly more errors on both the representational drawings and abstract design forms of the Petrides Self-Ordered Pointing Test compared to their healthy siblings and long-term survivors of Wilms' tumor.

2. It was predicted that the long-term survivors of ALL would have a mean BRIEF Working Memory subscale score that was significantly above (with higher scores indicating greater difficulties) that of their healthy siblings and long-term survivors of Wilms' tumor.
3. It was predicted that long-term survivors of ALL would have a mean score below (with lower scores indicating greater difficulty) that of the control groups on the Working Memory Index of the Children's Memory Scale/Wechsler Memory Scale – 3rd Edition.
4. It was predicated that long-term survivors of ALL would have a mean scaled score on the Finger Windows (spatial span) task that was significantly below that of their healthy siblings and long-term survivors of Wilms' tumor.
5. It was predicted that the long-term survivors of ALL would have poorer scores on the Digit Span Backwards compared to the Digit Span Forwards task due to the monitoring and manipulation component of the former task.

# METHOD

## Participants

The same children from Study One participated in this study. The study was approved by the Research Ethics Board at the Children's Hospital of Eastern Ontario and by the ethics committee of the Department of Psychology at Carleton University. Informed written consent was obtained for each participant from the parents, or from the participant themselves if they were 16 years or older.

## Measures and Procedures

The study was conducted at the Children's Hospital of Eastern Ontario in a small office that was quiet and without distraction. Each participant underwent approximately four hours of psychometric testing in one session. The principal investigator carried out most of the assessments. Seven participants required administration of the tests in the French language. A bilingual psychologist performed these evaluations. The principal investigator was blind to the medical history (group) of the child at the time of assessment.

Specific information regarding the materials (excluding the Self-Ordered Pointing Test), task demands, time requirements, and psychometric properties of each measure is available in Appendix C. In order to ensure accuracy, the normed measures were scored initially by the examiner, and then again by an independent psychometrist. A psychologist with provincial registration, who provided verbal feedback of the results to each family of the ALL survivors, supervised the assessments.

*The Petrides Self-Ordered Pointing Task (SOPT)*

Petrides and Milner (1982) developed the Self-Ordered Pointing Test. Although the administration of this test is standardized, it is used in experimental research and complete normative data for all age groups is not available to allow conversion of raw scores into standard scores based on age. Two versions of this task were administered. In one version, the stimuli were line drawings of common objects (representational drawings), while in the other version, the stimuli were black and white abstract designs.

In each version, the participant was shown 4 sets of pictures. The first set consisted of 6 items, the second 8, the third 10, and the fourth 12 items. Each set was presented three times. During each presentation, the participant was asked to point to a picture on each page that they had not pointed to previously. The arrangement of the pictures changed from one page to another, and the child was instructed not to point to the same location more than once. The pace of the task was rapid and set by the examiner who turned the pages and encouraged the child to point within a reasonable time frame (within 5 seconds). Five scores were derived for each version of the test. An overall score consisted of the total number of errors (i.e., choosing the same picture more than once during each presentation) for representational drawings and abstract designs. As well, the number of errors per picture set (6,8,10,12) was calculated for each version. These tasks were administered in a fixed order with representational drawings always preceding abstract pictures.

*Finger Windows*

The Finger Windows task from the Wide Range Assessment of Memory and Learning (Sheslow & Adams, 1990) was administered to each participant at the

beginning of the testing session. The Finger Windows subtest measures a child's memory of a "rote" visual pattern by manually reproducing a demonstrated spatial sequence. The examiner points to increasingly longer series of locations on a card, and the child is asked to reproduce the spatial sequences. The Finger Windows subtest is analogous to the Digit Span subtest in that discrete and relatively non-meaningful "bits of information" are presented for immediate recall. A discontinue rule of 3 consecutive errors is applied. The total number correct was calculated and converted to a scaled score using the normative data from the test manual. The Finger Windows task is an indicator of visuospatial sequential memory.

*Working Memory Index*

The subtests comprising the Working Memory Index from the Children's Memory Scale (Cohen, 1997) and the Wechsler Memory Scale, 3rd Edition (Wechsler, 1997b) were administered to each participant, depending on their age (Table 1). Participants 6 to 15 years of age were administered the Childrens Memory Scale. Those participants aged 16 and over were administered the Wechsler Memory Scale, 3rd Edition. Different subtests comprise the Working Memory Index on each of these memory batteries (Table 1). In the Children's Memory Scale, the Working Memory Index is comprised of Digit Span (forwards and backwards) and Sequencing, in which they are asked to perform several mental operations (e.g., count by 4's, say the months of the year backwards, as quickly as possible). In the Wechsler Memory Scale, 3rd Edition, the Working Memory Index is comprised of a Letter-Number span test, in which the child is asked to repeat back a series of numbers and letters after mentally reorganizing them into sequence, numbers first, in order, followed by letters in alphabetical order. The second

task is a Spatial Span test, in which the child is asked to repeat a spatial sequence demonstrated by the examiner. There is a forwards and backwards component to the test. The correlation between the Working Memory Indices of the Childrens Memory Scale and the Wechsler Memory Scale, 3rd Edition is 0.68.

*The Behavior Rating Inventory of Executive Function (BRIEF)*

This standardized questionnaire (Gioia et al., 2000) was given to one parent of each participant to complete on the day of testing. The questionnaire consists of 86 questions to which the parent could respond Never, Sometimes, or Always. Raw scores were totaled and converted to standard scores using the normative data from the test manual. The BRIEF yields a total score, called the General Executive Composite. Two subscores that contribute to the General Executive Composite are the Behavioural Regulation Index and the Metacognitive Index. The Behavioral Regulation Index is derived from three subscale scores: Inhibit, Shift, and Emotional Control. The Metacognitive Index is derived from five subscale scores: Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor.

Table 1.

*Subtests That Comprise the Working Memory Index of the Childrens Memory Scale (Ages 6 to 15) versus the Wechsler Memory Scale, 3rd Edition (ages 16 and over). The Correlation Between the Respective Working Memory Indices is 0.68 (Wechsler, 1997b).*

| Participants Less Than 16 Years of Age | Participants Older Than 16 Years of Age |
|---|---|
| **Childrens Memory Scale** | **Wechsler Memory Scale, 3rd Edition** |
| *Working Memory Index* | *Working Memory Index* |
| • Digit Span Forwards & Backwards | • Spatial Span Forwards & Backwards |
| • Sequencing | • Letter-Number Sequencing |

Statistical Analyses

The data were screened for outliers, floor or ceiling effects, distribution, and satisfaction of statistical assumptions. Raw scores on the standardized measures, the Finger Windows, Working Memory Index of the CMS/WMS-III, and the BRIEF subscales were totaled and converted to standard scores using the normative data provided for each respective test as per the respective test manuals. The Self-Ordered Pointing Test is not normed. Therefore, analyses were run on the SOPT Representational Drawings and Abstract Designs total error raw scores with age as a covariate.

A series of Multivariate Analysis of Variance (MANOVA) were run on the composite scores to test for group differences. The Finger Windows test yielded a standard score with a mean of 10 and a standard deviation of 3. The Working Memory Index of the CMS/WMS-III yielded a standard score with a mean of 100 and a standard deviation of 15. Group differences were assessed for the Finger Windows score and the Working Memory Index, separately because they are from different test batteries.

Standard scores on the BRIEF were presented as T-scores with a mean of 50 and a standard deviation of 10. An Analysis of Variance (ANOVA) was performed for groups on the General Executive Composite alone, since it is a composite of the Behavioral Regulation Index and the Metacognitive Index. A MANOVA for groups on the Behavioral Regulation Index and the Metacognitive Index was conducted. Two separate MANOVAs for groups were run on the subscales of the BRIEF, one on the three subscales that contribute to the Behavioural Regulation Index, and one on the five subscales that contribute to the Metacognitive Index.

To explore the effect of the type of modality tapped by each normed working memory subtest, the two subtests requiring the same type of processing (maintenance of information), but in different modalities, i.e., verbal and visuospatial, were compared. To that end, a MANOVA for groups was conducted on the Digit Span Forwards and Finger Windows subtests.

The Digit Span Forwards and Backwards components were analyzed separately to explore the effect of processing demand, independent of modality, in this sample, i.e., monitoring and manipulation (Digit Span Backwards) compared to just maintenance of information (Digit Span Forward). A MANOVA for groups was conducted on the Digit Span Forwards and Backwards components of this subtest.

In analyses that yielded a significant multivariate F statistic, univariate Analyses of Variance (ANOVA) were used to determine which of the dependent measures had group differences. Tukey test ($p < 0.05$) was used for posthoc pairwise comparisons between groups.

The impact of a number of independent variables was also examined: SES, the average number of days absent from school up to the completion of treatment, age at diagnosis, length of time off all treatment, participants age at the time of testing for this thesis, and whether or not the child has required special education services. First, a one-way analysis of variance was used to test for group differences for each variable. Second, a Pearson Product Moment correlation was used to investigate the relationships between these variables and performance on the BRIEF, Finger Windows, Working Memory Index, and the SOPT scores. If a correlation with the DV was significant, it was

included it in the analysis as a covariate. A Multivariate Analysis of Covariance (MANCOVA) was then run on these scores with the subsequent covariates.

The analyses up to this point were run on the pooled sample of ALL survivors regardless of whether or not they received cranial radiation therapy and at what dose. The final analysis explored the effect of cranial radiation therapy and its dosage on the BRIEF, Finger Windows, Working Memory Index, and SOPT scores using only the survivors of ALL sample. MANOVAs were used to explore the differences on all test scores between those survivors of ALL who had received cranial radiation therapy ($n$=7) as part of their treatment and those who had received chemotherapy only ($n$=9). MANOVAs were then used to explore for differences between those survivors of ALL who had received 1800 rads of cranial radiation therapy ($n$=3) and those who had received 2400 rads of cranial radiation therapy ($n$=4).

## RESULTS

The groups mean errors for the Petrides Self-Ordered Pointing Test representational drawings and abstract designs, as well as the mean errors per set of 6, 8, 10, and 12 pictures, are presented in Table 2. A MANOVA conducted on the total number of errors for representational drawings and abstract designs (raw scores), failed to reveal significant differences in errors between groups on either version of the Self-Ordered Pointing Test. In order to verify whether age was confounding, a second MANOVA with the same dependent variables was conducted with age as a covariate. This revealed that, in all groups, age was a significant covariate for both versions of this (unnormed) test, as well as for differences between the sets of 6, 8, 10, and 12. When the differences attributable to age were covaried from the analysis, no significant group differences were revealed. The age ranges for each group were as follows: 10 to 20 years for the ALL group, 8 to 20 years for the sibling group, and 6 to 19 years for the Wilms' tumor group. The distribution of age within each group did not differ across the ALL, sibling, and Wilms' tumor groups, as indicated by the Shapiro-Wilks test of normality, *statistic* = 0.95, 0.91, 0.96 ($p$>0.05), respectively. Pearson correlations between age at time of testing and number of errors on the Self-Ordered Pointing Test representational drawings and abstract designs indicated that as age increased, the number of errors decreased, $r(41)$=-0.45, $p$<0.01, and $r(41)$=-0.501, $p$=0.001, respectively. Although the sample size was not large enough to test for the effects of cranial radiation therapy versus no cranial radiation therapy, a qualitative examination of the data did not reveal a pattern of potential error

Table 2.

*Group Means and Standard Deviations for Total Errors and Number of Errors per Picture Set for Representational Drawings (RD) and Abstract Designs (AD).*

| Variable | A.L.L. *n*=16 | Siblings of A.L.L. *n*=11 | Wilms' Tumor *n*=16 |
|---|---|---|---|
| RD total errors | 14.0 (7.3) | 11.1 (6.4) | 13.4 (10.0) |
| RD 6 Pictures | 2.0 (1.6) | 1.2 (1.4) | 1.4 (1.5) |
| RD 8 Pictures | 3.0 (2.1) | 2.6 (1.6) | 2.4 (2.3) |
| RD 10 Pictures | 4.3 (2.4) | 4.0 (2.0) | 4.3 (3.8) |
| RD 12 Pictures | 4.8 (3.4) | 3.4 (2.4) | 5.4 (4.2) |
| AD total errors | 19.1 (10.7) | 15.9 (8.6) | 19.6 (9.6) |
| AD 6 Pictures | 2.3 (1.3) | 1.6 (1.6) | 2.6 (2.1) |
| AD 8 Pictures | 4.6 (2.6) | 4.1(2.5) | 4.7 (2.4) |
| AD 10 Pictures | 6.3 (3.1) | 4.5 (2.7) | 5.8 (3.2) |
| AD 12 Pictures | 6.1 (4.2) | 5.7 (3.2) | 6.6 (3.4) |

differences between these two groups. However, the correlation between age and number of errors was significant only when those who had received cranial radiation therapy ($n$=7) were included in the analysis.

The group means for Finger Windows, the Working Memory Index from the CMS/WMS-III, and the Digit Span Forwards and Backwards scores are presented in Table 3. Although the groups means were within normal limits, separate ANOVAs indicated significant group differences for Finger Windows, $F(2, 40) = 3.55$, $p < 0.05$, $p.eta^2$=0.15, *power*=0.63, and for the Working Memory Index, $F(2,41)$=6.36, $p < 0.01$, $p.eta^2$=0.25, *power*=0.88. Posthoc Tukey tests confirmed that the survivors of ALL achieved lower Finger Windows scores than did the survivors of Wilms' tumor. They did not differ significantly from their siblings. The ALL survivors, however, achieved lower Working Memory Index scores than both control groups. The control groups did not differ significantly from each other on either measure.

A MANOVA conducted on the Digit Span Forwards and Finger Windows subtests indicated significant group differences overall, $F(2.39)$=7.82, $p$=0.001, $p.eta^2$=0.29, *power*=0.936. Separate ANOVAs revealed that the groups differed on both the Digit Span Forwards, $F(2,39)$=6.33, $p$<0.01, $p.eta^2$=0.25, *power*=0.875, and Finger Windows, $F(2,39)$=4.32, $p$<0.05, $p.eta^2$=0.18, *power*=0.717, subtests. Posthoc Tukey tests confirmed that the survivors of ALL achieved lower Digit Span Forwards scores than did both control groups. As stated previously, the survivors of ALL achieved lower scores than the survivors of Wilms' tumor on the Finger Windows subtest, but did not differ from their siblings on this measure. The control groups were not significantly different from each other on either subtest.

Table 3.

*Group Means and Standard Deviations for Finger Windows, the Working Memory Index, Digit Span Forwards, and Digit Span Backwards. In Order to Facilitate Interpretation of the Different Test Means and Standard Deviations, the Pertinent Population Means and Standard Deviations are Presented Underneath the Variable Name in the First Column.*

| Variable | A.L.L. *n*=16 | Siblings of A.L.L. *n*=11 | Wilms' Tumor *n*=16 |
|---|---|---|---|
| Finger Windows[a] (μ=10, SD=3) | 9.5 (3.3) | 11.1 (2.4) | 12.0 (2.2) |
| Working Memory Index[b] (μ=100, SD=15) | 89.9 (19.0) | 108.2 (12.5) | 109.6 (17.1) |
| Digit Span Forwards[c] (*z* scores) | -0.93 (0.92) | 0.20 (0.83) | 0.13 (1.10) |
| Digit Span Backward[a] (*z* scores) | -0.68 (0.87) | 0.64 (0.98) | 0.30 (1.01) |

[a]ALL < Wilms' tumor, $p < 0.05$

[b]ALL < controls, $p<0.05$

[c]ALL < controls, $p<0.01$

A MANOVA conducted on the Digit Span Forwards and Backwards subtests indicated significant group differences overall, $F(2.39)=7.13$, $p<0.01$, $p.eta^2=0.27$, $power=0.912$. Separate ANOVAs revealed that the groups differed on both the Digit Span Forwards, $F(2,39)=6.32$, $p<0.01$, $p.eta^2=0.25$, $power=0.875$, and Backwards, $F(2,39)=4.40$, $p<0.05$, $p.eta^2=0.18$, $power=0.725$, subtests. Posthoc Tukey tests confirmed that the survivors of ALL achieved lower Digit Span Forwards scores than did both control groups. However, they achieved lower Digit Span Backwards scores compared to the survivors of Wilms' tumor only, performing comparably to their siblings on this component of the Digit Span subtest. The control groups were not significantly different from each other on either subtest.

The group means for the BRIEF Indices are presented in Table 4. T-scores 65 to 69 indicate a moderate level of difficulty, while T-scores >70 indicate a clinically significant level of difficulty. Although the mean scores for each group were within normal limits, analyses revealed significant group differences. The ANOVA indicated that the groups differed significantly on the General Executive Composite, $F(2,40) = 3.57$, $p < 0.05$, $p.eta^2=0.151$, $power=0.63$. Post-hoc tests using Tukey test indicated that the T-scores for survivors of ALL were greater than that of their healthy siblings, but not significantly higher than that of the survivors of Wilms' tumor. The two control groups were not different from each other. The MANOVA conducted on the Behavioral Regulation Index and the Metacognitive Index revealed significant differences between

Table 4.

*Group Means and Standard Deviations for the BRIEF Indices.*

| Variable (μ=50, SD=10) | ALL *n*=16 | Siblings *n*=11 | Wilms' tumor *n*=16 |
|---|---|---|---|
| Global Executive Composite Score[a] | 58.6 (11.5) | 47.3 (9.9) | 52.3 (11.3) |
| Behavioural Regulation Index | 54.6 (13.4) | 46.1 (10.0) | 52.9 (13.0) |
| Metacognition Index[a] | 59.8 (10.8) | 48.4 (10.5) | 51.6 (10.0) |
| Inhibit | 52.9 (11.6) | 49.1 (10.3) | 50.4 (10.2) |
| Shift | 55.3 (13.6) | 45.9 (8.4) | 52.6 (13.7) |
| Emotional Control | 53.8 (14.0) | 44.6 (9.0) | 54.6 (13.3) |
| Initiate | 57.9 (13.9) | 49.8 (10.4) | 50.0 (8.5) |
| Working Memory[b] | 63.1 (12.6) | 49.7 (10.5) | 49.8 (10.4) |
| Plan/organize[c] | 59.1 (12.7) | 48.5 (8.7) | 51.5 (11.4) |
| Organization of materials | 56.1 (9.8) | 48.6 (12.2) | 54.1 (7.7) |
| Monitor | 55.3 (10.0) | 46.0 (8.7) | 51.1 (10.6) |

[a] ALL < siblings, $p < 0.05$
[b] ALL < controls $p < 0.05$
[c] $p < 0.05$, no specific group differences revealed

groups, $F(10,72) = 2.62$, $p < 0.05$, $p.eta^2=0.12$, $power=0.71$. Consequently, univariate ANOVAs were conducted and indicated that groups differed significantly on the Metacognitive Index score, $F(2,40) = 4.48$, $p < 0.05$, $p.eta^2=0.18$, $power=0.74$, but not on the Behavioral Regulation Index score. Tukey post-hoc tests showed that the survivors of ALL were rated higher on the Metacognitive Index by their parents compared to their healthy siblings but not more than survivors of Wilms' tumor were. Again, the two control groups did not differ significantly from each other. A MANOVA on the five subscales that contribute to the Metacognitive Index revealed significant differences between groups, $F(4,78) = 1.97$, $p < 0.05$, $p.eta^2=0.22$, $power=0.83$. ANOVAs were then performed and these indicated that the survivors of ALL had significantly elevated scores, indicating more difficulties, compared to both control groups on the following subscales: Working Memory, $F(2,40) = 6.99$, $p < 0.01$, $p.eta^2=0.26$, $power=0.91$,and Plan/Organize, $F(2,40) = 3.26$, $p < 0.05$, $p.eta^2=0.14$, $power=0.58$. Group differences on the Monitor subscale approached significance, $F(2,40) = 2.82$, $p =$ ns, $p.eta^2=0.12$, $power=0.52$. Although the mean T-score for the ALL group on the Working Memory subscale was within normal limits, three survivors of ALL were in the clinically significant range on this subscale, compared to none of the siblings, and only one of the survivors of Wilms' tumor. An examination of the data did not indicate that these three children had more errors on the Petrides' SOPT, have lower scores on measures of IQ, memory, or working memory, or have more structural abnormalities on CT or MRI compared to other survivors of ALL. They did not receive greater amounts of CRT than the other survivors of ALL. The distribution of scores is illustrated in Figure 4. Post-hoc Tukey tests did not indicate specific group differences on the Plan/Organize subscale.

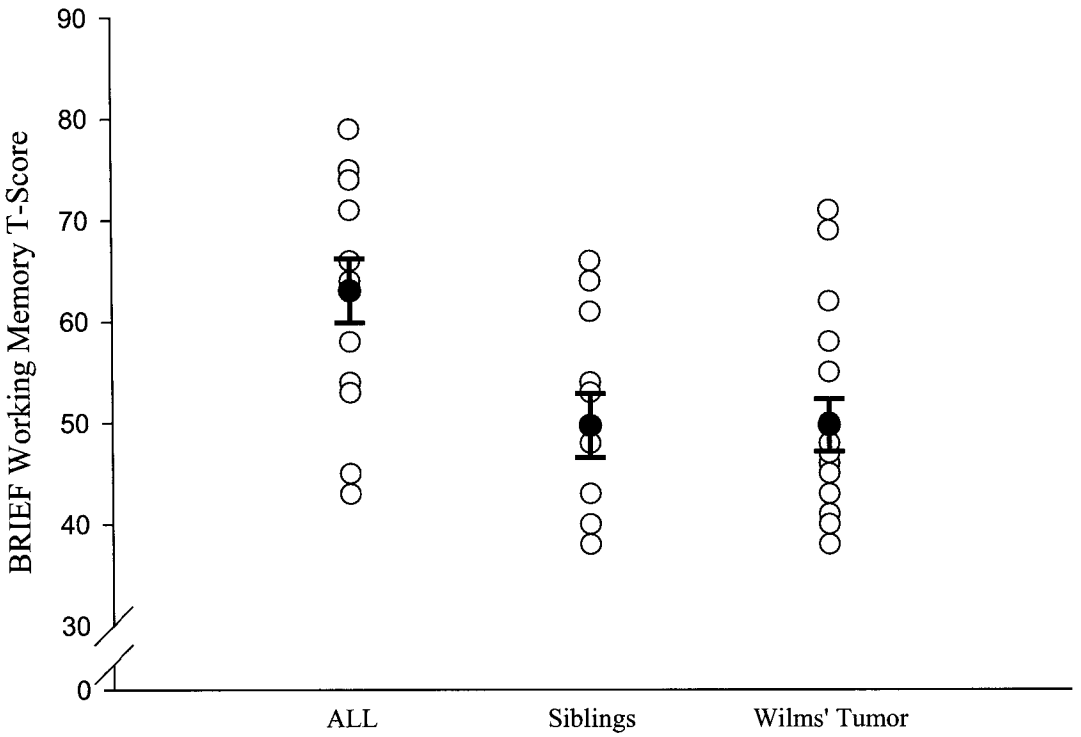



Figure 4. Distribution, Mean, and Standard Error of the Mean for Each Group on the BRIEF Working Memory Index

# DISCUSSION

Results of three of the four measures of working memory suggested that survivors of ALL have a relative weakness in working memory. Specifically, long-term survivors of ALL had significantly lower scores on the Working Memory Indices of the CMS/WMS-III compared to both control groups. They also had significantly lower scores on the Finger Windows test compared to the survivors of Wilms' tumor. Survivors of ALL were reported by their parents to more frequently display symptoms indicative of difficulties, specifically as measured by the Working Memory subscale of the BRIEF, as compared with parental report for both control groups. These results supported Hypotheses Two, Three, and Four.

The first hypothesis, that survivors of ALL would perform poorly compared to control groups on a task designed to measure the functional integrity of the dorsolateral prefrontal cortex, was not supported in this study. Neither version of the Petrides Self-Ordered Pointing Test distinguished the survivors of ALL from the control groups. It is possible that the sample size in this study was too small to detect potential group differences on the Self-Ordered Pointing Test, which was not normed. Alternatively, this sample may not have a deficit associated with the dorsolateral prefrontal lobes.

The differences in results across the working memory measures (i.e., the SOPT vs. Finger Windows, Working Memory Index, and BRIEF) could be accounted for by differences in the manner in which they measure working memory. It can be argued that the requirement for sequencing is the main difference between the SOPT and the standardized working memory measures. That is, the standardized measures require sequencing whereas the SOPT does not. The ventrolateral prefrontal region has been

implicated in sequential organization of information retrieved from posterior association regions (Owen, 1997; Petrides et al., 1993a, 1993b, 1994a, 1994b). It is possible that the ventrolateral prefrontal cortex was impacted to a greater extent than the dorsolateral prefrontal cortex. Petrides' research (1995a, 1995b) has indicated that the ventrolateral prefrontal regions are the most activated during externally ordered tasks. The conditioned spatial association test is an externally ordered task that requires the child to learn, through repeated trials, which spatial location matches a target item. It is possible that the administration of the conditioned spatial association test would have revealed deficits associated with damage in this brain region.

In the present sample, performance on the digit span and spatial span tests was worse in the survivors of ALL compared to the control groups for both the forwards and backward components of the test, which did not support the sixth hypothesis. Therefore, the requirement to maintain versus manipulate the rote information did not distinguish the groups. Furthermore, the type of information, i.e., auditory or spatial, was not a distinguishing feature in their performance (Digit Span Forwards and Finger Windows). These results are not readily interpretable using either Goldman-Rakic's or Petrides' models of working memory. Goldman-Rakic's model proposes that working memory is organized in the prefrontal cortex by domain. That is, the modality of the information will determine which area of the lateral prefrontal cortex will be involved. Petrides' proposes that information is organized according to the process required. That is, maintenance/monitoring and manipulation of information involve different regions of the lateral prefrontal cortex, respectively.

An alternative model could account for the findings. The results of this study implicate difficulties with the *central executive*, a component of working memory proposed by Baddeley (1986). The central executive is a theoretical construct proposed to interface with long-term memory and bring working memory into conscious awareness (Baddeley, 1998). The central executive is also thought to mediate the ability to focus, divide, and switch attention. It is assumed to be associated with the prefrontal lobes, but more research is needed to solidify this association (Baddeley, 2000). Given its interfacing role to long-term memory from working memory, difficulties with the central executive would be consistent with parent reports that the survivors of ALL have difficulty remembering material the next morning after supposedly mastering it the night before (Pui, 2000). Furthermore, the lower scores on both span measures (verbal and spatial), associated with the phonological loop and visuospatial sketchpad, respectively, suggest a defective execute component as opposed to a deficit in the slave systems. A follow-up study that tests the capacity of the central executive to coordinate activity in the two slave systems seems warranted. For example, one could ask participants to perform the digit span task, thus occupying the phonological loop, while simultaneously performing a visuospatial tracking task, thus occupying the visuospatial sketchpad. Adjusting task difficulty to a point where all study groups are operating at an equivalent level when the tasks are performed independently, scores on each task could then be compared between the survivors of ALL and the control groups. If the central executive were compromised, the survivors of ALL should have greater difficulty as the digit and visuospatial span increased, compared to the control groups.

# CHAPTER SIX

## GENERAL DISCUSSION

The purpose of this thesis was to investigate the iatrogenic effects of central nervous system prophylaxis in children treated for childhood ALL. The first study examined intelligence and short-term memory for verbal and visual information, as well as delayed memory and delayed recognition of verbal and visual information. The second study investigated the neuroanatomical integrity of the brains of the ALL survivors. The third study examined working memory using tests requiring maintenance, monitoring, and manipulation of verbal, visual, and spatial information.

A significant amount of effort was made to reduce the impact of confounding variables, as follows. To reduce sampling bias the entire cohort was approached for participation and 67% were enrolled in the study. Reasons for nonparticipation were documented and no child refused to participate for health reasons or due to medical history. Medical history was documented and no child had suffered extraneous medical problems such as head injury, seizures, or illness involving the central nervous system. Any children with central nervous system involvement at diagnosis of ALL were excluded. Long-term survivors of ALL received equivalent chemotherapy and differed only in whether or not they received cranial radiation therapy. To control for socioeconomic status, a sibling control group was included. To control for the effects of having a life threatening illness, a non-central nervous system control group, Wilms' Tumor, was included. The lack of randomization to central nervous system prophylaxis groups and a small sample size were two uncontrollable study limitations. However, this is the norm throughout the literature on this population. Certainly, the generalizability of

results to other childhood conditions that impact early brain development would be increased with a larger sample size, when possible. Power analyses were conducted in order to determine the probability of achieving significance under the same conditions, and effect size ($eta^2$) was indicated since it was not dependent on sample size. It should be noted that for almost all significant findings reported, power was at 0.75 or greater. Effect size showed that 15 or more percent of the variance could be explained by group membership, which is within expectations for a clinical study of this type. It is also important to note that all subjects were relatively intact other than the difficulties revealed by the testing. Thus, the effect sizes shown would be commensurate with subtle changes due to treatment.

Study One was conducted to measure intelligence and short-term verbal and visual memory in the sample of ALL survivors and to compare their scores to those of two control groups. Although mean IQ scores for the long-term survivors of ALL were in the Average range, they performed below the level of their siblings and Wilms' tumor survivors on all three IQ scales: Full Scale IQ, Verbal IQ and Performance IQ. This is consistent with reports in the literature in which cognitive assessments were conducted on long-term survivors of ALL two or more years after completing all treatment (e.g., Goff et al., 1980; Ochs et al., 1991). Mean scores on measures of short-term memory were within one standard deviation of the normative mean for all groups. There were no group differences on measures of Visual Immediate and Delayed or Delayed Recognition memory. Long-term survivors of ALL scored below the survivors of Wilms' Tumor on the General Memory Index. Differences between groups on the Immediate and Delayed Verbal Memory Indices approached, but did not reach, significance once a Bonferroni

correction was applied. Therefore, while results do indicate a deficit in general memory ability, power may have been too low to further determine whether the verbal or visual modalities, or both, were impacted.

Study Two investigated the prevalence of leukoencephalopathy in these survivors of ALL, using MRI and CT scans, which were obtained for all but one of the participants. It was expected that higher MRI and CT leukoencephalopathy scores (based on a 5-point likert scale, with a higher number indicating greater abnormality) would be negatively associated with IQ and memory scores. With a score of zero indicating no brain abnormalities, an examination of the neuroimages revealed that 40% had a score greater than zero on MRI, and 33% had a score greater than zero on CT. However, the results of the Common Toxicity Criteria scale were not predictive of performance on measures of IQ and Memory obtained in Study One, albeit, the male with severe abnormalities on both MRI and CT also had the lowest IQ scores of the ALL group. The lack of significant association between scan results and cognitive test scores was likely because all but two of the survivors of ALL with scores above 0 had scores of 1, which limited the range of scores. In general, the rate of abnormalities observed in this sample is in agreement with the majority of studies, albeit, the cognitive testing conducted in Study One suggested more cognitive impairment in this group than would be expected given the neuroimaging findings. The possibility that the MRI and CT techniques are sensitive to only gross abnormalities is an important consideration for future research.

Whether or not a participant received cranial radiation, and at what dose, was not associated with the presence of scan abnormalities. Of the two females scanned, one showed significant abnormalities. Because females are believed to be more vulnerable to

the late effects of treatment, it is possible that the male majority in this sample may have resulted in an underestimation of the rate of abnormalities in this population.

The third study focused on working memory. The idea of examining working memory in this population was inspired by the work of Ciesielski, Lesnik and their colleagues (1999; 1998). These researchers hypothesized that the later developing regions of the central nervous system should be most vulnerable to neurotoxicity because their development is more protracted and is still ongoing when treatment is administered. Their research implicated the neocerebellum and the prefrontal lobes. Research has indicated that the neocerebellum projects specifically to the dorsolateral prefrontal cortex (Middleton et al., 2001). For this reason, an unnormed test used in research, the Petrides Self-Ordered Pointing Test, was included in this study. Neuroimaging studies with human participants indicated that the Petrides Self-Ordered Pointing Test (Petrides & Milner, 1982) is sensitive to the integrity of mid-dorsolateral prefrontal function (Petrides, 1995). The three study groups were administered two versions of the Petrides Self-Ordered Pointing Test: the representational drawings and the abstract designs. However, the number of errors on both versions was negatively correlated with age at time of testing and no group differences were found once age was partialled out. If replicated, an effort should be made to gather as many participants as possible of each age, for each group, or to test only children of a certain age, so that any true differences on this task can be revealed.

The remaining tests administered to participants were all standardized tests of working memory. Although their overall mean scores were within normal limits, survivors of ALL were significantly lower than control groups on measures of Digit Span

Forwards and Backwards, Spatial Span Forwards and Backwards, and Sequencing. Neither the type of information (verbal vs. spatial) nor the process required for recall (monitoring vs. manipulation) distinguished the groups. This global weakness implicates a non-localized nature of structural deficits and suggests a single underlying deficit. Baddeley's theoretical construct, the central executive, may be the most useful for interpreting these findings. Incorporating measures designed to test the integrity of the central executive would be the next logical step in this research.

Speed of information processing was not directly measured in this thesis. But how much it contributed to the significantly lower cognitive scores in the survivors of ALL is a valid question, particularly considering the studies reporting white matter damage in this population (i.e., Price & Jamieson, 1975; Stehbens et al., 1991). Schatz, Kramer, Ablin, and Matthay (2000) evaluated the relationship between processing speed, working memory, and IQ in 27 long-term (off all treatment 3 or more years) survivors of ALL compared with 27 demographically matched controls. Fifteen of the 27 survivors of ALL had received 1800 rads of CRT and 3 had received 2400 rads of CRT. The rest received only chemotherapy for CNS prophylaxis. Working memory was assessed using four tasks that examined verbal and spatial memory span with and without a secondary task that elicits interference. Processing speed was evaluated using a series of reaction-time tasks completed on a computer. In this study, only the survivors of ALL who received either dose of CRT were significantly below controls on measures of intelligence, working memory, and processing speed. A simultaneous regression analysis with working memory as the dependent variable and group and processing speed as the independent variables indicated that processing speed was an important moderator of

working memory but group differences in working memory were not accounted for by processing speed alone. Although this study suggests that processing speed may not account for all of the differences on working memory tasks, this finding merits replication. The addition of tests of processing speed to future studies addressing working memory in long-term survivors of ALL is an important factor in delineating the nature of working memory deficits in this population.

Another area of consideration not addressed by standardized tests in this thesis, due to time constraints, was the relationship between memory and attention. Attentional processes have been investigated less frequently in long-term survivors of ALL. Attention is a prerequisite for memory and learning (Butler, 1998) and an important question is whether memory impairments in this population are rooted in problems with attention. However, attention is not a unitary construct and there is considerable ambiguity regarding the definition of the components of attention and concentration (Butler, 1998). The literature remains ambiguous regarding this topic, but the reader is referred to Brouwers and Poplack (1990), Lockwood, Bell, and Colegrove (1999), and Rodgers, Horrocks, Britton, and Kernahan (1999).

In summary, the results of the three studies provided a clear picture of this sample of survivors of ALL compared to the siblings and survivors of Wilms' tumor control groups. The survivors of ALL had lower overall intelligence compared to the control groups. Although their intelligence was within normal limits, significantly more survivors of ALL were below Average intellectually. Although the range of scores on the Common Toxicity Criteria scale, used to rate the CT and MRI scans, was limited, 33% of the survivors of ALL were found to have abnormalities on CT and 40% were

found to have abnormalities on MRI. Working memory deficits were observed in two measures: the Working Memory Index of the CMS/WMS-III, which were comprised of digit and spatial span tests, as well as the Finger Windows test, a spatial span task. Parents also reported more working memory difficulties on the Working Memory Index of the BRIEF questionnaire, such as difficulty following multi-step directions.

Taken together, these studies contribute to an understanding of how CNS prophylaxis impacts cognitive function in survivors of childhood ALL. Future research on the impact of the protocol administered to the current sample of survivors of ALL is unlikely given that the protocol is no longer in use. However, research on cancer treatment protocols, which use chemotherapy for CNS prophylaxis, continues to be important. With respect to investigating neurotoxicity in children, we suggest that research protocols incorporate measures of working memory as supported by the results of Study Three. Baddeley's model of working memory is the best fit for the results of that study. A proposed next step in this research is to include dual-task performance to test the capacity of the central executive to coordinate activity of the two slave systems. This is suggested based on the results of Study Three, which showed that survivors of ALL performed worse than controls on both measures of span, verbal and spatial, which tap the phonological loop and visuospatial sketchpad, respectively. It is proposed that an underlying executive process is the source of the weakness revealed on the standardized working memory tasks administered in this study.

In conclusion, this thesis demonstrated that working memory was impacted in a sample of long-term survivors of ALL compared to their siblings and to long-term survivors of Wilms' Tumor. The results of Study Three are best explained using

Baddeley's model of working memory. Specifically, difficulties with skills associated with the central executive were strongly implicated. The next step in this research is to more fully investigate the functioning of the central executive in this population.

## References


Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4 to 18 and 1991 Profile*. Burlington: University of Vermont, Department of Psychiatry.

Archibald, S. J. & Kerns, K. A. (1999). Identification and description of new tests of executive functioning in children. *Child Neuropsychology, 5*(2), 115-129.

*Army Individual Test Battery: Manual of Directions and Scoring.* Washington DC: War Dept., Adjutant General's Office.

Asato, R., Akiyama, Y., Ito, M., Kubota, M., Okumura R., Miki, Y., et al. (October 1, 1992). Nuclear magnetic resonance abnormalities of the cerebral white matter in children with acute lymphoblastic leukemia and malignant lymphoma during and after central nervous system prophylactic treatment with intrathecal methotrexate. *Cancer, 70*(7), 1997-2004.

Aur, Rhomes J. A., Simone, J. V., Hustu, H. O., & Verzosa, M. S. (1972). A comparative study of central nervous system irradiation and intensive chemotherapy early in remission of childhood acute lymphocytic leukemia. *Cancer, 29 (2),* 381-391.

Baddeley, A. D. (1986). *Working Memory*. Oxford: Oxford University Press.

Baddeley, A. D. (1998). Recent developments in working memory. *Current Opinion in Neurobiology, 8,* 234-238.

Baddeley, A. D. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences, 4 (11),* 417-423.

Baddeley, A. D. (2003). Working memory: Looking back and looking forward. *Nature Reviews, 4,* 829-839.

Baddeley, A. D., & Hitch, G. (1974). Working Memory. In G. A. Bower (Ed.), *The Psychology of Learning and Motivation.* New York: Academic Press.

Bakke, S. J., Fossen, A. & Storm-Mathiesen, I. (1993). Long-term cerebral effects of CNS chemotherapy in children with acute lymphoblastic leukemia. *Pediatric Hematology and Oncology, 10,* 267-270.

Balsom, W. R., Bleyer, A., Robison, L. L., Heyn, R. M., Meadows, A. T., Sitarz, A., et al. (1987). Intellectual functioning in long-term survivors of childhood acute lymphoblastic leukemia: Protective effect of pre-irradiation methotrexate? A children's cancer study group study. *Medical and Pediatric Oncology, 19,* 486-492.

Behin, A. & Delattre, J-Y. (2003). Neurologic sequelae of radiotherapy on the nervous system. In: David Schiff & Patrick Y. Wen (Eds.). *Cancer Neurology in Clinical Practice.* New Jersey: Humana Press, pp. 215-231.

Bleyer, W. A. (1995). Leukoencephalopathy detectable by magnetic resonance imaging: Much ado about nothing? Regarding Matsumoto et al., IJROBP 32:913-918; 1995. *International Journal of Radiation, Oncology, Biology & Physiology, 32*(4), 1251-1252.

Bleyer, W.A. (1988). Central nervous system leukemia. *Pediatric Clinics of North America, 35,* 789-814.

Bonner, J. A. (2000). Interaction of Chemotherapy and Radiation. In: Leonard L. Gunderson and Joel E. Tepper (Eds). *Clinical Radiation Oncology*. Pennsylvania: Churchill Livingstone, pp. 141-155.

Brass, M., Zysset, S., & von Cramon, D. Y. (2001). The inhibition of imitative response tendencies. *Neuroimage, 14,* 1416-1423.

Brickenkamp, R. (1981). Test d2 Aufmerksamkeits-Belastungs-Test. 7th ed. Gottingen, Germany, *Verlag fur Psychologie*. Dr. CJ Hogrefe.

Brouwers P. & Poplack D. (1990). Memory and learning sequelae in long-term survivors of acute lymphoblastic leukemia: association with attention deficits. *The American Journal of Pediatric Hematology/Oncology, 12*(2), 174-181.

Brouwers P., Riccardi R., Fedio P., & Poplack D. G. (1985). Long-term neuropsychologic sequelae of childhood leukemia: Correlation with CT brain scan abnormalities. *The Journal of Pediatrics, 106*(5), 723-728.

Brown, R. T., Madan-Swain, A., Walco, G. A., Cherrick, I., Ievers, C. E., Conte, P. M., et al. (1998). Cognitive and academic late effects among children previously treated for acute lymphocytic leukemia receiving chemotherapy as CNS prophylaxis. *Journal of Pediatric Psychology, 23 (5),*333-340.

Brown, R. T. & Madan-Swain, A. (1993). Cognitive, neuropsychological, and academic sequelae in children with leukemia. *Journal of Learning Disabilities, 26*(2), 74-90.

Brown, R. T., Madan-Swain, A., Pais, R., Lambert, R. G., Baldwin K., Casey R., et al. (1992a). Cognitive status of children treated with central nervous system prophylactic chemotherapy for acute lymphocytic leukemia. *Archives of Clinical Neuropsychology, 7*, 481-497.

Brown, R. T., Madan-Swain, A., Pais, R., Lambert, R. G., Sexson, S. & Ragab, A. (1992b). Chemotherapy for acute lymphocytic leukemia: Cognitive and academic sequelae. *The Journal of Pediatrics, 121*(6), 885-889.

Buschke, H., & Fuld, P. A. (1974). Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology, 24 (11)*, 1019-1025.

Butler R. W. (1998). Attentional processes and their remediation in childhood cancer. *Medical and Pediatric Oncology Supplement, 1*, 75-78.

Cetingul, N., Aydinok, Y., Kantar, M., Oniz, H., Kavakli, K., Yalman, O., et al. (1999). Neuropsychologic sequelae in the long-term survivors of childhood acute lymphoblastic leukemia. *Pediatric Hematology and Oncology, 16 (3),* 213-220.

Chugani, H. T., & Phelps, M. E. (1986). Maturational changes in cerebral function in infants determined by 18FDG positron emission tomography. *Science, 231 (4740),* 840-843.

Ciesielski, K. T., Lesnik, P. G., Benzel, E. C., Hart, B. L., & Sanders, J. A. (1999). MRI morphometry of mammillary bodies, caudate nuclei, and prefrontal cortices after chemotherapy for childhood leukemia: multivariate models of early and late developing memory subsystems. *Behavioral Neuroscience, 113*(3), 439-450.

Cohen C. (1997). *Manual for the Children's Memory Scale.* San Antonio, TX: The Psychological Corporation.

Cohen, R. A. (1993). *The Neuropsychology of Attention.* New York: Plenum Press.

Copeland D. R., Dowell R. E. Jr., Fletcher J. M., Bordeaux J. D., Sullivan M. P., Jaffe N., et al. (January 1988). Neuropsychological effects of childhood cancer treatment. *Journal of Child Neurology, 3,* 53-62.

Cousens P., Ungerer J. A., Crawford J. A., & Stevens M. M. (1991). Cognitive effects of childhood leukemia therapy: A case of four specific deficits. *Journal of PediatricPsychology, 16*(4), 475-488.

Cousens P., Waters B., Said J., & Stevens M. (1988). Cognitive effects of cranial irradiation in leukaemia: A survey and meta-analysis. *Journal of Child Psychology and Psychiatry, 29* (6), 839-852.

Della Sala, S., Gray, C., Baddeley, A., Allamano, N., & Wilson, L. (1999). Pattern span: a tool for unwelding visuo-spatial memory. *Neuropsychologia, 37,* 1189-1199.

D'Esposito, M., & Postle, B. R. (1999). The dependence of span and delayed-response performance on prefrontal cortex. *Neuropsychologia, 37,* 1303-1315.

D'Esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Atlas, S., & Grossman, M. (1995). The neural basis of the central executive system of working memory. *Nature, 378,* 279-281.

Diamond, A. (1985). Development of the ability to use recall to guide action, as indicated by infants' performance on AB. *Child Development, 56 (4),* 868-883.

Diamond, A. (1990). Developmental time course in human infants and infant monkeys, and the neural bases of, inhibitory control in reaching. *Annals New York Academy of Science, 608,* 669-676.

Diamond, A. (2002). Normal development of prefrontal cortex from birth to young adulthood: Cognitive functions, anatomy, and biochemistry. In: Donald T. Stuss & Robert T. Knight (Eds.). *Principles of Frontal Lobe Function.* New York: Oxford University Press, pp. 466-503.Diamond, A., & Doar, B. (1989). The performance of human infants on a measure of frontal cortex function, the delayed response task. *Developmental Psychobiology, 22 (3),* 271-294.

Diamond C. A., & Matthay K. K. (March 1988). Childhood acute lymphoblastic leukemia. *Pediatric Annals, 17*(3), 156-170.

Diamond, A., Kirkham, N., & Amso, D. (2002). Conditions under which young children can hold two rules in mind and inhibit a prepotent response. Developmental Psychology, 38 (3), 352-362.

Diamond, A., Prevor, M. B., Callender, G., & Druin, D. P. (1997). Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. *Monographs of Social Research in Child Development, 62 (4): i-v,* 1-208.

Dorland (1988). *Dorland's Illustrated Medical Dictionary, 27th Edition.* Philadelphia: W.B. Saunders Co.

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neuroscience, 23 (10),* 475-483.

Eiser, C. (1980). Effects of chronic illness on intellectual development. A comparison of normal children with those treated for childhood leukaemia and solid tumours. *Archives of Disease in Childhood, 55,* 766-770.

Eiser, C. & Tillman, V. (2001). Learning difficulties in children treated for acute lymphoblastic leukaemia (ALL). *Pediatric Rehabilitation, 4(3),* 105-118.

Esseltine, D. W., Freeman, C. R., Chevalier, L. M., Smith, R., O'Gorman, A. M., Dube, J., et al. (1981). Computed tomography brain scans in long term survivors of childhood acute lymphoblastic leukemia. *Medical and Pediatric Oncology, 9,* 429-438.

Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F. Jr., & Wolff, J. A. (1948). Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). *The New England Journal of Medicine, 238*(23), 787-793.

Ferguson Noyes, N. (1986). Chemotherapy. In: M.J. Hockenberry, & D. K. Coody (Eds.). *Pediatric Oncology and Hematology. Perspectives on Care. T*oronto: The C. V. Mosby Company, pp. 309-337.

Fiez, J. A., Raife, E. A., Balota, D. A., Schwarz, J. P., Raichle, M. E., & Petersen, S. E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. *The Journal of Neuroscience, 16*(2), 808-822.

Flanagan, D. P., & Ortiz, S. (2001). *Essentials of Cross-Battery Assessment.* Toronto, ON: John Wiley & Sons, Inc.

Fletcher, J. M., & Copeland, D. R. (1988). Neurobehavioral effects of central nervous System prophylactic treatment of cancer in children. *Journal of Clinical and Experimental Neuropsychology, 4,* 495-538.

Fox, N. A., & Bell, M. A. (1990). Electrophysiological indices of frontal lobe development. Relations to cognitive and affective behavior in human infants over the first year of life. *Annals New York Academy of Science, 608,* 677-698.

Frankel, S. R., Stock, W., Byrd J., & Bloomfield, C. D. (2001). Acute Lymphoblastic Leukemia. In: Charles M. Haskell (Ed.) *Cancer Treatment, 5th Edition.* Pennsylvania: WB Saunders Company, pp. 1438-1474.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: Evidence for mnemonic "scotomas". *The Journal of Neuroscience, 13 (4),* 1479-1497.

Funahashi, S., Chafee, M. V., & Goldman-Rakic, P. (1993). Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature, 365,* 753-756.

Fuster, J. M. (1990). Inferotemporal units in selective visual attention and short-term memory. *Journal of Neurophysiology, 64 (3),* 681-697.

Gamis, A. S., & Nesbit, M. E. (1991). Neuropsychologic (cognitive) disabilities in long-term survivors of childhood cancer. *Pediatrician, 1991,* 11-19.

Gaynon, P. S., Trigg, M. E., & Uckun, F. M. (2000). Childhood Acute Lymphoblastic Leukemia. In: Robert C. Blast Jr., Donald W. Kufe, Raphael E. Pollack, Ralph R. Weichselbaum, James F. Holland, & Emil Frei III (Eds.). *Cancer Medicine, 5th Edition.* Pennsylvania: WB Saunders, pp. 2140-2150.

Ghelani, K., Spiegler, B. J., & Humphries, T. (2000). Arithmetic processing in adolescents treated for leukemia. *Poster presentation*, Toronto, ON.

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). *BRIEF: Behavior Rating Inventory of Executive Function – Professional Manual.* Odessa, FL: Psychological Assessment Resources, Inc.

Giralt, J., Ortega, J. J., Olive, T., Verges, R., Forio, I. & Salvador, L. (1992). Long-term neuropsychologic sequelae of childhood leukemia: comparison of two CNS prophylactic regimens. *International Journal of Radiation, Oncology, Biology and Physiology, 24*, 49-53.

Goff, J. R., Anderson, H. R. & Cooper, P. F. (December 1980). Distractibility and memory deficits in long-term survivors of acute lymphoblastic leukemia. *Developmental and Behavioral Pediatrics, 1*(4), 158-163.

Goldman-Rakic, P. (1996). Regional and cellular fractionation of working memory. *Proceedings of the National Academy of Sciences U.S.A., 93 (24)*, 13473-13480.

Goldman-Rakic, P. (1995). Architecture of the prefrontal cortex and the central executive. Annals of the New York Academy of Science, 769, 71-83.

Goldman-Rakic, P. (1987). Development of Cortical Circuitry and Cognitive Function. *Child Development, 58,* 601-622.

Greenberg, D. B. (1998). Radiotherapy. In: Jimmie C. Holland (Eds.). *Psycho-Oncology.* New York: Oxford University Press, pp. 269-276.

Haaxma-Reiche, H. (2003). Leukemia. In: David Schiff & Patrick Y. Wen (Eds.). *Cancer Neurology in Clinical Practice.* New Jersey: Humana Press, pp. 215-231.

Halberg, F. E., Kramer, J. H., Moore, I. M., Wara, W. M., Matthay, K. K., & Ablin, A. R. (1991). Prophylactic cranial irradiation dose effects on late cognitive function in children treated for acute lymphoblastic leukemia. *International Journal of Radiation, Oncology, and Biological Physics, 22,* 13-16.

Halperin, E. C. (1986). Radiation therapy. In: M.J. Hockenberry, & D. K. Coody (Eds.). *Pediatric Oncology and Hematology. Perspectives on Care.* Toronto: The C. V. Mosby Company, pp. 339-346.

Harila-Saari A. H., Paakko E. L., Vainionpaa L. K., Pyhtinen J., & Lanning B. M. (1998). A longitudinal magnetic resonance imaging study of the brain in survivors of childhood acute lymphoblastic leukemia. *Cancer, 83*, 2608-2617.

Harten, G., Stephani, U., Henze, G., Langermann, H.-J., Riehm, H. & Hanefeld, F. (1984). Slight impairment of psychomotor skills in children after treatment of acute lymphoblastic leukemia. *European Journal of Pediatrics, 142*, 189-197.

Harwood-Nash D. C. F., & Reilly B. J. (Feb. 1970). Calcification of the basal ganglia following radiation therapy. American Journal of Roentogenology, Radium Therapy and Nuclear *Medicine, 108*(2), 392-395.

Haupt R., Fears T. R., Robison L. L., Mills J. L., Nicholson S., Zeltzer L. K., et al. (1994). Educational attainment in long-term survivors of childhood acute lymphoblastic leukemia. Journal of the American Medical Association, 272(18), 1427-1432.

Hertzberg H., Huk W. J., Ueberall M. A., Langer T., Meier W., Dopfer R., et al. (1997). CNS late effects after ALL therapy in childhood. Part I: neuroradiological findings in long-term survivors of childhood ALL - an evaluation of the interferences between morphology and neuropsychological performance. *Medical* and Pediatric Oncology, *28*, 387-400.

Hill, D. E., Ciesielski, K. T., Hart, B. L., & Jung, R. E. (2004). MRI morphometric and neuropsychological correlates of long-term memory in survivors of childhood leukemia. *Pediatric Blood and Cancer, 42,* 611-617.

Hill, J. M., Kornblith, A. B., Jones, D., Freeman, A., Holland, J. F., Glicksman, A. S., et al. (1998). A comparative study of the long term psychosocial functioning of childhood acute lymphoblastic leukemia survivors treated by intrathecal methotrexate with or without cranial radiation. *Cancer, 82 (1), 208-218.*

Hoffman Marymont, M. (2000). Leukemia and Non-Hodgkins Lymphoma. In: Leonard L. Gunderson and Joel E. Tepper (Eds). *Clinical Radiation Oncology.* Pennsylvania: Churchill Livingstone, pp. 1089-1104.

Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex – developmental changes and effects of aging. *Brain Research, 163 (2),* 195-205.

Huttenlocher, P. R. (1990). Morphometric study of human cerebral cortex development. *Neuropsychologia, 28 (6),* 517-527.

Jannoun. L., & Chessells, J. M. (1987). Long-term psychological effects of childhood leukemia and its treatment. *Pediatric Hematology and Oncology 4(4),* 293-308.

Johnston, C. (1985). Language ability in children treated with central nervous system prophylaxis for acute lymphocytic leukemia. *International Journal of Clinical Neuropsychology, 7,* 25-28.

Kaplan, D. M., Smith, A., & Grobstein, R. (1974). School management of the seriously ill child. *Journal of School Health, 44 (5),* 250-254.

Katz, J. A., Pollock, B. H., Jacaruso, D., & Morad, A. (1993). Final attained height in patients successfully treated for childhood acute lymphoblastic leukemia. *Journal of Pediatrics, 123 (4)*, 546-552.

Kimura, D. (1963). Right temporal lobe damage. *Archives of Neurology, 8,* 264-271.

Kingma, A., Mooyaart E. L., Kamps W. A., Nieuwenhuizen P., & Wilmink J. T. (1993). Magnetic resonance imaging of the brain and neuropsychological evaluation in children treated for acute lymphoblastic leukemia at a young age. *The American Journal of Pediatric Hematology/Oncology 15*(2), 231-238.

Kingma, A., Rammeloo L. A. J., van der Does-van den Berg A., Rekers-Mombarg L., & Postma A. (May 2000). Academic career after treatment for acute lymphoblastic leukaemia. *Archives of Disease in Childhood, 82(5)*, 353-357.

Kingma, A., van Dommelen, R., Mooyaart, E. L., Wilmink, J. T., Deelman, B. G., & Kamps, W. A. (2001). Slight cognitive impairment and magnetic resonance imaging abnormalities but normal school levels in children treated for acute lymphoblastic leukemia with chemotherapy only. *The Journal of Pediatrics, 139 (3),* 413-420.

Kirkham, N. Z., Cruess, L., & Diamond, A. (2003). Helping children apply their knowledge to their behavior on a dimension-switching task. *Developmental Science, 6 (5),* 449-476.

Klingberg, T., Kawashima, R., & Roland, P. E. (1996). Activation of multi-modal cortical areas underlies short-term memory. *European Journal of Neuroscience, 8 (9),* 1965-1971.

Knobf, M. T., Fasacreta, J. V., Valentine, A., & McCorkle, R. (1998). Chemotherapy, Hormonal Therapy and Immunotherapy. In: Jimmie C. Holland (Ed.). *Psycho-Oncology*. New York: Oxford University Press, pp. 277-285.

Koenderink, M. J., Uylings, H. B., & Mrzljak, L. (1994). Postnatal maturation of the layer III pyramidal neurons in the human prefrontal cortex: a quantitative Golgi analysis. *Brain Research, 653 (1-2),* 173-182.

Korkman, M. (1988). NEPSY. A proposed neuropsychological test battery for young, developmentally disabled children *[published doctoral dissertation]*. Helsinki: University of Helsinki.

Koslowski, B., & Bruner, J. S. (1972). Learning to use a lever. *Child Development, 43 (3),* 790-799.

Lahteenmaki P. M., Holopainen I., Krause C. M., Helenius H., Salmi T. T., & Heikki L. A. (2001). Cognitive functions of adolescent childhood cancer survivors assessed by event-related potentials. *Medical and Pediatric Oncology, 36*, 442-450.

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

Lansky, S. B., Cairns, N. U., Lansky, L. L., Cairns, G. F., Stephenson, L. & Garin, G. (Summer, 1984). Central nervous system prophylaxis. *The American Journal of Pediatric Hematology/Oncology, 6*(2), 183-190.

Lesnik, P. G., Ciesielski, K. T., Hart, B. L., Benzel, E. C., & Sanders, J. A.(Dec. 1998). Evidence for cerebellar-frontal subsystem changes in children treated with Intrathecal chemotherapy for leukemia. *Archives of Neurology, 55*, 1561-1568.

Levy, R., & Goldman-Rakic, P. S. (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental Brain Research, 133,* 23-32.

Lockwood K. A., Bell T. S., & Colegrove R. W. (1999). Long-term effects of cranial radiation therapy on attention functioning in survivors of childhood leukemia. *Journal of Pediatric Psychology, 24*(1), 55-66.

Luriia, A. R. (1966). *Human Brain and Psychological Processes.* New York: Harper & Row. [Translated by Basil Haigh].

Madan-Swain, A. & Brown, R. T. (1991). Cognitive and psychosocial sequelae for children with acute lymphocytic leukemia and their families. *Clinical Psychology Review, 11*, 267-294.

Markowitsch, H. J. (1988). Diencephalic amnesia: a reorientation towards tracts? *Brain Research, 472 (4),* 351-370.

McKenna, S. M., & Baehner, R. L. (1991). Diagnosis and treatment of childhood acute lymphocytic leukemia. In Peter H. Wiernik, George P. Canellos, Robert A. Kyle, & Charles A. Schiffer (Eds.), *Neoplastic Diseases of the Blood* (2nd Edition, pp. 231-252). New York, NY: Churchill Livingstone.

Meadows, A. T., Massari, D. J., Fergusson, J, Gordon, J, Littman, P., & Moss K. (1981). Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukemia treated with cranial irradiation. *The Lancet, November 7,* 1015-1018.

Meyer, D. E., Evans, J. E., Lauber, E. J., Gmeindl, L., Rubinstein, J., Junck, L., et al. (1998). The role of dorsolateral prefrontal cortex for executive cognitive processes in task switching. Poster presented to the Cognitive Neuroscience Society, San Francisco.

Middleton, F. A., & Strick, P. L. (2001). Cerebellar projections to the prefrontal cortex of the primate. *The Journal of Neuroscience, 21*(2), 700-712.

Miller, G. A., Galanter, E., & Pribram, K. H. (1960). *Plans and the Structure of Behavior.* New York: Holt.

Milner, B. (1962). Les troubles de la memoire accompagnant des lesions hippocampiques bilaterales. In *Physiologie de l'hippocampe (pp. 257-272).* Paris: Centre National de la Recherche Scientifique. English translation: B. Milner & S. Glickman (Eds.). Princeton: Van Nostrand, 1965 (pp. 97-111).

Milner, B. (1963). Effects of different brain lesions on card sorting. *Archives of Neurology, 9,* 90.

Milner, B. & Teuber, H-L. (1968). Alternations of perception and memory in man. Reflections on methods. In: Weiskrantz, L. (Ed.). *Analysis of Behavior.* New York: Harper and Row.

Mishkin, M., & Manning, F. J. (1978). Non-spatial memory after selective prefrontal lesions in monkeys. *Brain Research, 143 (2),* 313-323.

Moleski, M. (2000). Neuropsychological, Neuroanatomical, and Neurophysiological Consequences of CNS Chemotherapy for Acute Lymphoblastic Leukemia. *Archives of Clinical Neuropsychology, 15(7)*, 603-630.

Montour-Proulx, I., Kuehn, S. M., Keene, D. L., Barrowman, N. J., Hsu, E., Matzinger, M. A., Dunlap, H., & Halton, J. M. (2004). Cognitive changes in children treated for acute lymphoblastic leukemia with chemotherapy only according to the pediatric oncology group 9605 protocol. *Journal of Child Neurology, 20 (2),* 129-133.

Moore, I. M. (Ki), Kramer J. H., Wara W., Halberg F., & Ablin A. R. (November 1, 1991). Cognitive function in children with leukemia. Effect of radiation dose and time since irradiation. *Cancer, 68*, 1913-1917.

Moore, I. M., Packer, R. J., Karl, D. & Bleyer W. A. (1994). Adverse effects of cancer treatment on the central nervous system. In *Survivors of Childhood Cancer*, 81-95.

Moray, N. (1960). *Broadbent's filter theory: Postulate mental abilities [rev].* Chicago: Science Research Associates.

Moss, H. A., Nannis, E. D. & Poplack, D. G. (July 1981). The effects of prophylactic treatment of the central nervous system on the intellectual functioning of children with acute lymphocytic leukemia. *The American Journal of Medicine, 71*, 47-52.

Mulhern R. K., Fairclough D., & Ochs J. (August, 1991). A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy, or no cranial irradiation. *Journal of Clinical Oncology, 9*(8), 1348-1356.

Mulhern, R. K., Hancock, J. R. & Fairclough, D. (1992). Methodological issues in studies of neuropsychological function after treatment for acute lymphoblastic leukemia. In D. M. Green, & G. J. D'Angio (Eds.), *Late Effects of Treatment for Childhood Cancer* (pp. 31-39). New York, NY: Wiley-Liss.

Mulhern, R. K., Phipps, S., & White, H. (2004). Neuropsychological outcomes. In: W. Hamish, B. Wallace, & Daniel M. Green (Eds.). *Late Effects of Childhood Cancer*. London: Arnold, pp. 18-36.

Mulhern R. K., Wasserman A. L., Fairclough D., & Ochs J. (Feb. 1988). Memory function in disease-free survivors of childhood acute lymphocytic leukemia given CNS prophylaxis with or without 1,800 cGy cranial irradiation. *Journal of Clinical Oncology, 6*(2), 315- 320.

Neglia, J. P., & Robison, L. L. (1988). Epidemiology of the Childhood Acute Leukemias.

*Pediatric Clinics of North America, 35*(4), 675-692.

Noll, R. B., MacLean Jr., W. E., Whitt, J. K., Kaleita, T. A., Stehbens, J. A., Waskerwitz, M. J., Ruymann, F. B., Hammond, G. D. (1997). Behavioral adjustment and social functioning of long-term survivors of childhood leukemia: Parent and teacher reports. *Journal of Pediatric Psychology, 22 (6),* 827-841.

Ochs, J., Berg, R., Ch'ien, L., Coburn, T., & Parvey, L. (1982). Structural and functional central nervous system (CNS) changes in long-term acute lymphocytic leukemia (ALL) survivors (abstr). Proceedings of the American Society for Clinical Oncology, 1, 127.

Ochs, J., Parvey, L. S., & Mulhern, R. (1986). Prospective study of central nervous system changes in children with acute lymphoblastic leukemia receiving two different methods of central nervous system prophylaxis. *NeuroToxicology, 7 (2),*217-226.

Ochs, J., Mulhern, R., Fairclough, D., Parvey, L., Whitaker, J., Ch'ien, L., et al. (January 1991). Comparison of neuropsychologic functioning and clinical indicators of neurotoxicity in long-term survivors of childhood leukemia given cranial rdiation or parenteral methotrexate: A prospective study. *Journal of Clinical Oncology, 9*(1), 145-151.

Ochs, J. & Mulhern, R. K. (1992). Prospective evaluation of neuropsychological function following cranial irradiation or intermediate dose methotrexate. In D. M. Green, & G. J. D'Angio (Eds.), *Late Effects of Treatment for Childhood Cancer* (pp. 23-30). New York, NY: Wiley-Liss.

Ochs, J. J., Parvey, L. S., Whitaker, J. N., Bowman, W. P., Ch'ien, L., Campbell, M. et al. (December, 1983). Serial cranial computed-tomography scans in children with leukemia given two different forms of central nervous system therapy. *Journal of Clinical Oncology*, *12*(1), 793-798.

Osterreith, P. A. (1944). Le test de copie d'une figure complexe. *Archives of Psychology, 30,* 206-356. [Corwin, J., Bylsma, F. W., trans. *Clinical Neuropsychologist, 7,* 9-15.

Owen, A. M. (1997). The functional organization of working memory processes within human lateral frontal cortex: The contribution of functional neuroimaging. *European Journal of Neuroscience, 9*, 1329-1339.

Paakko, E., Vainionpaa. L., Lanning, M., Laitinen, J. & Pyhtinen, J. (December 1, 1992). White matter changes in children treated for acute lymphoblastic leukemia. *Cancer, 70*(11), 2728-2733.

Packer R. J., Meadows A. T., Rorke L. B., Goldwein J. L., & D'Angio G. (1987). Long-term sequelae of cancer treatment on the central nervous system in childhood. *Medical andPediatric Oncology, 15*, 241-253.

Papagno, C., & Vallar, G. (1992). Phonological short-term memory and the learning of novel words: the effect of phonological similarity and item length. *Quarterly Journal of Experimental Psychology, 44A,* 47-67.

Papagno, C., Valentine, T., & Baddeley, A. D. (1991). Phonological short-term memory and foreign language vocabulary learning. *Journal of Memory and Language, 30,* 331-347.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. J. (1993). The neural correlates of the verbal component of working memory. *Nature, 362,* 342-345.

Pavlovsky, S., Fisman, N., Arizaga, R., Castano, J., Chamoles, N., Leiguarda, R. et al. (Spring 1983). Neuropsychological study in patients with ALL. *The American Journal of Pediatric Hematology/Oncology, 5*(1), 79-86.

Peckham, V. C., Meadows, A. T., Bartel, N., & Marrero, O. (1988). Educational late effects in long-term survivors of childhood acute lymphocytic leukemia. *Pediatrics, 81,* 127-133.

Petrides, M. (2000a). Mapping prefrontal cortical systems for the control of cognition. In A. Toga, J. C. Mazziotta (Eds.), *Brain mapping: the systems* (pp. 157-176). San Diego, CA: Academic Press.

Petrides, M. (2000b). The role of the mid-dorsolateral prefrontal cortex in working memory. *Experimental Brain Research, 133*, 44-54.

Petrides, M. (1996). Lateral frontal cortical contribution to memory. *Seminars in the Neurosciences, 8*, 57-63.

Petrides, M. (1995). Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *The Journal of Neuroscience, 15*(1), 359-375.

Petrides, M. (1994a). Frontal lobes and behaviour. *Current Opinion in Neurobiology, 4,* 207-211.

Petrides, M. (1994b). Frontal lobes and working memory: Evidence from investigations of the effects of cortical excisions in nonhuman primates. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology* (pp. 59-82). New York, NY: Elsevier Science B. V.

Petrides, M. (1991). Monitoring of selections of visual stimuli and the primate frontal cortex. Proceedings of the Royal Society of London, B., 246, 293-298.

Petrides, M. (1990). Nonspatial conditional learning impaired in patients with unilateral frontal but not unilateral temporal lobe excisions. *Neuropsychologia, 28,* 137-149.

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia, 20*(3), 249-262.

Petrides, M., Alivisatos, B., & Evans, A. C. (1995). Functional activation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. *Proceedings of the National Academy of Science, 92*, 5803-5807.

Petrides, M., Alivisatos, B., Evans, A. C., & Meyer, E. (1993a). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Science, 90*, 873-877.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A. C. (1993b). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Science, 90,* 878-882.

Petrides, M., & Pandya, D. N. (1994). Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macque brain and corticocortical connection patterns. *European Journal of Neuroscience, 11,* 1011-1036.

Peylan-Ramu, N., Poplack, D. G., Pizzo, P. A., Adornato, B. T., & Di Chiro, G. (1978). Abnormal CT scans of the brain in asymptomatic children with acute lymphocytic leukemia after prophylactic treatment of the central nervous system with radiation and intrathecal chemotherapy. *The New England Journal of Medicine, 298*(15), 815-818.

Pfefferbaum-Levine, B., Copeland, D. R., Fletcher, J. M., Ried, H. L., Jaffe, N. & McKinnon, W. R. (Summer 1984). Neuropsychologic assessment of long-term survivors of childhood leukemia. The American Journal of Pediatric Hematology/Oncology, 6(2), 123-128.

Piaget, J. (1954). *The Construction of Reality in the Child.* Oxford: Basic Books.

Picard, E. M. & Rourke, B. P. (1995). Neuropsychological consequences of prophylactic treatment for acute lymphocytic leukemia. In *Syndrome of Nonverbal Learning Disabilities: Neurodevelopmental Manifestations* (pp. 282-230). New York, NY: Guilford Press.

Pollmann, S. (2001). Switching between dimensions, locations, and responses: the role of the left frontopolar cortex. *NeuroImage, 14,* 118-124.

Precourt, S., Robaey, P., Lamothe, I., Lassonde, M., Sauerwein, H. C., & Moghrabi, A. (2002). Verbal cognitive functioning and learning in girls treated for acute lymphoblastic leukemia by chemotherapy with or without cranial irradiation. *Developmental Neuropsychology, 21 (2),* 173-195.

Price, R. A., & Birdwell, D. A. (1978). The central nervous system in childhood leukemia, III. Mineralizing microangiopathy and dystrophic calcification. Cancer, 42 (2), 717-728.

Price, R. A. & Jamieson, P. A. (February 1975). The central nervous system in childhood leukemia II. Subacute Leukoencephalopathy. *Cancer, 35*(2), 306-318.

Pui C. H. (2000). *Childhood Leukemias.* Cambridge University Press.

Pui, C. H. (1997). Acute Lymphoblastic Leukemia. *Pediatric Clinics of North America, 44* (4), 831-846.

Pui, C. H. & Crist, W. M. (1995). Treatment of childhood leukemias. *Current Opinions* in Oncology, 7 (1), 36-44.

Pui, C. H., Simone, J. V., Hancock, M. L., Evans, W. E., Williams, D. L., Bowman, W. P., et al. (1992). Impact of three methods of treatment intensification on acute lymphoblastic leukemia in children: long-term results of St Jude total therapy study X. *Leukemia, 6 (2),* 150-157.

Raymond-Speden, E., Tripp, G., Lawrence, B., & Holdaway, D. (2000). Intellectual, neuropsychological, and academic functioning in long-term survivors of leukemia. *Journal of Pediatric Psychology, 25 (2),* 59-68.Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives of Psychology, 28,* 286-340.

Robaey, P., Dobkin, P., Leclerc, J-M., Cyr, F., Sauerwein, C., & Theoret, Y. (2000). A comprehensive model of the development of mental handicap in children treated for acute lymphoblastic leukaemia: A synthesis of the literature. *International Journal of Behavioral Development, 24 (1),* 44-58.

Romine, C. Burns, Reynolds, C. R. (2004). Sequential memory: A developmental perspective on its relation to frontal lobe functioning. *Neuropsychology Review, 14 (1),* 43-64.

Riccardi, R., Brouwers, P., Di Chiro, G. & Poplack, D. G. (January, 1985). Abnormal computed tomography brain scans in children with acute lymphoblastic leukemia: Serial long-term follow-up. *Journal of Clinical Oncology, 3*(1), 12-18.

Robison, L. L., Nesbit, M. E., Sather, H. N., Meadows, A. T., Ortega, J. A. & Hammond, G. D. (Summer 1984). Factors associated with IQ scores in long-term survivors of childhood acute lymphoblastic leukemia. *The American Journal of Pediatric Hematology/Oncology, 6* (2), 115-120.

Rodgers, J., Horrocks, J., Britton, P. G. & Kernahan, J. (1999). Attentional ability among survivors of leukemia. *Archives of Disease in Childhood, 80,* 318-323.

Said, J. A., Waters, B. G., Cousens, P., & Stevens, M. M. (1989). Neuropsychological sequelae of central nervous system prophylaxis in survivors of childhood acute lymphoblastic leukemia. Journal of Consulting and Clinical Psychology, 57 (2), 251-256.

Sather, H., Miller, D., Nesbit, M., Heyn, R., & Hammond, D. (1981). Differences in prognosis for boys and girls with acute lymphoblastic leukaemia. *Lancet,* 741-743.

Schacter, D. L., & Tulving, E. (1994). *Memory Systems 1994.* London: The MIT Press.

Schatz, J., Kramer, J.H., Ablin, A., & Matthay, K. (2000). Processing speed, working memory, and IQ: a developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychology, 14 (2),* 189-200.

Schlieper, A. E., Esseltine, D.W. & Tarshis, E. (1989). Cognitive function in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatric Hematology and Oncology, 6*(1), 1-9.

Schuler, D., Bakos, M., Borsi, J., Gacsaly, I., Kalmanchey, R., Kardos, G., et al. (1990). Neuropsychologic and CT examinations in leukemic patients surviving 10 or more years. *Medical and Pediatric Oncology, 18,* 123-125.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery, and Psychiatry, 20(1), 11-21.

Seltzer, B., & Pandya, D. N. (1989). Frontal lobe connections of the superior temporal sulcus in the rhesus monkey. Journal of Comparative Neurology, 281 (1), 97-113.

Shelby, M. D., Nagle, R. J., Barnett-Queen, L. L., Quattlebaum, P. D., & Wuori, D. F. (1998). Parental reports of psychosocial adjustment and social competence in child survivors of acute lymphocytic leukemia. *Children's Health Care, 27 (2),* 113-129.

Sheslow, D., & Adams, W. (1990). *WRAML: Wide range assessment of memory and learning – Administration Manual.* Wilmington, Delaware: Wide Range, Inc.

Shindy, W. W., Posley, K. A., Fuster, J. M. (1994). Reversible deficit in haptic delay tasks from cooling prefrontal cortex. *Cerebral Cortex, 4 (4),* 443-450.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283,* 1657-1661.

Smith, E. E., & Jonides, J. (1998). Neuroimaging analyses of human working memory. *Proceedings of the National Academy of Science, 95,* 12061-12068.

Smith, M. L., Leonard, G., Crane, J., & Milner, B. (1995). The effects of frontal- or temporal-lobe lesions on susceptibility to interference in spatial memory. Neuropsychologia, 33 (3), 275-285.

Smyth, M. M., & Pendleton, L. R. (1990). Space and movement in working memory. *Quarter Journal of Experimental Psychology, 42 (2),* 291-304.

Soni, S.S., Marten, G.W., Pitner, S. E., Duenas, D. A., & Powazek, M. (1975). Effects of central nervous system irradiation on neuropsychologic functioning of children with acute lymphocytic leukemia. New England Journal of Medicine, 293, 113-118.

Sowell, E. R., Thompson, P. M., Holmes, C. J., Jernigan, T. L., & Toga, A. W. (1999). In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nature Neuroscience, 2 (10), 859-861.

Squire, L. R. (1982). The neuropsychology of human memory. *Annual Reviews in Neuroscience, 5,* 241-273.

Squire, L. R. (1986). Mechanisms of memory. *Science, 232 (4758),* 1612-1619.

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. Neurobiology of Learning and Memory, 82, 171-177.

Squire, L. R. & Schacter, D. L. (2002). *Neuropsychology of Memory – Third Edition.* London: The Guilford Press.

Squire L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253(5026),* 1380-1386.

Squire, L. R., Haist, F., & Shimamura, A. P. (1989). The neurology of memory: Quantitative assessment of retrograde amnesia in two groups of amnesic patients. The Journal of Neuroscience, 9 (3), 828-839.

Stanfill, P., & Green A. (1986). Wilms' tumor. In: M.J. Hockenberry, & D. K. Coody (Eds.). *Pediatric Oncology and Hematology. Perspectives on Care.* Toronto: The C. V. Mosby Company, pp. 81-91.

Stehbens, J. A., Kaleita, T. A., Noll, R. B., MacLean Jr., W. E., O'Brien, R. T., Waskerwitz, M. J., et al. (1991). CNS prophylaxis of childhood leukemia: What are the long-term neurological, neuropsychological, and behavioral effects? Neuropsychology Review, 2(2), 147-177.

Stehbens, J. A., & Kisker, C. T. (1984). Intelligence and achievement testing in childhood cancer: Three years post diagnosis. *Developmental and Behavioral Pediatrics, 5,* 184-188.

Steinherz, P. G. & Simone, J. (1998). Biology of Childhood Cancers. In: Jimmie C. Holland (Ed.). *Psycho-oncology*, New York: Oxford University Press, pp. 881-896.

Tabachnik, B. G., & Fiddell, L. S. (2001). *Using Multivariate Statistics, 4th Edition.* Boston: Allyn & Bacon.

Taylor, E. M. (1959). *The Appraisal of Children with Cerebral Deficits.* Cambridge, MA: Harvard University Press.

Taylor H. G., Albo V. C., Phebus C. K., Sachs B. R., & Bierl P. G. (1987). Postirradiation treatment outcomes for children with acute lymphocytic leukemia: clarification of risks. *Journal of Pediatric Psychology, 12*(3), 395-411.

Thurstone, L. L., & Thurstone, T. G. (1962). *Primary mental abilities [rev].* Chicago: Science Research Associates.

Trautman, P. D., Erickson, C. Shaffer, D., O'Connor, P. A., Sitarz, A., Correra, A., et al. (June 1988). Prediction of intellectual deficits in children with acute lymphoblastic leukemia. *Developmental and Behavioural Pediatrics, 9*(3), 122-128.

Tulving, E. (1992). Memory systems and the brain. *Clinical Neuropharmacology, 15 (Suppl 1, Pt. A)*, 327A-328A.

Vallar, G., & Papagno, C. (2002). In Baddeley, A. D., Kopelman, M. D., & Wilson, B. A. (Eds.). *Handbook of Memory Disorders.* Chichester: Wiley, pp. 249-270.

Waber, D. P., Carpentieri S. C., Klar N., Silverman L. B., Schwenn M., Hurwitz, C. A., et al. (2000). Cognitive sequelae in children treated for acute lymphoblastic leukemia with dexamethasone or prednisone. *Journal of Pediatric Hematology/Oncology, 22*(3), 206-213.

Waber, D. P., Gioia, G., Paccia, J., Sherman, B., Dinklage, D., Sollee, N., et al. (1990). Sex differences in cognitive processing in children treated with CNS prophylaxis for acute lymphoblastic leukemia. *Journal of Pediatric Psychology, 15*(1), 105-122.

Waber, D. P. & Mullenix P. J. (2000). Acute lymphoblastic leukemia. In K. O. Yeates, M. D. Ris, & H. G. Taylor (Eds.), *Pediatric Neuropsychology: Research, Theory, and Practice* (pp. 300-319). New York, NY: The Guilford Press.

Waber, D. P., Shapiro, B. L., Carpentieri, S. C., Gelber, R. D., Zou G., Dufresne, A., et al. (2001). Excellent therapeutic efficacy and minimal late neurotoxicity in children treated with 18 grays of cranial radiation therapy for high-risk acute lymphoblastic leukemia. A 7-year follow-up study of the Dana-Farber Cancer Institute consortium. *Cancer, 92*(1), 15-22.

Waber, D. P., Tarbell, N. J., Fairclough, D., Atmore, K., Castro, R., Isquith, P., et al. (October, 1995). Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: Cranial radiation requires an accomplice. *Journal of Clinical Oncology, 13*(10), 2490-2496.

Wechsler, D. (1945). A standard memory scale for clinical use. *Journal of Psychology, 19,* 87-95.

Wechsler, D. (2002). *Wechsler Primary and Preschool Scale of Intelligence – Third Edition,* Manual Canadian Supplement. Toronto, ON: The Psychological Corporation.

Wechsler, D. (1997a). *Wechsler Adult Intelligence Scale - Third Edition.* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1996). *Wechsler Intelligence Scale for Children - Third Edition,* Manual Canadian Supplement. Toronto, ON: The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale - Third Edition.* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1993). *Wide Range Achievement Test – Third Edition.* San Antonio, TX: The Psychological Corporation.

Wen, P. Y. (2003). Central nervous system complications of cancer therapy. In: David Schiff & Patrick Y. Wen (Eds.). *Cancer Neurology in Clinical Practice.* New Jersey: Humana Press, pp. 215-231.

Williams J. M., & Davis K. S. (1986). Central nervous system prophylactic treatment for childhood leukemia: neuropsychological outcome studies. *Cancer Treatment Reviews, 13,* 113-127.

Williams, K. S., Ochs, J., Williams, J. M., & Mulhern, R. K. (1991). Parental report of everyday cognitive abilities among children treated for acute lymphoblastic leukemia. Journal of Pediatric Psychology, *16 (1)*, 13-26.

Wilson, D. A., Nitschke, R., Bowman, M. E., Chaffin, M. J., Sexauer, C. L., & Prince, J. R.,(1991). Transient white matter changes on MR images in children undergoing chemotherapy for acute lymphocytic leukemia: correlation with neuropsychologic deficiencies. *Radiology, 180 (1),* 205-209.

Wilson, F. A. W., O'Scalaidhe, S. P., & Goldman-Rakic, P. (1994). Functional synergism between putative γ-aminobutyrate-containing neurons and pyramidal neurons in prefrontal cortex. *Proceedings of the National Academy of Sciences, 91,* 4009-4013.

Zelazo, P. D., Reznick, J. S., & Pinon, D. E. (1995). Response control and the execution of verbal rules. *Developmental Psychology, 31,* 508-517.

Zola-Morgan, S., & Squire, L. R. (1990). The neuropsychology of memory: Parallel findings in humans and nonhuman primates. *Annals New York Academy of Science, 608,* 434-50.

Zola-Morgan, S., & Squire, L. R. (1993). Neuroanatomy of memory. *Annual Reviews in Neuroscience, 16,* 547-563.

# APPENDIX A

## Wilms' Tumour

Wilms' tumour is the most common primary kidney (rapid-growing) tumour in children, accounting for about 10% of all malignant tumours in childhood (Stanfill & Green, 1986). Seventy percent of Wilms' tumours occur before the age of 4, with 30% occurring before 1 year of age (Stanfill & Green, 1986). The distribution of cases is equal in all countries and appears stable over time. There is no sexual predominance, but familial cases have been reported. The left kidney is affected more than the right, and bilateral tumours occur in about 5% of these cases (Stanfill & Green, 1986).

Fifteen percent of cases present with metastases at diagnosis, and one third of cases develop metastases with 24 months of diagnosis. The most common site of metastasis is the lungs with single or multiple lesions occurring (Stanfill & Green, 1986). Disease-free survival has improved over the years to 80-90% with surgery, radiation, and chemotherapy in combination. This development of multimodal therapy has even resulted in disease-free survival in the presence of pulmonary metastases.

The surgical objectives of Wilms' tumour management are to remove the primary tumour even if metastases are present and to provide tissue for pathologic examination. If the mass is unusually large or initial diagnostic workup has indicated contraindications for immediate surgery, chemotherapy and irradiation may be used before surgery or alone to decrease tumour bulk.

The use of radiation therapy and/or chemotherapy postoperatively depends on the stage and histology of the tumour. The goal of radiation therapy is the control of microscopic residual disease and the treatment of metastases, particularly those in the

lungs. Radiation doses to the treatment field usually range from 2000 to 2600 rads delivered over 2 to 3 weeks. Dosages are varied by age and size of the child, stage of disease, and amount of residual or suspected residual tumour.

Actinomycin D, in combination with vincristine, and doxorubicin (Adriamycin) are the agents of choice to obliterate evidence of microscopic disease, residual tumour remaining after surgery, and metastases. Chemotherapy dosages and schedules are based on stage of disease. There is concern, however, regarding the possible late effects of chemotherapy, such as cardiotoxicity secondary to doxorubicin. Since a high percentage of patients with Wilms' tumour attain disease-free survival, the ultimate aim of therapy is to maintain or increase survival time while decreasing toxicities of treatment (Stanfill & Green, 1986).

Appendix B

The Boston Protocol

Systemic induction chemotherapy consisted of prednisone, vincristine, daunorubicin, and Lasparaginin followed by systemic consolidation therapy that included these four drugs. Maintenance consisted of prednisone, vincristine, methotrexate, and 6-mercaptopurine. This regimen was continued for a total of 36 months. Central nervous system preventive therapy was given during consolidation treatment and consisted of 1800 cGy or 2400 cGy of cranial irradiation (delivered in 200 cGy/day fractions from a 6-MeV linear accelerator) and intrathecal chemotherapy.

Patients also received intrathecal methotrexate (five doses at 12 mg/m2 maximum 12 mg) during the period of cranial radiation therapy and systemic consolidation therapy followed by monthly intrathecal methotrexate for 18 weeks. The cumulative systemic methotrexate dose on this protocol was approximately 2000 mg/m2. Methotrexate was administered intravenously during induction and orally during the remainder of treatment.

APPENDIX C

STANDARDIZED TESTS OF INTELLIGENCE:

Wechsler Intelligence Scale for Children - Third Edition (WISC-III)

*Test description* - The WISC-III is a standardized test of intelligence commonly used with children 6 to 16 years, 11 months of age. Intelligence ratings are derived from the child's collective performance across several subtests. Five subtests contribute to the *Verbal I.Q. rating*. Five subtests also contribute to the *Performance I.Q. rating*. An additional subtest that examines the child's ability to arrange sets of pictures into meaningful sequences also contributes to the Performance I.Q. rating. A Full Scale I.Q. rating, which is a composite of verbal and nonverbal abilities, can also be derived. Only one of three optional subtests was administered, as it contributes to a speed of processing factor. The WISC-III is administered individually by a psychometrist, and it requires approximately 60 minutes to complete these eleven subtests.

*Psychometric properties* - The WISC-III was recently re-normed using a Canadian sample of 1100 children, including 100 children (50 males, 50 females) in each of 11 age groups. Canada was divided into three major geographic regions based upon percentage of total school-age population for each province defined by Statistics Canada during the 1986 Census report. Further information regarding sample characteristics is available from the Canadian Supplement Manual. *Split-half reliability* coefficients for the Verbal, Performance, and Full Scale I.Q. ratings were .93, .89, and .95 respectively. Reliability coefficients for each of the non-speeded subtests (i.e., all but Coding and Symbol Search) ranged from .61 to .87. Confidence intervals are available for individual subtest scores and intelligence ratings. The following reliability computations were based upon

American norms. The inter-rater reliability for individual subtests were also in the .90s. *Test-retest reliability* was investigated by assessing a sample of 353 American children on two occasions. The intervals between testing ranged from *12 to 63 days with a median retest interval of 23 days*. The retest coefficients were corrected for the variability of the standardization sample in order to obtain accurate estimates of score stability in the population. The corrected correlation coefficients for the Verbal, Performance, and Full Scale I.Q. ratings ranged from .87 to .94 for children 6 to 15 years of age. These results suggest that the WISC-III provides relatively stable scores over short time periods. Improvements in the Performance I.Q. rating were observed with short-interval retesting. These improvements are consistent with the effects of practice. In clinical practice a minimum interval of 6 months is recommended between assessments in order to reduce the likelihood of inflating results due to practice effects. The *concurrent validity* of the WISC-III has been demonstrated by correlating the Full Scale I.Q. rating with other measures of global ability (ranged from .73 to .92).

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

*Test description* - The WAIS-III is a standardized test of intelligence commonly used with individuals 16 to 89 years of age. Intelligence ratings are derived from the individual's collective performance across several subtests. Six subtests contribute to the *Verbal I.Q. rating*. These subtests examine the individual's general knowledge; their ability to provide appropriate responses to social dilemmas; to define words; to use language to reason; to solve Arithmetic problems mentally; and to repeat sets of numbers immediately after presentation. Five subtests contribute to the *Performance I.Q. rating*. These subtests examine the individual's ability to copy symbols rapidly; to determine

what details are missing from pictures of common objects; to arrange sets of pictures into meaningful sequences of action; to reproduce geometric designs using blocks; and to complete abstract patterns or sequences. A Full Scale I.Q. rating, which is a composite of verbal and nonverbal abilities, can also be derived. Of the three optional subtests, only the one that contributes to speed of information processing will be administered. The WAIS-III is administered individually by a psychometrist, and it requires approximately 60 minutes to complete these twelve subtests.

*Psychometric properties* - The WAIS-III was normed on a sample of 2450 American adults, including 200 participants in each of 11 age groups ranging from 16 to 79 years of age, 150 adults aged 80 to 84 years of age, and 100 adults aged 85-89 years of age. *Split-half reliability* coefficients for the Verbal, Performance, and Full Scale I.Q. ratings were .97, .94, and .98, respectively. Reliability coefficients for all subtests ranged from .70 to .93. Confidence intervals are available for individual subtest scores and intelligence ratings. *Inter-rater reliability* is high, averaging in .90s. *Test-retest reliability* was investigated by assessing a sample of 394 participants on two occasions. The intervals between testing ranged from *2 to 12 weeks with a mean retest interval of 34.6 days.* Test-retest stability coefficients were calculated for four pooled age groups: 16-29, 30-54, 55-74, and 75-89. The corrected correlation coefficients for the Verbal, Performance, and Full Scale I.Q. ratings for the 16 to 29 years age group were .94, .88, and .95, respectively. The corrected correlation coefficients for each subtest at this age level ranged from .67 to .94. The lowest correlation coefficients occurred on the Picture Arrangement and Picture Completion subtests. The mean retest scores from the second assessment were higher than those from the first assessment. These improvements are

consistent with the effects of practice. In clinical practice a minimum interval of 6 months is recommended between assessments in order to reduce the likelihood of inflating results due to practice effects. The *concurrent validity* of the WAIS-III has been demonstrated by correlating the Full Scale I.Q. rating with the Standford-Binet Intelligence Scale - Fourth Edition (.88), and with the WISC-III (.88).

STANDARDIZED TESTS OF MEMORY FUNCTIONING:

Children's Memory Scale (CMS)

*Test Description* - The CMS is a standardized test of memory functioning used with children 5 to 16 years of age. The test was developed in 1997 as a downward extension of the Wechsler Memory Scale. The CMS consists of six core subtests, four of which contribute to a *General Memory* Index. The remaining two subtests contribute to an *Attention/Concentration* Index. The six subtests can be divided further into *Verbal* and *Visual Memory Indices*. In the Auditory Verbal Memory tasks, the child is asked to recall stories and pairs of words immediately after presentation, and to recall and recognize the information again after a delay. The Visual Memory subtests include a face recognition task and another task in which the child is asked to remember locations of dots on a board. Both of these tasks also have a delayed recall component. Thus, an *Immediate Memory and Delayed Memory Index* can be derived separately for visually and auditorially presented information. A supplementary subtest that examines the child's ability to learn a list of words after repeated presentations was administered. Reading is not required by the child in order to complete any of the subtests from the CMS. The test materials are colourful and the content is generally relevant to the

experiences of children. The CMS is administered individually by a psychometrist, and it requires approximately 60 minutes to complete all subtests.

*Psychometric properties* - The CMS was normed on a sample of 1000 children, in 10 age groups ranging from 5 to 16. Each age group (i.e., 5, 6, 7, 8, 9, 10, 11, 12, 13 to 14, and 15 to 16) included 100 children. A limited set of norms on children with neurological conditions, including traumatic brain injury, is also available for the CMS.

*Inter-rater reliability* was examined by having 112 randomly selected protocols re-scored by an independent examiner. The inter-rater reliability coefficients for all subtests ranged from .88 to 1.00. Confidence intervals are also available for individual subtest scores and indices ratings. *Test-retest reliability* was investigated by reassessing a sample of 125 children, divided into age bands of 5 to 8, 9 to 12, and 13 to 16 years of age. The retest interval ranged from 30 to 88 days, with a median of 65.3 days. As with the WISC-III, practice effects that enhanced performance on the second testing, were apparent on visual tasks. At the higher age range (i.e., 13 to 16) low correlation coefficients of .29 and .38 were obtained for the Visual Immediate and Visual Delayed Indices. Test-retest intervals that are longer in duration would be more likely to show smaller practice effects. The test-retest correlation coefficients for all remaining indices ranged from .56 to .89. In order to examine the stability of index scores further, the indices were then grouped into classifications of: impaired, borderline to low average, and average to above average. The *decision consistency stability coefficients* for all indices ranged from .61 to .93 across all age bands. The internal consistency of the test was examined by calculating split-half reliability coefficients for each subtest and index. The *mean split half reliability coefficients* for each of the indices was as follows: Auditory Verbal Immediate Memory,

.86; Auditory Verbal Delayed Memory, .84; Delayed Recognition, .80; Visual Immediate Memory, .76; Visual Delayed Memory, .76; and, General Memory. Mean reliability coefficients for each of the subtests across all ages ranged from .71 to .91.

The CMS is the first memory test to directly compare memory functioning with general intellectual abilities. Predicted CMS Index standard scores can be derived once estimates of a child's intellectual functioning have been obtained using the WISC III. This feature of the CMS is likely to be particularly useful with the head injured population where discrepancies between intellectual and memory functioning are common.

The *concurrent validity* of the CMS was investigated by correlating the CMS Indices with those of the Wide Range Assessment of Memory and Learning (WRAML) and the Wechsler Memory Scale - III. When the CMS and the WRAML were administered to 33 children in a counterbalanced order, low to high positive correlations were obtained between the respective general, verbal, visual and learning indices. The low correlation of .26 between the two visual memory indices likely reflects differences in the memory assessment paradigms of the two tests. A high correlation of .70 was obtained between the CMS Attention/Concentration Index and the WRAML Verbal Memory Index, suggesting that attention plays an important role in children's performance on the WRAML. The CMS and WMS-III were administered to eighty-six 16 year olds in counterbalanced order. The correlation coefficients ranged from .26 to .74, with the lowest correlation occurring, once again, on a visual index.

Finger Windows Subtest from the Wide Range Assessment of Memory and Learning (WRAML).

*Test description* – The Finger Windows subtest measures a child's memory of a "rote" visual pattern by manually reproducing a demonstrated spatial sequence. The examiner points to increasingly longer series of locations found on a card, and the child is asked to reproduce the spatial sequences. The Finger Windows subtest is analogous to the Digit Span subtest in that discrete and relatively non-meaningful "bits of information" are presented for immediate recall. A discontinue rule of 3 in a row wrong is applied. Principals components Factor Analysis indicated that Finger Windows loads best on the Visual Memory Index of the WRAML. Intercorrelations with other subtests ranged from .16 to .25. Internal consistency ranged from .71 to .84.

Wechsler Memory Scale - Third Edition (WMS-III)

*Test description* - The WMS-III is a standardized test of memory functioning commonly used with individuals 16 to 89 years of age. The test consists of eleven subtests. Four of these subtests contribute to the *Immediate Memory Index,* five contribute to the *General Memory Index* (which is a measure of delayed recall and recognition). These subtests can be divided further into *Auditory* and *Visual Memory Indices*. In the Auditory Memory tasks, the individual is asked to recall stories and pairs of words, immediately after presentation and again after a delay. The Visual Memory subtests include a face recognition task and another task in which the individual is asked to remember details from scenes. Both of these tasks also have a delayed recall component. Two additional subtests contribute to a *Working Memory Index*. In one task, the individual is asked to reorganize sets of numbers and letters by stating the numbers first in order followed by

the letters in alphabetical order, immediately after presentation, while in the other, they are asked immediately imitate a spatial sequence demonstrated by the examiner, first forwards then backwards.

*Psychometric properties* - The WMS-III was revised in 1997 and normed using a sample of 1250 American adults, including 100 participants in each of 11 age groups from 16 to 79 years of age, and 75 in each of the two oldest age groups. *Split-half reliability* coefficients were calculated for the Immediate Memory (.91), General Memory (.91), and Working Memory (.86) Indices. Reliability coefficients for each of the subtests ranged from .74 to .93. Confidence intervals are available for individual subtest scores and indices ratings. *Inter-rater reliability* is high, averaging in .90s. *Test-retest reliability* was investigated by assessing a sample of 297 participants on two occasions. The intervals between testing ranged from *2 to 12 weeks with a mean retest interval of 35.6 days*. The stability coefficients were calculated for two pooled age groups: 16-54 and 55-89. The corrected correlation coefficients for the Primary Indices for the 16 to 54 age group ranged from .62 to .87. The lowest coefficient was obtained for the Auditory Recognition Delayed Index, with .75 being the second lowest value. Mean subtest scores and mean Index scores increased by .33 SD to 1 SD from the first to the second testing. These improvements are consistent with the effects of practice. In clinical practice a minimum interval of 6 months is recommended between assessments in order to reduce the likelihood of inflating results due to practice effects. Given the recent availability of the WMS-III (i.e., 1997), validity studies that involve comparing the WMS-III to other measures of memory functioning are still in the preliminary stages.

THE BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION (BRIEF)

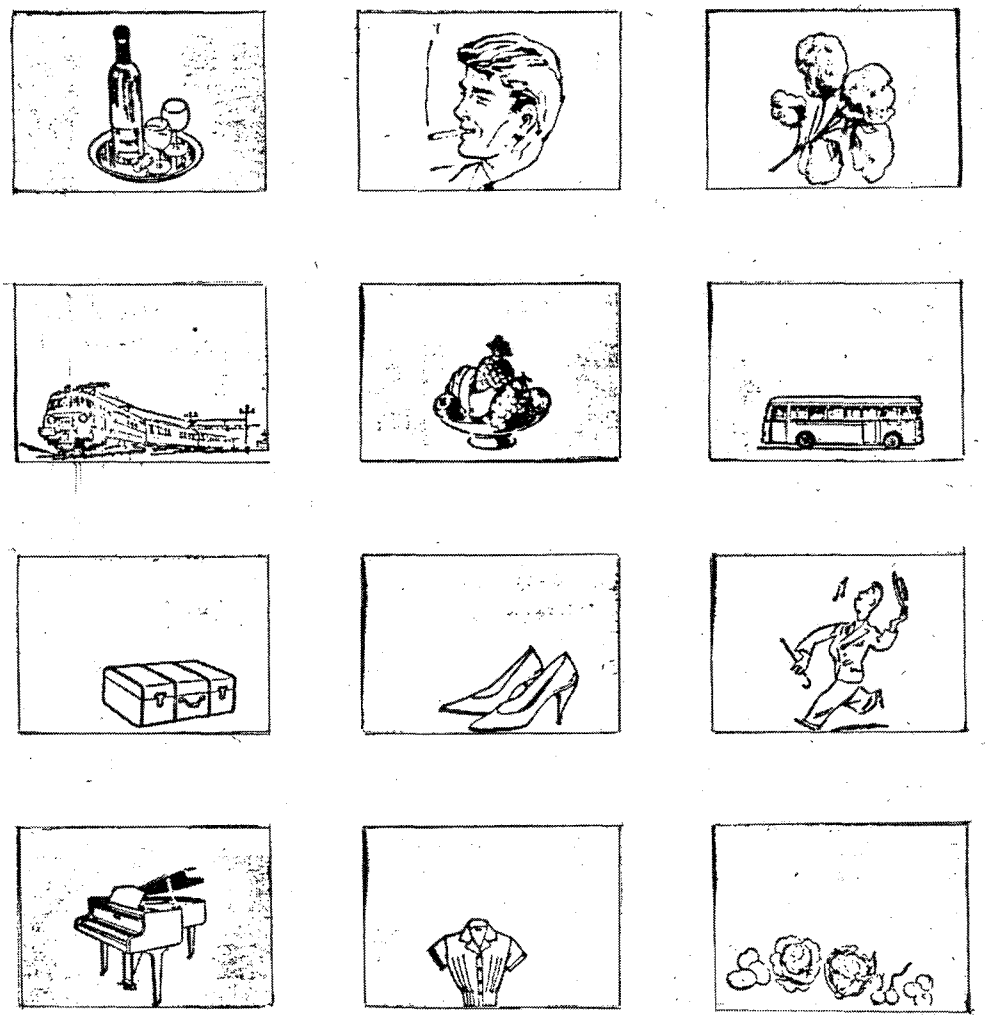
*Test description* – The BRIEF is a standardized questionnaire for parents and teachers of school age children that enables professionals to assess executive function behaviours in the home and school environments. It is designed for a broad range of children, ages 5 to 18 years, including those with learning disabilities and attentional disorders, traumatic brain injuries, lead exposure, pervasive developmental disorders, depression, and other developmental, neurological, psychiatric, and medical conditions. The parent and teacher forms of the BRIEF each contain 86 items within eight theoretically and empirically derived clinical scales that measure different aspects of executive functioning: *Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials,* and *Monitor*. There are also two validity scales: *Inconsistency* and *Negativity*. The clinical scales form two broader Indexes: *Behavioral Regulation Index* and *Metacognition*, as well as an overall *Global Executive Composite*.

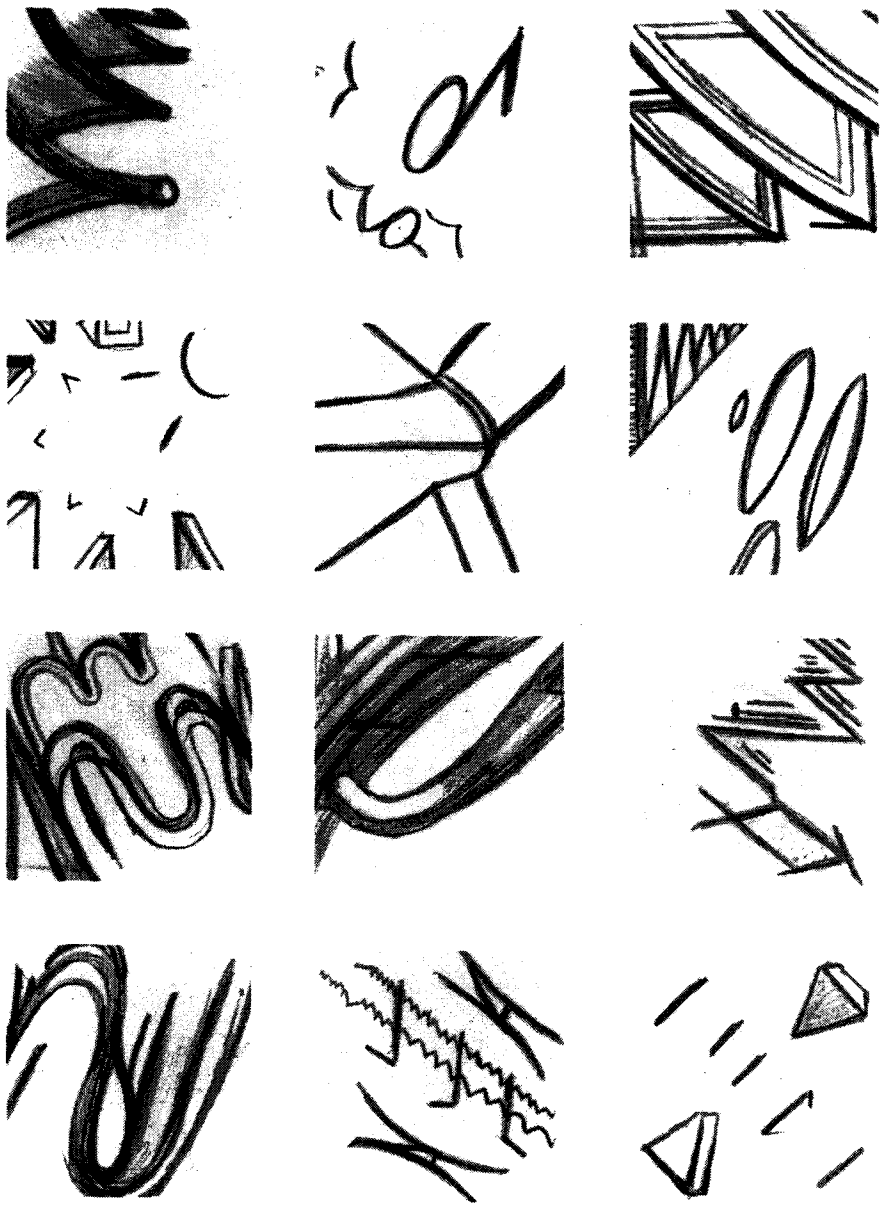
*Psychometric Properties* – The BRIEF normative sample was obtained through public and private school recruitment in urban, suburban, and rural settings in the State of Maryland, which has a full range of ethnicity's, socioeconomic classes, and population densities. A total of 25 schools were sampled, including 12 elementary, 9 middle, and 4 high schools. A total of 1, 419 Parent Forms (815 girls and 604 boys) and 720 Teacher Forms (403 girls and 317 boys) were completed. Gender and age were revealed as significant factors with respect to BRIEF scores for both forms requiring separate normative scales for these variables. Further information on test norming can be found in the BRIEF Professional Manual. *Internal Consistency*, for both forms of the BRIEF, was high, ranging from .80 to .98. *Interrater Reliability* between parent and teacher of the

same child, were moderate (mean=0.32). *Test-Retest Reliability* was measured in a subsample of 54 parents and ranged from .76 to .85 over an average interval of 2 weeks. For the teacher form, a subsample of 41 teachers completed the BRIEF. Interrater reliability was between .83 and .92 over an average 3.5 week interval. This suggests that the BRIEF provides relatively stable profiles over short periods of time. *Content Validity* – The BRIEF items were selected from clinical interviews with parents and teachers. Agreement was sought among several pediatric neuropsychologists and among the authors as to the fit of each item within the intended scale. *Construct Validity* was determined by correlating the BRIEF with several normed questionnaires that included the Behavioral Assessment System for Children, the Child Behavior Checklist, and the Connors' Attention Scales.

Appendix D

The Petrides Self-Ordered Pointing Test





# Appendix E

## Letters to Parents and Consent Forms

Children's Hospital of Eastern Ontario
Hôpital pour enfants de l'est de l'Ontario
A University of Ottawa Teaching Hospital / Un Hôpital d'enseignement affilié a l'Université d'Ottawa
401 SMYTH, OTTAWA, ONT. K1H 8L1 TELEPHONE (613) 737-7600

**Study Description/Information Letter**

**MEMORY FUNCTIONING IN LONG-TERM SURVIVORS OF ACUTE LYMPHOBLASTIC LEUKEMIA, WILMS' TUMOR, AND THEIR HEALTHY SIBLINGS**

Dear Parent,

Researchers in the fields of Psychology and Hematology/Oncology from the Children's Hospital of Eastern Ontario and Carleton University are conducting a project investigating the long-term effects of treatment for Acute Lymphoblastic Leukemia. The goal of this project is to improve understanding of the long-term effects of CNS prophylaxis on memory functioning in individuals who are a minimum of three years off treatment. In order to investigate this question we require the participation, not only of individuals with a history of ALL, but also their siblings, and other children who have been treated for cancer, specifically Wilms' tumor.

Most studies on the long-term effects of CNS prophylaxis have reported that long-term survivors of ALL typically function within the normal range on tests of global intellectual functioning. However, studies of memory functioning have produced conflicting results. Since memory has important implications for learning, we would like to investigate this potential source of difficulty further.

There are no established risks from participation in the study. All participants are free to withdraw from the study at any time. Your participation is not in any way related to the treatment your family receives at CHEO and no treatment will be altered or withheld if you decide not to participate in this study or to withdraw at any point. Furthermore, your participation in this study will not affect any future treatment that your family receives.

All information received about your family will be handled in a confidential manner. Participation will involve completing approximately 4 hours of tests in a single session **for each child**, to be scheduled at your convenience. A psychometrist under the supervision of a psychologist will administer these tests. The activities involve: answering questions, listening to stories; looking at pictures; drawing shapes; etc. None of these procedures are invasive or painful. An extended neuropsychological assessment that is comparable to the clinical service they would normally receive, will be provided for those participants with a history of ALL, but not their siblings or children with a history of Wilms' tumor. Communication of the test results will only be offered to families for those children with a history of ALL. In the event that the results for any children in the control groups (i.e., siblings, Wilms' tumor) suggest the presence of previously undetected cognitive difficulties, an appointment will be arranged to review these results with parents.

This research protocol also includes neuroradiological investigations. MRI and CT scans of the head will *only* be conducted on participants with a history of ALL. The appointments for the MRI and CT scans will be scheduled at a separate time within 6 months of your participation in the study.

Your contribution to the understanding of human memory and the late effects of treatment for leukemia is greatly appreciated and very important since only a small number of individuals are eligible for this study. Please note that the investigators will pay parking costs at the time of participation.

If you have any questions concerning this research you can contact Dr. Sally Kuehn at 737-2657 or Dr. Elizabeth Hsu at 737-2751. You may also contact the Chair of the Research Ethics Committee at CHEO for information regarding patient's rights in research studies at 738-3272. However, this person cannot provide any medical information with regard to this study.

Dr. Elizabeth Hsu,
Pediatric Oncologist
Children's Hospital of Eastern Ontario
Ottawa, Ontario

Dr. Sally Kuehn,
Staff Psychologist
Children's Hospital of Eastern Ontario
Ottawa, Ontario

Dr. Shelley Parlow
Associate Professor of Psychology
Department of Psychology
Carleton University
Ottawa, Ontario

Pauline Richards, M.A.
Ph.D. Candidate
Psychology Program
Carleton University
Ottawa, Ontario

Children's Hospital of Eastern Ontario
Hôpital pour enfants de l'est de l'Ontario
A University of Ottawa Teaching Hospital / Un Hôpital d'enseignement affilié a l'Université d'Ottawa
401 SMYTH, OTTAWA, ONT. K1H 8L1 TELEPHONE (613) 737-7600

**MEMORY FUNCTIONING IN LONG-TERM SURVIVORS OF ACUTE LYMPHOBLASTIC LEUKEMIA**

**CONSENT FORM**

I/My child,_____, consent to participation in a study examining the long-term effects of treatment for Acute Lymphoblastic Leukemia and comparing their memory functioning to that of their healthy siblings and survivors of Wilms' tumor.

I acknowledge that the research procedures have been explained to me, and that any questions that I had have been answered to my satisfaction. I know that I may contact either Dr. Kuehn or Dr. Hsu if I have further questions as they arise.

I have been assured that participation in this study poses no personal risk. The testing, which will take approximately 4 hours, will take place at CHEO.

I understand that there will be no direct benefit to me/my child from participating in this study.

I also understand that I/my child may withdraw from the study at any time, even after signing this form, and this will in no way affect current or future medical care received through CHEO. All information we receive from you/your child will be handled in a confidential manner.

Name: _____ Date:_____

Witness: _____ Date: _____

Witness' relationship to participant: _____

If you are interested in receiving the group results of the study upon its completion at a future date, please print your name and address clearly below.

Name: _____

Address: _____

_____

Children's Hospital of Eastern Ontario
Hôpital pour enfants de l'est de l'Ontario
A University of Ottawa Teaching Hospital / Un Hôpital d'enseignement affilliié a l'Université d'Ottawa
401 SMYTH, OTTAWA, ONT. K1H 8L1 TELEPHONE (613) 737-7600

**Description de l'étude/lettre d'information**

**Le fonctionnement de la mémoire chez les survivants à long terme de la leucémie lymphoblastique aiguë ou de la tumeur de Wilms, et chez leurs frères/soeurs en bonne santé**

Madame,
Monsieur,

Des chercheurs en psychologie et en hématologie/oncologie de l'Hôpital pour enfants de l'Est de l'Ontario et de l'Université Carleton mènent actuellement une étude sur les effets à long terme du traitement contre la leucémie lymphoblastique aiguë (LLA). Le projet vise à améliorer la compréhension des effets à long terme de la prophylaxie du système nerveux central (SNC) sur le fonctionnement de la mémoire des individus dont les traitements ont pris fin il y a au moins trois ans. Afin d'étudier la question, nous avons besoin non seulement de la participation de gens ayant été atteints de leucémie, mais aussi de celle de leurs frères et soeurs et d'autres enfants ayant subi des traitements contre le cancer, plus précisément, la tumeur de Wilms.

La plupart des études sur les effets à long terme de la prophylaxie du SNC ont signalé que les survivants de la LLA fonctionnaient généralement dans les limites de la normale aux tests de fonctionnement intellectuel global. Cependant, des études sur le fonctionnement de la mémoire ont donné des résultats contradictoires. Puisque la mémoire a une grande importance dans le processus d'apprentissage, nous aimerions étudier davantage cette source potentielle de difficulté.

Il n'existe aucun risque connu à participer à cette étude. Tous les participants peuvent s'en retirer à tout moment. Votre participation n'est aucunement liée au traitement que reçoit votre enfant à l'Hôpital pour enfants de l'est de l'Ontario. On ne modifiera ni ne refusera aucun traitement si jamais vous choisissez de ne pas participer à l'étude ou de vous en retirer. De plus, votre participation à l'étude n'influera nullement sur les traitements que votre famille pourraient recevoir dans l'avenir.

Tous les renseignements vous concernant, vous et votre enfant, demeureront confidentiels. Vous devrez passer des tests qui prendront environ quatre heures de votre temps en une seule séance **par enfant.** Cette séance aura lieu à un moment qui vous conviendra. Ils seront administrés par un psychométricien, sous la supervision d'un psychologue. Les activités comprennent: répondre à des questions, écouter des histoires, regarder des photos, tracer des formes, etc. Aucune de ces activités n'est envahissante ou douloureuse. Les participants ayant été atteints de leucémie, mais non leurs frères/soeurs ou les

enfants ayant eu une tumeur de Wilms, subiront une évaluation approfondie en neuropsychologie comparable à celle qu'ils recevraient normalement au service clinique. La communication des résultats obtenus aux tests sera offerte seulement aux familles des enfants ayant eu la leucémie lymphoblastique aiguë. Dans les cas où les résultats obtenus par tout autre enfant faisant partie du groupe contrôle (i.e., frère/soeur, tumeur de Wilms) suggèrent la présence de difficultés cognitives non identifiées auparavant, un rendez-vous sera fixé afin de discuter de ces résultats avec les parents de l'enfant.

Ce protocole de recherche comprend également des investigations neuroradiologiques. On procédera à des examens IRM et à des tomodensitométries de la tête *seulement* chez les participants ayant été atteints de leucémie. Les rendez-vous pour les IRM et tomodensitométries seront fixés pour une journée différente de l'évaluation pour la recherche, mais auront lieu au cours des premiers six mois suivant votre participation à l'étude.

Votre contribution à la compréhension de la mémoire humaine et des effets tardifs du traitement pour la leucémie est grandement appréciée et très importante puisque peu de gens sont admissibles à ce projet de recherche. Veuillez noter que les frais de stationnement seront couverts par les chercheurs au moment de votre participation.

Si vous avez des questions au sujet de cette recherche, communiquez avec le Dr Sally Kuehn au 737-2657 ou le Dr Elizabeth Hsu au 737-2751. Vous pouvez également communiquer avec le président du Comité d'éthique de la recherche (738-3272) pour connaître les droits des patients qui participent à une recherche. Cependant, cette personne ne peut vous transmettre aucune information médicale sur l'étude.

Nous apprécions vivement votre contribution à la compréhension de la mémoire humaine et des effets à long terme du traitement de la leucémie.

Dr Elizabeth Hsu
Oncologue pédiatrique
HEEO
Ottawa (Ontario)

Dr Sally Kuehn
Psychologue titulaire
HEEO
Ottawa (Ontario)

Pauline Richards, M.A.
Candidate au doctorat
Département de psychologie
Carleton University
Ottawa (Ontario)

Dr Shelley Parlow
Professeure associée en psychologie
Département de psychologie
Carleton University
Ottawa (Ontario)

Children's Hospital of Eastern Ontario
Hôpital pour enfants de l'est de l'Ontario
A University of Ottawa Teaching Hospital / Un Hôpital d'enseignement affilié a l'Université d'Ottawa
401 SMYTH, OTTAWA, ONT. K1H 8L1 TELEPHONE (613) 737-7600

**Le fonctionnement de la mémoire chez les survivants à long terme de la leucémie lymphoblastique aiguë**

**Consentement**

Je/mon enfant, _____, accepte de participer à une étude sur les effets à long terme du traitement de la leucémie lymphoblastique aiguë et sur la comparaison du fonctionnement de leur mémoire avec celui de leurs frères/soeurs en bonne santé et celui des survivants de la tumeur de Wilms.

Je reconnais qu'on m'a expliqué les procédures de recherche et qu'on a répondu à toutes mes questions de manière satisfaisante. Je sais que je peux communiquer avec les D[rs] Kuehn ou Hsu en tout temps si je venais à avoir d'autres questions.

On m'a assuré qu'il n'y a aucun risque personnel à participer à cette étude. Les tests, d'une durée approximative de quatre heures, auront lieu à l'Hôpital pour enfants de l'est de l'Ontario (HEEO).

Je comprends que ni mon enfant ni moi ne bénéficierons directement de notre participation à cette étude.

Je comprends également que moi et mon enfant pouvons nous retirer de l'étude à n'importe quel moment, même après avoir signé ce formulaire, et que cela n'aura aucun impact sur les soins médicaux obtenus par l'entremise de l'HEEO. Tous les renseignements que mon enfant et moi transmettrons demeureront confidentiels.

Nom : _____ Date : _____

Témoin : _____ Date : _____

Relation du témoin avec le participant : _____

Si vous désirez obtenir les résultats de l'étude, écrivez votre nom et votre adresse en caractères d'imprimerie ci-dessous.

Nom : _____

Adresse : _____