A multi-method study of neuropsychological functioning following treatment for pediatric acute lymphoblastic leukemia (ALL)

by

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Abstract

Cancer treatment, such as intrathecal chemotherapy and cranial radiation therapy, are frequently cited for their negative influence on neuropsychological functioning. Deficits have been noted in areas such as working memory, attention, IQ, and learning. The research reported herein used a multi-modal approach to explore the predictive value of inter-individual and treatment-related risk factors. In Study 1, I used a cross-sectional design to compare children treated for acute lymphoblastic leukemia (ALL) with a healthy control group for the association between predictive risk factors and deficits in verbal learning and memory, and IQ. In Study 2a, I analysed a longitudinal sample of individuals treated for pediatric ALL to explore changes in neuropsychological abilities over time, and evaluated their association with predictive risk factors. Finally, in Study 2b, I used the longitudinal sample from Study 2a to explore event-related potential components over time as a psychophysiological index of information processing, and the predictive risk factors associated with change over time. Treatment-related factors, such as chemotherapy protocol and total glucocorticoid dose emerged as significant predictors of impairment. The effects of radiation were more subtle than predicted. Sex, age at diagnosis, and indicators of parental well-being also predicted neurocognitive outcomes. This project filled a gap in the existing literature by answering specific questions about the nature of neuropsychological deficits following treatment for pediatric ALL, as well as helping to identify patients most at-risk for these impairments. To my knowledge, this is the first study to explore event-related potentials longitudinally in a pediatric cancer sample, and this technique may prove useful for tracking functional changes in neurocognitive function over time. The deleterious effects of treatment-related toxicity

extend beyond neuropsychological performance and can impact all facets of everyday life, including personal distress and trauma, and costs to educational and healthcare systems and social infrastructure. These results may help clinicians identify patients who are most at-risk for developing neurocognitive impairments, and/or require modified treatment protocols, long-term monitoring, or early intervention.

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List of Abbreviations

ALL . . . . . Acute lymphoblastic leukemia

CNS. . . . . Central nervous system

CRT . . . . . Cranial radiation therapy

CVLT-C. . . . California Verbal Learning Test – Children's Version

DFCI . . . . . .Dana Farber Cancer Institute

EEG. . . . . .Electroencephalogram

EOG. . . . . Electrooculogram

ERP . . . . . Event-related potential

FAI . . . . . Family Adversity Index

HPA. . . . . .Hypothalamic pituitary adrenal axis

IQ. . . . . Intelligence quotient

WISC . . . . . Wechsler Intelligence Scale for Children

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The last 50 years have marked a period of substantial research and innovation in the care and understanding of patients with pediatric cancer. As a result, there has been notable improvement in long-term rates of survival. That said, there are still meaningful consequences to the cure: although research has led to more effective treatments, these treatments are also associated with high rates of adverse effects that can impact nearly every bodily system, including the brain. Although significant resources have been directed to refine treatment protocols and minimize the most cognitively damaging adverse effects, functionally important differences between survivors persist (Peterson et al., 2008). For this reason, society is faced with a growing population of pediatric cancer survivors who continue to experience acute and late adverse effects that impact their day-to-day functioning. The impact of adverse effects is pervasive, and also affects survivors' families, educators, and communities.

Much research has explored the influence of anticancer therapy on the brain and the associated impairments in working memory, learning outcomes, intelligence, and academic achievement (e.g. Campbell et al., 2007). Notwithstanding, relatively little is understood about the development of these impairments following treatment, and research on inter-individual and treatment-related factors that might affect the development of these impairments lacks definitive answers. In the research reported herein, I used a multimodal design to examine possible inter-individual and treatment-related risk factors associated with the emergence of neuropsychological deficits following diagnosis in survivors of pediatric acute lymphoblastic leukemia (ALL).

My program of research was comprised of two studies, which were based on archival data. Overall, the aim was to explore the emergence and nature of neuropsychological deficits, to understand potential mediating relationships between variables, and to identify inter-individual factors that may have contributed to the development of these deficits with a cross-sectional sample including a control group, as well as in a longitudinal sample. In Study 1, I examined a retrospective cohort of children who received treatment for ALL and a group of healthy controls. All children in the treatment group received intrathecal chemotherapy in addition to cranial radiation therapy (CRT). A measure of verbal learning and memory, and a standardized measure of intelligence were administered to both groups in order to explore the differences between childhood cancer survivors and typically developing children. Predictive risk factors known to affect the emergence of late effects (i.e. group membership, sex, age at diagnosis, and delay between diagnosis and testing) were considered for their association with performance on these measures. In Study 1, mediating relationships between predictive risk factors and outcome variables were also explored based on past research.

In Study 2a, the same predictive risk factors tested in Study 1 were explored for their association with verbal learning and memory outcomes in pediatric ALL survivors over time. The aim of this study was to replicate previous findings with respect to certain risk factors (e.g., age at diagnosis, sex, use of CRT), and to expand the literature with the inclusion of total dose of glucocorticoids as a potential predictive risk factor.

The study rationale and predictive risk factors from Study 2a were applied to Study 2b, where cognitive abilities were measured psychophysiologically. Study 2b utilized a subset of the Study 2a sample. Event-related potentials (ERPs) derived from a

visual oddball task were used to measure the working memory updating process and as a marker of the brain network subtending working memory (Bledowski et al., 2004; Soltani & Knight, 2000). ERPs have been used in other studies of childhood cancer survivors, though few have examined outcomes longitudinally. Research with other populations (e.g. multiple sclerosis, Piras et al., 2003; mild cognitive impairment, Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2011) has suggested that ERP components, such as the P300, are sensitive to change over time. Past research has also demonstrated differences between the ERP components of typically developing children, and children treated for cancer (Lähteenmäki et al., 2001). Based on a search of the PubMed database conducted in August 2019, the present study was the first to examine changes in ERP components over time in survivors of pediatric ALL.

The studies contained in my program of research tested similar hypotheses, but varied in sample and methodology. By nature, the cross-sectional design of Study 1 prohibited the study of change over time, and did not incorporate a true baseline measure. It was also based on a relatively small sample. To address these limitations, Study 2a and 2b used a larger sample of children treated for ALL who were assessed at diagnosis (i.e. prior to the administration of treatment), and then approximately annually during the following four years. Participants in Study 2a and 2b were either treated with intrathecal chemotherapy alone, or with a combination of intrathecal chemotherapy and CRT, making it possible to tease out the effects of specific treatment modalities.

The goal of the project was to use a mixed methods research design to address questions relating to the association of treatment-related and inter-individual variables with neuropsychological outcomes. Previous research on the types of deficits associated

with anticancer therapy and variables associated with their emergence and development are summarized in the literature review that follows.

Pediatric Acute Lymphoblastic Leukemia (ALL) and Its Treatment

Acute lymphoblastic leukemia occurs as the result of an acquired genetic injury to the DNA of a single marrow cell, which produces uncontrolled growth, and an accumulation of abnormal cells (*lymphoblasts*) that impede the production of normal cells. ALL is most often diagnosed in the first decade of life, with the highest incidence occurring in children less than five years of age (National Cancer Institute, 2010). Typically, patients (or their parents/caregivers) initially notice symptoms like tiring more easily than usual, shortness of breath during normal physical activity, pale complexion, unusual bruising, and prolonged bleeding from minor cuts (The Leukemia & Lymphoma Society, 2012).

Though relatively rare, childhood cancer is the second leading cause of disease-related death for individuals between five and 15 years of age in Canada (Public Health Agency of Canada, 2012). ALL is the most common pediatric malignancy, and accounts for 25% of all childhood cancer diagnoses (Howlader et al., 2013). Although the overall incidence of childhood cancer in Canada has remained stable since 1984 (with an average age-standardised incidence rate of 153 cases per one million children), survival rates have increased significantly. These changes are largely attributed to improvements in treatment protocols (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2013).

Since the 1950s, the survival rate of pediatric ALL has risen nearly 80%, with several studies citing current five-year survival rates close to 90% (e.g. Pui & Evans,

2013). Much of this change may be credited to improvements to treatment protocols. Chemotherapy was first introduced to pediatric ALL patients in 1948 with the use of aminopterin in five patients (Farber, Diamond, Mercer, Sylvester, & Wolff, 1948). Over the next few decades, additional medications, such as mercaptopurine and methotrexate, were added to chemotherapy protocols, and survival rates improved. Historically, radiation therapy was also routinely administered, though it was associated with markedly deleterious outcomes like deficits in cognitive function, secondary malignancies, growth retardation, obesity, osteoporosis, and craniofacial deformities (Pui & Relling, 2002). In the 1980s, in response to significant radiation-related complications, triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabine (Sullivan, Chen, Dyment, Hvizada, & Steuber, 1982), and intermediate-dose intravenous methotrexate (Freeman et al., 1983) were introduced as alternatives to cranial radiation; these protocols highlighted the efficacy of methotrexate in improving patient outcomes.

In 1962, Donald Pinkel introduced "total therapy," which was comprised of four distinct phases of treatment: (1) remission induction; (2) central nervous system-directed therapy with CRT and intrathecal methotrexate, (3) intensification/consolidation, and (4) continuation, with promising results (Pinkel, 1971). Clinicians continue to administer treatment in these phases today. Currently, ALL treatment most often requires chemotherapy administered over several years, which becomes progressively less intense. During the first phase of chemotherapy (remission induction), patients typically receive vincristine, glucocorticoids (e.g. prednisone or dexamethasone), asparaginase, and often an anthracycline (e.g. doxorubicin or daunorubicin) for four to six weeks. In the consolidation phase, which lasts for six to nine months, patients receive a combination of

chemotherapeutic medications aimed at maximizing efficacy and minimizing drug resistance, and may include mercaptopurine, thioguanine, methotrexate, and cytarabine. The maintenance phase typically lasts two years, and consists of antimetabolite therapy with methotrexate and mercaptopurine. The final phase of treatment is directed at the CNS, regardless of CNS involvement at diagnosis; in the absence of CNS involvement at diagnosis, CNS-directed treatment is included as a prophylaxis (Cooper & Brown, 2015). Presently, the rate of patients who receive CRT ranges from 0% to 20%, depending on factors like disease characteristics (Vora et al., 2016).

Since the 1990s, researchers have attempted to identify the pathobiology of ALL, develop more precise risk classification (e.g. based on age at diagnosis, and/or white blood cell count) and targeted treatment for high-risk groups (e.g. infants), and further understand individual response to chemotherapeutic agents through mechanisms such as pharmacogenetics (Cooper & Brown, 2015; Pui & Evans, 2013). Large scale studies from the Children's Oncology Group, which includes over 21 000 participants, indicate that with more refined and directed treatments, survival rates have continued to improve for almost all patients, including those in high-risk subgroups (Hunger et al., 2012).

Presently, children diagnosed with ALL are surviving longer than ever (Kizilocak & Okcu, 2019). However, between two thirds and three quarters of survivors will experience one or more adverse effects following treatment (Public Health Agency of Canada, 2012). Survivors commonly experience adverse effects like cardiac abnormalities (Ness, Armenian, Kadan-Lottick, & Gurney, 2011), secondary malignancies (Ishida et al., 2014), and neuropsychological deficits (Iyer, Balsamo, Bracken, & Kadan-Lottick, 2015). In an attempt to minimize the risk of children

developing adverse effects, modern treatment protocols have progressively lessened the intensity of treatment aimed directly at the brain, including: reduction of cranial radiation exposure, restricting the use of radiation to only the most high-risk patients, and replacing radiation with chemotherapy (Pui & Evans, 2013). As a result of these efforts, the incidence of radiation-related side effects has decreased, though chemotherapy-related side effects are still relatively common and distressing. Today, chemotherapy-related adverse effects are typically smaller in magnitude than in the past, but they continue to significantly impact pediatric survivors' day-to-day functioning (Krull, Hardy, Kahalley, Schuitema, & Kesler, 2018).

Although some treatment-related side effects appear acutely (e.g., fatigue, nausea), *late effects* are those that typically do not emerge for several years after treatment is complete (Shannon, 2007). Behind stunted growth, impairments in neuropsychological or neurocognitive abilities are the second most commonly cited late effect (Haddy, Mosher & Reaman, 2009). Though overall differences between patients and healthy controls are relatively small, large differences in neuropsychological function persist between individual survivors (e.g. Waber et al., 2007; Waber, Forbes, Almli, Blood, & The Brain Development Cooperative Group, 2012). Survivors commonly experience disruption in their attention and concentration (Mulhern & Palmer, 2003; Butler & Copeland, 2002), processing speed (Peterson et al., 2008), and memory (Ashford et al., 2010). The full extent of long-term adverse effects is still largely unclear, though these effects are functionally important, particularly in the context of a growing cohort of survivors, as their impact extends to an individual's mental health (e.g. Kunin-Batson et al., 2016), quality of life (e.g. Kunin-Batson, Kadan-Lottick, & Neglia, 2014),

ability to function at school (e.g. Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005), and function as part of a family and member of society (e.g. Mody et al., 2008).

Neuropsychological Deficits Following Pediatric Cancer Treatment

When compared to healthy control groups, children treated for ALL significantly underperform on a range of neuropsychological skills and domains, including academic performance, general intelligence, working memory, attention, and learning. In a meta-analysis by Campbell et al. (2007) that included survivors of pediatric acute lymphocytic leukemia, significantly negative mean effect sizes were related to nine neurocognitive domains (overall cognitive functioning, academic achievement, attention, executive functioning, processing speed, psychomotor skills, verbal memory, visuospatial skills, and visuospatial memory; g = -.34 to -.71).

Marked differences have been noted amongst children treated for ALL, even between those who received the same treatment protocol. Some children experience little impairment, while others present with significant disturbance in their intellectual and cognitive abilities. These deficits take time to emerge and typically appear as a function of a reduced rate of cognitive development in comparison to their same-age peers (Harshman et al., 2012). Moreover, the gap between survivors and their peers tends to increase with time elapsed from diagnosis (Askins & Moore, 2008). Atypical neuropsychological development is often noticed first at school, though academic difficulties may not manifest until middle or high school as curriculums shift from a focus on rote-learning to more advanced skills like organization, reasoning, and time management (Nathan et al., 2007).

Neuropsychological impairments related to the use of radiation have been detected up to 20 years post-diagnosis (Harila, Winqvist, Lanning, Bloigu, & Harila-Saari, 2009). However, certain skills may not follow a linear developmental trajectory. For example, Krull et al. (2013b) noted that in adult survivors of pediatric ALL, Performance IQ and Full Scale IQ scores worsened over time elapsed from diagnosis (median years from diagnosis = 28.5), though the same pattern was not observed for Verbal IQ.

Academic functioning. Children who have undergone cancer treatment tend to have significantly lower levels of academic functioning compared to their healthy peers (Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000). As a result, survivors face a number of challenges at school, and many pediatric patients and survivors require extra attention or special services. According to a parent report study, childhood cancer survivors were more likely to repeat a grade, make use of learning disability or special education programs, and have issues with academic performance (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005). Additionally, Mitby et al. (2003) reported that 23% of childhood cancer survivors utilized special education services, compared to only 8% of their siblings. Children diagnosed prior to age six were most likely to rely on these resources. In a population-based study of pediatric cancer survivors, Harshman et al. (2012) found consistent declines in academic achievement between grades four and 11 (mean age at diagnosis = 7.2 years). The increase in academic expectations as students progress to higher grades may, at least in part, explain why deficits seem to worsen with time elapsed from diagnosis.

Previous findings suggest that survivors and typically developing children may also rely on different skills and strategies to learn. For example, a study by Kaemingk, Carey, Moore, Herzer, and Hutter (2004) examined differences in math performance between pediatric ALL survivors and healthy children. Their results indicated that the two groups relied on a different set of cognitive skills to complete the same task. Poorer performance on mathematical operations, mental calculations, and mathematical applications were most related to deficits in verbal and visual memory and dominant-hand psychomotor speed in children treated with chemotherapy. Conversely, mathematics performance of an age- and sex-matched control group was most closely related to rote reading skills and visual-motor integration skills.

Intelligence quotient (IQ). Prior research has demonstrated that IQ is negatively affected by anticancer therapy, and that scores tend to decline over time (Brown, Sawyer, Antoniou, Toogood & Rice, 1999). Outcomes are most alarming for those treated with CRT, particularly on older protocols that used 24Gy of radiation. Even with radiation doses reduced to 18Gy, survivors still present with significant neurocognitive deficits. For example, Jankovic et al. (1994) found that children treated with 18Gy radiation had significantly lower IQ scores compared to other survivors who were treated with chemotherapy alone. Further, the observed gap in IQ scores widened with time elapsed from diagnosis: IQ dropped almost four points per year from diagnosis in those who received radiation, while no change in IQ was observed for the chemotherapy-only group.

Memory. Working memory plays an integral role in other cognitive abilities, like attention and processing speed. In typically developing children, individual differences in processing speed directly affect working memory capacity, which in turn affects

individual differences in fluid intelligence (Fry & Hale, 1996; Fry & Hale, 2000) and other cognitive abilities. Research has suggested that working memory capacity may largely account for individual differences detected in intellectual function (Cowan, 1995), and academic achievement. It has also been suggested that working memory is a more accurate predictor of academic achievement than IQ (Alloway & Alloway, 2010).

Survivors of childhood cancer commonly experience impairments in memory, including working memory. In a study of children treated for ALL with chemotherapy alone (n = 26), Montour-Proulx et al. (2005) found that on four consecutive trials of a memory and learning task (Verbal Memory Index of the Wide Range Assessment of Memory and Learning), more than half of participants scored over one standard deviation below the normative mean. In another study, Monje et al. (2013) found differences in working memory function between survivors of pediatric ALL (n = 10) and healthy age- and sex-matched controls (n = 10), where survivors performed more poorly on a recognition task and had more false alarms (i.e. identified a novel stimuli as one that had been presented previously). Given the important role of memory in other cognitive abilities, it is imperative that treatment-related changes to memory observed in survivors are well-studied, well-understood, and are allocated adequate attention and resources.

Attention. Survivors of pediatric ALL frequently experience deficits in attention. Similar to impairments in working memory, attention deficits are commonly associated with other neuropsychological abilities or with inter-individual characteristics. For example, deficits in attention have been linked to specific difficulties with mathematics and reading skills (Rodgers, Horrocks, Britton, & Kernahan, 1999), as well as increased vulnerability to working memory deficits (Ashford et al., 2010).

Previous research has also linked attention deficits to specific behavioural concerns. Krull et al. (2011) used parent report to track the incidence of inattentive behavioural symptoms in daily life in children treated for cancer with radiation. Thirty-two percent of survivors demonstrated symptoms of distractibility, 22% were described as forgetful, and 20% experienced disorganization. Though researchers have yet to determine the academic implications of these behaviours, there is likely an association between distractibility, forgetfulness, disorganization, and poorer school performance. Individuals diagnosed with Attention-Deficit/Hyperactivity Disorder exhibit a similar pattern of academic struggles and attentional deficits, and these difficulties extend from kindergarten to postsecondary programs (Loe & Feldman, 2007).

Learning. Treatment-related disturbances to IQ, memory, and attention are often related to challenges in learning and to the use of specific learning strategies. For example, a study by Mabbott et al. (2005) demonstrated that independent of school absenteeism, declines in academic achievement were associated with reduced rates of skill acquisition in cancer survivors treated with CRT for a tumour of the posterior fossa (medulloblastoma or ependymoma).

Using a subset of the sample used for Study 1 in my thesis, Precourt et al. (2002) measured verbal learning, learning strategies, and working memory in a group of girls treated for ALL at an average of 30 months post-treatment. On the California Verbal Learning Test-Children's Version (CVLT–C), which is a span task repeated over several trials, after the third trial children treated with chemotherapy alone or with a combination of CRT and chemotherapy, recalled fewer words than children in the healthy control group. However, at the last trial, children treated with chemotherapy alone ultimately

matched the performance of healthy children. Both treatment groups performed more poorly than the control group on short- and long-delay recall trials. Moreover, the treatment groups used fewer serial associations than the control group, and performed more poorly on the Freedom from Distractibility Index of the Wechsler Intelligence Scale for Children-III (WISC-III), which measure working memory and attention. Patients treated with a combination of CRT and chemotherapy also demonstrated a unique pattern of correlations between the number of words recalled on the CVLT-C and their scores on the Backward Digit Span subtest of the WISC-III, especially during the last three trials. These results suggested that after three repetitions, working memory was still a limiting factor in auditory-verbal learning for those treated with CRT, though not for those treated with chemotherapy alone or typically developing children.

Individual Factors Associated with Differential Outcomes Following Pediatric Cancer Treatment

Age at diagnosis. Patients diagnosed with ALL earlier in life are more likely to develop neurocognitive impairments (Kizilocak & Okcu, 2019). These age-related differences in adverse effects associated with treatment toxicity may occur as a function of brain development. Since brain development occurs in stages, there are periods at which the brain is more vulnerable to insults. When an injury to the brain occurs at an earlier stage of development (i.e. at a younger age), the brain assimilates the damage into structural and neural networks. However, when an injury to the brain occurs at a later stage of development (i.e. at an older age, though still pre-puberty), functional, more adaptive changes in the brain occur as a result of compensation of cerebral structures (Andersen, 2003). Therefore, since treatments for ALL directly affect the brain (i.e.,

intrathecal chemotherapy, cranial radiation therapy), the severity of adverse effects may be influenced by the age at which treatment is administered.

Researchers have yet to determine an exact age threshold for heightened vulnerability to the risk of adverse effects. However, in most studies, children under five years of age are at the greatest risk for treatment-related impairments, such as poor academic achievement (Harshman et al., 2012) and attentional deficits (Buizer, de Sonneville, van den Heuvel-Eibrink, Njiokiktjien & Veerman, 2005; Schatz, Kramer, Ablin, & Matthay, 2004; Lockwood, Bell, & Colegrove, 1999). The magnitude of the impact of CRT is also dependent on age at diagnosis for outcomes like intelligence, academic achievement, and memory, where younger children are more sensitive to the harmful effects of treatment (Krull et al., 2013a). A population-based study by Waber et al. (2001) suggested that children diagnosed with high-risk ALL when they were less than three years old were more susceptible to treatment-related toxicity and performed more poorly on the Vocabulary and Digit Span subtests of the WISC-III. As mentioned previously, the highest incidence of ALL diagnosis occurs prior to five years of age (National Cancer Institute, 2010), which may explain the common occurrence of neurocognitive deficits in this population.

Sex. Sex differences in pediatric cancer survivors have been reported in many studies. Late effects influencing neurocognitive function are more commonly detected and severe in girls, even in those treated without central nervous system radiation (von der Weid et al., 2003). Global differences between sexes were reported in a meta-analysis by Peterson et al. (2008) where females' Full Scale IQ, Verbal IQ, and Performance IQ scores were significantly weaker than their male counterparts. In another study, Waber,

Tarbell, Kahn, Gelber, and Sallan (1992) found that the association between treatment intensity and neurocognitive outcome was sex-dependent, such that a high dose of methotrexate (a medication in chemotherapy protocols) was associated with a significant increase in the proportion of female survivors with an IQ below 90.

Female sex has been associated with specific patterns of neuropsychological impairment (Waber et al., 1990), as girls seem to be particularly vulnerable to deficits in attention and working memory (Brown et al., 1998; Jain, Brouwers, Okcu, Cirino & Krull, 2009). These effects are often associated with treatment-related factors. In one study, survivors of ALL treated on a chemotherapy-only protocol showed subtle visuomotor deficits one year after treatment, especially in conditions where higher order executive control was required. Children who received intensified treatment protocols demonstrated more considerable deficits on attentional flexibility, as well as sustained attention and visuomotor control. Dosage of methotrexate was a noted factor in post-treatment attentional deficits, and girls were significantly more vulnerable to impairments on several measures of attention (Buizer, de Sonneville, van den Heuvel-Eibrink & Veerman, 2005).

Post-treatment sex-related differences may be, at least in part, attributed to brain morphology and maturation related to grey and white matter development. White matter plays a critical role in complex cognitive functions, such as learning (Fields, 2011), and sex-related differences in white matter development may govern the observed differences in neuropsychological function. During development, brain regions differ in their rate of myelination, and white matter tends to develop more quickly in males. De Bellis et al. (2001) used structural neuroimaging to explore white and grey matter growth in a group

of healthy children and adolescents. They found that between six and 18 years old, white and grey matter volume increased more significantly in boys compared to girls, and these differences may account for some of the observed sex differences in cognitive abilities. A recent study of healthy adults also suggested that males typically have greater white matter volume in the occipital, temporal, insular, parietal, and frontal brain regions (Bourisly, Gejo, Hayat, Alsarraf, Dashti, & Di Paola, 2017). These results imply that greater white matter volume may protect males against the deleterious effects of anticancer therapy, while relatively smaller white matter volumes may leave females more vulnerable to impairments.

However, across studies, results with respect to grey and white matter volume and development are somewhat contradictory; often, these inconsistencies can be attributed to differences between samples, software, or procedures (i.e. controlling for intracranial volume versus whole brain volume). In the context of sex differences associated with treatment toxicity, some of the variance in results may be connected to an interaction between sex, age at diagnosis, and study methodology. Mills et al. (2016) conducted a study to account for some of the differences between studies and their results. They analysed four distinct longitudinal samples of healthy children, and while controlling for whole brain volume, they noted that cortical grey matter volume peaks in childhood and then declines throughout adolescence. As well, cortical white matter volume increases during childhood and plateaus in mid-to-late adolescence. The relationship between grey and white matter development and sex is complex and likely non-linear, and the relationship between brain development and sex is further complicated by age-related development.

Family well-being. Family well-being refers to the overall psychosocial functioning of a family unit, where the family is viewed as the primary influence on the behaviour and experience of its individual members, and is responsible for the creation and maintenance of each member's well-being (Caldwell, 2003). It is a dynamic construct comprised of several key indicators of stress and well-being, like psychological status and self-efficacy of the parents, family organizational structure, and interpersonal relationships (Armstrong, Birnie-Lefcovitch, & Ungar, 2005). Families are complex systems, and the well-being of individual members and/or the family as a whole may be dependent on a number of factors, such as family structure (e.g., dual-parent versus single parent, presence of illness, social support available to the family). The status of family well-being may explain how the impact of a cancer diagnosis, its treatment, and associated stress is absorbed into the family system, how it affects the well-being of each family member, and how chronic family stress can impact neuropsychological outcomes.

While family well-being is not well-studied in the pediatric cancer population, convincing links between components of well-being, including family well-being, and clinical outcomes have been reported (Armstrong, Birnie-Lefcovitch, & Ungar, 2005). Previous research has demonstrated significant associations between indicators of family well-being and clinical and psychological outcomes in a number of chronic disease populations, including children diagnosed with ALL (e.g. Iqbal & Siddiqui, 2002; Waters, Wake, Hesketh, Ashley, & Smibert, 2003), and other childhood cancers. For example, Ach et al. (2013) found that pediatric brain tumour survivors with lower levels of family support and higher levels of family conflict, underperformed on measures of academic achievement compared to their healthy peers. These associations remained

significant even after controlling for age at diagnosis, delay between treatment and testing, and type of chemotherapy and/or radiation. Ach et al.'s study highlights the significant influence of family functioning and well-being on neuropsychological outcomes.

Treatment-Related Factors Associated with Differential Outcomes Following Pediatric Cancer Treatment

Risk classification. Treatment intensity varies substantially between subsets of children with ALL based on risk classification. Standard-risk patients with favourable clinical and biological features (and who are thus more likely to have a positive outcome) can be spared a more intensive and toxic treatment protocol, and instead receive less aggressive and toxic therapies. Conversely, those with a lower probability of long-term survival are treated with more aggressive and toxic protocols (Smith et al., 1996). Considering that risk classification influences treatment intensity, risk classification may also impact the severity of neurocognitive functions, such as working memory and attention deficits. In one study, Ashford et al. (2010) found that pediatric ALL patients classified as standard- or high-risk performed more poorly on the Digit Span, Digit Span Backward (a measure of verbal working memory), and Digit Span Forward (a measure of attention and immediate recall) subtests of the WISC-III compared to participants classified as low-risk. Across groups, more patients performed below the normative mean on the Digit Span Backward compared to Digit Span Forward or Digit Span subtests, suggesting that working memory may be more sensitive to the effects of anticancer therapy compared to attention. Further, a regression analysis indicated that Digit Span

Backwards scores predicted estimated IQ scores after accounting for performance on the Digit Span Forward subtest, linking working memory with other neurocognitive abilities.

Cranial radiation therapy. The relationship between the use of CRT and the emergence of late neurocognitive deficits suggests that patients who receive radiation are at the highest risk for long-term impairment among all patients (e.g. Jankovic et al., 1994; Meshref, ElShazly, Nasr, & AbdElhai, 2013). Radiation-related impairments may emerge soon after treatment, or they may take time to develop. For example, Anderson, Godber, Smibert, Weiskop, and Ekert (2000) assessed children treated for cancer with a combination of chemotherapy and CRT, children treated with chemotherapy-alone, and a group of healthy controls. The cancer survivor groups were assessed at a minimum of two years post-diagnosis, and then again three years later. At the first assessment, children treated with CRT performed more poorly on measures of IQ and academic achievement compared to the other groups. At the second assessment, non-verbal and processing task performance had declined for children treated with CRT but remained relatively stable for children in the other groups. The results from this study indicate that impairments may not emerge or progress linearly, and that specific impairments in neuropsychological abilities may follow distinct timelines.

Radiation-related effects in survivors of pediatric cancer have been found to persist well into adulthood and to worsen with time. In a study of 102 adult survivors of pediatric ALL treated with CRT (median time from diagnosis = 28.5 years), verbal intelligence declined by an average of 10.3 points over the follow-up period, and the use of radiation was significantly associated with attention deficits in adulthood (Krull et al.,

2013b), echoing research cited earlier, which demonstrated a decline in IQ following radiation (Jankovic et al., 1994).

The adverse neurocognitive outcomes associated with CRT as treatment for ALL extend beyond IQ, also affecting academic achievement, attention, and memory (Spiegler et al., 2006). On a span task repeated over several trials, Precourt et al. (2002) noted that girls treated with CRT and chemotherapy recalled fewer words and relied more upon short-term memory compared to children treated with chemotherapy alone or typically developing children.

At the structural level, there is a well-established correlation between radiation therapy and changes in white matter volume that are associated with neurocognitive impairments (Filley & Kleinschmidt-DeMasters, 2001). Reddick et al. (2005) compared mean white matter volume in healthy children and children treated for a medulloblastoma with 35 to 45Gy of radiation. They found that white matter volume increased by 5.4% per year between the ages of six and 12 years for typically developing children, and decreased at a rate of -1.1% over the same period for children treated for cancer with radiation. A study by Reddick et al. (2006) produced similar results: children treated for ALL who were assessed at least 18 months following treatment with a combination of CRT and chemotherapy, showed white matter volume that was reduced by 9.6% compared to children who were treated with chemotherapy alone.

Reduction in white matter volume has been directly associated with attenuated intellectual functioning and academic skills, as well as with underlying attentional deficits (Reddick et al., 2014). The effects of radiation on the brain are persistent: by middle adulthood, survivors who received 24Gy of CRT as children experienced reduced

cognitive status and memory, which were associated with white matter anomalies in cortical regions essential for memory. These results are similar to findings in patients with early onset mild cognitive impairment, and some research has suggested that ALL survivors are at risk for early onset dementia (Armstrong et al., 2013).

The impact of CRT on the brain has also been detected in studies using ERPs. For example, Sato et al. (1992) found that participants who received a combination of CRT (18Gy) and intrathecal methotrexate had longer P300 latencies on an auditory oddball task compared to participants treated with chemotherapy alone, suggesting impaired information processing. Other studies have reported similar results (e.g., Heukrodt et al., 1988; Moore, Copeland, Ried, & Levy, 1992). In another study, Uberall et al. (1996) assessed long-term survivors of pediatric ALL with ERPs elicited by a visual oddball task. P300 latency was correlated with measures of non-verbal memory, attention, and intelligence, and longer P300 latencies were detected in individuals who received a combination of CRT and chemotherapy, compared to those treated with chemotherapy alone, while no significant difference was detected between survivors treated with chemotherapy alone, and a group of age and gender-matched healthy controls.

Chemotherapeutic agents. Glucocorticoids are well-regarded for their anti-inflammatory and immunosuppressive abilities, and are widely included in chemotherapy protocols (Coutinho & Chapman, 2011). Unfortunately, these medications are also associated with declines in specific neurocognitive functions, particularly those implicated in hippocampal-dependent processes, such as declarative memory (Phillips et al., 2019). The hippocampus may be especially vulnerable to the toxic effects of

glucocorticoids because it is the brain region with the highest concentration of glucocorticoid receptors in the brain (Sapolsky, Krey, & McEwen, 1984).

Neurocognitive outcomes may vary as a function of the type of glucocorticoid administered with chemotherapy, with some adverse effects being more severe than others. However, overall differences between survivors treated solely with chemotherapy tend to be subtler than those observed in individuals treated with CRT (Kadan-Lottick et al., 2009). Still, two thirds of children treated for ALL with chemotherapy alone experience neurocognitive decline to some degree (Moleski, 2000).

Dexamethasone and prednisone are two of the most frequently administered glucocorticoids, and the decision of which to include in a chemotherapy protocol is a recurring clinical question. The biochemical and physiological properties of dexamethasone and prednisone differ, and the nature and severity of their related side effects may also vary. Several studies have been aimed at determining optimal glucocorticoid type and dose. Prednisone:dexamethasone bioequivalence ratios vary from six to 10, and are most common at 6.67. At those ratios, dexamethasone may be more efficient in maximizing survivorship, though it is associated with a higher incidence of deleterious side effects (Inaba & Pui, 2010). Dexamethasone continues to be included in chemotherapy protocols due to its relative advantage over prednisone in outcomes of survival, such as five-year relapse rate and survival rates for patients with T-cell type ALL (Carlson, 2016).

Overall, studies have shown that the use of prednisone is associated with fewer adverse effects compared to dexamethasone (Mitchell et al., 2005; Bostrom et al., 2003). For example, Edelmann et al. (2013) compared a group of pediatric ALL survivors

treated with either dexamethasone (n = 18) or prednisone (n = 20) on measures of intelligence, academic achievement, and memory, and fMRI. Participants treated with dexamethasone performed more poorly on outcomes of intelligence, academic achievement, and several measures of memory. On fMRI, story memory was associated with altered activation in the left inferior frontal-temporal brain regions for those treated with dexamethasone.

Clinicians must also consider the total dosage when administering glucocorticoids. High-dose glucocorticoids have been associated with suppression of the hypothalamic-pituitary-adrenal (HPA) axis, which is associated with reduced resilience to stressors and impaired immune response (Gordijn, Rensen, Gemke, van Dalen, Rotteveel, & Kaspers, 2015). However, response to therapy may improve with dose (Schwartz et al., 2001), and the adrenal suppression caused by high-dose glucocorticoids may be relatively short-lasting (e.g. Einaudi, Bertorello, Masera, & Pastore, 2008).

Time elapsed from diagnosis. While some adverse effects emerge during or immediately following treatment, other effects take time to emerge. Compared to sibling controls, the risk of ALL survivors developing chronic medical conditions like cardiac or neurologic issues increases with time elapsed from diagnosis and treatment (Oeffinger et al., 2006). As well, research indicates that some deficits may worsen with time (Askins & Moore, 2008). In a sample of more than 500 long-term survivors of ALL (mean time from diagnosis = 26 years), Krull et al. (2013a) found that impairments in executive function worsened as a function of years elapsed from diagnosis for patients treated with CRT. The risk of impairment was six times greater for those treated with CRT compared

to patients treated without radiation at 45 years post-diagnosis. In addition, risk for self-reported behavioural problems increased by 5% with each year from diagnosis.

Mechanisms Of Impairments

Brain imaging technology has led to greater insight into the mechanisms impacting neuropsychological performance in individuals treated for pediatric cancers. Based on these techniques, white matter damage and oxidative stress have emerged as the most commonly cited mechanisms linked to treatment-related brain toxicity in the cancer survivor population. Damage to cortical and subcortical white matter is perhaps the most well-studied mechanism underlying treatment-related adverse effects. Demyelinating white matter damage is thought to be the primary mechanism responsible for delayed treatment-related toxicity (Cole & Kamen, 2006). Moreover, white matter seems to be especially vulnerable to CRT-related damage (Burger & Boyko, 1991), with up to half of patients treated with CRT showing progressive changes in white matter that do not resolve with time (Askins & Moore, 2008).

White matter damage is also associated with chemotherapy. Studies using MRI or fMRI technology have detected white matter differences between ALL survivors and healthy controls. For example, Edelmann et al. (2014) measured grey and white matter volume in a group of ALL survivors treated with CRT, a group of ALL survivors treated with chemotherapy only, and a group of typically developing participants. In comparison to the control group, both treatment groups had a lower ratio of white matter to intracranial volume in the frontal and temporal lobes. In those treated with chemotherapy alone, these findings were associated with poorer performance on neuropsychological tasks. In another study, Montour-Proulx et al. (2005) examined neuropsychological

performance in children treated for ALL with chemotherapy alone. In a sample subset of children who received an MRI (n = 23), 78% showed white matter changes reflective of leukoencephalopathy, though brain imaging data was not corroborated by neuropsychological findings in one third of cases.

Another mechanism underlying differential outcomes is oxidative stress, which refers to an imbalance between oxidants and antioxidants in the body (Sies, 1997). Aggressive and continuous chemotherapy exhausts the antioxidant defence system (Mazor, Abucoider, Meyerstein, & Kapelushnik, 2008), and elevated levels of oxidative stress have been detected in survivors of ALL (Battisti et al., 2008). Oxidative stress is correlated with impairments to executive functions (Caron et al., 2009), and may be induced by chemotherapy-related injury to the CNS. Methotrexate has been cited as an oxidant agent that suppresses the antioxidant system and increases oxidative stress in several organs. Its inclusion in chemotherapy protocols may predispose patients to elevated oxidative stress and its associated adverse effects. Children treated for cancer at a younger age tend to be more susceptible to oxidative stress (El-Sabagh, Ramadan, El-slam & Ibrahim, 2011), which may partially explain their increased vulnerability to treatment-related toxicity.

Research Objectives and Hypotheses

The current project describes a series of studies where a multi-method approach was utilized to assess neuropsychological function in survivors of pediatric ALL. The overarching goal of the project was to explore the effects of treatment, and to identify predictive risk factors for key components of neurocognitive function, including working memory, verbal learning, IQ, and information processing.

Broadly speaking, it was predicted that participants who received treatment would demonstrate greater impairment on neuropsychological tests compared to healthy individuals. As well, individuals with one or more predictive risk factors (i.e., female; diagnosed at a younger age relative to the sample; longer delay between diagnosis and testing; received cranial radiation therapy; longer hospital stay; received dexamethasone; received a higher total dose of glucocorticoids relative to the sample; poorer parental well-being) would demonstrate greater impairment on measures of neurocognitive function, compared to those without these traits. It was also predicted that change may not emerge or progress linearly; however, our sample did not have sufficient power to test any trends beyond linear. My thesis utilized two archival datasets, and their use was approved by the Carleton University Research Ethics Board-B (see Appendix A).

In Study 1, I compared a cross-sectional sample of survivors at four to eight years post-diagnosis to a sample of healthy controls on measures of verbal learning and memory, and intelligence. Study 1 was designed as a follow-up to a paper published by Precourt et al. (2002), which used a subset of the sample included in this project. The association of predictive risk factors was considered in relation to neuropsychological outcomes. The primary objective of this study was to replicate the overall impairment in working memory in children treated for ALL found previously in the literature, and to explore sex and age at diagnosis as predictive risk factors. The analyses also included a mediation analysis in which I explored the effect of working memory capacity (measured by the Digit Span Forward subtest) on verbal learning bindings (measured by the use of serial associations in a recall task) over successive recall trials.

The hypotheses for Study 1 were as follows:

i. Group effect: Individuals in the healthy control group would outperform those in the treatment group on all neuropsychological tests.
ii. Sex effect: Overall, males would outperform females on neuropsychological tests.
iii. Age effect: Children diagnosed at a younger age (below sample median) would perform more poorly compared to those diagnosed at an older age on neuropsychological tests.
iv. Delay between diagnosis and testing: Impairment on neuropsychological tests would worsen with time elapsed between diagnosis and assessment.
v. Short-term memory would mediate the use of learning strategies, such that children with greater memory capacity would use more semantic associations, reflecting a more efficient process of encoding and retrieval.

Study 2a used longitudinal data to explore verbal learning and memory over the first four years from diagnosis of pediatric ALL. In addition to the same predictive risk factors tested in Study 1, parental well-being, type of glucocorticoid included in the chemotherapy protocol, and total glucocorticoid dose were also included as predictive risk factors. The main hypothesis for Study 2a was that the absence of specific individual- and treatment-related risk factors would be associated with better verbal learning and memory performance over time elapsed from diagnosis.

i. It was expected that:
    a. males;
    b. participants diagnosed later in life;
    c. participants with greater parental well-being;
    d. participants treated with prednisone;

e. participants who did not receive cranial radiation therapy;

f. participants who spent relatively fewer days in hospital; and,

g. participants who were administered lower total doses of glucocorticoids,

would perform better on a measure of verbal learning and memory over time.

Study 2b explored variations in event-related potentials elicited by a visual oddball task in individuals treated for pediatric ALL over the first four years from diagnosis of pediatric ALL. Specifically, peak amplitude and latency of the P300 were used as outcome variables. The same predictive risk factors considered in Study 2a were again included in Study 2b, and were tested for their association with ERP variables over time. The main hypothesis for Study 2b was that the absence of specific individual- and treatment-related risk factors would be associated with shorter P300 latency and greater P300 peak amplitude over time.

i. It was expected that:

a. males;

b. participants diagnosed later in life;

c. participants with greater parental well-being;

d. participants treated with prednisone;

e. participants who did not receive cranial radiation therapy;

f. participants who spent relatively fewer days in hospital; and,

g. participants who were administered lower total doses of glucocorticoids,

would demonstrate shorter P300 latency over time.

ii. It was also expected that:

a. males;
b. participants diagnosed later in life;
c. participants with greater parental well-being;
d. participants treated with prednisone;
e. participants who did not receive cranial radiation therapy;
f. participants who spent relatively fewer days in hospital; and,
g. participants who were administered lower total doses of glucocorticoids,

would demonstrate greater P300 peak amplitude over time.

Study 1

The purpose of Study 1 was to compare a group of children treated for ALL with a group of healthy controls, and to test the effects of known individual and treatment-related risk factors for their association with verbal learning and memory performance, and IQ.

Method

Results derived from a subgroup of this sample were previously published in a paper by Precourt et al. (2002), and included data from the first 19 girls treated for ALL (10 with chemotherapy only, and nine with chemotherapy and radiation) and 10 healthy girls, as well as outcomes derived from the California Verbal Learning Test – Children's Version (CVLT-C) and the Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991). The present sample included an additional four females and 12 males in the treatment group, and nine additional males in the control group. Children

treated with chemotherapy only (i.e. those who did not receive CRT) were excluded from Study 1.

Participant characteristics. School-age children treated with a combination of intrathecal chemotherapy and cranial radiation therapy (n = 25), and healthy controls (n = 19) were recruited at the Ste-Justine Hospital (Montreal, Quebec) between January 1989 and January 1993. Patients were treated on one of two protocols, the Dana Farber Cancer Institute (DFCI) Acute Lymphoblastic Leukemia Consortium Protocol 87-01 (LeClerc et al., 2002), or DFCI 91-01 (Silverman et al., 2001). Both protocols included remission induction therapy with doxorubicin, asparaginase, methotrexate, vincristine, prednisone, and intrathecal cytarabine, and post-remission consolidation with weekly high-dose asparaginase, plus doxorubicin for high-risk patients. Children were considered high-risk if they presented with any of the following characteristics: < two years, or > nine years of age at diagnosis; presenting leukocyte count greater than 20,000/L; T-cell immunophenotype; an anterior mediastinal mass; or CNS leukemia. In order to prevent CNS relapse, high risk patients on both protocols, and standard risk males on 91-01, were treated with cranial radiation randomization, where they received treatment on either a conventional (18 Gy delivered in 10 1.8 Gy fractions, one fraction per day over 12 to 14 days), or hyperfractionated (18Gy delivered in 20 0.9 Gy fractions, with a minimum of six hours between the twice-daily treatments over 12 to 14 days) schedule, up to a total dose of 18Gy. CRT was always administered in combination with intrathecal methotrexate and cytarabine. Intrathecal therapy dose was based on patient age (<1 year, methotrexate 6 mg, cytarabine 15 mg; 1 to 1.99 years, methotrexate 8 mg, cytarabine 20 mg; 2 to 3 years, methotrexate 10 mg, cytarabine 30 mg; > 3 years, methotrexate 12 mg,

cytarabine 40 mg), and was administered every 18 weeks after the completion of initial CNS-intensive therapy, which consisted of four therapeutic lumbar punctures over a two-week period concurrent with CRT.

To be included in the present study, participants required a Full Scale IQ score greater than 85 but less than 130, with a maximum difference of 20 points between their Verbal IQ and Performance IQ. This cut off was based on American norms to improve comparability with previous studies (Precourt et al., 2002). None of the participants in the control group presented with any psychiatric disturbances other than simple phobias, as assessed by a computerized standardized interview conducted with a parent (Computerized Diagnostic Interview Schedule for Children, 1991). Participants did not receive any other treatments known to affect cognitive function. Descriptive statistics related to the sample are presented in Table 1. The procedures used in this study were reviewed and approved by the Institutional Review Ethics Board at Ste-Justine Hospital. Informed consent was obtained from all parents/legal guardians and assent was obtained from the children.

Table 1

Descriptive Statistics of Study 1 Sample

Statistic	Group		Total
	Treatment	Control	
Sample Size	25	20	45
Sex			
Male (♂)	12(48%)	10(50%)	22 (49%)
Mean Age at Diagnosis (*SD*)	3.44(1.79)	-	-
Mean Age at Testing (*SD*)	9.11(1.43)	9.21(1.19)	9.15(1.31)
Chemotherapy protocol			
DFCI 87-001	15 (♂= 6)	-	
DFCI 91-001	10 (♂ = 6)	-	
Type of cranial radiation therapy			
Standard	19 (♂ = 10)	-	
Hyperfractionated	6 (♂ = 2)	-	
Methotrexate Dose[1]			

High	16 (♂ = 9)	-
Low	9 (♂ = 3)	-

[1]In the 87-01 protocol, during remission induction, methotrexate (eight hours after the second dose of doxorubicin) was randomly assigned to high-dose (4 g/m^2 over one hour with leucovorin rescue beginning at hour 36) or low-dose 40 mg/m^2. In the 91-01 protocol, methotrexate dose was 4 g/m^2, eight to 24 hours after doxorubicin) with leucovorin rescue. Methotrexate was delivered intravenously.

Measures. The California Verbal Learning Test – Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994), was used to assess the strategies and processes involved in learning and recalling verbal information. The CVLT-C standardization sample was based on data for 920 individuals gathered in March 1988 by the United States Bureau of the Census, and was stratified by age, gender, race/ethnicity, geographic region, and parent education level. The CVLT-C uses an everyday memory task: recalling items from a shopping list, and involves multiple trials with two different lists of words. The lists (List A and List B) consist of 15 words each that can be evenly divided into three semantic categories. There are a number of variables that can be derived from the CVLT-C, including: number of words recalled on each of the first five trials of List A; total number of words recalled across the first five trials of List A (cumulative); number of words recalled on List B; number of words recalled on each of the short and long delay recall trials; proactive interference (where past learning interferes with future learning); retroactive interference (where later learning interferes with the memory of past learning); learning slope (average number of new words per trial acquired across the first five trials of List A); number of semantic associations (words recalled by category); number of serial associations (words recalled in the order in which they were presented); primacy effect (percent of the first four words recalled from List A over the first five trials); and recency effect (percent of the last four words recalled from List A over the first five trials).

All individual subtests of the WISC-III (Wechsler, 1991), including: Full Scale IQ, Verbal IQ, Performance IQ, and all composite factors (Freedom from Distractibility, Perceptual Organization, Processing Speed, and Verbal Comprehension), were administered to the participants.

Procedure. Testing took place between 41 and 105 months (M = 68 months) after diagnosis. On the first five trials of the CVLT-C, the experimenter read List A aloud, and participants were asked to immediately recall the items verbally. During the sixth trial, the experimenter read List B aloud, and participants were asked to immediately verbally recall the items from that list. Participants were then asked to verbally recall as many items as possible from List A, without the experimenter repeating the list (i.e. short delay free-recall trial). This was followed by a cued recall trial of items on List A (i.e. short delay cued-recall trial). After a 20-minute delay, the final two trials, a free recall of List A (i.e. long delay free-recall trial) and a cued recall of List A (i.e. long delay cued-recall trial) were administered.

Statistical analysis. A series of analyses of variance were conducted to examine the effect of between-group variables. Specifically, the effect of sex was tested between the treatment and control group. The effects of treatment and age at diagnosis were tested within the treatment group. The treatment group was not divided according to protocol (87-01 vs. 91-01), type of radiation, or dose of methotrexate, as the number of subjects per cell was too small. Sex was treated as a dichotomous variable, where males were coded as ‘1,’ and females were coded as ‘2.’ Repeated measures ANOVAs were used to test effects across trials on the CVLT-C. Two-way ANOVAs were used in all other cases. The mediation analysis was conducted using an SPSS macro with a bootstrap approach

(Preacher & Hayes, 2004; Preacher & Hayes, 2008). Effect sizes were calculated with an online effect size calculator ("Effect Size Calculator," 2019). Hedge's *g* was primarily used due to unequal group sizes. In line with general guidelines, <0.3 was considered a small effect size, <0.5 was considered a medium effect size, and <0.8 was considered a large effect size. In long-delay recall trials, the number of words learned on the final learning trial (i.e. Trial 5) of the CVLT-C was controlled for in order to test retention (rather than learning) as the dependent variable (Crocker, Vaurio, Riley, & Mattson, 2011).

I hypothesized that there would be an age-related sensitivity to treatment, where younger children performed more poorly compared to older children. Age at diagnosis was entered as a categorical (versus continuous) variable. Children were divided into two groups based on the median age at diagnosis (32 months). Children who were diagnosed at or prior to 32 months of age were coded as '1,' and children who were diagnosed after 32 months of age were coded as '2.'As noted in the introduction section of this paper, past research has suggested that children treated for ALL before five years of age are at the greatest risk of developing neuropsychological deficits (e.g. Buizer, de Sonneville, van den Heuvel-Eibrink, Njiokiktjien & Veerman, 2005). Thus, the median age of 32 months represents not just the median age of the sample, but also a critical period of brain development when children are presumably more vulnerable to the effects of treatment. By taking a dichotomous approach, I was able to detect age-related sensitivity to treatment by participants treated at earlier or later stages of brain development[1].

[1]Due to the concern that using dichotomous variables can lead to spurious results (e.g. MacCallum, Zhang, Preacher, & Rucker, 2002), the analysis was also run as a regression with age as a continuous variable. When age was entered as a continuous variable, there were several changes to the results. Specifically, age at diagnosis significantly predicted number of words recalled on the first five trials of List A (β = .46, t(23)

Results

California Verbal Learning Test – Children's Version (CVLT-C)

Treatment effect. Across all participants, a learning effect was found on List A Trials 1 to 5 ($F(2.98, 128.30) = 78.79$, $p<.001$, $\varepsilon = 0.75$). The effect of learning was also evident when comparing the number of words recalled between List A Trial 1, and the short- and long-delay free recall trials ($F(1.64, 70.71) = 88.80$, $p< .001$, $\varepsilon = 0.82$). Participants in the control group, on average, recalled more words than participants in the treatment group on the long-delay free recall ($F(1, 42) = 5.41$, $p = .03$, $g = 0.70$) and cued recall ($F(1, 42) = 5.27$, $p = .03$, $g = 0.71$) trials. Means and standard deviations for CVLT-C variables are displayed in Table 2.

= 2.45, $p = .02$) and short-delay recall trial ($\beta = .45$, $t(23) = 2.44$, $p = .02$), as well as the use of serial associations on List B ($\beta = .50$, $t(23) = 2.76$, $p = .01$). The above three variables were not significantly associated with age at diagnosis when it was entered as a dichotomous variable. Some findings also became non-significant: word recall on the free and cued long-delay recall trials, number of words recalled on the recency section of List A, and serial associations on the first five trials of List A. While it is possible that the results presented with age as a dichotomous variable are spurious, since the median age (i.e. 32 months) represents a functionally important developmental stage with respect to cancer treatment, the analysis with age as a dichotomous variable was retained in the main text.

Table 2

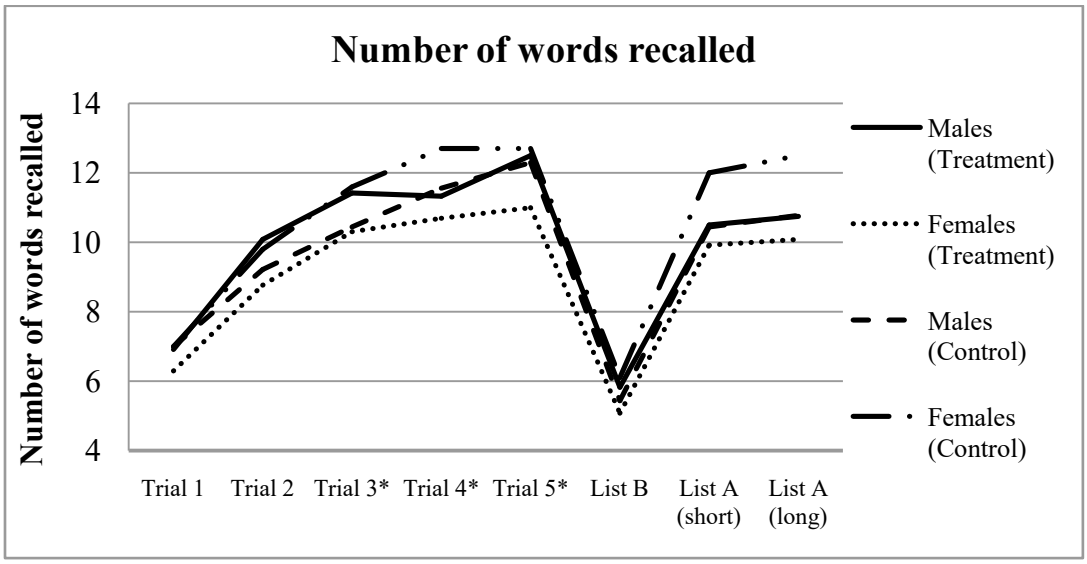
Means and Standard Deviations on the CVLT-C by Sex and Age at Diagnosis.

Variable	Sex				Age at diagnosis			
	Treatment		Control		Treatment		Total	
	Males (n = 12)	Females (n = 13)	Males (n = 10)	Females (n = 10)	Younger (n = 13)	Older (n = 12)	Treatment (n = 25)	Control (n = 20)
Trial 1 recall	6.92(1.44)	6.31(2.56)	7.00(1.58)	7.00(2.16)	6.38(2.29)	6.83(1.90)	6.60(2.08)	7.00(1.86)
Trial 2 recall	10.08(2.71)	8.77(4.07)	9.22(2.22)	9.80(1.55)	7.54(3.48)	11.42 (2.15)***	9.40(3.48)	9.52(1.87)
Trial 3 recall	11.42(1.24)**	10.31(2.25)	10.44(1.67)	11.60(1.90)**	9.92(1.85)	11.83 (1.40)***	10.84(1.89)	11.05(1.84)
Trial 4 recall	11.33(1.72)*	10.69(1.65)	11.56(1.59)	12.70(1.16)*	10.69(1.44)	11.33(1.92)	11.00(1.68)	12.16(1.46)
Trial 5 recall	12.50(1.62)*	11.00(1.73)	12.33(1.73)	12.70(1.83)*	11.08(1.61)	12.42(1.83)*	11.72(1.81)	12.53(1.74)
Trial 1 to 5 recall	51.17(6.04)	47.08(10.01)	50.67(5.57)	53.80(5.63)	45.38(7.70)	53.00(7.60)	49.04(8.44)	52.32(5.68)
List B recall	5.83(1.85)	5.08(1.50)	5.44(1.51)	6.10(1.52)	5.23(1.96)	5.67(1.37)	5.44(1.69)	5.79(1.51)
List A short-delay recall	10.50(2.75)	9.92(2.53)	10.44(2.07)	12.00(1.83)	9.08(2.43)	11.42(2.27)	10.20(2.60)	11.26(2.05)
List A long-delay free recall	10.42(2.94)	9.62(2.84)	11.00(1.66)	12.40(1.90)	8.92(3.12)	11.17(2.08)**	10.00(2.86)	11.74 (1.88)**
List A long-delay cued recall	10.75(1.76)	10.08(2.06)	10.78(1.39)	12.50(1.51)	10.00(2.16)	10.83(1.59)	10.40(1.91)	11.68 (1.67)**
Primacy effect (%)	27.08(2.91)	29.12(4.07)	31.70(4.63)	31.04(2.95)	27.69(4.00)	28.63(3.30)	28.14(3.64)	31.35 (3.78)***
Recency effect (%)	29.08(3.70)	28.29(5.06)	25.79(3.12)	25.47(2.27)	30.42(4.49)**	26.77(3.53)	28.67 (4.39)***	25.62(2.63)
Serial associations (Trial 1-5)	4.42(2.81)	3.62(2.40)	3.67(2.65)	8.30(4.50)***	3.15(1.72)	4.92(3.09)*	4.00(2.58)	6.11(4.35)**
Serial associations (List B)	.17(.58)	.23(.44)	.67(.71)	.70(.95)	.08(2.8)	.33(.65)	.20(.50)	.68(.82)***
Serial associations (short-delay recall)	.92(1.31)	.46(.78)	.78(1.64)	1.90(1.97)	.38(.87)	1.00(1.21)	.68(1.07)	1.37(1.86)
Serial associations (long-delay free recall)	.75(1.22)	.77(1.24)	.33(.71)	2.90(3.35)**	.08(.28)	1.50 (1.38)***	.76(1.20)	1.68(2.75)
Serial cluster ratio	2.01(1.17)	1.84(1.17)	1.67(1.13)	3.68(1.85)***	1.68(1.01)	2.18(1.27)	1.92(1.15)	2.73(1.83)
Semantic associations (Trial 1-5)	17.25(5.50)	13.08(3.84)	16.00(4.80)	16.10(6.45)	13.84(4.54)	16.42(5.47)	15.08(5.07)	16.05(5.57)

Semantic associations (List B)	1.50(1.24)	1.23(1.09)	1.33(1.22)	1.40(1.07)	1.77(1.36)	.92(.67)	1.36(1.15)	1.37(1.12)
Semantic associations (short-delay recall)	4.00(2.52)	3.54(1.61)	4.89(2.21)	4.30(2.50)	3.69(2.02)	3.83(2.21)	3.76(2.07)	3.92(2.16)
Semantic associations (long-delay free recall)	4.25(2.49)	3.62(1.85)	4.33(2.35)	3.30(2.45)	3.31(1.93)	4.58(2.27)	4.58(2.32)	3.79(2.39)
Semantic cluster ratio	1.49(.26)	1.26(.28)	1.39(.43)	1.23(.45)	1.37(.28)	1.38(.30)	1.37(2.88)	1.31(4.38)

*p < .10; **p < .05; ***p < .01

Though there was no overall group effect on the number of words recalled across the first five trials of List A, a significant group difference was detected on the number of words recalled on the long-delay trials (see Figure 1). Children in the treatment group recalled fewer words than children in the control group on the long-delay free recall trial ($F(1, 42) = 5.27$, $p = .03$, $g = .70$) and long-delay cued recall trial ($F(1, 42) = 5.41$, $p = .03$, $g = .71$). However, the group effects were no longer significant when using the number of words recalled in Trial 5 as a covariate for the long-delay free recall ($F(1,40) = 0.32$, $p = 0.57$), and for the long-delay cued recall ($F(1,40) = 0.88$, $p = 0.35$) trials.



*p<.10

Figure 1. Number of words recalled across trials by sex and group (Study 1)

Significant differences in learning strategies were detected between groups. Over the first five trials of List A, children in the treatment group tended to recall fewer words in the order they were presented (number of serial associations) across Trials 1 to 5 ($F(1, 42) = 4.02$, $p = .05$, $g = .61$), and on the List B recall trial ($F(1,42) = 5.87$, $p = 0.02$, $g = .73$; see Figure 2). The groups also differed in their propensity to recall words primarily from the beginning or the end of List A (treatment by order interaction: $F(1, 42) = 11.35$,

p = .002). Children in the control group recalled more words from the beginning of the list (primacy effect) compared to those in the treatment group (F(1, 42) = 8.21, p = .01, g = .87). Conversely, children in the treatment group recalled more words from the end of the list (recency effect) compared to those in the control group (F(1, 42) = 7.18, p = .01, g = .82).

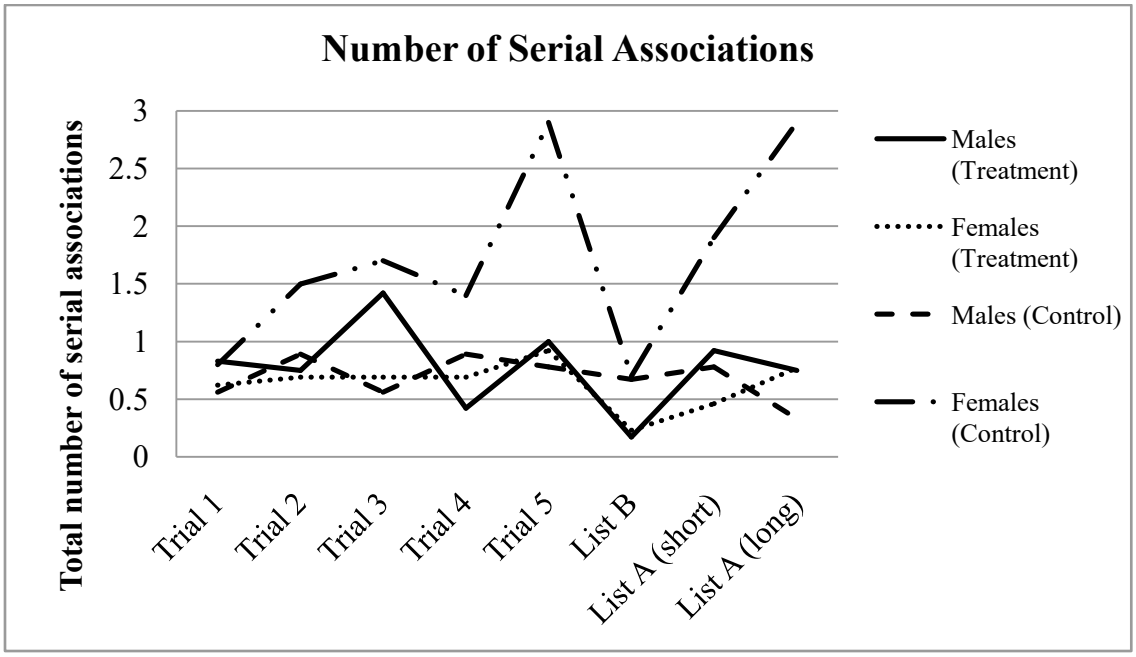


Figure 2. Use of serial associations (scaled score) by trial and sex across groups (Study 1)

Group by sex interaction. A trend towards a group by sex interaction emerged on word recall of the first five trials (F(1,40) = 2.63, p = .11, d = .56), where healthy girls tended to recall more words than boys, but boys in the treatment group tended to recall more words than girls. When trials were analysed individually, there was no significant effect at Trials 1 and 2, but the interaction approached statistical significance for the last three trials (Trial 3 (F(1,40) = 4.18, p = .05, d = .65), Trial 4 (F(1,40) = 3.51, p = .07, d = .82) and Trial 5 (F(1,40) = 3.15, p = .08, d = .21)), indicating that this trend was driven by later repetitions.

A significant group by sex interaction emerged on the number of serial associations on the first five trials (group by sex interaction: $F(1, 40) = 8.07$, $p = .01$, $g = .61$), where healthy girls were twice as likely to use this strategy compared to healthy boys ($F(1, 17) = 7.26$, $p = .03$, $\Delta = 1.63$). No significant difference was detected in the treatment group, though boys tended to use serial associations more than girls. This interaction remained significant when tested using the serial cluster ratio ($F(1, 40) = 7.13$, $p = .01$, $g = .54$), which controls for association by chance as a function of the total number of words recalled. The serial cluster ratio was twice as large in girls in the control group ($F(1, 17) = 7.98$, $p = .01$, $d = 1.31$), while no sex difference was found in the treatment group. A group by sex interaction effect on serial associations was also significant on the long-delay free-recall trial ($F(1, 40) = 5.01$, $p = .03$, $g = .45$). In the control group, girls relied more upon serial associations compared to boys ($F(1, 17) = 5.06$, $p = .04$), though there was no difference by sex in the treatment group. This group by sex interaction was no longer significant when the number of words recalled on Trial 5 was used as a covariate ($F(1, 39) = 2.16$, ns) to test retention.

Age at diagnosis. Over the first five trials of List A, children diagnosed at a younger age (relative to the sample) recalled fewer words, especially at Trial 2 ($t(23) = -3.32$, $p<.01$, $g = 1.33$), Trial 3 ($t(23) = -2.89$, $p<.01$, $g = 1.16$), and Trial 5 ($t(23) = -1.95$, $p = .06$, $g = .78$). They also recalled fewer words on the long-delay free-recall trial ($t(23) = -2.10$, $p = .05$, $g = .84$). Children diagnosed earlier demonstrated a stronger recency effect ($t(23) = 2.25$, $p = .04$, $g = .90$), and tended to rely less on serial associations across the first five trials of List A ($t(23) = -1.78$, $p = .09$, $g = .72$), and on the long-delay free-recall trial ($t(11.8) = 3.50$, $p<.005$, $g = 1.46$). Note that with the inclusion of age as a

dichotomous variable, there is a significant probability that at least some of these findings are spurious (see footnote on page 34).

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

Means and standard deviations for WISC-III subtests and subscores are displayed in Table 3.

Treatment effects. Participants in the control group outperformed participants in the treatment group on the Picture Completion ($F(1, 43) = 5.21$, $p = .03$, $g = .68$), Block Design ($F(1, 43) = 9.76$, $p = .003$, $g = .94$), Object Assembly ($F(1, 43) = 8.40$, $p = .01$, $g = .87$), Information ($F(1, 43) = 19.05$, $p = .000$, $g = 1.31$), Similarities ($F(1, 43) = 10.62$, $p = .002$, $g = .98$), Arithmetic ($F(1, 43) = 4.09$, $p = .05$, $g = .61$), Vocabulary ($F(1, 43) = 12.34$, $p = .001$, $g = 1.05$), Comprehension ($F(1, 43) = 7.43$, $p = .01$, $g = .82$), Digit Span ($F(1, 43) = 6.73$, $p = .01$, $g = .78$), and Digit Span forward ($F(1, 42) = 9.11$, $p = .004$, $g = .91$) subtests, the Verbal ($F(1, 43) = 17.00$, $p = .000$, $g = 1.24$) and Full Scale ($F(1, 43) = 23.21$, $p = .000$, $g = 1.44$) IQ, and the Verbal Conceptualization ($F(1, 43) = 17.43$, $p = .000$, $g = 1.25$), Perceptual Organization ($F(1, 43) = 18.78$, $p = .000$, $g = 1.30$), and Freedom from Distractibility ($F(1, 43) = 8.47$, $p = .01$, $g = .87$) indices.

Group by sex interaction. Results indicated a significant group by sex interaction on the Freedom from Distractibility Index ($F(1, 41) = 4.48$, $p = .04$, $g = .87$). Girls in the treatment group were more distractible than boys ($F(1, 23) = 8.32$, $p<.01$, $g = 1.16$), though there was no sex difference in the control group. Among the subtests contributing to the Freedom from Distractibility Index, a significant group by sex interaction was found on the Forward Digit Span subtest ($F(1, 40) = 9.01$, $p<.01$, $g = .92$), where girls in the treatment group had significantly lower scores than boys ($F(1, 22) =$

5.88, $p = 0.02$, $g = .99$); however, girls in the control group typically outperformed boys ($F(1, 18) = 3.45$, $p = .08$, $d = .83$).

Age at diagnosis by sex interaction. A significant age at diagnosis by sex interaction was detected on processing speed ($F(1, 21) = 4.67$, $p = .04$, $g = .46$). Girls diagnosed later in life tended to perform more poorly than boys diagnosed later in life ($F(1, 10) = 4.23$, $p = .07$). Boys diagnosed at a younger age tended to perform more poorly than girls diagnosed at a younger age, though this difference was not significant.

Table 3

Wechsler Intelligence Scale for Children-III Mean and Standard Deviation Subscores (Study 1)

	Treatment		Control		Treatment		Total	
Subscore	Males (n = 12)	Females	Males (n = 10)	Females	Younger (n = 13)	Older	Treatment (n = 25)	Control (n = 20)
Wechsler Intelligence Scale for Children – III								
Picture completion	9.42(3.82)	9.77 (3.39)	11.90 (2.96)	11.50 (1.65)	9.31 (3.79)	9.92(3.37)	9.60(3.35)	11.70 (2.34)**
Coding	9.33(3.87)	9.46 (2.82)	9.70 (2.75)	11.20 (3.05)	9.54 (3.23)	9.25(3.49)	9.40(3.29)	10.45 (2.93)
Picture arrangement	11.25 (2.77)	8.46 (3.07)	12.10 (3.96)	11.70 (3.16)	8.77 (3.30)	10.92 (2.81)	9.80(3.20)	11.90 (3.49)*
Block design	13.00 (4.12)	9.46 (2.50)	14.60 (2.50)	13.80 (2.25)	10.08 (3.71)	12.33 (3.70)	11.16(3.80)	14.20 (2.35)***
Object assembly	10.17 (1.95)	9.38 (3.10)	12.00 (1.70)	11.30 (1.25)	9.46 (3.31)	10.08 (1.56)	9.76(2.59)	11.65 (1.50)***
Symbol search	10.58 (2.94)	9.92 (2.25)	12.20 (1.55)	11.10 (3.00)	9.62 (1.85)	10.92 (3.12)	10.24 (2.57)	11.65 (2.39)*
Information	9.42(2.54)	7.23 (2.31)	12.10 (2.60)	10.80 (1.40)	8.23 (2.13)	8.33(3.17)	8.28(2.62)	11.45 (2.14)***
Similarities	10.50 (2.15)	7.54 (3.13)	11.70 (2.41)	11.40 (1.71)	8.54 (3.55)	9.42(2.47)	8.96(3.05)	11.55 (2.04)***
Arithmetic	11.17 (2.32)	8.69 (2.59)	12.30 (3.53)	10.90 (2.23)	9.77 (2.83)	10.00 (2.73)	9.88(2.73)	11.60 (2.96)**
Vocabulary	10.17 (2.82)	7.08 (2.40)	11.90 (3.35)	11.60 (2.91)	8.69 (2.87)	8.42 (3.26)	8.56(3.00)	11.75 (3.06)***
Comprehension	9.42 (3.09)	7.38 (2.93)	10.70 (1.95)	10.50 (2.46)	8.39 (3.18)	8.33 (3.20)	8.36(3.12)	10.60 (2.16)***
Digit span	9.92 (3.15)	7.23 (2.95)	10.20 (2.62)	11.60 (2.84)	8.00 (2.83)	9.08 (3.75)	8.52(3.12)	10.90 (2.75)***
Performance IQ	105.50 (11.26)	96.15 (11.32)	103.80 (33.56)	112.80 (6.91	96.92 (11.38)	104.67 (11.87)	100.64 (12.04)	108.30 (24.03)
Verbal IQ	105.50 (10.48)	86.46 (12.87)	110.30 (11.07)	106.20 (9.17)	92.54 (13.33)	93.92 (14.39)	93.20 (13.58)	108.25 (10.11)***

Full scale IQ	103.42 (9.45)	90.23 (10.71)	113.00 (8.51)	110.20 (7.61)	94.46 (10.77)	98.83 (13.26)	96.56 (11.98)	111.60 (7.99)***
Verbal conceptualization	99.67 (10.65)	85.62 (12.87)	109.00 (11.66)	106.10 (8.10)	91.92 (13.46)	92.83 (14.43)	92.36 (13.64)	107.55 (9.89)***
Perceptual organization	106.50 (10.61)	96.31 (11.71)	116.50 (9.23)	113.10 (6.21)	97.15 (12.19)	105.58 (10.91)	101.20 (12.13)	114.80 (7.85)***
Freedom from distractibility	104.17 (12.66)***	89.38 (12.93)	107.60 (10.77)	108.10 (11.15)	94.69 (13.46)	98.42 (16.16)	96.48 (14.62)	107.85 (10.67)***
Processing Speed	102.92 (14.39)	99.92 (8.75)	106.00 (7.07)	107.10 (13.84)	99.23 (11.22)	103.67 (12.13)**[3]	101.36 (11.64)	106.55 (10.71)
Digit Span forward	7.63 (1.69)***	5.92 (1.75)	7.70 (1.34)	9.00 (1.76)*	6.42 (1.66)[2]	7.00 (2.34)	6.71(1.89)[1]	8.35 (1.66)***
Digit Span backward	4.64(1.69)	3.62 (1.98)	4.50 (1.72)	4.80(1.48)	3.08 (1.62)[2]	5.08 (1.62)	4.08(1.88)[1]	4.65 (1.56)

[1]*n* = 24; [2]*n* = 12; [3]age at diagnosis x sex interaction;
*p < .10; **p < .05; ***p < .01

Mediation Analysis

Based on the results of the CVLT-C and WISC-III analyses, two exploratory mediation analyses were conducted. The mediation analyses followed Preacher and Hayes's (2008) bootstrap procedure.

In Study 1, children in the treatment group performed more poorly on the long-delay recall trials, and used fewer serial associations. However, when word recall on Trial 5 was entered as a covariate, the treatment effect on the long-delay recall trials was no longer significant. This suggests that poorer recall on the long-delay trials may be explained by a treatment effect on learning, rather than on retention after learning. Further, it also raises questions about the relationship between the effect of treatment, short-term memory, and the use of learning strategies. Mediation analysis was used to elucidate these associations. To limit the known effects of sex on CVLT-C performance, sex was controlled for in both mediation analyses.

The first mediation analysis suggested that while controlling for sex, the indirect effect of treatment on the total number of words recalled on the long-delay free recall trial of the CVLT-C was mediated by the number of serial associations used on the first five trials of List A (M = 0.71; SE = .36; 95% CI:.09-1.49). In a second mediation analysis, still controlling for sex, the indirect effect of treatment on the number of serial associations used on the first five trials of List A was mediated by the Forward Digit Span subscore of the WISC-III (as an index of short-term memory), and this was also significant (M = .92; SE:.48; 95% CI:0.13-2.00). In other words, short-term memory influenced the degree to which treatment affected the use of a serial association strategy.

The use of a serial association strategy also influenced the degree to which treatment affected long-term memory. The mediation models are depicted in Figure 3.

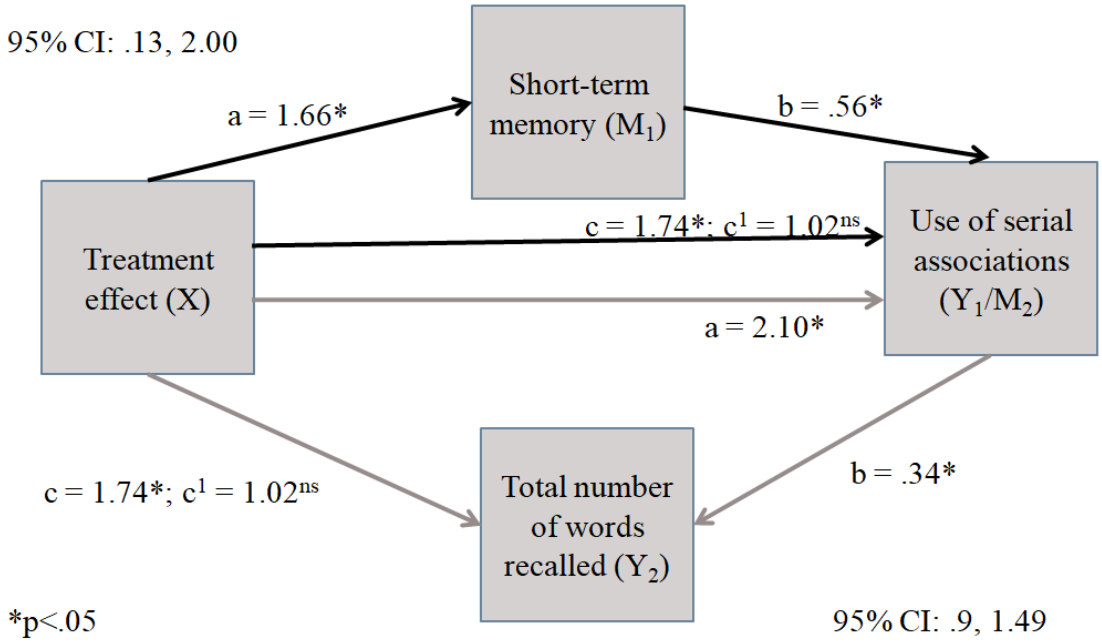


Figure 3. Mediation models (Study 1)

Correction for Multiple Testing

To correct for multiple testing, the Benjamini-Hochberg False Discovery Rate adjustment (Benjamini & Hochberg, 1995) was applied to p-value thresholds. The p-value threshold was calculated as p = rank/total tests * .05, where the total number of tests performed was 22 for the CVLT-C and 21 for the WISC-III. After correction, the majority of treatment effects that were reported as significant survived correction. However, the group effect on the long delay trials and the use of serial associations on the first five trials of List A (CVLT-C) did not survive the multiple testing correction. On the WISC-III, only the treatment difference on the Arithmetic subtest did not survive correction. The effect of age at diagnosis on the CVLT-C, the group by sex interaction on

the CVLT-C and the WISC-III, and the age by sex interaction on the WISC-III also did not survive correction for multiple tests.

Discussion

In Study 1, group differences between pediatric ALL survivors and a sample of healthy children were tested for their association with verbal learning and memory, and indices of IQ. As well, two mediation models were tested to further understand the relationships between treatment effects, learning strategies, and memory. As expected, children in the control group outperformed children in the treatment group overall. Although groups did not differ significantly in word recall on the first five trials of the CVLT-C, significant differences were found on long-delay trials. However, these differences were not significant when Trial 5 of the CVLT-C was used as a covariate, which suggests that poorer long-delay recall was explained by a treatment effect on learning rather than on retention after learning. Children in the treatment group used fewer serial associations, which was consistent with Precourt et al. (2002), who used a female subset of the current sample. However, this finding did not survive correction for multiple testing.

Associations between neuropsychological outcomes were tested in a mediation model. Short-term memory mediated the effect of treatment on the use of serial associations. Additionally, the use of serial associations mediated the effect of treatment on long-term memory capacity. This suggests that the impact of treatment on short-term memory deficits may affect long-term memory in verbal learning, particularly for those using a serial strategy.

In the healthy control group, girls relied more on a serial strategy in the learning trials than boys, but this finding was not evident in the treatment group. The same pattern was observed for the use of serial associations in long-term recall, and for the Freedom from Distractibility Index. Of note, these findings did not survive correction for multiple testing. However, the literature suggests that certain neuropsychological outcomes may be more vulnerable to treatment effects in girls, and these results do support previous research which demonstrated that girls have a higher risk of developing cognitive impairments after treatment. For instance, sex has been found to predict performance on the Digit Span (Waber et al., 1990) and Freedom from Distractibility (Brown et al., 1998) subtests of the WISC, suggesting heightened distractibility or difficulties with attention and concentration (Briere, Scott, McNall, & Adams, 2008). Female survivors have demonstrated greater difficulty in sustained attention more than five years post-diagnosis (Jain, Brouwers, Okcu, Cirino, & Krull, 2009). More than 10 years after diagnosis, female sex increases the risk for impaired intelligence and academics (Krull et al., 2013a). Thus, females are at long-term risk for developing adverse neurocognitive outcomes, and should be monitored accordingly.

Females' heightened vulnerability to the effects of treatment that have been reported within the literature may be explained by sex differences in brain development and cognition. At a structural level, white matter abnormalities are a commonly observed late-delay change in ALL survivors (Dellani et al., 2008; Porto et al., 2008; Reddick, Glass, Johnson, Laningham, & Pui, 2009). Moreover, white matter connectivity predicts nonverbal abilities (Ferrer, Whitaker, Steele, Green, Wendelken, & Bunge, 2013; Kim, Davis, Sandman, Sporns, O'Donnell, Buss, & Hetrick, 2016), and verbal abilities,

especially in children (Broce, Bernal, Altman, Tremblay, & Dick, 2015). During typical development, males have larger white matter volume from birth to adolescence (Giedd et al., 1999; Lenroot et al., 2007; Wilke, Krageloh-Mann, & Holland, 2007), and the growth rate of white matter volume is faster in males (Waber et al., 1990), even after controlling for global cerebral volume (De Bellis et al., 2001; Lenroot et al., 2007). Larger white matter volume in males compared to females persists into adulthood. However, white matter tends to reach maturation earlier in girls (Asato, Terwilliger, Woo, & Luna, 2010; De Bellis et al., 2001; Paus & Toro, 2009). This might explain why the correlation between white matter organization (as measured by fractional anisotropy) and cognitive abilities becomes increasingly positive during girls' childhood and adolescence (Schmithorst, 2009), especially for verbal abilities (Wang et al., 2012). Adult females' general intelligence seems to be related more to white matter compared to males (Haier, Jung, Yeo, Head, & Alkire, 2005). The girls in the Study 1 sample received treatment for ALL during a critical developmental period characterized by faster white matter maturation and higher verbal abilities, making them more vulnerable to the combined toxicity of chemotherapy and irradiation. On the other hand, boys may have had a larger 'reserve' of white matter, which could protect them against more severe cognitive impairment. Taken together with the existing literature, these results suggest that there is likely an interaction between the effects of sex and age at diagnosis, and that the relationship between these two factors, and the trajectory of adverse effects may not be linear.

As predicted, children diagnosed earlier in life tended to perform more poorly on measures of working memory and verbal learning compared to those diagnosed later in

life. Interestingly, girls diagnosed later demonstrated slower processing speed compared to boys, though there was no sex difference for children diagnosed earlier in life. While these results did not survive correction for multiple testing, they are consistent with research which indicated that faster white matter development occurs in younger children (Hermoye et al., 2006; Tanaka, Matsui, Uematsu, Noguchi, & Miyawaki, 2012), and younger children have increased vulnerability to neuropsychological impairments (e.g., Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2005; Ng, Lin, Ariffin, Zainab, Lam, & Chan, 2000).

Study 1 had several limitations. Firstly, although the groups were homogenous in terms of diagnosis, treatment, and age range, the sample size was relatively small. Consequently, I was not able to analyse subgroups within the sample (e.g., chemotherapy protocol, methotrexate dose). Given the small sample size, and that many findings did not survive correction for multiple testing, findings should be interpreted with caution. Follow up with a larger sample size is warranted.

Secondly, the data were obtained in a cross-sectional manner at an average of 5.9 years post-diagnosis. It is unknown how sex and age at diagnosis would influence these outcomes with a greater length of time elapsed from diagnosis. Longitudinal data should be used to provide a more complete picture of the development of these deficits. In addition, I did not find differences related to time elapsed since diagnosis, possibly because inter-individual differences were too small.

Thirdly, since the introduction of the DFCI 2000-01 protocol, irradiation has been substituted with intensive intrathecal chemotherapy in low-risk patients, and irradiation doses have been diminished to 12Gy for some high-risk patients. However, irradiation at

18Gy is still used in combination with triple intrathecal chemotherapy in a subset of ALL patients and in children with other cancers (e.g. brain tumours), so the present results may still be relevant for these patients.

Another concern is the issue of power, where several tests were conducted on a relatively small sample size. To compensate for power-related concerns, Hopkin, Hoyle, and Gottfredson (2015) suggest that other features of the study, such as reliability of measures, are augmented. To that end, both the WISC-III and the CVLT-C are widely recognized as highly reliable neuropsychological tests. Additionally, effect sizes were calculated, and many tests produced medium to large effect sizes. Notwithstanding, even findings with large effect sizes had wide confidence bands, which results in difficulty ruling out small and null effects.

From a clinical perspective, the adverse effects of treatment on the long-delay recall trials may be traced back to limited use of serial learning strategies, which is linked to a deficit in working memory. One possible strategy to improve outcome might be to compensate for these memory impairments by allowing children to use more repetitions, and giving them more time to learn verbal material at school. It may also be useful to teach semantic learning strategies, to produce more efficient encoding (Campoy & Baddeley, 2008). However, the role of working memory in learning verbal material should be further investigated before more specific treatment approaches are developed (e.g. cognitive rehabilitation).

Study 2a

To understand their association with the emergence and occurrence of neuropsychological deficits over time, the same predictive risk factors considered in

Study 1 were tested in Study 2a in a longitudinal fashion. The Study 2 sample was distinct from the Study 1 sample. Study 2a included the use of CRT, chemotherapy protocol, the number of days in hospital (taken as an index of treatment-related complications), maternal and paternal family well-being scores (taken as an indicator of chronic stress), and total glucorticoid dose as predictive risk factors in the analysis. These variables were tested for their association with verbal learning and memory over time.

Method

This sample was previously included in two published journal articles, one dissertation, and my own Master's thesis (Aronovitch, 2012). The first published article (Krajinovic et al., 2005) considered the effect of genetic polymorphisms on IQ, and found a link between a specific variant (NOS3 894TT genotype) and a reduction in IQ over time as a function of the use of CRT. Two other risk factors (young age at diagnosis and treatment protocol) were also linked to changes in IQ. The second published article (Marcoux, Robaey, Krajinovic, Moghrabi, & Laverdière, 2012) was based on a dissertation submitted by Sophie Marcoux. It explored the impact of predictive risk factors on behavioural issues, and found that children had more difficulty resolving internalized behavioural problems in the presence of medical variables. As well, the use of dexamethasone was linked to a greater incidence of externalized behavioural issues. In Aronovitch (2012), when predictive risk factors were combined into a single multilevel model, the use of CRT emerged as a marginally significant predictor of proactive interference on the CVLT-C. None of the other predictive risk factors tested (sex, age at diagnosis, number of days in hospital, chemotherapy protocol) were significant predictors of other outcome variables (i.e. t-score equivalents for total number of words recalled

across trials one to five; List A trial one; List A trial five; List B recall; short-delay free recall trial; proactive interference; retroactive interference; learning slope). Willow Amber, a PhD student at the University of Montreal is also currently using this dataset for her dissertation. She is examining psychosocial outcomes, such as marital status and family functioning as they relate to cancer treatment.

Participant characteristics. Children treated for acute lymphoblastic leukemia were recruited at Ste-Justine Hospital (Montreal, Quebec) between 1993 and 1999. Inclusion criteria were as follows: (1) must be ≤ 18 years of age at diagnosis; (2) ALL must be the first cancer occurrence; and (3) must have normal or corrected to normal hearing and vision. Participants did not receive any additional treatment known to impact cognitive function.

The initial sample consisted of 138 participants who completed various portions of a multi-arm project. Testing included neuropsychological assessment, magnetic resonance imaging, psychosocial assessment, and event-related potential assessment. Of 138 participants, 107 were included in the Study 2a analysis; thirty-one participants were excluded due to missing data (i.e. they did not complete the neuropsychological assessment portion of the original project due to parent availability, and thus no data were available). Descriptive statistics relating to this sample are presented in Table 4.

Table 4

Descriptive Statistics of Study 2a Sample

Statistic	Total (n = 107)
Sex[1]	
Male	56
Mean Age at Diagnosis (*SD*), Years[2]	7.19(4.12)
Age Range at Diagnosis, Years	0.72 – 18

Chemotherapy protocol[1]	
DFCI 91-01	39
DFCI 95-01	62
Mean total effective dose of corticosteroid received during induction (*SD*)[3]	13 313.63(9460.96)
Type of cranial radiation therapy[1]	
Standard	47
Hyperfractionated	30
Did not receive cranial radiation therapy	24
Mean number of days in hospital (*SD*)[4]	31.01(9.91)
Maternal family well-being scores	
At diagnosis[5]	2.38(.54)
At three months post-diagnosis[6]	2.55(.72)
Paternal family well-being scores	
At diagnosis[7]	2.32(.65)
At three months post-diagnosis[8]	2.46(.62)
Incidence of patient relapse	10
Incidence of patient death	11

Note: sample sizes varied due to missing data.[1]*n*=101; [2]*n*=106; [3]*n*=89; [4]*n*=103; [5]*n*=34; [6]*n*=71; [7]*n*=28; [8]*n*=63

Patients were treated on one of two chemotherapy protocols: Dana Farber Cancer Institute (DFCI) Protocol 91-01, or DFCI 95-01. Treatment details are summarized in Table 5. For a full description of the differences between DFCI 91-01 and DFCI 95-01, see Barry et al. (2007).

Table 5

Comparison of Dana Farber Cancer Institute Chemotherapy Protocols 91-01 and 95-01

	Treatment Protocol	
Antileukemic Agent	91-01	95-01
Glucocorticoid	Dexamethasone	Prednisone
Asparaginase	E. Coli, PEG, or Erwinia	E. Coli, PEG, or Erwinia
Doxorubicin		
Maximum dose	360 mg/m^2	300 mg/m^2
6-mercaptopurine	Per os or intravenous	-

Source: Marcoux, Robaey, Krajinovic, Moghrabi, &Laverdière, 2012

Procedure. Data were collected at five time points, beginning at diagnosis and continuing annually for four years. Assessments were conducted approximately one year apart (e.g., first assessment taken at baseline/diagnosis, second assessment taken at one

year post-diagnosis, third assessment taken at two years post-diagnosis, etc.). However, due to logistical factors (e.g. patient or parent availability) there was some variability in the follow-up period. To account for this variability and to measure time elapsed from diagnosis with the most accuracy possible, time was measured individually for each participant as number of days elapsed from diagnosis (i.e. rather than grouped by follow-up). Descriptive variables related to the measurement of time elapsed from diagnosis are presented in Table 6, and the time between the date of diagnosis and assessment per participant are displayed in Figure 4.

Table 6

Time Elapsed from Diagnosis Measured in Days (Study 2a)

Assessment	*n*	Min.-Max.	Mean(*SD*)
First assessment	34	4 – 414	30(95.86)
Second assessment	48	82 – 745	455.38(101.98)
Third assessment	61	30 – 994	808.00(129.04)
Fourth assessment	65	838 – 1546	1213.71(99.80)
Fifth assessment	89	1113 – 2246	1609.78(170.10)

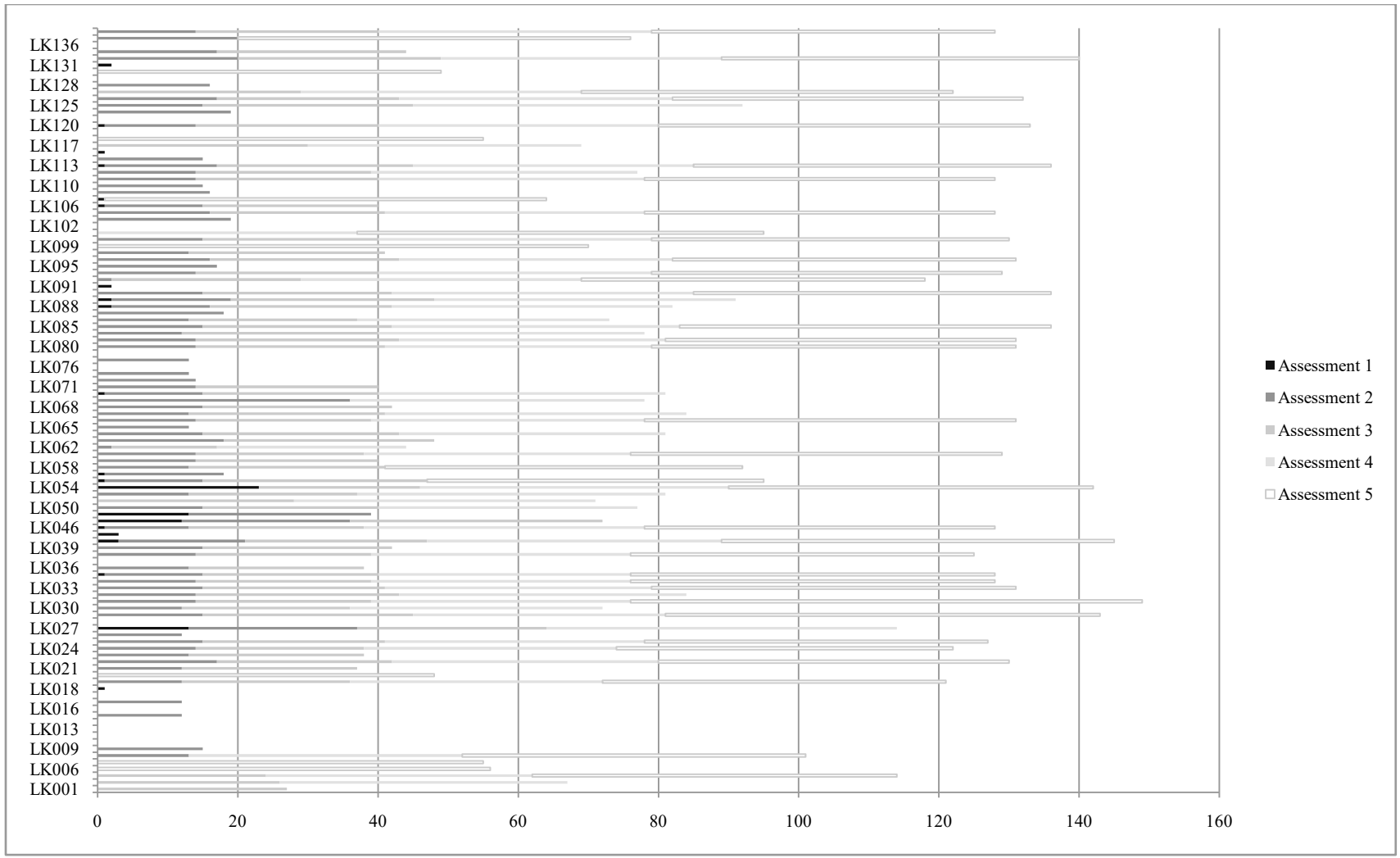


Figure 4. Time between date of diagnosis and assessment per participant (months)

The procedures used in this study were reviewed and approved by the Institutional Review Ethics Board at Ste-Justine Hospital (see Appendix B). Informed consent was obtained from all parents/legal guardians and assent was obtained from the children.

Measures. The California Verbal Learning Test – Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994) was used to test verbal memory and learning using the same procedure described in Study 1. Though the CVLT-C is intended for children between the ages of five and 16, data from patients up to 22 years of age were included in order to maximize sample size. Scores from participants who were 16 years and older at their assessment(s) were standardized using the standard score equivalents for 16 years of age (Delis, Kramer, Kaplan, & Ober, 1994). To control for a potential confound between age and time, standard score equivalents of raw scores were used for all outcome variables. Scores were converted to z-scores and t-scores that were provided in the CVLT-C test manual. Participants' scores were converted to z- or t-scores corresponding with their age at a given assessment. For example, as per the CVLT-C test manual, the mean number of words recalled on Trial 1 for a nine year old is six words; therefore, a nine-year-old who recalled six words from Trial 1 would have a converted score of zero, regardless of how many assessments they completed, or the age at which they were diagnosed and treated. A nine-year-old who recalled four words from Trial 1 would have a converted score of -1, a nine-year-old who recalled eight words from Trial 1 would have a converted score of one, and so on. Since these converted scores were used in the analyses, the outcome measure represents a relative score, rather than a participant's absolute performance. Their relative score reflects how closely a given participant is performing relative to the expected norm or mean. For example, a participant might have

a score of zero for the number of words recalled on Trial 1 across several time points. This means that the participant recalled the mean number of words on Trial 1 corresponding with their age at that particular assessment, and that their score has not changed relative to the mean for their given age. It does not imply that the participant recalled zero words on Trial 1, or that they recalled the same number of words across several time points.

In Study 2a, I examined relationships between family well-being, inter-individual and treatment-related risk factors, and neuropsychological outcomes in pediatric ALL survivors. Maternal and paternal family well-being scores were tested for their influence on CVLT-C outcomes, and whether predictive risk factors influenced CVLT-C outcomes. The Family Well-Being Assessment Tool (Caldwell, 2001) was used to assess family well-being on a continuum from wellness to stress, where *family* was defined as "an interaction system consisting of two or more members." Family structure (i.e., units that make up a family), family roles, and vulnerability to influences (genetic, physiological, sociological, or psychological) were assessed, and combined to determine the level of well-being of a given family. The Family Well-Being Assessment Tool has sufficient face-, construct-, and content validity, and interrater agreement between .90 and 1.00. Test-retest reliability based on 11 families over a course of one to three weeks was r = .88, and internal consistency was high (α = .90). The Family Well-Being Assessment Tool consists of 57 items that are rated on a six-point Likert scale, and takes approximately 15 to 20 minutes to complete. A total well-being score is calculated by adding the mean scores of each subscale. A low score represents a high level of well-being and a high score represents a low level of family well-being (i.e., a low score

represents a low level of stress and a high score represents a high level of stress). A measure of family well-being was selected over a stress assessment of the child due to large variability in age within the sample, which would have resulted in poor measurement reliability. The Family Well-Being Assessment Tool was administered at baseline and at three months post-diagnosis. Since mothers and fathers often fulfill different roles within the family (e.g., one parent fulfills more logistical and organizational roles within the family; one parent is more physically and/or emotionally present, etc.), maternal and paternal scores were considered separately. Of note, maternal and paternal family well-being scores taken at diagnosis were moderately positively corrected ($r(81) = .33$, $p = .04$), and maternal and paternal family well-being scores taken three months post-diagnosis were strongly correlated ($r(59)$, $= .59$, $p = .001$). This may be attributed to role overlap, family culture, and/or shared parental perspectives.

Total glucocorticoid dose was calculated by Sophie Marcoux. Actual glucocorticoid dose was drawn from medical charts. Relapse risk, treatment protocol, and treatment assignation arm were taken into account in the theoretical dose calculation. Theoretical doses were converted in milligrams of prednisone-equivalents, and dose deviations were calculated using the following formula: (theoretical dose – actual dose)/theoretical dose*100 (Marcoux, Chapdelaine, Robaey, Sinnett, Krajinovic, & Laverdiere, 2014). The theoretical dose was based on the chemotherapy protocol itself, while actual dose represents the amount of glucocorticoid that was administered to the participant. Actual and theoretical dose may vary slightly based on patient characteristics and clinical judgement.

Statistical analysis. Multilevel modeling was used to analyse this dataset. Time points were nested within participants, and predictive risk factors were entered at level two. The hypotheses were developed to examine whether the effect of specific predictive risk factors on outcome variables varied as a function of time elapsed from diagnosis. Where a significant interaction with time was identified, post-hoc ANOVAs were conducted to examine the specific effects. Table 7 includes the hypotheses and multi-level models tested.

Age at diagnosis, days in hospital, glucocorticoid dose, and family well-being were treated as continuous variables. Sex, the use of cranial radiation therapy, and chemotherapy protocol were treated as categorical variables, where '0' represented males, no radiation delivered, and DFCI 91-01. Conversely, females, the administration of cranial radiation therapy, and DFCI 95-01 were coded as '1' in the dataset.

Individual-level data for all dependent variables were plotted on spaghetti plots, and a linear approach was used for all models. Based on examination of QQ plots, there was some deviation from normality for intrusions on the cued recall trial at the third, fourth, and fifth assessments. Since the other two assessment points did not violate the assumption of normality, no changes were made to the variable to avoid complicating its interpretation.

Table 7

Hypotheses and Multi-level Models Tested (Study 2a)

Hypothesis	Analysis
Base model (constant)	Outcome variable$_{ti}$ = π_{0i} + e_{ti}
Developmental model (Level-1 model)	Outcome variable$_{ti}$ = π_{0i} + π_{1i}*(TIME FROM DIAGNOSIS$_{ti}$) + e_{ti}
It was expected that boys	Outcome

would have more favourable outcomes (e.g., increasing reliance on semantic associations, more words recalled by and across trials, etc.) over time elapsed from diagnosis.	$variable_{ti} = \pi_{0i} + \pi_{1i}*(TIME\ FROM\ DIAGNOSIS_{ti}) + e_{ti}$ *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}*(SEX_i) + r_{0i}$ $\pi_{1i} = \beta_{10} + \beta_{11}*(SEX_i) + r_{1i}$
It was expected that older children would have more favourable outcomes over time elapsed from diagnosis.	Outcome $variable_{ti} = \pi_{0i} + \pi_{1i}*(TIME\ FROM\ DIAGNOSIS_{ti}) + e_{ti}$ *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}*(AGE\ AT\ DIAGNOSIS_i) + r_{0i}$ $\pi_{1i} = \beta_{10} + \beta_{11}*(AGE\ AT\ DIAGNOSIS_i) + r_{1i}$
It was expected that children who did not receive radiation would have more favourable outcomes over time elapsed from diagnosis.	Outcome $variable_{ti} = \pi_{0i} + \pi_{1i}*(TIME\ FROM\ DIAGNOSIS_{ti}) + e_{ti}$ *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}*(CRT_i) + r_{0i}$ $\pi_{1i} = \beta_{10} + \beta_{11}*(CRT_i) + r_{1i}$
It was expected that children who were treated with prednisone (i.e. protocol DFCI 95-01) would have more favourable outcomes over time elapsed from diagnosis.	Outcome $variable_{ti} = \pi_{0i} + \pi_{1i}*(TIME\ FROM\ DIAGNOSIS_{ti}) + e_{ti}$ *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}*(CHEMOTHERAPY\ PROTOCOL_i) + r_{0i}$ $\pi_{1i} = \beta_{10} + \beta_{11}*(CHEMOTHERAPY\ PROTOCOL_i) + r_{1i}$
It was expected that children who received lower total doses of glucocorticoids would have more favourable outcomes over time elapsed from diagnosis.	Outcome $variable_{ti} = \pi_{0i} + \pi_{1i}*(TIME\ FROM\ DIAGNOSIS_{ti}) + e_{ti}$ *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}*(GLUCOCORTICOIDDOSE_i) + r_{0i}$ $\pi_{1i} = \beta_{10} + \beta_{11}*(GLUCOCORTICOIDDOSE_i) + r_{1i}$
It was expected that children who spent less time in hospital would have more favourable outcomes over time elapsed from diagnosis.	Outcome $variable_{ti} = \pi_{0i} + \pi_{1i}*(TIME\ FROM\ DIAGNOSIS_{ti}) + + e_{ti}$ *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}*(DAYS\ IN\ HOSPITAL_i) + r_{0i}$ $\pi_{1i} = \beta_{10} + \beta_{11}*(DAYS\ IN$

	$HOSPITAL_i) + r_{1i}$
It was expected that children with subjectively better family well-being would have more favourable outcomes over time elapsed from diagnosis.	Outcome variable$_{ti} = \pi_{0i} + \pi_{1i}$*(TIME FROM DIAGNOSIS$_{ti}$) + e_{ti} *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}$*(FAMILY WELL-BEING$_i$) + r_{0i} $\pi_{1i} = \beta_{10} + \beta_{11}$*(FAMILY WELL-BEING$_i$) + r_{1i}

Results

The fixed effects models that were tested, their parameters, and all results are summarized in Appendix C. The results of the Study 2a cross-level interactions are summarized in Table 8.

Time elapsed from diagnosis. The following variables increased with time elapsed from diagnosis: recall consistency (b = .09, p = .02); perseverations (b = .08, p = .04); intrusions on the free-recall trials (b = .05, p = .03); intrusions on the cued-recall trials (b = .07, p = .04); and percent of words recalled from the recency region of List A (b = .07, p = .05). The following variables decreased with time elapsed from diagnosis: number of correct words recalled on the first five trials of List A (b = -.26, p = .01); number of correct words recalled on List B (b = -.09, p = .02); maternal family well-being scores taken at diagnosis (b = -.07, p< .01); paternal family well-being scores taken at diagnosis (b = -.06, p = .04); and proactive interference (b = -.15, p = .02).

Sex. Being male was associated with increased recall of correct words on List B (b = -.15, p = .05), and higher paternal family well-being scores (i.e. more subjective stress as experienced by the participant's father; b = -.32, p = .05) at the first assessment. The effect of sex on intrusions on free-recall (b = .11, p = .01) and cued-recall trials (b = .14, p = .04) varied as a function of time. Over time elapsed from diagnosis, boys tended

to make more intrusions on both types of trials, while intrusions made by girls remained relatively stable.

Age at diagnosis. Participants who were treated at a younger age (relative to the sample) recalled more words from the primacy region of List A (b = -.06, p = .04), and relied more on a semantic association strategy (b = -.05, p< .0001) at baseline. The effect of age at diagnosis on the number of correct words recalled on the first five trials of List A (b = .28, p = .03) varied as a function of time, where children diagnosed at a younger age demonstrated a more rapid rate of decline in number of correct words recalled compared to children diagnosed later in life. The effect of age at diagnosis on the number of perseverations (b = -.02, p = .02) also varied as a function of time, where all children tended to make more preservations over time elapsed from diagnosis with a more rapid increase observed in children diagnosed at a younger age.

Use of cranial radiation therapy. The effect of the use of cranial radiation therapy on number of correct words recalled on List B varied as a function of time (b = .28, p<.01). Initially, children who did not receive CRT recalled more words from List B compared to children who did receive radiation, though this difference was not significant. By the fifth assessment, children who did not receive CRT recalled significantly fewer words compared to children who did receive radiation (F(1, 82) = 13.58, p< .001). Figure 5 illustrates the mean number of correct words recalled by trial on the CVLT-C for participants who did and not receive CRT at each time point.

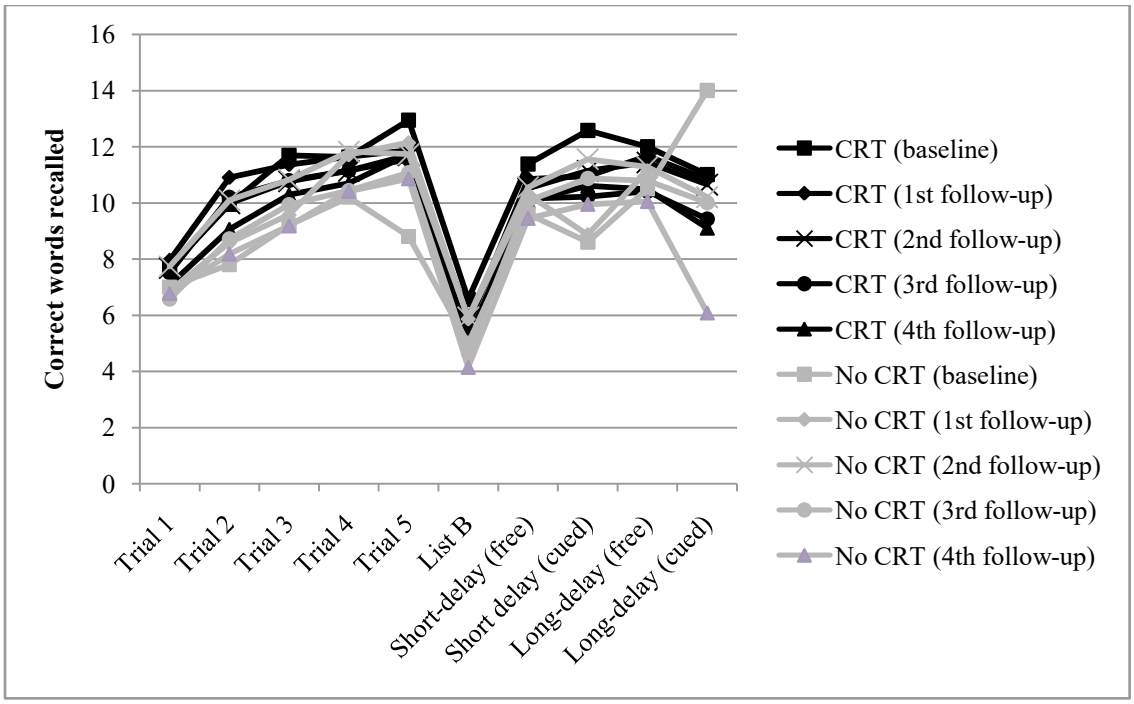


Figure 5. Correct word recall on the CVLT-C with and without cranial radiation therapy

Chemotherapy protocol. At baseline, children treated with DFCI 91-01 recalled significantly more words on Trial 1 compared to children treated with DFCI 95-01 (b = -.89, p = .02). However, by the fourth follow-up the difference between groups was not significant. A similar effect was observed with number of perseverations: at baseline, children treated with DFCI 91-01 made significantly fewer preservations compared to children treated with DFCI 95-01 (b = .58, p = .03). Though this trend persisted past treatment (b = -.19, p = .02), by the fourth follow-up, the difference between groups was not significant.

Glucocorticoid dose. A higher total dose of glucocorticoids was associated with more perseverations (b = .00002, p = .05) at the first assessment. Higher total doses were associated with fewer words recalled across the first five trials of List A (b = -.003, p = .04), and on the short-delay free recall trial (b = -.0001, p = .02), with an increased reliance on a semantic association strategy at baseline (b = -.00001, p = .01).

There was an effect of glucocorticoid dose on the number of correct words recalled on the first five trials of List A (b = .0001, p = .01), Trial 1 (b = .00001, p = .04), and the short-delay free recall trial (b = .00002, p = .01), which varied as a function of time elapsed from diagnosis. At the first assessment, children who received higher doses tended to recall fewer words on these trials compared to children who received lower doses. However, at subsequent assessments, the gap between groups lessened and became non-significant by the fourth follow-up. Glucocorticoid dose also impacted the percent of words recalled from the primacy region of List A (b = .000007, p = .04) which varied as a function of time elapsed from diagnosis, where those who received higher doses tended to recall fewer words from the primacy region compared to children who received lower doses, though all children recalled increasingly more words from the first third of the list over time.

Days in hospital. Over time, children who spent fewer days in the hospital tended to demonstrate more rapid rates of learning (learning slope; b = -.01, p = .03), and recalled more words from the short-delay free recall trial (b = .02, p< .01).

Maternal family well-being scores taken at diagnosis. Participants with less subjective stress as experienced by their mothers tended to recall more correct words on Trial 1 (b = .51, p = .01) at baseline. Participants with more subjective stress experienced by their mothers had steeper learning slopes (b = -.80, p = .03) at baseline.

Paternal family well-being scores taken at diagnosis. Participants with less subjective stress as experienced by their fathers tended to recall more words from the recency region of List A at baseline (b = -.56, p = .03). At baseline, participants with less subjective stress as experienced by their fathers also tended to make fewer intrusions on

the free-recall trials (b = .41, p<.01) though the difference between groups lessened with time elapsed from diagnosis (b = -.14, p< .01).

Maternal family well-being scores taken three months post-diagnosis. Participants with more subjective stress as experienced by their mothers tended to make more intrusions on the free-recall trials at baseline (b = .27, p = .03), though this difference lessened with time elapsed from diagnosis (b = -.10, p = .01).

Paternal family well-being scores taken three months post-diagnosis. At baseline, participants with more subjective stress as experienced by their fathers typically showed more rapid rates of learning (learning slope; b = .32, p< .01), and recalled more correct words from Trial 5 (b = .54, p = .05). Participants with more subjective stress as experienced by their fathers also tended to recall fewer words from the recency region of List A at baseline (b = -.41, p = .03), and this persisted with time elapsed from diagnosis (b = .16, p = .01).

Table 8

Fixed Effects Estimate and Standard Error of Study 2a Results (Cross-Level Interactions)

	CRT x Time	Sex x Time	Glucocorticoid dose x Time	Days in hospital x Time	DFCI protocol x Time	Age at diagnosis x Time	Maternal FWB, diagnosis x Time	Paternal FWB, diagnosis x Time	Maternal FWB, 3mo x Time	Paternal FWB, 3mo x Time
Recall consistency	-.03(.09)	-.03(.08)	<.00(<.00)	.13(.09)	.04(.09)	<.00(.01)	.<.00(.10)	-.08(.11)	-.03(.07)	-.11(.07)
Perseverations	.05(.09)	-.04(.08)	<.00(.00)*	.01(.01)	-.19(.08)**	-.02(.01)**	.03(.08)	.03(.08)	.02(.07)	.08(.08)
Intrusions (free recall)	.02(.05)	-.11(.04)***	<.00(<.00)	.00(.00)	-.07(.05)	<.00(.01)	-.04(.05)	-.14(.05)***	-.10(.04)***	-.04(.04)
Intrusions (cued recall)	.04(.07)	-.14(.06)**	<.00(<.00)	-.01(.00)*	-.10(.07)	<.00(.01)	-.06(.08)	.03(.09)	-.08(.04)*	-.05(.05)
Primacy	.02(.08)	-.05(.07)	<.00[1](<.00)**	-.01(.00)	-.07(.08)	<.00(<.00)	-.09(.07)	-.09(.07)	.01(.05)	-.10(.06)*
Middle	-.92(.08)	.08(.06)	<.00(<.00)	.00(.00)	.06(.07)	-.00(.01)	.08(.08)	-.01(.09)	-.01(.05)	-.07(.06)
Recency	.03(.08)	-.01(.07)	<.00(<.00)	-.00(.00)	.03(.07)	-.00(.01)	.05(.05)	.13(.07)*	.02(.06)	.16(.06)**
Semantic ratio (scaled)	-.01(.03)	.00(.03)	<.00(<.00)	-.00(.00)	-.05(.03)	-.00(.00)	-.03(.03)	.00(.03)	.01(.02)	.02(.03)
Serial ratio (scaled)	-.01(.17)	.02(.15)	<.00(<.00)	.00(.01)	.02(.15)	-.01(.02)	.04(.15)	.30(.18)	.14(.11)	.19(.14)
Words recalled on Trial 1 to 5	.35(1.19)	1.78(.97)*	.00[2](.00)***	.09(.06)	1.78(1.06)*	.28(.13)**	.54(1.32)	-.74(1.13)	-.31(.85)	-1.08(.98)
Learning slope	-.03(.06)	.02(.05)	<.00(<.00)	-.01(.00)**	.22(.06)	-.00(.01)	-.08(.07)	.08(.07)	.00(.04)	-.06(.04)
Words recalled on Trial 1	.04(.13)	.02(.11)	.00(<.00)	.01(.00)	.29(.11)	.01(.01)	.15(.15)	.05(.15)	-.03(.09)	-.10(.11)

*p< .10, **p< .05, ***p< .01

[1].000007; [2].000134

Correction for multiple testing. To correct for multiple testing, the Benjamini-Hochberg False Discovery Rate adjustment (Benjamini & Hochberg, 1995) was applied to p-value thresholds. The p-value threshold was calculated as p = rank/total tests * .05, where the total number of tests performed was 12. After correction, the majority of treatment effects that were reported as significant did not survive correction. Specifically, after correction, none of the dependent variables varied significantly with time elapsed from diagnosis, sex, chemotherapy protocol, glucocorticoid dose, days in hospital, or maternal or paternal family well-being. The effect of age at diagnosis on the use of semantic associations at baseline, and all reported effects associated with the use of cranial radiation therapy survived correction. Other effects reported as being influenced by age at diagnosis did not survive correction for multiple testing.

Discussion

In Study 2a, treatment-related and interindividual risk factors (i.e., sex, age at diagnosis, use of radiation, total glucocorticoid dose, glucocorticoid type, number of days in hospital, and parental well-being) were tested for their association over time with verbal learning and memory in a sample of pediatric ALL survivors. Individuals treated for pediatric ALL followed an atypical pattern of development from the first to final assessment. Variables that would typically become greater over time (e.g. number of correct words recalled) instead decreased, and variables that would typically decrease with time (e.g., number of perseverations, number of intrusions) instead increased. These findings support previous studies that reported interrupted, or halted cognitive development following treatment for childhood cancer. Within the pediatric cancer survivor population, impaired performance has been demonstrated on measures of Verbal

IQ (Annett et al., 2015), attention and academic achievement (Jacola, Krull, Pui, Pei, Cheng, Reddick, & Conklin, 2016), and processing speed and verbal memory (Peterson, et al., 2008), among others. However, in my study, these results did not survive correction for multiple testing.

The use of radiation produced a surprising result, where children who did not receive radiation recalled fewer words from the List B trial compared to irradiated children at the last assessment. This finding was significant at a single time point only, and was not indicative of change over time measured; there was no significant difference between groups at the first assessment or at any other time point prior to the fifth assessment. It would be important to track performance on this outcome variable for further follow-up to determine whether this finding was an anomaly, or indicative of a long-term trend over time. An alternative explanation is that another factor, such as sex or age differences, may have impacted these results. It is more than likely that this finding represents a statistical anomaly and occurred as a result of an imbalanced sample (i.e. 77 participants who received radiation compared to 24 participants who did not receive radiation), and should be interpreted with considerable caution.

Over time elapsed from the first assessment, boys made more intrusions on cued and free recall trials, while the number of intrusions made by girls remained relatively stable. No significant differences were detected between groups over time elapsed from diagnosis. According to the CVLT-C manual, a high number of intrusions may reflect difficulty discriminating relevant from irrelevant responses (Delis, Kramer, Kaplan, & Ober, 1994). This finding was counter to my hypothesis that males would outperform females, and is not supported by the majority of previous research. However, these results

were consistent with a study of adults with frontal lobe lesions who, compared to typically developing individuals, had poorer word recall, were more likely to make intrusions, and were less likely to use a semantic clustering strategy on the California Verbal Learning Test-II (Baldo, Delis, Kramer, & Shimamura, 2002). Alternatively, my results may be attributable to a female sex advantage observed in typical populations that could protect against toxic treatment effects by providing a cognitive reserve (Barulli & Stern, 2013), or to the non-linear nature of sex-differentiated brain development and response to cancer treatment.

The CVLT-C was very sensitive to the effects of glucocorticoid dose. While the medication was being administered, significant differences were observed between groups. However, these effects did not persist over time; by the fourth follow-up, differences no longer met significance criteria. These findings are indicative of an acute treatment effect for children treated with high dose glucocorticoids that does not persist to four years post-diagnosis. A similar result was associated with chemotherapy protocol, where acute treatment effects were observed during administration of medications, but did not persist to the final assessment. Early or short-term intervention may alleviate some of the concerns that arise soon after treatment, and it is promising that these effects appear to lessen with time.

Children diagnosed at a younger age showed a more rapid rate of decline in the number of words recalled and tended to make more perseverations over time. Some of the observed age-related differences in adverse effects may have occurred as a function of developmental stages, as brain injuries that occur earlier in life are often assimilated into structural and neural networks, while injuries that occur later in life may represent

functional and adaptive changes (Andersen, 2003). Previous research has reported similar impairments associated with age at diagnosis; in a long-term follow up study (six to 26 years post-diagnosis) of adults treated with radiation and chemotherapy for pediatric ALL, Edelstein et al. (2011) found that young age at diagnosis (< 5.5 years of age) was associated with lower scores on standardized neurocognitive tests, including tests of speed and accuracy.

At the first assessment, differences were detected in family well-being scores; overall, participants with less subjective stress as experienced by their parents demonstrated better performance on the CVLT-C (e.g., fewer intrusions, more words recalled). However, these differences did not persist to four years post-diagnosis. In fact, differences between groups tended to lessen with time elapsed from diagnosis. In other words, although family-well being did impact certain verbal learning and memory outcomes with time elapsed from diagnosis, their effect on CVLT-C outcomes was mitigated over the four-year follow-up. The impact of aspects of family well-being on academic achievement has been reported in the literature (e.g. Ach et al., 2013), and there is an overlap in the skills recruited to perform on a measure of academic achievement and a measure of verbal learning and memory (e.g. working memory). This may account for the effect of family well-being on CVLT-C performance. However, that the effect seems to resolve within four years from diagnosis suggests that another factor may be driving the association. For example, one possibility is that a genetic component underlies both family dysfunction and academic achievement.

No significant effects over time were detected with either the use of a semantic or serial association learning strategy. In typical populations, serial clustering strategies tend

to increase with age (Meijs, Hurks, Kalff, Slaats-Willemse, Rozendaal, & Jolles, 2009), and is predictive of word recall (Meijs, Hurks, Rozendaal, & Jolles, 2013). It is likely that over time, children treated for cancer do not demonstrate the same patterns of learning or rely upon the same strategies. Thus, atypical development may account for the lack of significant results with respect to learning strategies.

Overall, the results of this study indicate the presence of an acute treatment effect that is influenced by a number of predictive risk factors, but does not persist to four years post-diagnosis. It is important to note that effects associated with sex, chemotherapy protocol, glucocorticoid dose, days in hospital, and family well-being did not survive correction for multiple testing, while some of the effects associated with age at diagnosis and all effects associated with the use of cranial radiation therapy did survive correction. In some instances, the effects did not persist beyond cessation of treatment (i.e., glucocorticoid dose, family well-being). My results suggest that any adverse effects present within the first few years may ameliorate over time. However, large scale studies have shown that cognitive effects related to treatment toxicity persist several decades beyond cessation of treatment (Mody et al., 2008). The relatively short-term nature of the deficits detected in my study may suggest that adverse effects emerge later in life once certain developmental milestones have passed, or when the demands of school or work shift towards more complex skills like synthesis and analysis of information. Continual and long-term follow-up of this population is important to detect possible future change in verbal learning and memory function.

Study 2b

In Study 2b, the same predictive risk factors considered in Study 2a were explored in a longitudinal analysis of event-related potentials (ERPs). The purpose of this study was to extend the literature by utilizing ERPs longitudinally in a pediatric cancer sample, which has not been previously done.

Method

Participant characteristics. The sample used in Study 2b was drawn from the same sample of 138 participants used for Study 2a. However, there were several participants who did not attend the specific event-related potential assessments (e.g. due to logistical factors, such as availability), and were thus excluded from the Study 2b sample. One hundred and thirteen participants were included in Study 2b. Descriptive statistics for this study are displayed in Table 9.

Table 9

Descriptive Statistics of Study 2b Sample

	Total (n = 113)
Sex	
Male	46
Mean Age at Diagnosis (*SD*), Years	6.91(4.38)
Age Range at Diagnosis, Years	0.92 – 18
Chemotherapy protocol	
DFCI 91-01	41
DFCI 95-01	72
Mean total effective dose of corticosteroid received during induction[1] (*SD*)	12333.25(6102.70)
Type of cranial radiation therapy	
Standard	49
Hyperfractionated	36
Did not receive cranial radiation therapy	28
Mean number of days in hospital (*SD*)	30.93(9.87)
Maternal family well-being scores	
At diagnosis[2](SD)	2.44(.62)
At three months post-diagnosis[3](SD)	2.56(.76)
Paternal family well-being scores	

At diagnosis[4](SD)	2.39(.67)
At three months post-diagnosis[5](SD)	2.45(.69)

Note: sample size varied due to missing data. [1]*n*=103; [2]*n*=97; [3]*n*=79; [4]*n*=85; [5]*n*=70

Measures. Event-related potentials (ERPs) were used as a psychophysiological measure of working memory, which indicate change in function at an overt neuropsychological and covert psychophysiological level. Event-related potentials are regularly used to assess memory function. They represent internal oscillatory activity linked to a time-locked stimulus (see Appendix D for a more thorough description of ERPs). ERPs are based on recordings from an electroencephalogram (EEG) which measures electrical activity that is naturally generated by the brain. The ERP is subsequently extracted from the EEG data using an averaging process.

The P300 (*P* for positive; *300* for the estimated post-stimulus latency in typical adults) is one of the most commonly examined ERP components, particularly in the context of working memory assessment. The P300 is associated with the dorsolateral and ventrolateral prefrontal cortex, supramarginal gyrus, cingulate cortex, medial temporal cortex (hippocampal and peripheral), superior temporal sulcus, superior parietal cortex, and posterior parietal cortex (Bledowski, Prvulovic, Hoechstetter, Scherg, Wibral, Goebel, & Linden, 2004; Halgren, Marinkovic, & Chauvel, 1998; Picton, 1992; Polich, 2012). The P300 has been linked to memory processes like searching and selecting the most relevant stimuli from a given set of data or environment, and is easily extracted from data from an auditory-, or visual oddball paradigm. It is often studied as two separate components: the P3a and the P3b, where the former is recognized by its relatively short peak latency recorded from frontal areas, and the latter by its longer peak latency and recorded by temporal and parietal leads (Polich, 2007).

Patterns of EEG and ERP activity are dependent on an individual's age, developmental trajectory (i.e. typical or atypical), and cognitive state. For example, in typically developing children, slower frequency bands (e.g., delta waves, theta waves) tend to decrease with age, while faster frequency bands (e.g., alpha waves, beta waves) tend to increase, and shift to higher frequencies as an individual ages (Yordanova & Kolev, 2008). In atypically developing individuals (e.g. those with Attention-Deficit/Hyperactivity Disorder), and in clinical populations (e.g. those with Parkinson's disease), certain latencies are prolonged and may have smaller overall amplitudes (Pearlstein, Whitten, & Haerich, 2006). Diminished amplitudes have also been observed in survivors of pediatric cancer (e.g. Järvelä et al., 2011). In typically developing children, a negative correlation has been demonstrated between reaction time, peak latency, peak amplitude, and age, such that P300 amplitude and latency tend to decline with age. Pfueller et al. (2011) reported that reaction time and peak latency decreased in typically developing children until approximately 11 years of age, at which point the rate of decline slowed, though change was still linear. Greater P300 amplitude in children who were 10 years of age or younger was also observed.

There are several advantages to ERPs: (1) they reflect neuro-electric mechanisms of information processing, rather than the neurobiological maturation of the brain alone; (2) they parse out functionally different, but temporally simultaneously generated responses from various ranges of frequency; and (3) they provide insight into developmental differences relating to the synchrony of neuroelectric responses (Yordanova & Kolev, 2008). They are also relatively quick to administer, and more cost-

effective compared to other psychophysiological measures of neural activity, such as fMRIs.

In this study, ERPs were recorded during a visual oddball task using the InstEP data acquisition program. Images of a moose (*non-target stimuli*; 75%) or a raccoon (*target stimuli*; 25%) were presented to participants on a computer screen located directly in front of them. Participants were asked to respond to the images as quickly as possible. The stimuli were black and white drawings presented on a white background. Participants each completed one stimulus block consisting of 160 stimuli, where individual stimuli were presented for 100 milliseconds. Typically, between 20 and 30 repetitions of a stimulus are considered sufficient to produce reliable data (Pearlstein, Whitten, & Haerich, 2006). The length of time between stimuli varied randomly between 2200 milliseconds and 2800 milliseconds. Stimuli were presented quasi-randomly so that two target stimuli were never presented in succession. All participants received the same stimulus presentation.

Similar to Study 2a, family well-being was measured with the Family Well-Being Assessment Tool (Caldwell, 2001). It was administered at diagnosis and at three months post-diagnosis.

Procedure. The procedures used in this study were reviewed and approved by the Institutional Review Ethics Board at Ste-Justine Hospital in Montreal, Quebec (see Appendix B). Informed consent was obtained from all parents or legal guardians, and assent was also obtained from participants.

Data were collected at five time points beginning at diagnosis, and repeated approximately annually for four years. Assessments were conducted approximately one

year apart (i.e., first assessment taken at baseline/diagnosis, second assessment taken at one-year post-diagnosis, third assessment taken at two-years post-diagnosis, fourth assessment taken at three-years post-diagnosis, fifth assessment taken at four-years post-diagnosis). Due to logistical factors (e.g. patient availability), there was some variability in the date at which assessments took place. To account for this variability, and to measure time elapsed from diagnosis with the most accuracy possible, time was measured individually for each participant by number of years elapsed from diagnosis (i.e., rather than grouped by first, second, third, fourth, or fifth assessment regardless of length of time elapsed from diagnosis). This was the same procedure described in Study 2a. Of note, in Study 2a time was measured in days from diagnosis and in Study 2b time was measured in years from diagnosis; while this impacts the magnitude of coefficients, it does not influence the relationships between variables. Descriptive variables related to the measurement of time elapsed from diagnosis are presented in Table 10.

Table 10

Time Elapsed from Diagnosis Measured in Years (Study 2b)

Assessment	*n*	Min.-max. years	Mean(SD)
First assessment	54	-.04 – .05	.001(.01)
Second assessment	63	.01 – 3.11	1.22(.31)
Third assessment	74	1.05 – 6.15	2.33(.52)
Fourth assessment	73	2.41 – 7.13	3.33(.50)
Fifth assessment	87	3.79 – 8.11	4.40(.54)

ERPs were derived from electroencephalogram signals recorded from 30 scalp electrodes affixed with an electrode cap (ElectroCap International Inc.). Twenty electrodes were based on standard International 10-20 system positions: Fz, Cz, Pz, Oz, FP1, F7, F3, T3, P3, T5, C3, O1, FP2, F8, F4, T4, P4, T6, C4, and O2. Ten additional

electrodes were positioned as follows: midway between FP1/FP2 and F3/F4; midway between F3/F4 and C3/C4; midway between C3/C4 and P3/P4; midway between T3/T4 and T5/T6; and midway between C3/C4 and Cz. See Figure 6 for an illustration of the 10-20 system. Impedance at all sites was < 5.0 kΩ. All electrodes were referenced to linked earlobes, and vertical and horizontal electrooculograms (EOG) were recorded with electrodes affixed to the supra- and infra-orbital ridge of the left eye and on the outer canthus of each eye.

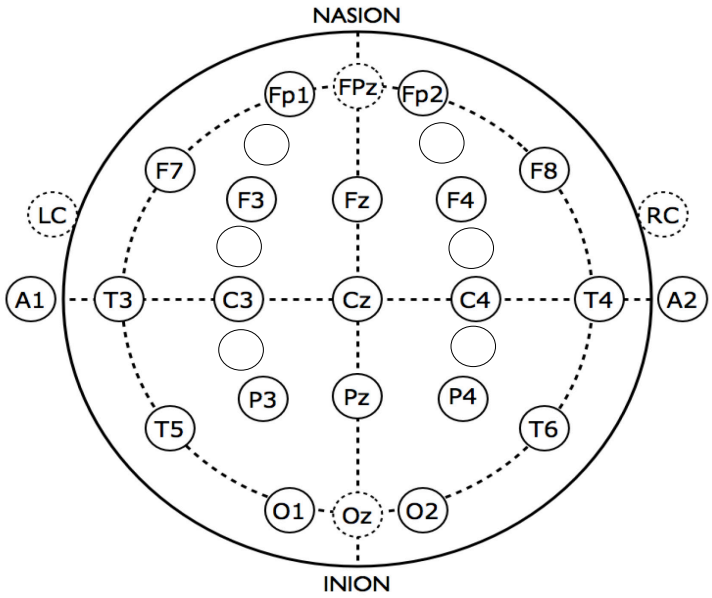


Figure 6. International 10-20 system

Participants were instructed to keep their lower arms rested on a table with each hand lightly placed over one of two response buttons (each five centimetres in diameter) attached to the table. They were asked to respond as rapidly as possible following presentation of the stimulus by pressing the left-hand button for non-target stimuli and the right-hand button for target stimuli. Responses were correct if participants pressed the correct button within 200 to 1600 milliseconds from stimulus presentation. The task

lasted approximately seven minutes total, and the same procedure was repeated at each assessment.

The IWave 7.2 software package (which accompanies the InStEP data acquisition program) was used to process the EEG and ERP data. The ERP components were extracted from the EEG recording through an averaging process, which isolated time-locked sections of data linked to the stimulus presentation over many trials. To quantify the observed response, peak amplitude and latency of the P300 response were measured from responses within a set timeframe. All available channels were processed initially, and data were processed as single trial averages. Artefact reject was enabled to eliminate responses +/-150 Hz, which would have occurred due to equipment error or muscle movement. Artefact reject was set to reject data from a single electrode; data from the other electrodes at the same point in time were retained. Separate averages were computed for peak amplitude and peak latency associated with target and non-target stimulus presentation.

EOG correction (i.e. removal of data which occurred due to eye movements, such as blinking) was processed for all channels. Blink template parameters were set as follows: blink amplitude = 200 uV; blink duration = 250 ms; A/D clipping interval = 100 milliseconds. EOG correction was completed with the multiple regression approach, which is based on data derived from EOG and EEG recorded during the experiment. It uses correction factors computed separately for blinks and eye movements, and are computed on measurements at each time point on each trial after event-related activity has been subtracted from the data (see Gratton, Coles, & Donchin, 1983 for a full description of this method).

To determine at which topographical site the P300 waveform was most evident in the sample, the P300 was examined by age groups based on developmental milestones: five to seven years; eight to 11 years; 12 to 17 years; and 18 to 22 years. In the two youngest age groups, the P300 was not visible at the frontal sites, and was most easily detectable at the central and parietal sites. In the 12 to 17 age group, the P300 was most clear at the parietal sites. It was also visible at the central sites, but occurred slightly later, and was not detectable at the frontal or occipital sites. In the oldest age group, the P300 was most evident at the parietal sites and was not visible at the frontal or occipital sites. It was detectable at the central sites, though similarly to the 12 to 17 age group, it occurred slightly later. Given that parietal sites produced the most consistent waveforms across age groups, the P3b was used as a marker (see Figure 7). Across all age groups, the P300 was most consistently detected at the left and right parietal sites (i.e., P3 and P4). The P300 was not generally visible at the frontal or occipital sites, and was delayed or difficult to clearly identify at the central sites. These observations were congruent with previous research indicating that the maximum amplitude for a visual P300 occurs over parietal electrode sites; as a result, researchers frequently limit analysis of the P300 to sites situated over the parietal lobe (Handy, 2005). Given these observations, and corroborating research, only data collected from the left and right parietal sites were included in the current project.

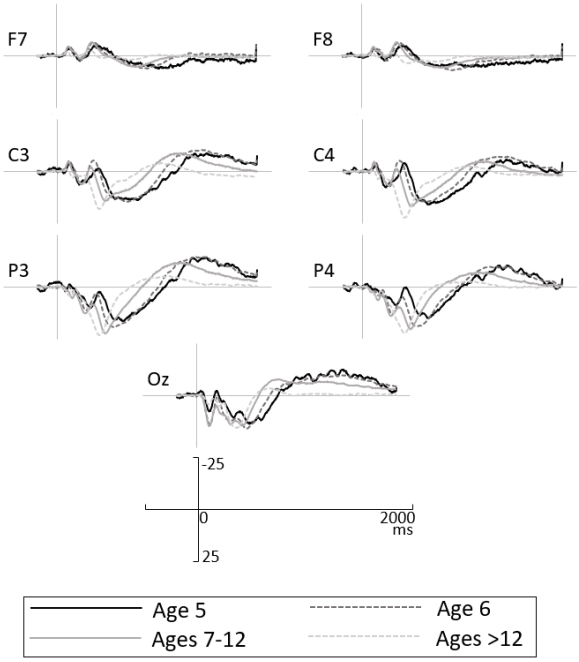


Figure 7. P300 across age groups

Based on a grand average of the sample (shown in Figure 8), the P3b was most clearly identifiable between 372 and 732 milliseconds post-stimulus, with a peak at 444 milliseconds post-stimulus. These findings were congruent with previous research suggesting that the P300 peaks as early as 300 milliseconds, and as late as 900 milliseconds post-stimulus (e.g. Kuperberg, 2004; Linden, 2005). P300 response to target (i.e. standard) and non-target (i.e. deviant) stimuli is presented in Figure 9.

Left parietal site *Right parietal site*

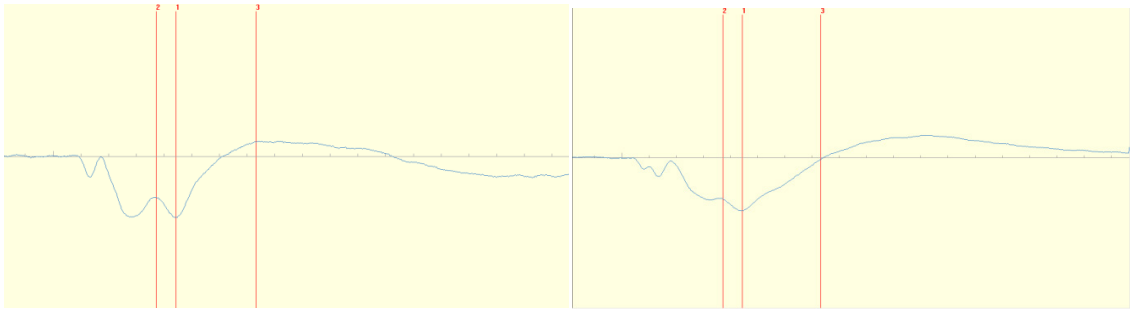


Figure 8. ERP grand average (milliseconds)

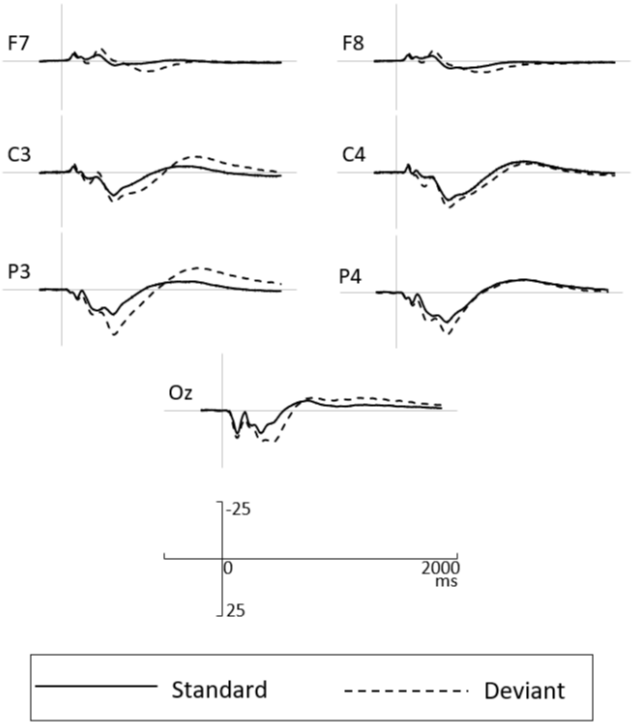


Figure 9. P300 response to target (standard) and non-target (deviant) stimuli

Statistical analysis. Multilevel modeling (SAS University Edition) was used to test change in peak amplitude and peak latency of the P3b waveform over time elapsed from diagnosis. Probability values <.05 were considered statistically significant. The hypotheses were developed to examine whether the effect of specific predictive risk factors on outcome variables varied as a function of time elapsed from diagnosis. Time points were nested within participants, and predictive risk factors were entered at level two. The predictive risk factors tested were sex, age at diagnosis, the use of cranial radiation therapy, chemotherapy protocol, total glucocorticoid dose, number of days in hospital (as a proxy for treatment-related complications), and maternal and paternal family well-being scores. The outcome variables were peak amplitude to target and non-target stimuli at P3 (i.e. left parietal site), peak amplitude to target and non-target stimuli at P4 (i.e. right parietal site), latency of the response to target and non-target stimuli at

P3, latency of the response to target and non-target stimuli at P4, the difference between the amplitude of a response to target versus non-target stimuli at P3 (i.e. (target – non-target) based on raw values), the difference between the amplitude of a response to target versus non-target stimuli at P4, the difference between the latency of a response to target versus non-target stimuli at P3 (i.e. (target – non-target) based on raw values), and the difference between the latency of a response to target versus non-target stimuli at P4. By using difference scores as the outcome variable, I was able to examine the additional time (i.e. latency) and amplitude to process target versus non-target stimuli, and to better capture the functional aspect of the process indexed by the P300. Where a significant interaction with time was identified, post-hoc ANOVAs were conducted to examine the specific effects. In order to account for age effects on ERP outcome variables, age at assessment was included as a covariate in all analyses. Table 11 presents the models tested.

As in Study 2a, age at diagnosis, days in hospital, glucocorticoid dose, and family well-being were treated as continuous variables. Sex, the use of cranial radiation therapy, and chemotherapy protocol were treated as categorical variables, where '0' represented males, no radiation delivered, and DFCI 91-01. Conversely, females, the administration of cranial radiation therapy, and DFCI 95-01 were coded as '1' in the dataset.

Table 11

Study 2b Statistical Models and Hypotheses

Hypothesis	Analysis
Base model (constant)	Outcome variable$_{ti}$ = π_{0i} + e_{ti}
Developmental model (Level-1 model)	Outcome variable$_{ti}$ = π_{0i} + π_{1i}*(TIME FROM DIAGNOSIS$_{ti}$) + π_{2i}*(AGE AT ASSESSMENT$_{ti}$) + e_{ti}
The rate of change	Outcome variable$_{ti}$ = π_{0i} + π_{1i}*(TIME

with time elapsed since diagnosis will be larger in girls.	*FROM DIAGNOSIS$_{ti}$) + π_{2i}*(AGE AT ASSESSMENT$_{ti}$) + e_{ti}* *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}$*(SEX$_i$) + r_{0i} $\pi_{1i} = \beta_{10} + \beta_{11}$*(SEX$_i$) + r_{1i} $\pi_{2i} = \beta_{20} + \beta_{12}$*(SEX$_i$) + r_{2i}
The rate of change with time elapsed since diagnosis will be larger in children diagnosed at a younger age.	Outcome variable$_{ti} = \pi_{0i} + \pi_{1i}$*(TIME FROM DIAGNOSIS$_{ti}$) + π_{2i}*(AGE AT ASSESSMENT$_{ti}$) + e_{ti} *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}$*(AGE AT DIAGNOSIS$_i$) + r_{0i} $\pi_{1i} = \beta_{10} + \beta_{11}$*(AGE AT DIAGNOSIS$_i$) + r_{1i} $\pi_{2i} = \beta_{20} + \beta_{12}$*(AGE AT DIAGNOSIS$_i$) + r_{2i}
The rate of change with time elapsed since diagnosis will be larger in those treated with cranial radiation therapy in addition to chemotherapy.	Outcome variable$_{ti} = \pi_{0i} + \pi_{1i}$*(TIME FROM DIAGNOSIS$_{ti}$) + π_{2i}*(AGE AT ASSESSMENT$_{ti}$) + e_{ti} *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}$*(CRT$_i$) + r_{0i} $\pi_{1i} = \beta_{10} + \beta_{11}$*(CRT$_i$) + r_{1i} $\pi_{2i} = \beta_{20} + \beta_{12}$*(CRT$_i$) + r_{2i}
The rate of change with time elapsed since diagnosis will be larger in those treated with dexamethasone (DFCI protocol 91-01) compared to those treated with prednisone (DFCI protocol 95-01).	Outcome variable$_{ti} = \pi_{0i} + \pi_{1i}$*(TIME FROM DIAGNOSIS$_{ti}$) + π_{2i}*(AGE AT ASSESSMENT$_{ti}$) + e_{ti} *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}$*(CHEOMTHERAPY PROTOCOL$_i$) + r_{0i} $\pi_{1i} = \beta_{10} + \beta_{11}$*(CHEMOTHERAPY PROTOCOL$_i$) + r_{1i} $\pi_{2i} = \beta_{20} + \beta_{12}$*(CHEMOTHERAPY PROTOCOL$_i$) + r_{2i}
The rate of change with time elapsed since diagnosis will be larger in those treated with higher doses of glucocorticoids.	Outcome variable$_{ti} = \pi_{0i} + \pi_{1i}$*(TIME FROM DIAGNOSIS$_{ti}$) + π_{2i}*(AGE AT ASSESSMENT$_{ti}$) + e_{ti} *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}$*(GLUCOCORTICOIDDOSE$_i$) + r_{0i} $\pi_{1i} = \beta_{10} + \beta_{11}$*(GLUCOCORTICOIDDOSE$_i$) + r_{1i} $\pi_{2i} = \beta_{20} + \beta_{12}$*(GLUCOCORTICOIDDOSE$_i$) + r_{2i}
The rate of change with time elapsed since	Outcome variable$_{ti} = \pi_{0i} + \pi_{1i}$*(TIME FROM DIAGNOSIS$_{ti}$) + π_{2i}*(AGE

diagnosis will be larger in those who spent more days hospitalized during the induction phase of treatment.	$AT\ ASSESSMENT_{ti}) + e_{ti}$ *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}$*(DAYS IN $HOSPITAL_i) + r_{0i}$ $\pi_{1i} = \beta_{10} + \beta_{11}$*(DAYS IN $HOSPITAL_i) + r_{1i}$ $\pi_{2i} = \beta_{20} + \beta_{12}$*(DAYS IN $HOSPITAL_i) + r_{2i}$
The rate of change with time elapsed since diagnosis will be larger in those with poorer family well-being scores.	Outcome variable$_{ti} = \pi_{0i} + \pi_{1i}$*(TIME $FROM\ DIAGNOSIS_{ti}) + \pi_{2i}$*(AGE $AT\ ASSESSMENT_{ti}) + e_{ti}$ *Where:* $\pi_{0i} = \beta_{00} + \beta_{01}$*(FAMILY WELL-$BEING_i) + r_{0i}$ $\pi_{1i} = \beta_{10} + \beta_{11}$*(FAMILY WELL-$BEING_i) + r_{1i}$ $\pi_{2i} = \beta_{20} + \beta_{12}$*(FAMILY WELL-$BEING_i) + r_{2i}$

Normality of data distribution for all continuous variables was assessed (IBM SPSS Statistics Version 23) with histograms, stem-and-leaf plots, and the Shapiro-Wilk test. Variables adhered to a normal distribution, with the exception of age at diagnosis (in years), number of days in hospital, and difference scores in amplitude at P3 and latency at P3 and P4. Aside from difference in amplitude at P3, all variables skewed to the left. For age at diagnosis, the results indicated that the majority of our sample was younger than six years of age at diagnosis. Since most ALL cases are diagnosed between three and five years of age (St. Jude Children's Research Hospital, 2018), this was not unexpected, and was not corrected. The skew observed in latency was also expected, with the majority of responses occurring within 16 milliseconds at the left parietal site (P3), and within eight milliseconds at the right parietal site (P4). This (and non-normality of P3 amplitude) was examined more closely with outlier analysis.

Amplitude and latency of the P3b waveform were checked for outliers with target and non-target stimulus presentation at the left and right parietal sites using box plots. Data

points that were greater than three box lengths from the lower or upper hinge of the interquartile range were considered extreme outliers. There were no extreme outliers identified at either parietal site for difference scores in amplitude. For difference scores in latency, at the left parietal site there were two extreme outliers, and at the right parietal site there were five extreme outliers identified. All extreme outliers were further examined for group membership to predictive risk factor groups, age, and assessment time point. There were no significant associations with any of the above variables and extreme outlier scores. In sum, all extreme outliers were individually visually examined in IWave, and all appeared to be true outliers and not due to measurement error. Therefore, they were left uncorrected.

Results

Behavioural data were calculated at each time point, and the average number of correct responses (out of 160), average number of non-responses (omission errors; out of 160), average number of incorrect responses (commission errors; out of 160), and early and late responses are displayed in Table 12. Early responses were defined as those that occurred more than 200 milliseconds before stimulus presentation, and late responses were defined as those that occurred more than 1600 milliseconds after stimulus presentation.

Table 12

Behavioural Data (Study2b)

Assessment	Correct responses M(*SD*)	Commission errors M(*SD*)	Omission errors M(*SD*)	Early responses M(*SD*)	Late responses M(*SD*)
First	88.43%	5.44%	4.89%	.18%	1.06%
Second	93.21%	2.98%	2.91%	.17%	1.12%
Third	91.83%	2.36%	4.55%	.16%	1.12%

Fourth	93.63%	3.96%	1.76%	0%	.83%
Fifth	92.91%	4.04%	1.99%	.01%	1.06%

Overall, at the first assessment, participants made fewer correct responses, more commission and omission errors, and more early responses. Over time and with practice, participants generally made more responses in general – especially correct responses. The number of late responses remained relatively stable over time, and the incidence of early responses increased slightly from the third assessment onwards.

Mean reaction time to target and non-target stimuli was calculated in milliseconds by assessment time point, and is displayed in Figure 10. Overall, participants became quicker to respond after the first assessment. The dip in reaction time at the second assessment represents a difference of .06 milliseconds and is unlikely to represent meaningful change. The subsequent improvement in reaction time may indicate recovery and a return to a participant's pre-treatment function.

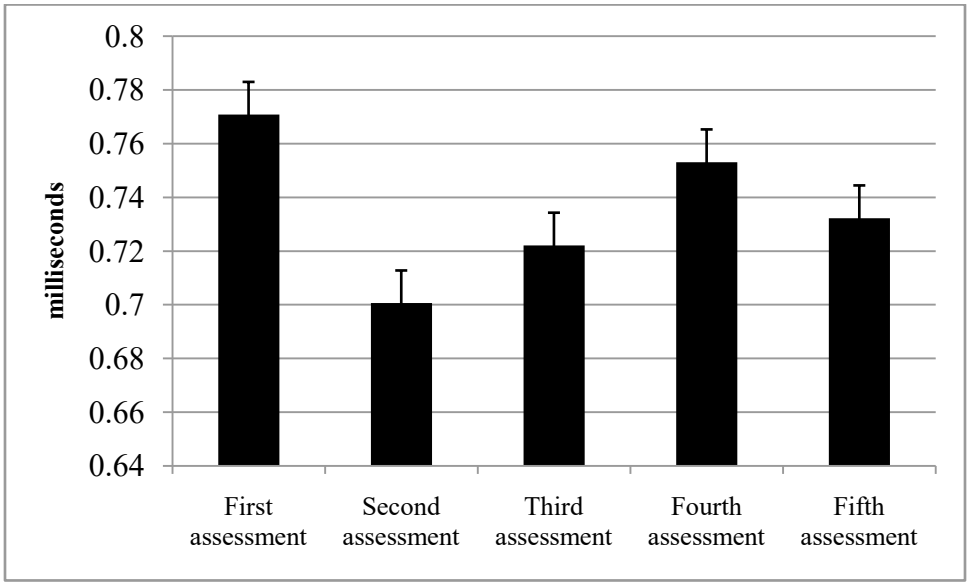


Figure 10. Mean reaction time (milliseconds) over time elapsed from first assessment (standard error)

The fixed effects models that were tested, their parameters, and all results are summarized in Appendix E. The results of the cross-level interactions tested in Study 2b are presented in Table 13.

Sex. Male or female sex did not predict change in latency or amplitude in any of the outcome variables tested.

Age at diagnosis.

Amplitude. Age at diagnosis did not predict change in amplitude in any of the outcome variables tested.

Latency. Overall, latency decreased with time elapsed from diagnosis, and this effect was most pronounced in participants who were diagnosed at a younger age (P3, target stimuli: t = -2.57, b = -.31, p = .01). The greatest change was observed in participants who were diagnosed at a younger age, as they had longer latencies at diagnosis (P3 target: t = 4.64, b = 2.12, p<.0001; P4 target: t = 3.99, b = 1.62, p< .01; P4 non-target: t = 2.64, b = 1.23, p< .01).

Use of cranial radiation therapy.

Amplitude. The use of cranial radiation therapy did not predict change in amplitude in any of the outcome variable considered.

Latency. Overall, latency decreased over time; this decrease attenuated with time elapsed from diagnosis. Thus, for participants of the same age, those with a greater amount of time elapsed from diagnosis had longer latencies than those who were treated more recently.

For participants who did not receive cranial radiation therapy, the difference in latency between target and non-target stimuli decreased with age (P3: t = -2.02, b = -

19.67, p = .05), and with time elapsed from diagnosis (P3: t = -2.10, b = -6.05, p = .04). The use of cranial radiation therapy nearly cancelled these developmental changes; in irradiated patients, the difference in latency between target and non-target stimuli was estimated at 20 milliseconds, and the change over time and with age was not significant.

Moreover, for participants who did not receive cranial radiation therapy, the difference in latency between target and non-target stimuli decreased over time (P3: t = 2.35, b = -182.92, p = .02), and the rate of change was greater in older participants. Processing time for targets and non-targets was more similar for participants who did not receive CRT. Across all participants, the difference in latency between targets and non-targets increased with years elapsed from diagnosis (P3: t = -2.02, b = -19.67, p = .05), and this effect was greatest for older participants. Processing time for non-targets shortened in comparison to targets. See Figure 11 for a graphical representation of these effects. Note that the y-axis represents a difference score (i.e. target – non-target), which accounts for the negative values. The y-axis is presented in milliseconds, where zero represents stimulus presentation.

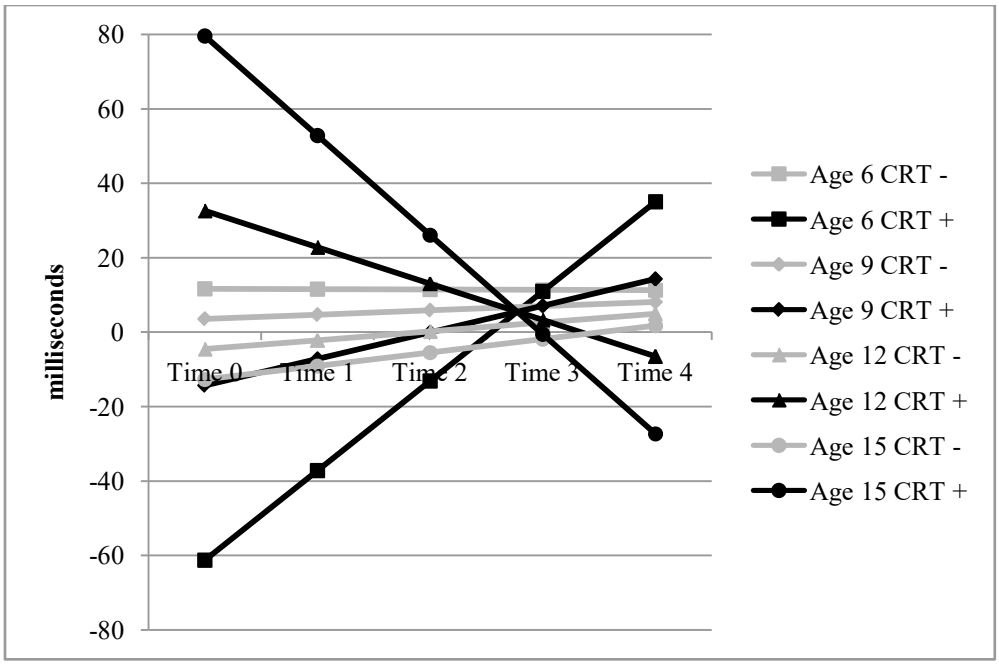


Figure 11. The effect of cranial radiation therapy on P3b latency (milliseconds)

The effect of cranial radiation was significant only on the latency of the P3b to target stimuli. The effect of radiation was observed to increase the latency to target stimuli, and this effect was larger for older participants. Overall, for irradiated participants, the decrease in latency with age was much smaller than for non-irradiated patients (P3: $t = 2.10$, $b = 2.62$, $p = .04$; P4: $t = 2.07$, $b = 19.49$, $p = .04$).

Chemotherapy protocol.

Amplitude. Chemotherapy protocol did not predict change in amplitude in any of the outcome variables tested.

Latency. The effect of the DFCI protocol (91-01 vs. 95-01) was significant on the latency of the P3b to both target and non-target stimuli. Overall, the latency of the P3b to non-target stimuli decreased with age (P3: $t = -3.77$, $b = -1.62$, $p<0.01$), as did the latency of the P3b to target stimuli (P3: $t = -4.71$, $b = -13.93$, $p<0.0001$). The 95-01 protocol was associated with a small increase in latency of the P3b to non-targets (P3: $t = 2.08$, $b =$

77.79, $p = 0.04$), which attenuated with time (P3: $t = -2.47$, $b = -27.87$, $p = 0.02$). Both effects tended to be larger in younger children (P3: $t = 1.88$, $b = 1.80$, $p = 0.06$). The same effects were observed for the latency of the P3b to targets: an increase of the P3b latency in patients treated with the 95-01 attenuated with time, more clearly in younger children. As a consequence, patients treated with the DFCI 91-01 protocol showed an effect of age, but only very small changes with time. The most significant decrease in latency occurred for participants treated with DFCI 95-01; a relatively more moderate decrease was observed for participants treated with DFCI 91-01. This trend was observed across most sites and type of stimuli (P3, target stimuli: $t = -3.18$, $b = -34.02$, p = .01; P4 target stimuli: $t = 2.58$, $b = 1.94$, $p = .01$; P4 non-target stimuli: $t = 2.43$, $b = 2.32$, $p = .02$), and the effect was most clear in the youngest participants.

Glucocorticoid dose.

Amplitude. Total glucocorticoid dose did not predict change in amplitude in any of the outcome variables tested.

Latency. The effect of the total dose of glucocorticoid was significant only on the latency of the P3b to non-target stimuli. The children who received glucocorticoids at a dose above the median dose showed an increase in P3b latency (P3: $t = -2.92$, $b = -.003$, $p = 0.01$), but this effect was attenuated in older children (P3: $t = 2.55$, $b = .0002$, $p = 0.03$) and over time (P3: $t = 2.55$, $b = .0002$, $p = 0.01$). As a consequence, among the youngest participants, those who received a higher total dose of glucocorticoids had longer latencies, and the decrease with time elapsed from diagnosis was steeper.

Days in hospital.

Amplitude. The number of days in hospital did not predict change in amplitude in any of the outcome variables tested.

Latency. Overall, latency decreased with time elapsed from diagnosis; this effect was observable at the left (t = -2.43, b = 157, p = .02) and right (t = -2.16, b = -115.25, p = .03) parietal sites in response to target stimuli. Those who were hospitalized for more than 30 days demonstrated a steeper increase in latency as they tended to have longer latencies at the beginning of follow-up. The most significant decrease in latency was observed in the youngest participants, especially for those who were hospitalized for more than 30 days, and this effect was also observable at the left (t = -2.03, b = -40.37, p = .04) and right (t = -2.21; b = -41.32, p = .03) parietal sites in response to target stimuli.

Maternal family well-being scores.

Amplitude. The effect of maternal family well-being scores taken at diagnosis on the difference between responses to target and non-target stimuli varied as a function of time elapsed from diagnosis at the right parietal site (t = -2.00, b = -1.60, p = .05). Across groups, the difference between amplitude in response to target and non-target stimuli tended to decrease with time elapsed from diagnosis for the younger participants, and tended to increase with time elapsed from diagnosis for the older participants with maternal family well-being scores taken at three months post-diagnosis (P3: t = 2.03, b = .19, p = .05). This difference became smaller over time when there was reported greater subjective stress experienced by participants' mothers at three months post-diagnosis (P3: t = -2.44, b = -2.45, p = .01).

Latency. Maternal family well-being scores did not predict change in latency in any of the outcome variables tested.

Paternal family well-being scores. Paternal family well-being scores did not predict change in amplitude or latency in any of the outcome variables tested.

Supplementary analysis. Study 2a and 2b utilized different techniques but aimed to measure similar constructs: information processing, learning, memory, and attention. To examine the association between the neuropsychological (CVLT-C in Study 2a) and electrophysiological tasks (ERP elicited with a visual oddball task in Study 2b) administered in the current project, and to explore to what extent these differing assessment modalities measured the same constructs, I ran a correlation analysis between total number of words recalled on the first five recall trials of the CVLT-C and latency of the response to rare stimuli at the left parietal site. Controlling for age at assessment on the relationship between total number of words recalled on the first five trials of the CVLT-C and latency of the response to rare stimuli at the left parietal site, the following partial correlations were detected at each assessment point: first assessment (baseline): r = -.17, p = .50; second assessment: r = -.01, p = .95; third assessment: r = -.27, p = .07; fourth assessment: r = -.32, p = .03; fifth assessment: r = -.25, p = .12).

Correction for multiple testing. To correct for multiple testing, the Benjamini-Hochberg False Discovery Rate adjustment (Benjamini & Hochberg, 1995) was applied to p-value thresholds. The p-value threshold was calculated as p = rank/total tests * .05, where the total number of tests performed was six for latency, and six for amplitude. After correction, all reported effects associated with age at diagnosis and chemotherapy protocol remained significant. None of the effects associated with the use of cranial radiation therapy, number of days in hospital, maternal family well-being, or glucocorticoid dose survived correction.

Table 13

Fixed Effects Estimate and Standard Error of Study 2b Results (Cross-Level Interactions)

	CRT x Time x Age at assessment	Sex x Time x Age at assessment	Glucocorticoid dose x Time x Age at assessment	Days in hospital x Time x Age at assessment	Chemotherapy protocol x Time x Age at assessment	Age at diagnosis x Time x Age at assessment	Maternal FWB, diagnosis x Time x Age at assessment	Paternal FWB, diagnosis x Time x Age at assessment	Maternal FWB, 3mo x Time x Age at assessment	Paternal FWB, 3mo x Time x Age at assessment
Latency										
Rare stimuli (P3)	-3.71(2.94)	-.09(1.08)	.0001(6.7E-05)**	.14(.08)*	2.41(.90)***	-.31(.12)***	-.90(.71)	-.12(1.22)	-.98(.92)	-1.10(1.02)
Frequent stimuli (P3)	2.28(2.85)	.73(1.08)	.0002(.0001)***	.06(.08)	1.80(.96)*	-.02(.13)	-.08(.62)	-1.65(1.07)	-.17(.78)	.05(.83)
Rare stimuli (P4)	-.22(2.43)	.63(.85)	7.9E-05(5.7E-05)	.12(.08)	1.94(.75)***	-.14(.10)	-.25(.52)	-.17(.92)	-.24(.75)	.09(.83)
Frequent stimuli (P4)	1.19(2.87)	1.34(1.06)	.0002(7.2E-05)***	.04(.08)	2.32(.96)**	-.02(.13)	-.77(.57)	-1.52(1.07)	.0004(.79)	.06(.90)
Difference score[1](P3)	-6.05(2.92**	-.60(1.02)	-.00003(6.9E-05)	.07(.08)	.68(.92)	-.22(.12)	-.16(.67)	1.71(1.13)	-.48(.79)	-.56(.87)
Difference score[1] (P4)	-3.60(2.59)	-.85(.92)	-.0001(.0001)	.05(.07)	-.13(.84)	-.04(.11)	.51(.53)	1.52(.94)	-.13(.69)	.30(.79)
Amplitude										
Rare stimuli (P3)	-.33(.40)	.10(.16)	2.40E-06(8.76E-06)	.01(.01)	-.10(.14)	-.002(.02)	.02(.09)	.25(.14)	.09(.11)	.07(.12)

Frequent stimuli (P3)	-.27(.27	.02(.11)	-6.12E-06(8.03E-06)	-.01(.01)	.01(.11)	-.01(.01)	-.07(.07)	.11(.11)	-.08(.08)	-.02(.08)
Rare stimuli (P4)	-.07(.39)	.01(.16)	6.24E-06(.00001)	<.00(.01)	-.08(.15)	.003(.02)	.05(.10)	.16(.14)	.03(.12)	-.02(.12)
Frequent stimuli (P4)	-.16(.29)	-.01(.12)	5.19E-07(8.09E-07)	-.01(.01)	-.10(.11)	.002(.01)	-.04(.07)	-.07(.09)	-.09(.09)	.55(.32)
Difference score[1] (P3)	.05(.34)	.09(.12)	6.88E-06(7.47E-06)	.01(.01)	-.13(.11)	.002(.02)	.05(.07)	.11(.12)	.20(.09)**	.13(.10)
Difference score[1] (P4)	.32(.30)	.03(.10)	5.59E-6(6.92E-06)	.01(.01)	.003(.09)	.001(.01)	.08(.06)	.02(.11)	.13(.09)	.07(.09)

*p< .10, **p< .05, ***p< .01

[1]Difference score calculated as (response to rare stimuli – response to frequent stimuli)

Discussion

In Study 2b, visual ERPs elicited with an oddball paradigm were used to examine the P3b response in a sample of children treated for pediatric ALL. The results of this study suggested that specific treatment-related factors (i.e., chemotherapy protocol, total glucocorticoid dose) influenced change in the P3b over time elapsed from diagnosis in participants diagnosed with pediatric ALL. Certain inter-individual factors (e.g., the number of days in hospital, age at diagnosis, maternal family well-being scores) also influenced P3b outcomes, though others (e.g., sex, paternal family well-being scores) did not have a significant effect. Of note, after correction for multiple testing, only change associated with age at diagnosis and chemotherapy protocol remained significant.

The behavioural data analysis showed that this sample responded in a way that would be expected in a typically developing population, particularly in a repeated measures design. Overall, participants' responses became quicker and more accurate over time, suggesting that learning occurred progressively at each subsequent assessment. Participants generally made fewer omission errors and early responses, and they made more correct responses over time.

During typical development, ERP latency tends to decrease with age. However, typical amplitude and latency trajectories may not be present in individuals with diminished cognitive function (e.g. Jonkman et al., 1997). In Study 2b, latency to target and non-target stimuli decreased with time elapsed, as would be expected in a typically developing population. However, young age at diagnosis, chemotherapy protocol, total glucocorticoid dose, and parental well-being were associated with adverse effects to neurocognitive function, such as slowed processing time.

Given that the developmental changes often attenuated with time elapsed from diagnosis, age and time could be measured separately. In other words, age and time did not necessarily progress at the same rate, and I was able to parse out their differences. Development by age occurred more slowly than by time. Therefore, it is of note that the effects of radiation were influenced by age but not time, and that the effects of glucocorticoid dose, chemotherapy protocol, and age at diagnosis were influenced by age, time, and the interaction between age and time. In a typically developing population, latency is expected to decrease with age, so my results may suggest that there were some negative effects of the cancer treatment. The above-noted findings are in line with previous research, which found an association between the use of radiation, atypical ERP performance, and cognitive deficits (e.g. Sato, Miyao, Muchi, Gunji, Iizuka, & Yanagisawa, 1992; Uberall, Haupt, Meier, Hertzberg, Beck, & Wenzel, 1996). Cancer treatment may negatively impact the conclusion of a cognitive encoding process of an event, and other mechanisms implicated in the ERP response phenomenon. Notable impairment to these processes may be associated with diminished categorization or differentiation behaviour. In our everyday lives, we use these skills to understand our environment, such as recognizing when to cross the street, or selecting a writing implement or kitchen utensil (Soltani & Knight, 2000).

A greater decrease in latency over time was observed in participants who were treated with DFCI 95-01, while a relatively more modest decrease in latency was observed for participants treated with DFCI 91-01, and this trend was most clearly observed in the youngest participants. This finding supports an attenuation of typical developmental changes, and may suggest that treatment with DFCI 91-01 is associated

with slowed development. This is supported by previous research suggesting that dexamethasone (which is a component of DFCI 91-01) is associated with more adverse outcomes than prednisone (which is a component of DFCI 95-01). As well, for younger participants, higher total doses of glucocorticoids were associated with slowed development. Of note, there are other differences between the 91-01 and 95-01 protocols, which may account for at least some of these results. These differences include the elimination of an investigational window of glucocorticoids in DFCI 95-01 and lower total doses of doxorubicin in DFCI 95-01 (Barry et al., 2007).

An acute effect of treatment (i.e. longer latency) was associated with a comparatively longer stay in hospital, where number of days in hospital was taken as an index of treatment-related complications. This effect waned by the fifth assessment, suggesting that treatment-related complications may not be a reliable indicator of long-term cognitive outcome.

Greater familial stress was associated with atypical development (i.e. the time to process targets versus non-targets became more similar over time elapsed from diagnosis). This effect was particularly strong for younger participants. These results indicate that maternal family well-being scores taken shortly after diagnosis might be an important and useful predictive tool for attentional outcomes several years later.

Overall, the results of Study 2b suggested that cancer treatment and specific inter-individual risk factors are associated with adverse outcomes on cognitive functions, such as attention and processing speed, and are in line with previous research. For example, Lähteenmäki et al. (2001) analysed the P300 response elicited by an oddball paradigm in adolescent survivors of childhood cancer (including survivors of leukemia, as well as

solid tumours), and healthy controls; the cancer survivors had prolonged latencies. Other research has indicated that prolonged P300 latency is linked to slower information processing and poorer performance on neuropsychological tests, such as subtests of the Wechsler Intelligence Scale; in a healthy population this relationship was detected on the Digit Span Backward subtest (Lefebvre, Marchand, Eskes, & Connolly, 2005) and in a pediatric cancer survivor population, it was noted on the Verbal IQ index (Järvelä et al., 2011).

The findings of Study 2b suggest that P3b latency and amplitude provide early brain markers of long-term neurophysiological outcome following the use of dexamethasone or high dose glucocorticoids. Previous studies using alternate methods of assessment have indicated that significant cognitive deficits emerge later in life, suggesting that long-term toxicity to anti-cancer therapy remains a concern for survivors (e.g. Edelstein et al., 2011). The present study corroborated these findings and brought additional value by examining not just the outcomes, but by tracing their emergence. The sample size in this study is also an advantage, especially considering the nature of the data.

That I did not find strong associations with some predictive risk factors was surprising, though other studies have also failed to find associations with certain factors, such as sex (e.g. Lähteenmäki, Holopainen, Krause, Helenius, Salmi, & Heikki, 2001). Notwithstanding, there is enough evidence to suggest that ERPs are a valuable method to detect brain markers in the pediatric cancer survivor population, which may be used to identify children who are most at risk of developing short- or long-term sequelae, and to guide targeted interventions.

General Discussion

The purpose of this research was to assess and evaluate the role of predictive risk factors in neurocognitive outcomes in two samples of individuals treated for pediatric cancer. It is important to note that a major limitation of the project was the inclusion of relatively small sample sizes (as a whole in Study 1, and between groups in Study 2) and a comparatively large number of comparisons. Many results did not survive correction for multiple testing. The discussion herein includes a summary of the results of all three analyses prior to correction, followed by a more thorough discussion of the limitations of each study.

Study 1. In Study 1, group differences between ALL patients and healthy control participants were tested with a measure of verbal learning (CVLT-C) and intelligence (WISC-III) at a mean of 5.67 years post-treatment. Patients were treated with chemotherapy alone, or with chemotherapy and radiation. The aim of this study was to replicate existing findings related to group differences (e.g. between males and females), and to confirm the presence of known associations between treatment and neurocognitive impairment that have been shown in the literature.

Overall, as expected, the healthy control group outperformed the treatment group; predictably, children in the control group recalled more words from the first and final thirds of word recall lists of the CVLT-C. Differences were also detected in the use of learning strategies on the verbal learning task: children in the treatment group used fewer serial associations compared to their healthy peers. A group by sex interaction indicated that healthy girls relied more on a serial association recall strategy on short- and long-

delay recall trials compared to healthy boys. However, in the treatment group, there was no difference in the use of serial associations between sexes.

A mediation model was conducted, and short-term memory capacity mediated the effect of treatment on the use of serial associations, while the use of serial associations mediated the effect of treatment on long-term memory capacity. This model indicated that treatment effects on short-term memory function may also influence long-term memory associated with verbal learning, particularly for individuals relying on a serial association recall strategy. Study 1 utilized a cross-sectional sample, and did not test the effects of predictive risk factors over time.

Study 2a. In Study 2a, predictive risk factors were tested for their association with verbal memory and learning longitudinally in a sample of pediatric ALL survivors. The purpose of Study 2a was to replicate existing findings within the literature, such as the long-lasting impact of predictive risk factors on learning and memory over time, and to extend the literature by testing the impact of exact total dose of glucocorticoids over time.

Participants were assessed at diagnosis, and then approximately annually for four years post-diagnosis. At the base model (i.e. without level-2 variables entered into the model), verbal learning and memory was significantly negatively impacted during treatment, though these effects appeared to be relatively short-lasting; by the fourth follow-up, differences were no longer significant. Specifically, children who received higher total glucocorticoid doses recalled fewer words across the first five recall trials (i.e. recall of List A), and especially for the first five words (i.e., first third, or primary region) of each trial. Participants treated with dexamethasone made more perseveration

errors over time, compared to participants treated with prednisone. Males made more intrusion errors on free and cued word recall trials, while poorer maternal and paternal well-being measured close to diagnosis was also associated with fewer intrusion errors. As expected, poorer paternal well-being close to diagnosis was associated with weaker word recall from the last third of the first five recall trials. Overall, learning was negatively impacted by number of days in hospital, which was interpreted as a proxy for treatment-related complications. Finally, young age at diagnosis was associated with more perseveration errors and with fewer words recalled on the first five recall trials.

Study 2b. Study 2b used a subset of the longitudinal sample from Study 2a to test the influence of predictive risk factors on event-related potentials (ERPs), which were elicited with a visual oddball paradigm; participants were assessed at diagnosis and then reassessed approximately annually for four years. Specifically, the effect of predictive risk factors was tested for their impact on the latency and amplitude of the P300 waveform, which reflects an updating memory process when stimuli are presented in succession, as well as information processing and attention. The purpose of Study 2b was to extend the literature by testing the impact of exact total glucocorticoid dose over time, and to test the effects of the same predictive risk factors included in Study 2a with a less overt measure of attention and information processing. To my knowledge, this was the first study to utilize ERPs longitudinally in a pediatric cancer sample.

At the base model, the results of Study 2b suggested that the P300 latency and amplitude remained relatively constant over the four-year follow-up. However, as expected, differences in latency of the P300 response were detected in response to rare and frequent stimuli (i.e., frequent = 449 milliseconds; rare = 475 milliseconds) at the left

parietal site (i.e. P3). Amplitude of the P300 response also differed between rare and frequent stimuli (i.e. frequent = 15 mV; rare = 25 mV); this effect occurred in the expected direction, and no change was detected over the follow-up period. Significant effects primarily occurred on measures of latency; there were few significant effects on amplitude. Several factors influenced latency, including age at diagnosis, total glucocorticoid dose, chemotherapy protocol, and parental well-being. Latencies were longer for participants diagnosed at a younger age, and the observed decrease in latency with years elapsed from diagnosis was also larger in younger children. Additionally, participants who received higher doses of glucocorticoids had longer latencies during treatment, but their latency decreased over time as would be expected in normative populations, indicating that on average, these effects resolved with time. Similarly, while controlling for total glucocorticoid dose, participants treated with prednisone (i.e. on chemotherapy protocol DFCI 95-01) showed a decrease in latency over time, while those treated with dexamethasone (i.e. on chemotherapy protocol DFCI 91-01) did not demonstrate this trend, suggesting that dexamethasone was associated with atypical latency. Poorer maternal well-being close to diagnosis was associated with atypical amplitude, and these effects persisted over the duration of follow-up.

Study 2a and 2b. A correlation analysis was conducted to examine the relationship over time between the results of Study 2a (i.e. neuropsychological testing) and 2b (i.e. ERP outcomes). While controlling for age, the total number of words recalled on the first five trials of the CVLT-C and latency of the response to rare stimuli at the left parietal site were increasingly correlated with time; however, this effect only became significant at three years post-diagnosis. These results suggest that while Study 2a and 2b

utilized vastly different assessment modalities, there was some overlap in the underlying neurocognitive functions tested, suggesting that similar effects may be detectable with measures of different levels. The general lack of correlation between Study 2a and 2b outcomes seems to indicate that changes in amplitude and latency are not reflected in a word recall task, and thus may signify activation of different brain regions or neurocognitive functions. For example, latency may be taken as an index of information processing, but not directly of short-term memory, while word recall more directly indexes short-term memory. More research may be useful to determine whether changes in ERP outcomes over time translate to other functional and meaningful variables (e.g. other cognitive or behavioural outcomes).

Comparison with Previous Research

Treatment-related factors. In my thesis, total glucocorticoid dose and glucocorticoid type impacted neurocognitive outcomes. Previously, the effects of radiation were more damaging to neurocognitive function compared to chemotherapy administered on its own. These effects were evident in two older studies that examined the influence of pediatric cancer treatment on ERPs. Moore, Copeland, Ried, and Levy (1992) compared the P300, reaction time, and neurocognitive function in pediatric cancer survivors who received radiation and chemotherapy, chemotherapy alone, and without central nervous system prophylaxis. The use of methotrexate was associated with slowed reaction time and longer P300 latency, most significantly when it was administered in combination with radiation. In another study, Ueberall et al. (1996) looked at the P300 waveform in adult survivors of pediatric ALL who were treated with radiation and methotrexate, with methotrexate without radiation, and a healthy control group. They

reported that P300 latency was prolonged most substantially in the group that received radiation, suggesting that it was primarily the effects of radiation that were damaging to the individual. That there was no significant effect of radiation in either Study 2a or 2b suggests that refinements to treatment protocols have had the desired effect of minimizing the most traditionally damaging effects. Another possibility is that my study lacked sufficient power to detect an effect of radiation.

However, on more modern treatment protocols, chemotherapy also has deleterious effects that can equal those of radiation. For example, Waber et al. (2012) assessed the cognitive function of four-year survivors of childhood ALL who were classified as standard-risk or high-risk, and were treated on one of the same chemotherapy protocols as participants in Study 2a and 2b of the current project (i.e. DFCI 95-01). Additionally, some (randomized) standard-risk patients received 18Gy radiation, and all high-risk patients received 18Gy radiation. Participants in both treatment groups had scores that fell significantly below standardized norms on a span task, a verbal learning task, tests of visual perception, and some indicators of executive function, suggesting that in some cases the effects of chemotherapy were comparably deleterious to the effects of 18Gy radiation. In my thesis, radiation was also administered at 18Gy. As in Waber et al.'s (2012) study, in Study 2a and 2b, there was no significant difference detected between participants treated with radiation and chemotherapy, and those treated with chemotherapy alone. However, the effect of total glucocorticoid dose and chemotherapy protocol impacted verbal learning and memory and ERP outcomes, suggesting that the effects of chemotherapy were most impactful to neurocognitive outcome. The effect of total glucocorticoid dose was tested in Study 2a and 2b, and found

to negatively impact neurocognitive function, including poorer word recall and longer ERP latencies.

The above-described results may reflect the dependence of the tasks used in Study 2 on the hippocampus. The hippocampus plays an important role in verbal learning (Savage et al., 2001) and visual oddball tasks (Crottaz-Herbette, Lau, Glover, & Menon, 2005; Huetell & McCarthy, 2004), and although glucocorticoids are effective chemotherapeutic agents, they can also cause apoptosis in non-lymphoid cells and tissue. The hippocampus is especially vulnerable to the effects of synthetic glucocorticoids due its high concentration of glucocorticoid receptors and mineralocorticoid receptors (Judd et al., 2014). Thus, in the context of glucocorticoid use, these hippocampus-dependent tasks may have been impacted by cancer treatment.

The results of my thesis results support the occurrence of overall dysfunctional memory processes for individuals treated for pediatric cancer. The link between neurocognitive function, glucocorticoid use, and hippocampal integrity was highlighted in a study by Zając-Spychała, Pawlak, Karmelita-Katulska, Pilarczyk, Derwich, and Wachowiak (2017), who compared mean volume of brain structure in three groups of children who had been diagnosed with ALL: one group who had been treated with chemotherapy and radiation, one group who had been treated with chemotherapy alone, and one group who had yet to initiate treatment (control group). Differences were detected between the chemotherapy-only and control groups on caudate nucleus volume, between the radiation and control groups on volume of the hippocampus, caudate nucleus, globus pallidus, and brain ventricles, and between both treatment groups on hippocampal volume. Further, in a regression analysis of memory, attention, executive

functions, and brain volume, a significant relationship was detected between auditory-verbal memory and hippocampal volume across groups. Thus, the importance of the hippocampus in the Study 2 tasks and the vulnerability of the hippocampus to glucocorticoids may explain some of the effects to neurocognitive function (e.g., word learning, P300 latency) reported in my thesis.

Treatment-related changes to hippocampus-dependent functions may also be attributed to inhibition of neurogenesis (i.e. creation of new neurons), which is triggered by specific elements of cancer treatment, such as the use of glucocorticoids. There is evidence that cranial radiation and some chemotherapeutic agents will substantially decrease neurogenesis in the hippocampus, which would then be further inhibited from regeneration with the use of glucocorticoids. The effect of cancer treatment on hippocampal neurogenesis was demonstrated in a post-mortem analysis of four individuals (ranging from newborn to adult) treated for cancer (i.e. medulloblastoma or acute myelogenous leukemia) up to 23 years prior, with age- and sex-matched controls. Hippocampal neurogenesis in the individuals treated for cancer was at least 10 times less than the control group (Monje, 2008). Neurogenesis is necessary for normal hippocampal function, and its inhibition is associated with disruptions to hippocampus-dependent tasks, including certain types of memory, such as episodic memory (Monje, Thomason, Rigolo, Wang, Waber, Sallan, & Golby, 2013). However, as several findings related to treatment factors did not persist to four years post-diagnosis, they may be more related to an acute treatment effect rather than hippocampal damage or inhibition of neurogenesis.

Within the literature and in my thesis, differences between neurocognitive outcomes linked to the use of specific chemotherapeutic agents have been detected. The

use of dexamethasone is typically associated with more adverse effects compared to prednisone. Teuffel et al. (2011) systematically reviewed the literature comparing the effects of dexamethasone and prednisone use in pediatric ALL patients, and reported that individuals who received dexamethasone were four times more likely to develop adverse neuropsychological effects. Several other studies also noted differences between neurocognitive outcomes in individuals administered dexamethasone or prednisone. For example, Waber et al. (2013) compared the neuropsychological functioning of children diagnosed with ALL who were randomly treated with prednisone or dexamethasone at a median 5.8 years post-diagnosis; the chemotherapy protocol used (DFCI 00-01) was an updated version of the protocols included in Study 1 and Study 2 (i.e. DFCI 87-01, 91-01, and 95-01) of my thesis. In Waber et al.'s (2013) study, individuals classified as high-risk also received 12 or 18Gy radiation. Participants' scores differed significantly only on a measure of non-verbal (i.e. fluid) reasoning, and those treated with dexamethasone underperformed compared to those treated with prednisone. As well, there was a trend towards the use of special education programs associated with dexamethasone use: 33% of participants treated with dexamethasone were enrolled in special education programs and 20% of participants treated with prednisone were enrolled in the same programs (p = .09). In line with the above-described studies, in Study 2a and 2b, dexamethasone more negatively impacted CVLT and P300 outcomes compared to prednisone. Specifically, the use of dexamethasone was associated with more errors across trials, which may reflect impaired episodic memory or learning. It was also associated with atypical P300 latency, indicating disturbed attentional function and information processing. Importantly,

dexamethasone is typically more effective at central nervous system penetration, and thus continues to be used in chemotherapy protocols.

Of note, in Waber et al. (2013), scores across measures generally approximated population means, suggesting that impairments following treatment were overall relatively mild, even for those who received radiation. The differences detected between groups in my thesis were also subtle. For example, in Study 2a, while the effect of greater subjective stress as experienced by participants' fathers had a significant effect on word recall from the recency region of List A at baseline, the coefficient (b = -.41) suggests that there was less than a one word difference in recall between participants whose fathers experienced greater versus less subjective stress. It is important to consider whether a difference of less than one word represents meaningful change in function to an individual treated for cancer, which it likely does not. Moreover, the difference in word recall of the recency region by paternal family well-being lessened over time elapsed from diagnosis (b = .16).While there were many statistically significant effects in Study 2, it is important to keep in mind their questionable functional and practical meaning. Additionally, many effects either lessened with time or were no longer significant by four years post-diagnosis, suggesting that the effects detected in my thesis were not only subtle, but also relatively short-lasting.

In sum, the observed treatment-related effects may have occurred due to the vulnerability of the hippocampus to glucocorticoids, as glucocorticoids trigger a decrease in neurogenesis within the hippocampus, impacting its functioning. The central role of the hippocampus in the measures used in my thesis may account for many of my findings.

Interindividual-related factors. In my thesis, the effect of specific risk factors on neurocognitive outcomes, including sex, age at diagnosis, and parental well-being were present on measures of verbal learning and memory, attention, and information processing, and these effects were largely in line with findings of previous studies.

Sex. Typically, females experience more significant impairments compared to males following treatment for pediatric cancer (e.g. on measures of IQ; Peterson et al., 2008). Sex differences were detected in Study 2a, where males made more intrusion errors. Though these results seem counter-intuitive, intrusion errors on the CVLT-C are primarily related to frontal lobe function (Baldo, Delis, Kramer, & Shimamura, 2002). Faster rate of frontal lobe development in females compared to males may be protective (Lenroot, et al., 2007). The results may also be attributed to the nature of the verbal learning task, as adult females typically possess stronger verbal skills compared to males, and increased cerebral blood flow in the temporal lobe has been linked to better verbal learning in females (Ragland, Coleman, Gur, Glahn, & Gur, 2000). Sex differences were also detected in Study 1, but only between healthy males and females.

The effect of sex was not present on ERPs in Study 2b; however, within the broader literature, little is known about sex differences in ERPs, so it is unclear whether the lack of sex effects in Study 2b reflects typical or atypical development. Sex differences on ERP variables may only become apparent in adulthood. A meta-analysis by van Dinteren, Arns, Jongsma, and Kessels (2014) indicated that the P300 of male and female children follow a similar developmental trajectory, and sex differences only emerge in adulthood where males tended to have shorter latencies than females, though the analysis produced a small effect size.

Age at diagnosis. Pediatric cancer survivors who were diagnosed earlier in life are more likely to develop neurocognitive impairment than survivors who were diagnosed at an older age, especially in those diagnosed before five years old (Harshman et al., 2012). In line with the literature, in my thesis, participants diagnosed at a younger age in the Study 1 and 2 samples were more vulnerable to the effects of anticancer therapy. Being younger at diagnosis may render the brain more susceptible to the effects of cancer treatment due to vulnerability in early stages of development of white and gray matter (e.g. Ebel & Beaulieu, 2017). In a typically developing brain, vast cell growth and mylenation occur during the first few years of life. After approximately five to six years of age, programmed cell death (apoptosis) of neurons begins to occur. Throughout the lifespan, gray and white matter differ in their proliferation; gray matter typically increases until four years old and then decreases slowly over the lifespan, while white matter increases relatively linearly and peaks in the mid-20s. Since impairments that arise secondary to radiation are often thought to occur as a result of damage to gray and white matter, research suggests that the brain is most vulnerable to the effects of radiation during those first years of rapid white matter mylenation in childhood (Bledsoe, 2016), explaining the vulnerability of younger patients to cancer treatment.

Parental well-being. Generally speaking, stressors within an individual's environment, such as the well-being of parents or caregivers, negatively impact cognitive outcomes in children. In other populations, such as pre-term children, research has indicated that parenting and characteristics of the parent-child relationship influence the development of executive function (Zvara, Keim, Boone, & Anderson, 2019), and other research has found a mediating role of aspects of parental well-being (e.g. mood

symptomatology) on the relationship between parenting and behavioural issues in children (Huang, Bornheimer, Dankyi, & de-Graft Aikins, 2018). In Study 2a, poorer paternal well-being was associated with diminished word recall from the recency section (i.e. last third) of the word recall lists. Within the literature, the influence of a parent's well-being on their child's psychology and development has been similarly demonstrated. For example, in a sample of children with retinoblastoma and their parents, Willard et al. (2017) reported that parental stress at baseline predicted developmental functioning (e.g., fine and gross motor skills, learning) and adaptive functioning (e.g., motor skills, communication skills) over five years; in this same study, overall levels of parental stress at baseline and at five years old was normative (i.e. stress levels fell below the 50th percentile).

Implications

Following treatment for pediatric cancer, there are long-term implications for neurocognitive abilities like learning, episodic memory, attention, information processing, and task efficiency (Cheung et al., 2018). The neurocognitive effects of cancer treatment in pediatric cancer survivors are well-documented, easily detectable, and occur across genders, age groups, and cancer types and treatments (Krull, Hardy, Kahalley, Schuitema, & Kesler, 2018). Some of the results of my thesis highlighted the occurrence of these deficits and their persistence over time, though the limitations of my thesis (i.e. likelihood that some results are spurious or represent false positives) should be considered when weighing the significance of the results. Within the literature, deficits in neurocognitive function have been shown to be pervasive and to manifest across

domains. Acute, late, and chronic effects impact schooling, interpersonal relationships, and activities of daily living (e.g. Kunin-Batson, Kadan-Lottick, & Neglia, 2014).

Survivors' day-to-day functioning is impacted by the experience of cancer diagnosis and treatment, and they are at risk for developing secondary mental health concerns (Kirchhoff et al., 2011). During treatment, quality of life typically declines for patients, particularly when they are classified as high-risk, are older at diagnosis, or are female (Mitchell et al., 2016). Moreover, in the years following treatment, survivors' social functioning declines (Sung et al., 2011). Additionally, pediatric cancer survivors present with higher rates of mood and anxiety symptomatology (Kunin-Batson et al., 2016; Myers et al., 2014).

The impact on neurocognition following treatment is commonly observed at school, where childhood cancer survivors are more likely to repeat a grade (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005) and to rely on special education services (Mitby et al., 2003). Changes to neurocognitive function also have implications for specific academic skills. Armstrong and Briery (2004) highlighted several academic concerns associated with cancer survivorship, including periods of inattention, which affects learning; difficulty with handwriting, which affects performance on essays, written tests, and other written assignments; increased difficulty learning information involving symbols and sequences or visual information; reluctance or inability to comprehend what has been read, despite the capacity to recognize and read words; difficulty with organization and planning; suboptimal task completion, reflecting an impairment in processing speed; and, difficulty with some math calculations, though not always math concepts.

The impact of pediatric cancer and its treatment extends beyond the patient's mental well-being and academic functioning. Families are also impacted by the experience of cancer diagnosis and treatment. In the year following treatment, parents of children diagnosed with standard-risk ALL treated with chemotherapy (including methotrexate) were at a greater risk of loss of employment, divorce, and relocation, or were less likely to have more children, compared to 2010 American Census averages (Lauet al., 2014). Furthermore, there is an impact on society as a whole. Survivors of pediatric ALL at a mean 21.2 years follow-up, including 62% who received radiation, had lower rates of marriage, college graduation, employment (only for females), and health insurance, compared to their siblings. Survivors also presented with higher rates of chronic medical conditions (e.g., musculoskeletal, such as joint replacement, and cardiac, such as congestive heart failure) and mental health concerns. Overall, the above-noted issues were most likely to occur in individuals treated with radiation or who had experienced a relapse (Mody et al., 2008). Results from the Childhood Cancer Survivor Study indicate that at a mean 23.1 years post-treatment, 18.2% of survivors experience cardiopulmonary complications and 22.9% of survivors experience endocrine-related complications; moreover, through path analysis, it was determined that these physical health concerns are associated with impaired task efficiency and emotion dysregulation (Cheung et al., 2018). In Canada, higher rates of physical and mental health concerns in pediatric cancer survivors translates to a need for additional monetary and personnel resources in the public healthcare system.

Given the pervasive nature of the deficits associated with pediatric cancer treatment, it is important that the risks of treatment are communicated to families and

educators, so they can make informed decisions regarding treatment, recognize issues or deficits early on, and advocate on behalf of the child or adolescent for intervention and support. Communication of the risks and potential impairments is also important to provide context, and to avoid the likelihood of making dispositional or characteristic attributions, which may have detrimental effects to a child's self-image (e.g. attributing behaviour to laziness, rather than cancer treatment-related memory impairment). Importantly, although neurocognitive deficits are concerning and should be communicated, deficits are often subtle and survivors are able to adapt. Above all else, survivorship must be prioritized.

Given the potential for meaningful, pervasive, and long-lasting changes to neurocognitive function following treatment for pediatric cancer, early identification and availability of intervention is critical. Neurocognitive testing and intervention might benefit survivors at cessation of treatment, during times of transition (e.g. between middle and high school), and/or on a routine intermittent basis (Krull, Hardy, Schuitema, & Kesler, 2018).

Biomarkers and baseline testing. Taking into account stages of brain development, and brain changes following brain injury, early intervention may represent the best chance of cognitive remediation in survivors of childhood cancers, such as ALL. Thus, the development of markers to identify individuals most at-risk for presenting with neurocognitive sequelae is imperative. A review by Castel, Denouel, Lange, Tonon, Dubois, and Joly (2017) suggested that biomarkers, such as plasma inflammatory responses (e.g. cytokine levels), non-inflammatory biomarkers in blood or serum (e.g. haemoglobin), hormone factors (e.g. thyroid-stimulating hormone), genetic factors, and

biological factors in cerebrospinal fluid (e.g. phospholipid or lysophosphatidylcholine concentrations) will be useful to identify patients who are most at-risk for developing adverse effects, like impaired processing speed, fatigue, impairments to visual and verbal memory, and reduced hippocampal volume. In my thesis, specific functional markers of late effects, such as prolonged ERP latency, were identified, and may be used to identify survivors most in need of early intervention and treatment. These biomarkers may also be used to predict which individuals are least at-risk for developing adverse effects following treatment for pediatric cancer, as well as those who are most likely to recover full neurocognitive function. This is an area for future researchers to explore the potential associations between the presence and absence of change to ERP variables and positive response to intervention, such as rehabilitation and remediation programs. Such associations would further improve the process of identifying individuals who are most in need of early and targeted intervention.

Baseline testing might also be an important tool to detect late effects, especially some of the more subtle effects. For example, cognitive testing or brain imaging and blood panels (e.g., thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone) may serve as important markers of changing health status (Schwartz, 1999). Early identification of these individuals provides clinicians the opportunity to modify treatment protocols, introduce early or more frequent screenings, and to direct targeted interventions, which would hopefully minimize either the development of these effects, or at least produce the most favourable and least deleterious outcomes.

Psychological intervention and assessment. There have been several initiatives and research projects aimed at minimizing the neurocognitive deficits observed in the

pediatric cancer survivor population and limiting the progression of impairment. A review article by Castellino, Ullrich, Whelen, and Lange (2014) noted that many interventions, such as cognitive remediation, computerized training programs, school-based programs, and social skills training were associated with improved academic achievement, working memory, self-regulation, and social skills outcomes. For example, Butler and Copeland (2002) introduced a 50-hour, six-month cognitive rehabilitation program aimed at bettering attentional and neuropsychological outcomes. After six months, children who participated in the program demonstrated improved attention compared to children who did not receive the intervention. In a pilot project, Moore et al. (2000) delivered an academic arithmetic program to eight pediatric cancer survivors; after 40 to 50 hours of participation in the program, participants who received the intervention demonstrated stable academic achievement in arithmetic, while the control group (who received no intervention) exhibited declining arithmetic skills. Survivors who participated in computerized cognitive training have demonstrated improvements in working memory, attention, processing speed, and executive function (Conklin et al., 2015), and these changes persisted to at least six months post-intervention (Conklin et al., 2017). These interventions may be useful for some of the participants in the current project, particularly those who received higher total doses of glucocorticoids and subsequently demonstrated impaired word learning. Computerized programs may be especially appealing, as they can be completed from a distance which may lessen some of the logistical and monetary burdens associated with additional appointments and interventions.

Psychoeducational assessment might also be helpful to gain in-depth understanding of an individual's learning profile, including their strengths and areas of need. Subsequently, Individual Education Plans and academic accommodations should be implemented, when warranted and appropriate. Accommodations, like extra time on tests and written instructions, may support students who take longer to recall information or respond to questions, or present with memory impairments. Where possible, classroom strategies should also be adjusted to suit a student's learning needs (e.g. increased repetition of materials).

Due to the higher rates of mood and anxiety symptomatology and variable self-image in pediatric cancer survivors, psychotherapy may be helpful to support an individual's emotional needs during and after treatment. Families and others who are close with the patient may also benefit from psychotherapy or other forms of emotional support. Resources are accessible through organizations like the Canadian Cancer Society, and through institutions such as Sick Kids Hospital (Toronto, Ontario).

Pharmacological intervention. Pharmacological treatment has also been proposed as a potential intervention for pediatric cancer survivors who are experiencing deficits in neurocognition and executive functions, such as sustained attention. Methylphenidate has been suggested as a potential prescription for cancer survivors based on behavioural similarities with individuals diagnosed with Attention-Deficit/Hyperactivity Disorder. However, there are few studies which have empirically tested the use of stimulant medication in the cancer survivor population, and older studies produced mixed results. In one study, methylphenidate was administered to 12 children who were in remission from malignant brain tumours or ALL; eight children had a

positive response to the medication, two had a "fair" response, and two experienced adverse effects, such as suppressed appetite (DeLong, Friedman, Friedman, Gustafson, & Oakes, 1992). In another study, Thompson et al. (2001) used a randomized, double-blind design to test the efficacy of methylphenidate in a sample of children who were in remission from cancer and who were demonstrating suboptimal academic achievement and attentional vigilance. Ninety minutes following the administration of the medication, participants made fewer omissions and had overall improved scores on a continuous performance test, though other neuropsychological measures (e.g., CVLT-C, Visual-Auditory Learning Test on the Woodcock-Johnson Cognitive Battery) failed to show significant effects. Pediatric cancer survivors in another study also demonstrated improved performance on a continuous performance test after one year taking methylphenidate; additionally, participants improved on self-reported attentional skills, and parent-reported social skills and behavioural problems (Conklin et al., 2010). A systematic literature review suggested that behavioural outcomes are favourable for pediatric cancer survivors trialing stimulant mediation, particularly for males, individuals treated for cancer at an older age, and those with higher IQ (Smithson, Phillips, Harvey, & Morrall, 2013).

Contribution to the Field

Study 1 was intended to expand upon the work of Precourt et al. (2002). By including males in the sample, I was able to compare sex effects and found that girls treated for ALL were more distractible than boys treated for ALL. Additionally, I tested two mediation models to further understand the nature of the relationships between CVLT-C and WISC-III variables and the effect of pediatric ALL treatment. These

models suggested that the impact of treatment on short-term memory deficits may impact long-term memory in verbal learning, and this relationship was most evident for participants who relied on a serial recall strategy. Notwithstanding, Study 1 included a small sample and many comparisons were carried out; as such, the results should be interpreted with caution.

I analysed the same sample used in Study 2a in my Master's thesis (Aronovitch, 2012). For my doctoral dissertation, the data were completely re-coded and re-analysed, and additional predictive and outcome variables were added. Namely, learning strategies variables were added to explore any differences in the use of serial or semantic associations, and the addition of total glucocorticoid dose as a predictive variable represents a novel addition to the literature. Study 2a also contributed to the literature by exploring predictive risk factors of cognitive change over time, whereas most studies are cross-sectional. Study 2b was the first longitudinal study of ERP variables over time in pediatric ALL survivors, and added to the literature by contributing knowledge about development and change in psychophysiological markers of cognitive function (i.e. information processing) during and following treatment. Study 2 is also notable for its relatively salient findings with respect to the effect of glucocorticoid type and dose, seemingly over the use of cranial radiation. Historically, the effects of radiation were much more pronounced than the effects of chemotherapy. The findings of Study 2 may suggest that refinements to treatment protocols have been effective in reducing radiation-related adverse effects, though further research and follow-up would be needed to confirm these results.

It is important to note that Study 1, Study 2a, and Study 2b were based on archival data that was collected over two decades ago. However, as noted previously, glucocorticoids are still a cornerstone of ALL treatment, and these results may be useful in furthering the understanding of the effect of ALL treatment on neurocognitive function. Cranial radiation continues to be administered to a minority of patients, though in lower doses. Importantly, given the limitations of my thesis, these results should not be taken on their own to inform decisions around treatment.

Limitations of the Current Project

In the current project, radiation dose, chemotherapy protocol, and glucocorticoid dose were not randomized, but assigned based on risk classification, which took into account variables such as disease severity and age at diagnosis. Consequently, participants in the high-risk group were, on average, older at diagnosis, and therefore it was not feasible to completely control for the potential effects of risk classification or age at diagnosis. Of note, participants were randomized within risk groups. Age-normed scores were used where possible, though some independent effects may not be entirely accounted for. The absence of a randomized control design and confound with disease characteristics limits the ability to make definitive conclusions relating to the causal role of treatment in neurocognitive deficits. While this type of confound is common within the psycho-oncology literature and is a general limitation of research with clinical populations, it is important to highlight and to refrain from making definitive causal inferences based on the results of this project.

The data used in this study were collected between 1993 and 2004. Since that time, treatment protocols have been updated, and future protocols may continue to shift

more significantly towards personalized medicine (e.g. pharmacogenetics) and the use of newer medications, and medications at different doses or in different combinations. Notwithstanding, radiation and chemotherapy remain the most common treatments for childhood cancers. For the participants included in my study, chemotherapy was administered as total therapy (i.e. in four phases), which remains the standard. Radiation is less commonly used to treat leukemia, but is frequently administered at high doses to patients with brain tumours. Glucocorticoids, such as dexamethasone and prednisone, are still routinely administered and considered a key component of chemotherapy protocols. It is important to continue to track participants following the administration of these treatments and to monitor them for potential adverse effects on specific cognitive outcomes, especially as survivorship rates increase.

In my thesis, participant follow-up only extended until approximately four years post-diagnosis. Previous research has demonstrated that neuropsychological function in childhood cancer survivors tends to decline over time from diagnosis (Espy et al., 2001). Although many of my results supported this finding, many did not, and it is possible that some effects do not emerge until beyond four years post-treatment while other effects resolve after a number of years. Notwithstanding, based on the results of my thesis, a four-year follow-up was a sufficient timeframe to detect certain effects (e.g. effects of total glucocorticoid dose), though possibly not others (e.g. long-term effects on learning strategies).

There were several important limitations of my thesis relating to group size within and between studies. Study 1 employed a relatively small sample, which limited the power and scope of the analysis. For example, I was not able to compare chemotherapy

protocols by group or to compare any treatment-related factors. Across all samples, there was insufficient data to analyse varying doses of methotrexate, which is an important chemotherapeutic agent and may account for some differences in neurocognitive function between patients. Additionally, I performed a great number of comparisons relative to the sample size. While I corrected for multiple comparisons using the Benjamini-Hochberg False Discovery Rate adjustment, it is still possible that some results presented are spurious, and should be interpreted with caution.

In Study 2a and 2b, the sample size varied by time point, and group size at certain time points was relatively small. There was substantial variability in group size between variables in Study 2a and 2b. For example, in Study 2a, 34 participants had data for maternal family well-being scores at diagnosis (of a possible $n = 107$, representing a 30% response rate); in Study 2b, 97 participants had data for maternal family well-being scores at diagnosis (of a possible $n = 113$, representing an 86% response rate). In Study 2a, 28 participants had data for paternal family well-being scores at diagnosis (i.e. 26% response rate); in Study 2b, 63 participants had data for paternal family well-being scores at diagnosis (i.e. 56% response rate). Differences between group sizes were much smaller for parental family well-being at three months post-diagnosis. As with other missing data in Study 2, the difference between group sizes may be attributed to logistical factors, such as parental availability. This variability in group size somewhat limits the comparability of variables, though the use of MLM would account for some of the effects of missing data.

In the current project, Study 1 used a cross-sectional design, whereas Study 2a and 2b utilized a longitudinal design. In the cross-sectional study, a control group was

included to help illustrate treatment-related differences between participants and groups. In the longitudinal studies, with measurements taken at baseline, each participant's baseline is conceptualized as a reference point to which subsequent measurements are compared.

Future Directions

Future research projects should continue to carefully monitor survivors of childhood cancer for the persistence or amelioration of adverse effects, as findings have indicated that neurocognitive deficits are an ongoing concern for adult survivors of childhood cancer. In the St. Jude Lifetime Cohort Study, after 10 years' survival, 48% of patients presented with some degree of neurocognitive impairment. The most commonly impacted functions were mathematical ability, memory, and processing speed (Hudson et al., 2013). For this reason, continued monitoring of pediatric cancer survivors, including those in my thesis, is imperative. At this time, a 20-year follow-up project that includes the same participants from Study 2 of my thesis is underway at Ste-Justine Hospital in Montreal, Quebec. This long-term follow up study utilizes technologies, such as magnetoencephalography (MEG) and magnetic resonance imaging (MRI). The project will provide further insight as to the evolution of the effects detected in my thesis over a greater period of time.

Childhood cancer treatment protocols are regularly revised, and researchers will continue to assess the acute, chronic, and late effects associated with existing and new treatments. New therapies, such as immunotherapy, and new chemotherapeutic agents are being introduced with promising results. For example, pegylated asparaginase is associated with fewer allergic reactions and has a long-half life, and liposomal

danorubicin and liposomal vincristine are associated with reduced risk for cardiotoxicity. Medications more often used in adult treatment protocols, such as bortezomib, are also being investigated for their potential use in the pediatric population (Saletta, Seng, & Lau, 2014). Further developments in chemotherapy protocols may continue to reduce the need for radiation, which would eliminate some of the most historically cited adverse effects associated with cancer treatment.

Going forward, researchers might also focus on better understanding some of the inter-individual variables associated with neurocognitive outcome. For example, researchers should examine sex differences in children using ERPs, which may further illuminate the lack of sex differences detected in Study 2b of my thesis. ERP-related sex differences in children treated for cancer and healthy children could be compared and contrasted. Additional investigation is also warranted as to whether the effects of parental well-being are short-lasting, as has been suggested in previous studies. For example, a meta-analysis of pediatric oncology studies which measured parental psychological stress indicated that parents tend to experience intense feelings of stress at the time of diagnosis. Though these feelings often lessen over the first year from diagnosis, a subset of parents continued to experience elevated feelings of anxiety at five years post-diagnosis. Risk factors for these elevated and prolonged levels of stress and anxiety were identified as a high level of emotional distress (relative to other parents) at diagnosis, lower levels of education, and a lower socioeconomic status. Protective factors were also identified, and included adaptive coping strategies, high levels of social support, and stable family functioning (Vrijmoet-Wiersma et al., 2008). Future research should be aimed at identifying not just risk factors for neurocognitive deficits following treatment

for pediatric cancer, but also protective factors, such as high IQ or giftedness, low total glucocorticoid dose, avoidance of radiation, and avoidance of prophylactic treatments.

As support and intervention for pediatric cancer survivors continues to be developed and implemented, researchers should consider whether improvements following the implementation of these programs is influenced by the presence or absence of the same treatment-related and inter-individual risk factors considered in my thesis (e.g. whether one sex benefits from these programs more than the other). Questions might also be raised with respect to whether these programs are still effective for patients who receive the most aggressive treatments or who are likely to be the most vulnerable to treatment-related effects (e.g. younger age at diagnosis).

Conclusion

Overall, the results of my thesis suggested that individuals treated for pediatric ALL are at a significant risk of developing adverse effects associated with treatment-related toxicity and interindividual factors. Some effects persisted for up to approximately four years post-treatment, and were detectable on a verbal learning and memory measure, as well as by ERPs elicited by a visual oddball task. Study 1 used a small, but well-controlled retrospective cohort in a cross-sectional design, and tested short-term memory as a mediator of the use of learning strategies. In order to address the limitations of a cross-sectional design, Study 2a and Study 2b used a prospective, randomized controlled study design. A major strength of this project was the multimodal approach taken towards the exploration of neuropsychological performance in survivors of pediatric ALL. This type of mixed methods design provides a high degree of reliability in conclusions where similar findings are reported from an array of assessment

modalities, as the probability of chance findings is diminished. Several effects emerged across studies (e.g. treatment-related effects), providing strong evidence that childhood cancer survivors remain at risk for developing adverse effects associated with treatment-related and inter-individual factors.

My thesis is unique in its inclusion of total glucocorticoid dose as a predictive risk factor for change to neurocognitive function, and for the longitudinal exploration of ERP components in a sample of pediatric cancer survivors. The results suggested that the use of glucocorticoids continues to negatively impact verbal learning, episodic memory, and information processing in this population, and highlights the importance of long-term monitoring of survivors. ERPs may be a useful tool for clinicians and researchers to identify patients most at-risk of developing impairments and for tracking change in neurocognitive function over time. They are relatively inexpensive and quick to administer, though they do require a designated space and specialized equipment, and assessors would require appropriate training.

The concerns noted in the limitations section relating to study design and age of the data might raise doubts about the dependability and relevance of the data to today's pediatric cancer patient. It is possible that many, if not most, of the results reported herein are false positives or anomalies, and caution is advised in the interpretation of the results of this project. These results should not be used to inform treatment decisions, but instead may guide future research towards furthering our understanding of the nature and emergence of adverse effects to neurocognitive function following treatment for pediatric cancer, particularly with respect to the usability of ERPs as an assessment tool in clinical and research settings.

Oncologists continue to be faced with the responsibility of selecting treatment protocols to maximize survivorship, while minimizing adverse effects in the growing cohort of childhood cancer survivors. Given the potentially subtle nature of the impact of treatment-related and interindividual risk factors to neurocognitive function, my thesis highlights the importance of specific and directed neurocognitive follow-up, as well as early intervention for survivors of childhood cancer. Though typically subtle, some deficits have been shown to be long-lasting and have the potential to impair academic achievement, family functioning, mental health, and other meaningful outcomes. Furthering our understanding of the potential for the development of these deficits, as well as their severity and duration will benefit patients currently receiving treatment, as well as those who will undergo treatment in the future, their families, educators, and communities.

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Appendix A

Carleton University Review Ethics Board-B Approval

Office of Research Ethics
503 Robertson Hall | 1125 Colonel By Drive
Ottawa, Ontario K1S 5B6
613-520-2600 Ext: 4085
ethics@carleton.ca

CERTIFICATION OF INSTITUTIONAL ETHICS CLEARANCE

The Carleton University Research Ethics Board-B (CUREB-B) has granted ethics clearance for the research project described below and research may now proceed. CUREB-B is constituted and operates in compliance with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS2).

Ethics Protocol Clearance ID: Project # 111344

Research Team: Ms. Blair Aronovitch (Primary Investigator)
Michael Wohl (Co-Investigator)
Dr. Philippe Robaey (Co-Investigator)

Project Title: A multi-method study of neuropsychological functioning following treatment for pediatric acute lymphoblastic leukemia (ALL)

Funding Source (If applicable):

Effective: **September 04, 2019** Expires: **September 30, 2020.**

Please ensure the study clearance number is prominently placed in all recruitment and consent materials: CUREB-B Clearance # 111344.

Restrictions:

This certification is subject to the following conditions:

1. Clearance is granted only for the research and purposes described in the application.
2. Any modification to the approved research must be submitted to CUREB-B via a Change to Protocol Form. All changes must be cleared prior to the continuance of the research.
3. An Annual Status Report for the renewal of ethics clearance must be submitted and cleared by the renewal date listed above. Failure to submit the Annual Status Report will result in the closure of the file.If funding is associated, funds will be frozen.
4. A closure request must be sent to CUREB-B when the research is complete or terminated.
5. During the course of the study, if you encounter an adverse event, material incidental finding, protocol deviation or other unanticipated problem, you must complete and submit a Report of

Adverse Events and Unanticipated Problems Form, found here:
https://carleton.ca/researchethics/forms-and-templates/

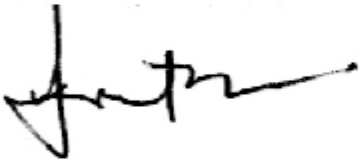
Failure to conduct the research in accordance with the principles of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 2ndedition* and the *Carleton University Policies and Procedures for the Ethical Conduct of Research* may result in the suspension or termination of the research project.

Upon reasonable request, it is the policy of CUREB, for cleared protocols, to release the name of the PI, the title of the project, and the date of clearance and any renewal(s).

Please contact the Research Compliance Coordinators, at ethics@carleton.ca, if you have any questions.

CLEARED BY: **Date: September 04, 2019**

Natasha Artemeva, PhD, Chair, CUREB-B



Janet Mantler, PhD, Vice-Chair, CUREB-B

Appendix B

Review Ethics Board Approval from St. Justine Hospital (Study 2a & 2b)

Le 27 février, 2004

Dr Philippe Robaey
Psychophysiologie
Étage A Bloc 8

CENTRE
DE RECHERCHE
DE L'HÔPITAL
SAINTE-JUSTINE
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

OBJET: Titre du projet: FUNCTIONAL, ANATOMICAL AND NEUROPSYCHOLOGICAL BRAIN TOXICITY AFTER CRANIAI RADIATION THERAPY IN CHILDHOOD LEUKEMIA.

Responsables du projet: Philippe Robaey M.D., Jean-Claude Décarie, M.D., Albert Moghrabi, M.D., Yves Théorêt, Ph.D., Mulherm Raymond, Ph.D., W.E. Reddick, M.D. et Véronique Bohbot, Ph.D.

Cher Docteur,

Les membres du Comité d'éthique de la recherche ont examiné votre demande de renouvellement du projet cité en rubrique à leur réunion du 26 février dernier.

Afin de renouveler votre projet, nous vous demandons de répondre, avant le 17 mars prochain, aux commentaires ci-joints du Comité.

Recevez, Cher Docteur, nos salutations distinguées.

Jean-Marie Therrien, Ph.D., éthicien
Président du Comité d'éthique de la recherche

JMT/ic

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Appendix C

Study 2a Fixed Effects Tables

Fixed effects for model predicting recall consistency

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	.26(.07)***
Level 1	
Time (years)	09(.04)*
Level 2	
Cranial Radiation Therapy	-.03(.34)
Sex	.23(.27)
Glucocorticoid Dose	< .00(<.00)
Days in Hospital	-.65(.39)
Chemotherapy Protocol	.09(.31)
Age at Diagnosis	.01(.04)
Family Well-Being, Maternal, Diagnosis	.02(.26)
Family Well-Being, Paternal, Diagnosis	.22(.21)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	.13(.23)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	.31(.07)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-.03(.09)
Time x Sex	-.03(.08)
Time x Glucocorticoid Dose	< .00(< .00)
Time x Days in Hospital	.13(.09)
Time x Chemotherapy Protocol	.04(.09)
Time x Age at Diagnosis	< .00(.01)
Time x Family Well-Being, Maternal, Diagnosis	< .00 (.10)
Time x Family Well-Being, Paternal, Diagnosis	-.08(.11)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.03(.07)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.11(.07)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting perseverations

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	.03(.07)
Level 1	
Time (years)	.08(.03)**
Level 2	
Cranial Radiation Therapy	.02(.31)

Sex	.01(.25)
Glucocorticoid Dose	< .00(< .00)**
Days in Hospital	-.02(.02)
Chemotherapy Protocol	.58(.26)**
Age at Diagnosis	.05(.03)
Family Well-Being, Maternal, Diagnosis	.24(.26)
Family Well-Being, Paternal, Diagnosis	.21(.28)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.07(.22)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.04(.25)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.05(.09)
Time x Sex	-.04(.08)
Time x Glucocorticoid Dose	< .00(< .00)*
Time x Days in Hospital	.01(.00)
Time x Chemotherapy Protocol	-.19(.08)**
Time x Age at Diagnosis	-.02(.01)**
Time x Family Well-Being, Maternal, Diagnosis	.03(.08)
Time x Family Well-Being, Paternal, Diagnosis	.03(08)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.02(.07)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.08(.08)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting intrusions (free recall trial)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-.30(.05)***
Level 1	
Time (years)	.05(.02)**
Level 2	
Cranial Radiation Therapy	.21(.15)
Sex	.11(.12)
Glucocorticoid Dose	< .00(< .00)
Days in Hospital	-.01(.01)
Chemotherapy Protocol	.15(.14)
Age at Diagnosis	.03(.02)
Family Well-Being, Maternal, Diagnosis	.03(.15)
Family Well-Being, Paternal, Diagnosis	.41(.14)**
Family Well-Being, Maternal, 3 Months Post-Diagnosis	.27(.12)**
Family Well-Being, Paternal, 3 Months Post-Diagnosis	.19(.15)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.02(.05)
Time x Sex	-.11(.04)***
Time x Glucocorticoid Dose	< .00(<.00)

Time x Days in Hospital	< .00(< .00)
Time x Chemotherapy Protocol	-.07(.05)
Time x Age at Diagnosis	< .00 (.01)
Time x Family Well-Being, Maternal, Diagnosis	-.04(.05)
Time x Family Well-Being, Paternal, Diagnosis	-.14(.05)***
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.10(.04)***
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.04(.04)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting intrusions (cued recall trial)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-.65(.05)***
Level 1	
Time (years)	.07(.03)**
Level 2	
Cranial Radiation Therapy	.21(.14)
Sex	.25(.14)*
Glucocorticoid Dose	< .00(< .00)
Days in Hospital	.02(.01)**
Chemotherapy Protocol	.12(.16)
Age at Diagnosis	.03(.02)*
Family Well-Being, Maternal, Diagnosis	.09(.18)
Family Well-Being, Paternal, Diagnosis	.06(.19)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	.08(.11)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	.08(.15)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.04(.07)
Time x Sex	-.14(.06)**
Time x Glucocorticoid Dose	< .00(< .00)
Time x Days in Hospital	-.01(< .00)*
Time x Chemotherapy Protocol	-.10(.07)
Time x Age at Diagnosis	<.00(.01)
Time x Family Well-Being, Maternal, Diagnosis	-.06(.08)
Time x Family Well-Being, Paternal, Diagnosis	.03(.09)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.08(.04)*
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.05(05)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting words recalled from the primacy region of List A

Parameter	Estimate

	(Standard Error)
Fixed Effects	
Intercept	.13(.06)**
Level 1	
Time (years)	.01(.04)
Level 2	
Cranial Radiation Therapy	-.23(.28)
Sex	.23(.23)
Glucocorticoid Dose	< .00(< .00)
Days in Hospital	.02(.02)
Chemotherapy Protocol	.10(.27)
Age at Diagnosis	-.06(.03)**
Family Well-Being, Maternal, Diagnosis	.27(.21)
Family Well-Being, Paternal, Diagnosis	.25(.20)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.01(.16)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	.18(.19)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.02(.08)
Time x Sex	-.05(.07)
Time x Glucocorticoid Dose	< .00(< .00)**
Time x Days in Hospital	-.00(< .00)
Time x Chemotherapy Protocol	-.07(.08)
Time x Age at Diagnosis	< .00(< .00)
Time x Family Well-Being, Maternal, Diagnosis	-.09(.07)
Time x Family Well-Being, Paternal, Diagnosis	-.09(.07)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.01(.05)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.10(.06)*

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting words recalled from the middle region of List A

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	.06(.05)
Level 1	
Time (years)	-.06(.03)*
Level 2	
Cranial Radiation Therapy	.20(.27)
Sex	-.25(.21)
Glucocorticoid Dose	< .00(< .00)
Days in Hospital	-.02(.02)
Chemotherapy Protocol	-.35(.24)
Age at Diagnosis	-.01(.03)
Family Well-Being, Maternal, Diagnosis	-.19(.24)

Family Well-Being, Paternal, Diagnosis	.33(.24)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	.07(.15)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	.22(.17)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-.92(.08)
Time x Sex	.08(.06)
Time x Glucocorticoid Dose	< .00(< .00)
Time x Days in Hospital	.00(.00)
Time x Chemotherapy Protocol	.06(.07)
Time x Age at Diagnosis	-.00(.01)
Time x Family Well-Being, Maternal, Diagnosis	.08(.08)
Time x Family Well-Being, Paternal, Diagnosis	-.01(.09)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.01(.05)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.07(.06)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting words recalled from the recency region of List A

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-.27(.05)***
Level 1	
Time (years)	.07(.03)**
Level 2	
Cranial Radiation Therapy	.14(27)
Sex	-.03(.22)
Glucocorticoid Dose	< .00(< .00)
Days in Hospital	.00(.02)
Chemotherapy Protocol	.10(.25)
Age at Diagnosis	.05(.03)*
Family Well-Being, Maternal, Diagnosis	-.09(.16)
Family Well-Being, Paternal, Diagnosis	-.52(.22)**
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.13(.17)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.41(.19)**
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.03(.08)
Time x Sex	-.01(.07)
Time x Glucocorticoid Dose	< .00(< .00)
Time x Days in Hospital	-.00(<.00)
Time x Chemotherapy Protocol	.03(.07)
Time x Age at Diagnosis	-.00(.01)
Time x Family Well-Being, Maternal, Diagnosis	.05(.05)
Time x Family Well-Being, Paternal, Diagnosis	.13(.07)*
Time x Family Well-Being, Maternal, 3 Months Post-	.02(.06)

Diagnosis	
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.16(.06)**

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting scaled semantic ratio

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-3.14(.03)***
Level 1	
Time (years)	.00(.01)
Level 2	
Cranial Radiation Therapy	-.06(.11)
Sex	-.02(.10)
Glucocorticoid Dose	-.00(< .00)***
Days in Hospital	<.00(.00)
Chemotherapy Protocol	.14(.11)
Age at Diagnosis	-.05(.01)***
Family Well-Being, Maternal, Diagnosis	.06(.11)
Family Well-Being, Paternal, Diagnosis	-.07(.10)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.04(.07)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.11(.09)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-.01(.03)
Time x Sex	.00(.03)
Time x Glucocorticoid Dose	< .00(< .00)
Time x Days in Hospital	<-.00(.00)
Time x Chemotherapy Protocol	-.05(.03)
Time x Age at Diagnosis	-.00(.00)
Time x Family Well-Being, Maternal, Diagnosis	-.03(.03)
Time x Family Well-Being, Paternal, Diagnosis	.00(.03)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.01(.02)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.02(.03)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting scaled serial ratio

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	.08(.42)
Level 1	
Time (years)	-.06(.07)
Level 2	

Cranial Radiation Therapy	-.16(.60)
Sex	.06(.49)
Glucocorticoid Dose	< .00(.00)
Days in Hospital	-.02(.03)
Chemotherapy Protocol	.18(.50)
Age at Diagnosis	-.04(.06)
Family Well-Being, Maternal, Diagnosis	.59(.41)
Family Well-Being, Paternal, Diagnosis	-.21(.50)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.08(.35)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.34(.39)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-.01(.17)
Time x Sex	.02(.15)
Time x Glucocorticoid Dose	< .00(< .00)
Time x Days in Hospital	<.00(.00)
Time x Chemotherapy Protocol	.02(.15)
Time x Age at Diagnosis	-.01(.02)
Time x Family Well-Being, Maternal, Diagnosis	.04(.15)
Time x Family Well-Being, Paternal, Diagnosis	.30(.18)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.14(.11)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.19(.14)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting number of words recalled on trials 1 to 5 (age-normed)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	55.66(.85)***
Level 1	
Time (years)	-1.26(.50)**
Level 2	
Cranial Radiation Therapy	-.31(3.96)
Sex	-3.79(3.14)
Glucocorticoid Dose	-.00(.00)**
Days in Hospital	-.34(.22)
Chemotherapy Protocol	-5.86(3.39)*
Age at Diagnosis	-.44(.41)
Family Well-Being, Maternal, Diagnosis	-3.05(3.17)
Family Well-Being, Paternal, Diagnosis	1.00(3.14)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	.86(2.60)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	2.76(2.88)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.35(1.19)
Time x Sex	1.78(.97)*

Time x Glucocorticoid Dose	.00(.00)***
Time x Days in Hospital	.09(.06)
Time x Chemotherapy Protocol	1.78(1.06)*
Time x Age at Diagnosis	.28(.13)**
Time x Family Well-Being, Maternal, Diagnosis	.54(1.32)
Time x Family Well-Being, Paternal, Diagnosis	-.74(1.13)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.31(.85)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-1.08(.98)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting learning slope

Parameter	Estimate (Standard Error)
Fixed effects	
Intercept	.97(.05)***
Level 1	
Time (years)	.01(.03)
Level 2	
Cranial Radiation Therapy	-.00(.22)
Sex	-.02(.19)
Glucocorticoid Dose	< .00(< .00)
Days in Hospital	.03(.01)**
Chemotherapy Protocol	.06(.22)
Age at Diagnosis	-.00(.02)
Family Well-Being, Maternal, Diagnosis	.51(.19)***
Family Well-Being, Paternal, Diagnosis	.07(.18)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	.07(.12)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	.32(.11)***
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-.03(.06)
Time x Sex	.02(.05)
Time x Glucocorticoid Dose	< .00(< .00)
Time x Days in Hospital	-.01(.00)**
Time x Chemotherapy Protocol	.22(.06)
Time x Age at Diagnosis	-.0(.01)
Time x Family Well-Being, Maternal, Diagnosis	-.08(.07)
Time x Family Well-Being, Paternal, Diagnosis	.08(.07)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.00(.04)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.06(.04)
Random effects	
Within-person variability	

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting number of words recalled on Trial 1

Parameter	Estimate (Standard Error)
Fixed effects	
Intercept	.67(.09)***
Level 1	
Time (years)	-.08(.05)
Level 2	
Cranial Radiation Therapy	-.03(.41)
Sex	.08(.34)
Glucocorticoid Dose	-.00(.00)
Days in Hospital	-.02(.02)
Chemotherapy Protocol	-.89(.36)
Age at Diagnosis	.03(.04)
Family Well-Being, Maternal, Diagnosis	-.79(.36)
Family Well-Being, Paternal, Diagnosis	-.24(.39)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	.02(.27)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	.19(.31)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.04(.13)
Time x Sex	.02(.11)
Time x Glucocorticoid Dose	.00(< .00)
Time x Days in Hospital	.01(.01)
Time x Chemotherapy Protocol	.29(.11)
Time x Age at Diagnosis	.01(.01)
Time x Family Well-Being, Maternal, Diagnosis	.15(.15)
Time x Family Well-Being, Paternal, Diagnosis	.05(.15)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.03(.09)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.10(.11)
Random effects	
Within-person variability	

*p < .10, **p < .05, ***p < .01

Appendix D

Event-Related Potentials

Event-related potentials (ERPs) were developed to explore the neurobiological basis of cognitive processing, and have been used in practice for more than 50 years (Pearlstein, Whitten, & Haerich, 2006). ERPs are derived from an electroencephalogram (EEG), which is produced by electrodes that are applied to the scalp in specific locations based on the International 10-20 system. The ERP components of the EEG are those which are specifically tied to a time-locked stimulus. Since ERPs are relatively small in comparison to the full array of EEG activity, a signal-averaging process is applied to the raw EEG data in order to isolate electrical activity elicited by the stimuli, and to cut out information that is either irrelevant or produced by non-neural sources (e.g., eye blinks, muscle movement).

Electrical activity from the brain can be divided into brainwaves based on bandwidths measured in hertz (Hz). Brainwave activity changes with age and development. In children, ERPs tend to be dominated by slow waves such as delta (.1 – 4 Hz) and theta (4 – 7 Hz), and the amplitude of these waves typically declines with time. Higher cognitive processes, such as memory and attention, are often correlated with theta activity. Alpha waves (8 – 15 Hz) are associated with memory, motor behaviour, and primary sensory processing. Peak alpha amplitude occurs around 10 or 11 years of age, and declines into adulthood. Gamma waves (30 – 70 Hz) are associated with basic brain functions, like conscious perception, and attention and memory. There are few changes in gamma during development; this bandwidth is particularly stable between nine and 16 years of age (Yordanova & Kolev, 2008).

ERPs may be separated into components, which relate to various neuropsychological abilities, such as the P300, P600, and the N1[2]. The P300 component is the most extensively researched component (Key, Dove, & Maguire, 2005), and the most relevant to my thesis. The P300 (also called the 'P3'), can be further divided into the P3a, which is oriented towards the front of the scalp, and the P3b, which is oriented towards the posterior region (Friedman, Cycowicz, & Gaeta, 2001). This phenomenon, which is related to response to a novel event, is most commonly elicited with an auditory or visual oddball task. When a change occurs in an otherwise invariant environment (i.e. the 'oddball' stimulus is presented), the brain responds with a type of ERP signal called mismatch negativity at an average of 120 milliseconds after the event. If the event is sufficiently deviant, the mismatch negativity is then followed by the P300. The mechanism by which this occurs is not fully understood, but researchers theorize that the P300 occurs once the information is transferred from the mismatch negativity system to the frontal lobe, making the event accessible to consciousness and behavioural control (Friedman, Cycowicz, & Gaeta).

[2] For a full description of ERP components beyond the scope of this project, see Key, Dove, and Maguire (2005).

Appendix E

Study 2b Fixed Effects Tables

Fixed effects for model predicting P3b latency (P3 rare stimuli)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	475.66(6.99)***
Level 1	
Time (years)	-14.08(6.63)***
Age at assessment (years)	-17.64(1.84)***
Time x Age at assessment	1.71(.48)***
Level 2	
Cranial Radiation Therapy	-162.23(81.76)**
Sex	36.14(39.74)
Glucocorticoid Dose	.0004(.003)
Days in Hospital	6.54(2.66)**
Chemotherapy Protocol	86.62(38.15)**
Age at Diagnosis	2277.40(11814.00)
Family Well-Being, Maternal, Diagnosis	-19.92(32.71)
Family Well-Being, Paternal, Diagnosis	7.66(42.73)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-63.45(30.05)**
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-54.45(37.85)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	22.62(10.75)**
Time x Sex	4.55(12.26)
Time x Glucocorticoid Dose	-.002(.001)*
Time x Days in Hospital	-1.88(.82)**
Time x Chemotherapy Protocol	-34.17(10.76)***
Time x Age at Diagnosis	.24(1.67)
Time x Family Well-Being, Maternal, Diagnosis	8.44(8.85)
Time x Family Well-Being, Paternal, Diagnosis	4.01(12.82)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	16.33(10.02)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	14.93(11.72)
Age at assessment x Cranial Radiation Therapy	22.62(10.75)**
Age at assessment x Sex	-2.29(3.84)
Age at assessment x Glucocorticoid Dose	-.0003(.0003)
Age at assessment x Days in Hospital	-.48(.26)*
Age at assessment x Chemotherapy Protocol	-6.82(3.68)*
Age at assessment x Age at Diagnosis	2.12(.46)***
Age at assessment x Family Well-Being, Maternal, Diagnosis	2.73(3.16)
Age at assessment x Family Well-Being, Paternal, Diagnosis	-1.42(4.23)

Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	5.05(2.93)*
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	4.01(3.37)
Time x Age at assessment x Cranial Radiation Therapy	-3.71(2.94)
Time x Age at assessment x Sex	-.09(1.08)
Time x Age at assessment x Glucocorticoid Dose	.0001(6.7E-05)**
Time x Age at assessment x Days in Hospital	.14(.08)*
Time x Age at assessment x Chemotherapy Protocol	2.41(.90)***
Time x Age at assessment x Age at Diagnosis	-.31(.12)***
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	-.90(.71)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	-.12(1.22)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.98(.92)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-1.10(1.02)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b latency (P3 frequent stimuli)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	444.84(6.67)***
Level 1	
Time (years)	-8.74(5.81)
Age at assessment (years)	-14.29(1.78)***
Time x Age at assessment	1.15(.51)**
Level 2	
Cranial Radiation Therapy	29.20(77.69)
Sex	52.80(38.20)
Glucocorticoid Dose	.01(.003)**
Days in Hospital	2.03(2.67)
Chemotherapy Protocol	77.79(37.46)**
Age at Diagnosis	-154.02(11643.00)
Family Well-Being, Maternal, Diagnosis	-40.51(30.18)
Family Well-Being, Paternal, Diagnosis	-38.02(39.33)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-35.09(29.48)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-19.00(34.83)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-35.04(23.92)
Time x Sex	-5.59(12.25)
Time x Glucocorticoid Dose	-.003(.001)***
Time x Days in Hospital	-.52(.85)

Time x Chemotherapy Protocol	-27.87(11.30)**
Time x Age at Diagnosis	-2.08(1.76)
Time x Family Well-Being, Maternal, Diagnosis	9.01(7.94)
Time x Family Well-Being, Paternal, Diagnosis	18.63(11.33)*
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	4.11(8.55)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	1.21(9.46)
Age at assessment x Cranial Radiation Therapy	2.85(10.19)
Age at assessment x Sex	-4.47(3.71)
Age at assessment x Glucocorticoid Dose	-.001(.0003)*
Age at assessment x Days in Hospital	-.16(.26)
Age at assessment x Chemotherapy Protocol	-5.67(3.61)
Age at assessment x Age at Diagnosis	1.16(.45)***
Age at assessment x Family Well-Being, Maternal, Diagnosis	3.56(2.98)
Age at assessment x Family Well-Being, Paternal, Diagnosis	2.92(3.94)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	2.80(2.96)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.77(3.20)
Time x Age at assessment x Cranial Radiation Therapy	2.28(2.85)
Time x Age at assessment x Sex	.73(1.08)
Time x Age at assessment x Glucocorticoid Dose	.0002(.0001)***
Time x Age at assessment x Days in Hospital	.06(.08)
Time x Age at assessment x Chemotherapy Protocol	1.80(.96)*
Time x Age at assessment x Age at Diagnosis	-.02(.13)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	-.08(.62)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	-1.65(1.07)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.17(.78)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.05(.83)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b latency (P4 rare stimuli)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	468.43(6.93)***
Level 1	
Time (years)	-7.67(4.32)*
Age at assessment (years)	-16.27(1.66)***
Time x Age at assessment	1.20(.35)***
Level 2	

Cranial Radiation Therapy	-120.50(70.08)*
Sex	57.98(35.24)
Glucocorticoid Dose	.003(.003)
Days in Hospital	6.73(2.25)***
Chemotherapy Protocol	52.54(35.17)
Age at Diagnosis	3076.13(10294.00)
Family Well-Being, Maternal, Diagnosis	1.15(27.92)
Family Well-Being, Paternal, Diagnosis	12.92(35.33)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-33.35(28.94)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-11.53(34.35)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	8.46(20.36)
Time x Sex	-1.92(9.89)
Time x Glucocorticoid Dose	-.001(.001)
Time x Days in Hospital	-1.64(.82)**
Time x Chemotherapy Protocol	-27.04(9.05)***
Time x Age at Diagnosis	-.65(1.35)
Time x Family Well-Being, Maternal, Diagnosis	.14(6.83)
Time x Family Well-Being, Paternal, Diagnosis	1.36(9.86)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	5.24(8.26)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-1.01(9.44)
Age at assessment x Cranial Radiation Therapy	19.49(9.42)***
Age at assessment x Sex	-4.73(3.49)
Age at assessment x Glucocorticoid Dose	-.0003(.0003)
Age at assessment x Days in Hospital	-.49(.21)**
Age at assessment x Chemotherapy Protocol	-4.89(3.49)
Age at assessment x Age at Diagnosis	1.62(.41)***
Age at assessment x Family Well-Being, Maternal, Diagnosis	1.15(2.81)
Age at assessment x Family Well-Being, Paternal, Diagnosis	1.46(2.22)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	3.03(2.94)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.91(3.14)
Time x Age at assessment x Cranial Radiation Therapy	-.22(2.43)
Time x Age at assessment x Sex	.63(.85)
Time x Age at assessment x Glucocorticoid Dose	7.9E-05(5.7E-05)
Time x Age at assessment x Days in Hospital	.12(.08)
Time x Age at assessment x Chemotherapy Protocol	1.94(.75)***
Time x Age at assessment x Age at Diagnosis	-.14(.10)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	-.25(.52)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	-.17(.92)

Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.24(.75)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.09(.83)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b latency (P4 frequent stimuli)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	451.48(6.79)***
Level 1	
Time (years)	-9.37(5.71)*
Age at assessment (years)	-15.47(1.86)***
Time x Age at assessment	1.23(.50)**
Level 2	
Cranial Radiation Therapy	-1.90(79.40)
Sex	55.84(39.80)
Glucocorticoid Dose	.01(.003)***
Days in Hospital	1.85(2.75)
Chemotherapy Protocol	68.83(39.77)*
Age at Diagnosis	-551.89(12169)
Family Well-Being, Maternal, Diagnosis	-33.43(30.45)
Family Well-Being, Paternal, Diagnosis	-40.99(39.64)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-34.40(29.75)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-23.56(36.25)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-27.10(23.94)
Time x Sex	-9.47(12.02)
Time x Glucocorticoid Dose	-.003(.001)***
Time x Days in Hospital	-.37(.85)
Time x Chemotherapy Protocol	-30.98(11.16)***
Time x Age at Diagnosis	-1.93(1.73)
Time x Family Well-Being, Maternal, Diagnosis	6.47(7.55)
Time x Family Well-Being, Paternal, Diagnosis	16.58(11.38)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	2.51(8.72)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	1.62(10.22)
Age at assessment x Cranial Radiation Therapy	7.97(10.43)
Age at assessment x Sex	-5.37(3.88)
Age at assessment x Glucocorticoid Dose	-.001(.0003)*
Age at assessment x Days in Hospital	-.17(.27)
Age at assessment x Chemotherapy Protocol	-5.56(3.85)
Age at assessment x Age at Diagnosis	1.23(.47)***
Age at assessment x Family Well-Being, Maternal, Diagnosis	3.50(3.02)

Age at assessment x Family Well-Being, Paternal, Diagnosis	3.49(3.94)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	2.97(2.97)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	1.37(3.28)
Time x Age at assessment x Cranial Radiation Therapy	1.19(2.87)
Time x Age at assessment x Sex	1.34(1.06)
Time x Age at assessment x Glucocorticoid Dose	.0002(7.2E-05)***
Time x Age at assessment x Days in Hospital	.04(.08)
Time x Age at assessment x Chemotherapy Protocol	2.32(.96)**
Time x Age at assessment x Age at Diagnosis	-.02(.13)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	-.77(.57)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	-1.52(1.07)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.0004(.79)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.06(.90)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b latency (P3 difference)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	27.84(3.69)***
Level 1	
Time (years)	-2.54(5.01)
Age at assessment (years)	-2.70(1.55)*
Time x Age at assessment	.41(.42)
Level 2	
Cranial Radiation Therapy	-182.94(77.83)**
Sex	-3.33(36.00)
Glucocorticoid Dose	-.002(.003)
Days in Hospital	3.74(2.57)
Chemotherapy Protocol	20.55(36.43)
Age at Diagnosis	4347.07(11653.00)
Family Well-Being, Maternal, Diagnosis	10.77(28.26)
Family Well-Being, Paternal, Diagnosis	53.48(36.18)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-11.97(26.35)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-10.91(31.82)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	60.45(24.12)**
Time x Sex	8.54(11.46)
Time x Glucocorticoid Dose	.001(.001)

Time x Days in Hospital	-1.14(.85)
Time x Chemotherapy Protocol	-7.71(10.82)
Time x Age at Diagnosis	.70(1.59)
Time x Family Well-Being, Maternal, Diagnosis	1.35(8.34)
Time x Family Well-Being, Paternal, Diagnosis	-17.18(11.86)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	7.99(8.50)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	6.92(9.97)
Age at assessment x Cranial Radiation Therapy	18.34(9.89)*
Age at assessment x Sex	.99(3.38)
Age at assessment x Glucocorticoid Dose	2.7E-05(.0003)
Age at assessment x Days in Hospital	-.27(.24)
Age at assessment x Chemotherapy Protocol	-2.06(3.38)
Age at assessment x Age at Diagnosis	.61(.42)
Age at assessment x Family Well-Being, Maternal, Diagnosis	-.26(2.61)
Age at assessment x Family Well-Being, Paternal, Diagnosis	-5.03(3.52)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.99(2.52)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	1.01(2.79)
Time x Age at assessment x Cranial Radiation Therapy	-6.05(2.92)**
Time x Age at assessment x Sex	-.60(1.02)
Time x Age at assessment x Glucocorticoid Dose	-.00003(6.9E-05)
Time x Age at assessment x Days in Hospital	.07(.08)
Time x Age at assessment x Chemotherapy Protocol	.68(.92)
Time x Age at assessment x Age at Diagnosis	-.22(.12)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	-.16(.67)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	1.71(1.13)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.48(.79)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.56(.87)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b latency (P4 difference)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	16.52(3.50)***
Level 1	
Time (years)	4.32(4.67)
Age at assessment (years)	-.26(1.37)

Time x Age at assessment	-.09(.40)
Level 2	
Cranial Radiation Therapy	-121.40(69.73)*
Sex	6.65(31.05)
Glucocorticoid Dose	-.05(.003)*
Days in Hospital	3.28(2.32)
Chemotherapy Protocol	3.60(31.45)
Age at Diagnosis	5428.49(9975.42)
Family Well-Being, Maternal, Diagnosis	28.53(25.90)
Family Well-Being, Paternal, Diagnosis	60.24(32.07)*
Family Well-Being, Maternal, 3 Months Post-Diagnosis	7.26(23.38)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	27.49(28.47)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	37.39(21.41)*
Time x Sex	9.81(10.30)
Time x Glucocorticoid Dose	.002(.0008)**
Time x Days in Hospital	-.82(.74)
Time x Chemotherapy Protocol	-.14(9.80)
Time x Age at Diagnosis	-.24(1.46)
Time x Family Well-Being, Maternal, Diagnosis	-5.63(6.86)
Time x Family Well-Being, Paternal, Diagnosis	-17.48(9.96)*
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	1.64(7.46)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-6.47(9.05)
Age at assessment x Cranial Radiation Therapy	11.75(8.91)
Age at assessment x Sex	.31(2.92)
Age at assessment x Glucocorticoid Dose	.00002(.00002)
Age at assessment x Days in Hospital	-.23(.22)
Age at assessment x Chemotherapy Protocol	-.68(2.92)
Age at assessment x Age at Diagnosis	.08(.37)
Age at assessment x Family Well-Being, Maternal, Diagnosis	-1.93(2.42)
Age at assessment x Family Well-Being, Paternal, Diagnosis	-5.07(3.11)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.47(2.24)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-1.60(2.49)
Time x Age at assessment x Cranial Radiation Therapy	-3.60(2.59)
Time x Age at assessment x Sex	-.85(.92)
Time x Age at assessment x Glucocorticoid Dose	-.0001(.0001)
Time x Age at assessment x Days in Hospital	.05(.07)
Time x Age at assessment x Chemotherapy Protocol	-.13(.84)
Time x Age at assessment x Age at Diagnosis	-.04(.11)
Time x Age at assessment x Family Well-Being,	.51(.53)

Maternal, Diagnosis	
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	1.52(.94)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.13(.69)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.30(.79)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b amplitude (P3 rare stimuli)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-25.26(.70)***
Level 1	
Time (years)	.77(.82)
Age at assessment (years)	.19(.26)
Time x Age at assessment	-.02(.07)
Level 2	
Cranial Radiation Therapy	-10.40(10.98)
Sex	1.76(5.54)
Glucocorticoid Dose	-.0002(.0004)
Days in Hospital	.34(.39)
Chemotherapy Protocol	-3.50(5.52)
Age at Diagnosis	2425.90(1691.63)
Family Well-Being, Maternal, Diagnosis	-.73(4.08)
Family Well-Being, Paternal, Diagnosis	2.98(4.97)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.54(4.18)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-4.34(4.72)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	1.10(3.35)
Time x Sex	-.54(1.75)
Time x Glucocorticoid Dose	2.61E-06(.00001)
Time x Days in Hospital	-.07(.12)
Time x Chemotherapy Protocol	2.72(1.64)*
Time x Age at Diagnosis	-.28(.25)
Time x Family Well-Being, Maternal, Diagnosis	-1.19(1.15)
Time x Family Well-Being, Paternal, Diagnosis	-2.38(1.52)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-1.57(1.25)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-1.21(1.35)
Age at assessment x Cranial Radiation Therapy	1.70(1.44)
Age at assessment x Sex	-.39(.54)
Age at assessment x Glucocorticoid Dose	8.76E-06(.00004)
Age at assessment x Days in Hospital	-.02(.04)

Age at assessment x Chemotherapy Protocol	.12(.53)
Age at assessment x Age at Diagnosis	.003(.07)
Age at assessment x Family Well-Being, Maternal, Diagnosis	.25(.39)
Age at assessment x Family Well-Being, Paternal, Diagnosis	-.46(.49)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.05(.41)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.28(.43)
Time x Age at assessment x Cranial Radiation Therapy	-.33(.40)
Time x Age at assessment x Sex	.10(.16)
Time x Age at assessment x Glucocorticoid Dose	2.40E-06(8.76E-06)
Time x Age at assessment x Days in Hospital	.01(.01)
Time x Age at assessment x Chemotherapy Protocol	-.10(.14)
Time x Age at assessment x Age at Diagnosis	-.002(.02)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	.02(.09)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	.25(.14)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.09(.11)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.07(.12)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b amplitude (P3 frequent stimuli)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-15.45(.51)***
Level 1	
Time (years)	.26(.59)
Age at assessment (years)	-.03(.20)
Time x Age at assessment	-.003(.05)
Level 2	
Cranial Radiation Therapy	-6.18(7.18)
Sex	1.13(4.11)
Glucocorticoid Dose	-.0003(.0003)
Days in Hospital	-.15(.27)
Chemotherapy Protocol	3.13(4.22)
Age at Diagnosis	1816.36(1284.05)
Family Well-Being, Maternal, Diagnosis	-1.90(3.12)
Family Well-Being, Paternal, Diagnosis	3.11(3.84)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-2.37(2.99)

Family Well-Being, Paternal, 3 Months Post-Diagnosis	-2.85(3.42)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	1.43(2.26)
Time x Sex	.28(1.25)
Time x Glucocorticoid Dose	.0001(.0001)
Time x Days in Hospital	.05(.08)
Time x Chemotherapy Protocol	.19(1.23)
Time x Age at Diagnosis	-.07(.17)
Time x Family Well-Being, Maternal, Diagnosis	.56(.86)
Time x Family Well-Being, Paternal, Diagnosis	-1.46(1.09)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.73(.88)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.05(.96)
Age at assessment x Cranial Radiation Therapy	.85(1.01)
Age at assessment x Sex	-.27(.40)
Age at assessment x Glucocorticoid Dose	.00002(.00003)
Age at assessment x Days in Hospital	.03(.03)
Age at assessment x Chemotherapy Protocol	-.28(.41)
Age at assessment x Age at Diagnosis	-.02(.05)
Age at assessment x Family Well-Being, Maternal, Diagnosis	.11(.31)
Age at assessment x Family Well-Being, Paternal, Diagnosis	-.27(.39)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.19(.30)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.24(.31)
Time x Age at assessment x Cranial Radiation Therapy	-.27(.27)
Time x Age at assessment x Sex	.02(.11)
Time x Age at assessment x Glucocorticoid Dose	-6.12E-06(8.03E-06)
Time x Age at assessment x Days in Hospital	-.01(.01)
Time x Age at assessment x Chemotherapy Protocol	.01(.11)
Time x Age at assessment x Age at Diagnosis	-.01(.01)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	-.07(.07)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	.11(.11)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.08(.08)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.02(.08)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b amplitude (P4 rare stimuli)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-24.22(.69)***
Level 1	
Time (years)	.92(.82)
Age at assessment (years)	.07(.27)
Time x Age at assessment	-.03(.07)
Level 2	
Cranial Radiation Therapy	-7.59(10.90)
Sex	-2.99(5.77)
Glucocorticoid Dose	7.18E-06(.001)
Days in Hospital	.23(.39)
Chemotherapy Protocol	-3.20(5.85)
Age at Diagnosis	2127.34(1789.80)
Family Well-Being, Maternal, Diagnosis	.32(4.44)
Family Well-Being, Paternal, Diagnosis	-.08(5.19)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-1.20(4.36)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-9.30(4.94)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.15(3.25)
Time x Sex	.45(1.75)
Time x Glucocorticoid Dose	-.00003(.0001)
Time x Days in Hospital	-.04(.12)
Time x Chemotherapy Protocol	1.87(1.69)
Time x Age at Diagnosis	-.33(.24)
Time x Family Well-Being, Maternal, Diagnosis	-1.56(1.21)
Time x Family Well-Being, Paternal, Diagnosis	-1.49(1.52)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-1.16(1.27)
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.02(1.36)
Age at assessment x Cranial Radiation Therapy	.88(1.44)
Age at assessment x Sex	.06(.56)
Age at assessment x Glucocorticoid Dose	-.11(.15)
Age at assessment x Days in Hospital	-.01(.04)
Age at assessment x Chemotherapy Protocol	.20(.57)
Age at assessment x Age at Diagnosis	-.01(.07)
Age at assessment x Family Well-Being, Maternal, Diagnosis	.09(.43)
Age at assessment x Family Well-Being, Paternal, Diagnosis	-.19(.52)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.15(.43)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.61(.45)

Time x Age at assessment x Cranial Radiation Therapy	-.07(.39)
Time x Age at assessment x Sex	.01(.16)
Time x Age at assessment x Glucocorticoid Dose	6.24E-06(.00001)
Time x Age at assessment x Days in Hospital	<.00(.01)
Time x Age at assessment x Chemotherapy Protocol	-.08(.15)
Time x Age at assessment x Age at Diagnosis	.003(.02)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	.05(.10)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	.16(.14)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.03(.12)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.02(.12)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b amplitude (P4 frequent stimuli)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-17.96(.55)***
Level 1	
Time (years)	.84(.62)
Age at assessment (years)	.22(.21)
Time x Age at assessment	-.05(.06)
Level 2	
Cranial Radiation Therapy	-9.20(8.18)
Sex	-2.59(4.34)
Glucocorticoid Dose	-.0003(.0003)
Days in Hospital	-.20(.29)
Chemotherapy Protocol	-1.27(4.40)
Age at Diagnosis	2055.92(1344.19)
Family Well-Being, Maternal, Diagnosis	-2.26(3.25)
Family Well-Being, Paternal, Diagnosis	2.50(3.88)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	-4.02(3.22)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-6.43(3.52)*
Cross-Level Interaction	
Time x Cranial Radiation Therapy	.09(2.44)
Time x Sex	.67(1.31)
Time x Glucocorticoid Dose	-.04(.12)
Time x Days in Hospital	.04(.09)
Time x Chemotherapy Protocol	1.95(1.28)
Time x Age at Diagnosis	-.06(.18)
Time x Family Well-Being, Maternal, Diagnosis	.06(.89)
Time x Family Well-Being, Paternal, Diagnosis	-1.54(1.13)
Time x Family Well-Being, Maternal, 3 Months Post-	.67(.94)

Diagnosis	
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.57(.98)
Age at assessment x Cranial Radiation Therapy	1.31(1.08)
Age at assessment x Sex	.02(.43)
Age at assessment x Glucocorticoid Dose	.00003(.00003)
Age at assessment x Days in Hospital	.03(.03)
Age at assessment x Chemotherapy Protocol	-.01(.43)
Age at assessment x Age at Diagnosis	-.04(.05)
Age at assessment x Family Well-Being, Maternal, Diagnosis	.24(.32)
Age at assessment x Family Well-Being, Paternal, Diagnosis	-.24(.39)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.36(.32)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.55(.32)*
Time x Age at assessment x Cranial Radiation Therapy	-.16(.29)
Time x Age at assessment x Sex	-.01(.12)
Time x Age at assessment x Glucocorticoid Dose	5.19E-07(8.09E-07)
Time x Age at assessment x Days in Hospital	-.01(.01)
Time x Age at assessment x Chemotherapy Protocol	-.10(.11)
Time x Age at assessment x Age at Diagnosis	.002(.01)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	-.04(.07)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	-.07(.09)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.09(.09)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.55(.32)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b amplitude (P3 difference)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-10.11(.48)***
Level 1	
Time (years)	.55(.60)
Age at assessment (years)	.23(.20)
Time x Age at assessment	-.02(.05)
Level 2	
Cranial Radiation Therapy	-2.33(9.29)
Sex	1.52(4.43)
Glucocorticoid Dose	9.3E-05(.0003)

Days in Hospital	.53(.31)*
Chemotherapy Protocol	-7.14(4.36)*
Age at Diagnosis	736.40(1418.57)
Family Well-Being, Maternal, Diagnosis	1.06(3.36)
Family Well-Being, Paternal, Diagnosis	-1.42(4.08)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	2.85(3.17)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	.36(3.62)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-1.07(2.81)
Time x Sex	-.99(1.34)
Time x Glucocorticoid Dose	-.0001(9.5E-05)
Time x Days in Hospital	-.14(.10)
Time x Chemotherapy Protocol	2.56(1.25)**
Time x Age at Diagnosis	-.18(.19)
Time x Family Well-Being, Maternal, Diagnosis	-1.42(.89)
Time x Family Well-Being, Paternal, Diagnosis	-.54(1.25)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-2.52(1.00)**
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-1.74(1.11)
Age at assessment x Cranial Radiation Therapy	.55(1.19)
Age at assessment x Sex	-.18(.42)
Age at assessment x Glucocorticoid Dose	7.14E-06(.00003)
Age at assessment x Days in Hospital	-.05(.03)
Age at assessment x Chemotherapy Protocol	.50(.41)
Age at assessment x Age at Diagnosis	.03(.05)
Age at assessment x Family Well-Being, Maternal, Diagnosis	.17(.31)
Age at assessment x Family Well-Being, Paternal, Diagnosis	-.08(.40)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.23(.31)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.12(.32)
Time x Age at assessment x Cranial Radiation Therapy	.05(.34)
Time x Age at assessment x Sex	.09(.12)
Time x Age at assessment x Glucocorticoid Dose	6.88E-06(7.47E-06)
Time x Age at assessment x Days in Hospital	.01(.01)
Time x Age at assessment x Chemotherapy Protocol	-.13(.11)
Time x Age at assessment x Age at Diagnosis	.002(.02)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	.05(.07)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	.11(.12)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.20(.09)**

Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.13(.10)

*p < .10, **p < .05, ***p < .01

Fixed effects for model predicting P3b amplitude (P4 difference)

Parameter	Estimate (Standard Error)
Fixed Effects	
Intercept	-6.34(.43)***
Level 1	
Time (years)	.26(.51)
Age at assessment (years)	-.11(.17)
Time x Age at assessment	-.004(.04)
Level 2	
Cranial Radiation Therapy	7.08(8.10)
Sex	.57(3.83)
Glucocorticoid Dose	.0004(.0003)
Days in Hospital	.45(.28)
Chemotherapy Protocol	-1.99(3.82)
Age at Diagnosis	130.42(1203.05)
Family Well-Being, Maternal, Diagnosis	2.94(3.02)
Family Well-Being, Paternal, Diagnosis	-3.10(3.81)
Family Well-Being, Maternal, 3 Months Post-Diagnosis	3.33(2.90)
Family Well-Being, Paternal, 3 Months Post-Diagnosis	-2.16(3.39)
Cross-Level Interaction	
Time x Cranial Radiation Therapy	-1.24(2.47)
Time x Sex	-.45(1.17)
Time x Glucocorticoid Dose	-6.92E-06(8.8E-05)
Time x Days in Hospital	-.07(.09)
Time x Chemotherapy Protocol	-.04(1.10)
Time x Age at Diagnosis	-.23(.16)
Time x Family Well-Being, Maternal, Diagnosis	-1.60(.80)**
Time x Family Well-Being, Paternal, Diagnosis	.25(1.16)
Time x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-1.90(.92)**
Time x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.69(1.05)
Age at assessment x Cranial Radiation Therapy	-1.25(1.04)
Age at assessment x Sex	-.02(.36)
Age at assessment x Glucocorticoid Dose	-.00004(2.7E-05)
Age at assessment x Days in Hospital	-.04(.03)
Age at assessment x Chemotherapy Protocol	.24(.36)
Age at assessment x Age at Diagnosis	.02(.04)
Age at assessment x Family Well-Being, Maternal, Diagnosis	-.16(.28)

Age at assessment x Family Well-Being, Paternal, Diagnosis	.08(.37)
Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	-.25(.28)
Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	-.02(.30)
Time x Age at assessment x Cranial Radiation Therapy	.32(.30)
Time x Age at assessment x Sex	.03(.10)
Time x Age at assessment x Glucocorticoid Dose	5.59E-6(6.92E-06)
Time x Age at assessment x Days in Hospital	.01(.01)
Time x Age at assessment x Chemotherapy Protocol	.003(.09)
Time x Age at assessment x Age at Diagnosis	.001(.01)
Time x Age at assessment x Family Well-Being, Maternal, Diagnosis	.08(.06)
Time x Age at assessment x Family Well-Being, Paternal, Diagnosis	.02(.11)
Time x Age at assessment x Family Well-Being, Maternal, 3 Months Post-Diagnosis	.13(.09)
Time x Age at assessment x Family Well-Being, Paternal, 3 Months Post-Diagnosis	.07(.09)

*p < .10, **p < .05, ***p < .01