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## Cognitive, Academic, and Neuropsychological Effects of Treatment

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## **Abstract**

This study explored the effects of number of intrathecal chemotherapies and time off therapy on cognitive, achievement, and neuropsychological functioning of post treatment children with Acute Lymphocytic Leukemia (ALL). Participants consisted of sixteen sibling pairs between the ages of eight and fourteen who were grouped into the high or low group for number of intrathecal chemotherapies (IT), and then regrouped for high or low time off therapy (TOT). Participants were administered a battery of cognitive, achievement, and neuropsychological tests. Matched sibling difference scores from these tests were analyzed. Results found that children with ALL performed in the average range, although below their healthy siblings in some domains, indicating that treatments appear to be doing less harm than anticipated from the past literature. Results indicate that on reading composite (comprehension and pseudoword reading) and math reasoning the high IT children with ALL, when compared with low IT children with ALL, performed more poorly than their healthy siblings. A large effect size for intelligence quotient indicated that high IT children with ALL, when compared with low IT children with ALL, performed more poorly than their healthy siblings. Large effect sizes also were noted for time off therapy (TOT) for reading composite and math reasoning, with the high TOT children with ALL performing more poorly than the low TOT children with ALL, relative to their healthy siblings. Nevertheless, there is cause for optimism.

This study replicated prior research on the effects of high number of intrathecal chemotherapies on the intellectual, reading, and math performance of children with ALL, with late effects becoming most apparent at five or more years post therapy. However, post hoc analyses cautioned that these results should be interpreted conservatively, given the study's methodological limitations.

**Cognitive, Academic, and Neuropsychological Effects of Treatment  
For Childhood Acute Lymphocytic Leukemia**

By

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Dissertation

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Special Education Syracuse University

Syracuse University  
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I would also like to thank my parents. This dissertation is done in part as a fulfillment of one of my father's dreams, who is a professor in every way with the exception of the letters after his name. This dissertation was only possible due to my mother, who advocated for my K-12 education unwaveringly. Without her belief in me as a learner, college in any form would have been unattainable.

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# **Cognitive, Academic, and Neuropsychological Effects of Treatment for Children with Acute Lymphocytic Leukemia**

## **Chapter 1: Introduction**

According to the American Cancer Society, approximately 10,380 children under the age of fifteen develop some form of cancer each year (American Cancer Society, 2016). In the United States there are approximately 60,000 survivors of childhood cancer under the age of 15 (Siegel et al., 2012). Approximately 3,000 of these children are diagnosed with acute lymphocytic leukemia (ALL), the most common of all childhood cancers. ALL is also one of the most treatable childhood cancers, with current survivor estimates of 90% (American Cancer Society, 2016). However, treatment comes with a price, as approximately 40% of children with ALL experience a deficit in some aspect of neurocognitive functioning (Nathan et al., 2007).

Leukemia is a cancer of the blood that causes rapid mitosis (cell division) of immature white blood cells. This rapid mitosis causes the bone marrow to fill up quickly with the leukemia cells, leaving little room for platelets and red blood cells. These immature cells do not perform the function of normal, healthy white blood cells and place the child at risk for death due to overwhelming infection. The illness presents with bleeding, bruising, and anemia (Armstrong & Mulhern, 1999). Because blood moves throughout all organs of the body, leukemia is known to migrate into the central nervous system (CNS). Leukemia cells also are known to hibernate in the CNS. Historically, the prognosis for children with leukemia was very poor when receiving only systemic chemotherapies (chemotherapies given through intravenous injection, orally, or intramuscularly), as these treatments could not pass through the blood-brain barrier and enter the central nervous system. Survival rates increased when treatment protocols of the 1970s started to include CNS radiation treatment, giving lifesaving treatment directly into the central nervous

system. Therefore, all current leukemia treatment protocols require systemic chemotherapy and some form of therapy to terminate leukemia cells in the CNS, the blood stream, and bone marrow. These treatment protocols include cranial-spinal radiation, intrathecal chemotherapy (chemotherapy treatments administered directly into the epidural space at the base of the spinal cord, via a spinal tap), or stem cell bone marrow transplant.

Since the 1970s, researchers have examined the cognitive and educational impact of childhood cancer and treatments (see Armstrong, Blumberg, & Toledano, 1999; Campbell et al., 2007; Peterson et al., 2008; Robinson et al., 2009). During the 1970s and early 1980s, most children with ALL received a treatment regimen consisting of cranial-spinal radiation, systemic chemotherapy (SC) (administered orally, intravenously, or intramuscularly), and intrathecal chemotherapy (IT) (Armstrong et al., 1999). These protocols were effective in curing 70 - 80% of children. However, a series of studies showed high toxicity levels caused by these treatments, resulting in considerable losses in intellectual, achievement, and information processing abilities.

Meadows et al. (1981) conducted one of the first comprehensive studies regarding long-term intellectual and achievement outcomes of post therapy children with ALL who received cranial-spinal radiation treatment. All participants ( $n = 31$ ) in this study received baseline testing within the first month of diagnosis and, prior to receiving radiation therapy, they all tested in the average range of intelligence. Twenty-eight of the participants were tested again 12-34 months after treatment and eighteen were again tested three years later. Follow-up testing demonstrated that the majority of the participants demonstrated lower global intellectual and academic functioning than when first diagnosed. Participants with a baseline IQ between 86 – 109 averaged an 8 point drop in IQ at the time of follow-up testing. Participants with a baseline IQ between 110 – 132 averaged a 23.5 point decrease at follow up testing. In addition, a significant

age effect showed greater relative delays in intellectual functioning for younger than older children. This was the first study to demonstrate that age at diagnosis coupled with cranial-spinal radiation therapy (CRT) played an important role in detrimental cognitive late effects.

Following the influential work of Meadows et al. (1981), numerous studies in the 1980s and 1990s focused on the relationship between cranial-spinal radiation therapy and cognitive/achievement effects after children with ALL had completed treatment. Four factors showed the strongest relationship with cognitive difficulties. Researchers found a consistent pattern in the amount of time off therapy being correlated with greater negative effects. Cognitive late effects most typically would present between two to five years off therapy and then level off (Brown et al., 1992; Copeland et al., 1988; Jankovic et al., 1994). Research also found strong evidence that children diagnosed and treated under the age of 5 were more likely to have cognitive late effects than children diagnosed at older ages (Cousens, Waters, Said, & Stevens, 1988). Additional research demonstrated links between gender and cognitive late effects, with poorer outcomes for females (Robison et al., 1984; Waber, et al., 1990). Finally, a number of studies found that higher doses of intrathecal chemotherapy were linked to greater long-term cognitive deficits (Kingma, et al., 2002; Lansky, Cairns, & Zwarzies, 1984; Williams, Ochs, Davis, & Daniel, 1986). Many of these earlier studies had methodological issues that persist today when studying children who had been treated for ALL.

An important limitation with studying this population of children is that many studies focusing on neuropsychological effects of treatment include low numbers of children with ALL. For example, of the 28 studies in Campbell et al.'s (2007) meta-analysis of long-term neuropsychological effects on survivors of childhood ALL, 14 studies had groups of ALL children with fewer than 20 participants. Seven of the studies had groups of participants that

ranged from 10 to 15 post therapy children with ALL. Studies with small sample sizes are common when conducting a single site study with children with ALL, which create data analysis and generalization issues. Another complicating factor is that children with the same type of cancer may be treated on different protocols and receive different amounts of the same chemotherapy agent, or very different chemotherapy agents. This presents an analysis problem in studies with small sample sizes. Despite the preponderance of small  $n$  studies, Campbell's meta-analysis served to confirm the cognitive and academic late effects of treatments that include cranial-spinal radiation, as well as methodological issues in designing such studies.

The studies from the 1980s and 1990s continued to find relationships between cranial-spinal radiation therapy and cognitive and academic decrements. Given this evidence, the leading pediatric association recommended treating children with low or standard risk ALL using systemic and intrathecal chemotherapy, without cranial-spinal radiation therapy. They believed these new protocols would eliminate the neurocognitive late effects experienced by children, without compromising mortality rates. Protocols that excluded the use of radiation and only included systemic chemotherapy (SC) and intrathecal chemotherapy (IT) were developed. These protocols demonstrated effectiveness at curing leukemia at rates similar to protocols that included cranial-spinal radiation. A large scale study by Mitby et al. (2003) estimated that approximately 40% of survivors of childhood ALL would receive some special education services during their school years, though causation was unclear. To what extent number of intrathecal chemotherapies and time off therapy impact neurocognitive late effects needed further exploration, with more adequate controls. Regardless, this shift in treatment protocols then led to a number of studies that evaluated the effects of leukemia SC and IT chemotherapy protocols on toxicity of treatment and neurocognitive late effects, as well as the relationship of

time off therapy to the appearance of these weaknesses. Evidence from many of these studies found that large doses of IT chemotherapy adversely affects brain structures, particularly white matter, which is believed to lead to information processing challenges, which cause the weaknesses in achievement functioning.

The current study was designed to assess the neurocognitive outcomes of non-radiation ALL treatment in relation to number of intrathecal injections and time off therapy, while using healthy siblings as controls for the cancer experience. It was predicted that participants with ALL in the high IT and high TOT groups would show greater neurocognitive weaknesses than the low IT and low TOT groups, when compared to their healthy siblings. This study expanded on the achievement and neuropsychological variables measured in prior studies. It also controlled for family factors by using siblings as controls. The results were expected to have implications for treatment protocols and psycho-educational interventions that would allay predictable weaknesses related to ALL therapy.

Chapter 2 presents a more in-depth understanding of childhood ALL treatment and the effects of cranial-spinal radiation and/or, systemic and intrathecal chemotherapy, on the cognitive, academic achievement, and neuropsychological outcomes for children who had been treated for ALL.

## **Chapter 2: Literature Review**

Due to the negative cognitive, achievement, and neuropsychological outcomes of the treatment protocols that included cranial-spinal radiation treatment, treatment of childhood ALL shifted to systemic and intrathecal chemotherapy protocols that did not include any radiation. This review will explore the literature comparing the neurocognitive outcomes of protocols that included cranial-spinal radiation to those that did not. This review also will explore the systemic and intrathecal treatment literature that focuses on neurocognitive late effects for children with acute lymphocytic leukemia.

### **Effects of Cranial-Spinal Radiation Treatment Compared to Systemic and Intrathecal Chemotherapy Treatment**

Smibert, Anderson, Godber, and Ekert (1996) conducted one of the first studies to compare cranial-spinal radiation to systemic and intrathecal chemotherapy treatment approaches. This study was interested in the long-term intellectual and academic outcomes for post therapy children with ALL. A large sample ( $n = 100$ ) of childhood leukemia participants treated with both irradiation and chemotherapy was compared to a healthy control group ( $n = 100$ ) and a comparison group of children with mixed cancers ( $n = 50$ ) who received chemotherapy, but not radiation, as part of their therapy. The study found that children who received cranial-spinal radiation performed more poorly on measures of intelligence and academic achievement than either the healthy control group or the mixed cancer comparison group that received SC or SC + IT but no radiation. Additionally, a younger age at treatment ( $< 5$  years) and a higher amount of radiation were predictive of poorer intellectual and academic performance. The participants who received SC or SC +IT chemotherapy without radiation performed similarly to the healthy control group. One limitation of the Smibert et al. study was that the chemotherapy only group ( $n$

= 50) was a mix of different childhood cancers, some who received intrathecal chemotherapy ( $n = 24$ ) and others only systemic chemotherapy ( $n = 26$ ). Similar findings were noted by several other studies (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Langer et al., 2002; Raymond-Speden, Tripp, & Lawrence, 2000; Spiegler et al., 2006). While all of these studies used comparison groups, none utilized any type of matched controls; thus demographic factors such as socio-economic status (SES), parent education level, gender, and age were left unaccounted for. Regardless of the methodological limitations, significant negative effects of cranial-spinal radiation on cognition and academic achievement when compared with SC and IT treatment was undeniable.

Hill et al. (1998) reported similar findings when comparing long-term effects on children with ALL treated with systemic and intrathecal chemotherapy (specifically, methotrexate), with and without cranial-spinal radiation ( $n = 110$ ). This study also focused on psychosocial long-term effects, as participants were between 14 years - 4 months to 14 years - 9 months since the time of diagnosis. In addition to poorer academic outcomes, this study found that children with ALL who received systemic and intrathecal chemotherapy and radiation treatment reported having a poorer self-image and greater psychological stress than children with ALL who received systemic and intrathecal chemotherapy treatment without radiation. This study used subjective, self report psychosocial measures to examine psychosocial outcomes for children with ALL.

In addition to intellectual and academic difficulties, researchers have found gender specific effects of ALL treatment as well. Précourt et al. (2002) were interested in the long-term effects of verbal learning ability for female children with ALL. They compared girls who received systemic chemotherapies, intrathecal chemotherapies, and cranial-spinal radiation ( $n = 9$ ) to girls who received only systemic chemotherapies and intrathecal chemotherapies ( $n = 10$ ).

The study used a healthy control group of girls ( $n = 10$ ). Only the group receiving systemic and intrathecal chemotherapies plus cranial-spinal radiation performed more poorly than the control group on verbal learning and passage comprehension.

Around this same time, researchers became particularly concerned with the late effects of one chemotherapy agent, IT methotrexate. This chemotherapy agent was found to cause greater cognitive late effects in female children with ALL than other chemotherapies, when injected into the central nervous system. However, IT methotrexate also had been found more effective in treating the disease (Mulhern, Fairclough, & Ochs, 1991; Williams, Ochs, Davis, & Daniel, 1986). Methotrexate, when used as a systemic chemotherapy agent, had not been found to cause neurocognitive late effects in children being treated for cancers other than leukemia (Anderson, Smibert, Ekert, & Godber, 1994; Lansky et al., 1984).

Looking at neuropsychological outcomes of treatment, Campbell et al. (2007) conducted a meta-analysis of childhood ALL studies that used systemic and intrathecal chemotherapy, with or without cranial-spinal radiation. Twenty-eight studies from 1980–2004 were used. The participants were in first remission and nationally normed psychometric measures were normed nationally. The meta-analysis found evidence that cranial-spinal radiation, in combination with systemic and intrathecal chemotherapy, has a detrimental effect on overall intellectual functioning when compared with non-ALL controls. Age at time of diagnosis and time off therapy provided mixed results in this meta-analysis.

A national Canadian study (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005) reviewed the educational and social outcomes for survivors of various childhood cancers ( $n = 800$ ) and compared these outcomes with healthy age and gender-matched controls ( $n = 923$ ). The findings indicate that survivors who received central nervous system treatments—such as cranial



radiation alone, or cranial radiation together with systemic chemotherapy and intrathecal chemotherapy, or systemic chemotherapy and intrathecal chemotherapy—were more likely to struggle in school, be placed in special education, and be at greater risk for academic and social difficulties at school than survivors of childhood cancers that required no central nervous system treatment. Of the 800 childhood cancer survivors, 293 were leukemia survivors. The leukemia survivors were considerably more likely than the control group to be enrolled in special education, be identified with a specific learning disability, repeat a grade, and have other school problems. This study found that one of the academic areas in which survivors struggled was English, but did not distinguish if reading and writing were of particular concern for this population. Survivors with central nervous system tumors (such as brain tumors) and who received cranial radiation demonstrated the greatest difference from the control population, followed by participants who received central nervous system treatment for leukemia. Leukemia patients treated with cranial radiation were more likely than those treated with systemic and intrathecal chemotherapy to demonstrate the above school issues.

Some investigators focused more particularly on how survivors' attention and information processing impact their academic and social experiences. Spiegler et al. (2006) compared neurocognitive outcomes of ALL treatment with or without cranial-spinal radiation. The study also included two groups that received systemic and intrathecal chemotherapy, but no radiation: the high dose methotrexate group ( $n = 32$ ) (HD-MTX), and the very high dose methotrexate group ( $n = 22$ ) (VHD-MTX). An additional group received cranial-spinal radiation but no intrathecal chemotherapy ( $n = 25$ ) (CRT). As with previous research, the CRT group performed significantly worse than the HD-MTX and the VHD-MTX groups on intelligence, memory, and academic measures. On an attention measure, children with ALL treated with HD-

MTX and VHD-MTX protocols performed close to the population norms, with the exception of greater impulsivity on the Delay task of the Gordon Diagnostic System.

Over time, treatment protocols for children with ALL have excluded cranial-spinal radiation because of its strong association with cognitive late effects. Investigations subsequently explored the more subtle difficulties of post therapy children with ALL who received intrathecal and systemic chemotherapy treatments without cranial-spinal radiation.

### **Effects of Systemic and Intrathecal Chemotherapy Treatment**

The treatment effects of childhood ALL chemotherapy-only protocols is an important area of study. All childhood ALL treatment protocols require some IT chemotherapy to achieve curative effects. The first treatments of this kind began in the mid-1980s. By eliminating cranial radiation (CRT) from the treatment regimen, it was hoped that children with ALL would not experience any neurocognitive late effects. However, research on *combined* systemic and intrathecal treatments made clear that children with ALL were still at risk for neurocognitive and achievement delays, even when treated without cranial-spinal irradiation (Armstrong et al., 1999; Butler & Copeland, 2002; Cousens et al., 1998; Essig et al., 2014; Hill et al., 1998). The focus of late effects research sought to understand which treatment variables most predicted specific neurocognitive and educational risk areas for survivors treated with systemic and intrathecal chemotherapy.

Based on findings from the 1990s, ALL researchers increasingly controlled for age, gender, cumulative dosage, and time off therapy to better understand the neurocognitive and achievement decrements revealed by the research. Research began to focus more specifically on processing issues such as attention, memory, visual-motor performance, and processing speed. Among the sizable number of studies conducted in the 1990s and early 2000s, the neurocognitive

late effects findings often were mixed. The findings of studies that targeted specific aspects of information processing are reviewed below.

### **Intelligence and achievement.**

A national study by von der Weid, Mosimann, and Hirt (2003) compared 132 children with ALL who had received systemic and intrathecal chemotherapy treatments in Switzerland to 100 childhood cancer survivors who received no central nervous system treatment. The findings demonstrated both age (less than six at age of diagnosis) and gender (female) as risk factors for decreased intellectual functioning in children with ALL after treatment was concluded. A meta-analysis by Peterson et al. (2008) found relative delays in intelligence, mathematics, reading, attention, perceptual reasoning, processing speed, verbal memory, and executive functioning among post therapy children with ALL. Campbell et al. (2007) and Lyer, Balsamo, Bracken, and Kadan-Kottick (2016) also found weaknesses in intelligence, academic achievement, and several neuropsychological domains.

Espy et al. (2001) was one of the first studies to use growth curve analysis to explore treatment-related neuropsychological outcomes in children treated with SC + IT protocols. The investigators administered a psycho-educational assessment battery that included traditional tests of intelligence and achievement and a comprehensive memory and processing battery. Participants were tested at eight months, two, three, and four years post-diagnosis. Compared to test norms, the investigators found declines in arithmetic skills, visual-motor integration, and verbal fluency for children with ALL at four years post therapy. There was no relationship between the rate of decline and the specific SC + IT protocol.

**Attention.**

Mennes et al. (2005) focused on attention and the processing speed of children with ALL. Twenty-three post therapy children with ALL who were treated on two European protocols that included systemic and intrathecal chemotherapies were compared to 23 age and gender matched controls. No difference was found between the two groups on sustained attention, inhibition, organization tasks, and simple baseline speed (the study used a simple mouse click response time activity). However, on more complex executive function tasks, children with ALL performed significantly worse than their healthy peers on focused attention tasks, memory recall, and memory search. Carey et al. (2008) and Butler et al. (2016) also found that post therapy children with ALL who had received systemic and intrathecal chemotherapies demonstrated lower performance on attention tasks, mental flexibility, visual-construction skills, and math achievement than the healthy control group.

**Fine-motor.**

In a sibling control study, Jansen et al. (2008) focused on the neuropsychological function over time of children with ALL who had received systemic and intrathecal chemotherapies. Forty-nine children with ALL were compared to 29 healthy siblings on fine-motor and perceptual functioning, memory and learning, sustained attention, speed, and executive functioning, at two time points: 3 to 6 months off therapy and 2.5 years off therapy. The study had two significant findings: 1) children with ALL demonstrated significantly weaker fine-motor skills over time than the sibling control group, and 2) children with ALL who expressed greater pain or fatigue during treatment demonstrated poorer sustained attention years after completion of treatment, in comparison to the sibling control group.

**Memory.**

Kingma et al. (2002) conducted a seven-year longitudinal study that focused on memory, intelligence, attention, processing speed, and motor skills of 20 children with ALL who had received systemic and intrathecal chemotherapy. Compared to a healthy control group, findings demonstrated relative delays in memory and fine-motor ability for post therapy children with ALL. In a similarly designed study, Kaemingk, Carey, Moore, Herzer, and Hutter (2004) compared children with ALL who had received systemic and intrathecal chemotherapy treatment with 15 healthy controls. The control group was comprised of matched age and gender participants utilizing siblings and friends. While the children with ALL performed mostly in the normal range, relative difficulties in memory, psychomotor speed, math calculation, math reasoning, attention, and visual-motor ability were noted.

In a small single site study, Hill et al. (1998) controlled for age, gender, SES and handedness to strengthen their study. This was one of the first studies to use a normed memory measure (the Wide Range Assessment of Memory and Learning). The research focused on the impact of systemic and intrathecal treatment on visual and verbal memory. Ten post therapy children with ALL were compared with ten healthy controls. The study showed relative delays in visual and verbal short-term memory, planning, and inattention issues for the children with ALL, in addition to 10-20 point deficits in intellectual scores.

In Ashford et al.'s (2010) childhood ALL study of working memory, post therapy children with ALL were placed into either low- or high-risk groups based on cumulative treatment dosage and number of intrathecal treatments: 13 to 18 treatments in the low risk group and 16 to 25 treatments in the high-risk group. This study found that the high-risk treatment

group underperformed when compared to normative data on tests of Digit Span Forward (DSF), Digit Span Backwards (DSB), and Total Digit Span (TDS). The low-risk treatment group had difficulty with the Digit Span Backwards only.

### **Processing speed.**

Mahone, Prahme, Ruble, Mostofsky, and Schwartz (2007) compared the motor processing speed of children with ALL ( $n = 22$ ), who had received systemic and intrathecal chemotherapy treatment, with age and gender matched healthy controls. Participants completed computer-based motor timed tasks as part of a larger neuropsychological battery. The ALL group performed more poorly than the control group on motor processing speed and in ability to estimate durations of time. Other studies also have noted relative delays with visual-motor speed (Buizer et al., 2005; Cheung & Krull, 2016; Kaemingk et al., 2004; Kingma et al., 2002).

Using a sibling comparison group, Reeves et al. (2007) assessed whether post therapy children with ALL have delays in processing speed and if this relates to behavioral symptoms. Eighty post therapy children with ALL and 19 sibling controls were studied using processing speed and achievement measures, and an abbreviated IQ test (three WISC-IV subtests: Information, Similarities, and Block Design). Behavior was measured using the Child Behavior Checklist (CBCL). The study found that children who had been treated for ALL had more processing speed delays than their sibling controls. The siblings scored higher than the ALL group on all measures of intelligence and academics, with the exception of numerical operations.

In summary, the findings from research on cognitive, achievement, and information processing functioning of children with ALL who had received SC and IT treatment suggests they are at greater risk for mild difficulties in intellectual functioning, academic achievement, memory, fine-motor skills, processing speed, and attention even without receiving cranial

radiation therapy. Today, the combined SC and IT therapy remains the most common treatment approach for childhood ALL (Anderson et al., 2009; Brown et al., 1998; Copeland et al., 1996; Espy et al., 2002; Lansky et al., 1984). Although lifesaving, these treatments come with neurocognitive risks. Therefore, continued study of neurocognitive outcomes for children with ALL is necessary.

The findings from these studies raise questions about whether there are ways that the medical community can modify protocols and intervene preventatively if ALL treatment late effects are likely. If not, are there ways that educators and therapists can monitor, prevent, and remediate weaknesses more effectively? Are there therapy protocols that have less negative outcomes? To better understand the relationship between treatment and cognitive, academic and neuropsychological functioning, researchers have studied the effects of time off therapy, and they are increasingly utilizing a combination of brain imaging and neuropsychological testing to research these complicated effects.

### **Time off Therapy Effects of Systemic and Intrathecal Chemotherapy**

Time off therapy has continued to be a focus of study, as neurocognitive and achievement delays may not be visible immediately after treatment, but do become evident over time. Copeland, Moore III, Francis, Geffee and Culbert (1996), for example, compared the cognitive and academic effects experienced by 51 children with ALL, who had received systemic and intrathecal chemotherapy treatment, to 48 children with other cancers who had received only systemic chemotherapy. Intelligence, memory, language, achievement, fine-motor, perceptual-motor, and tactile-spatial skills were assessed. Both groups showed declines on achievement scores, with time off therapy (TOT) becoming an important variable by three years post treatment. For the children with ALL, being treated at a young age (< 5 years) and the more time

off therapy (5 to 11 years), the greater the decline in perceptual-motor ability. On the performance intelligence quotient, children with ALL who had received systemic and intrathecal chemotherapy treatments scored approximately 10 points lower than their childhood cancer counterparts who received no central nervous system treatment. During the baseline year, which began at the time of diagnosis, the IQ scores of both groups had been equivalent.

Brown et al.'s (1996) study compared children with ALL who had been treated with systemic and intrathecal chemotherapy ( $n = 38$ ) to children with other childhood cancer diagnoses who received only systemic chemotherapy treatment ( $n = 25$ ). For the children with ALL, a steady decline was evident on the reading, writing, and arithmetic sections of the Wide Range Achievement Test over the four-year period from diagnosis. There were no cognitive or achievement deficits for the mixed-cancer comparison group. The declines for the post therapy children with ALL were attributed to the intrathecal chemotherapy treatment.

In another study, Brown et al. (1998) examined the cognitive and academic late effects among 47 children and adolescents with ALL who had been treated with the same systemic and IT chemotherapy protocol. All of the participants had been off treatment for two to seven years at the time of assessment. The study found a negative gender effect on nonverbal tasks for girls who were treated for ALL, when compared to the test's normative data and to boys treated with the same protocol. The females with ALL scored close to one standard deviation below the mean on performance tasks, whereas the males with ALL scored within low average to average ranges.

A study by Mulhern, Fairclough, and Ochs (1991) found that children with ALL who had received SC and IT therapy had average intelligence and achievement scores at one year off therapy. At four years off therapy intelligence scores held stable, but achievement scores, though still in the average range, had declined. In a similar study, Ochs et al. (1991) found that at a mean



time of six years off therapy, children with ALL showed decreases in Full Scale IQ and Verbal IQ scores, as well as math achievement. Late effects for achievement began to show sometime between two and four years, with IQ late effects presenting between four and six years post-therapy.

Espy et al. (2001) too found that children with ALL demonstrated declines in verbal fluency, math, and visual-motor processing skills if they were more than two years off therapy. In their study, Kingma, Van Dommelen, and Mooyaart (2001) studied late effects at two time points: 3-6 months post treatment (T1) and approximately 2.5 years post treatment (T2). No intellectual changes were found from T1 to T2, but auditory memory and fine-motor difficulties did become apparent at T2. In a study published a year later, Kingma et al. (2002) report that at 5 years off therapy the children with ALL ( $n = 20$ ) had lower Verbal IQ and attention when compared to the healthy control group.

Finally, Jansen et al. (2006), Lyster et al. (2016), and Nathan et al. (2006) found small decreases over time in intellectual function for children with ALL. These studies were longitudinal in nature and focused on time off therapy of under two years post treatment and again at 5 + years post treatment. Collectively, these studies suggest there is a likelihood of late effects becoming apparent in intelligence, achievement, perceptual-motor skills, auditory memory, and attention skills at approximately 5 or more years post therapy. Sometimes effects present as early as two years off treatment on verbal fluency, spelling, reading, math, visual-motor, auditory memory, and fine-motor skills.

These studies were critical to the understanding that, despite the exclusion of cranial-spinal radiation as part of curative therapy for childhood ALL, systemic and intrathecal chemotherapy combined can still cause skill decrements, especially as time off therapy increases.

These studies provide some depth of knowledge regarding neurocognitive and achievement late effects among children with ALL who had been treated with SC and IT chemotherapy. More recently, research has approached the issue of late effects of childhood ALL by utilizing more extensive neuropsychological batteries together with brain imaging techniques.

### **Brain Physiology Research on Post Therapy Children with ALL**

As the neurocognitive effects of ALL systemic and intrathecal chemotherapy treatment have become evident, understanding the biological mechanisms that underpin these changes has become a priority. The brain is the primary organ of interest for children with ALL in relation to late effects. What is unclear is which biological system(s) within the brain are responsible for cognitive difficulties faced by ALL survivors. Among the more robust theories is that ALL treatments may affect brain matter in ways that make cognitive development more difficult. The brain consists of what is commonly referred to as white and gray matter. White matter is important because its neuron networks support messages being passed from one section of the brain (gray matter) to another. A prevailing theory is that damage to the white matter due to radiation or chemotherapy may disrupt this network (Reddick et al., 2003).

To best research changes in brain structures, studies primarily have utilized MRIs, which create static images of the participant's white and gray matter. For example, Montour-Proulx et al. (2005) conducted a study that included traditional MRI imaging technology for children with ALL who had been treated with SC and IT. This study used Growth Curve Analysis to study how participants ( $n = 24$ ) performed on measures of intelligence and memory. The advantage of using this regression technique is that the researchers could analyze both group and individual effects over time. This study took place over two time periods: Time 1 was while on treatment, and Time 2 was sometime between 9 months to 2.5 years off therapy. The results of this study

demonstrated a reduction in white matter over the two time points that correlated with a significant reduction in Performance IQ scores.

Reddick et al. (2006) utilized imaging technology with neuropsychological testing and demonstrated that post therapy children with ALL between the ages of six and eighteen ( $n = 112$ ) had neurocognitive delays and reduced white matter associated with those relative delays, when compared to healthy siblings ( $n = 33$ ). The findings demonstrated statistically significant academic and attention delays for the children with ALL, who received cranial-spinal radiation plus systemic and intrathecal chemotherapy. Attention delays were more than one *SD* below the norm. Regarding the white matter, participants who received systemic and intrathecal chemotherapy without radiation had considerably more white matter than their peers treated with chemotherapy and cranial-spinal radiation, but both groups had less white matter than the healthy sibling controls. Smaller white matter volumes were associated with relative delays in attention, IQ, and academics. More aggressive treatments produced more detrimental physiological and cognitive outcomes.

Ashford et al. (2010) conducted the only brain imaging study that focused on the number of ITs, as they relate to neuropsychological outcomes. Their study examined the difference in white matter volumes between a high IT (16-25) and a low IT (13-18) group of post therapy children with ALL. IT groupings were based on a combination of number of ITs and total dosage of chemotherapy. The findings indicated that the high IT group exhibited a greater risk for leukoencephalopathy (white matter disease), working memory weaknesses, and attentional difficulties.

Other structural differences in the brains of children treated for ALL have been suggested by Lesnik, Ciesielski, Hart, Benzel, and Sanders (1998). Lesnik et al. conducted an imaging

study of 6-13 year old childhood participants with ALL ( $n = 10$ ) who had received systemic and intrathecal chemotherapy. Results were compared to matched age and gender controls. Structural brain differences in children with ALL demonstrated reduction in both left and right prefrontal cortical areas, which corresponded with delays on tasks of visual-spatial attention, short-term memory, and visual-motor organization.

Oxidized cerebral spinal fluid is also implicated in delays that follow SC + IT treatment for ALL. Caron et al. (2009) measured oxidative stress (the body's increase in oxidizing of blood and a decrease in levels of antioxidants) over the first two years of treatment by collecting spinal fluid during scheduled lumbar punctures, and then analyzing the oxidative levels in the cranial spinal fluid. Executive functioning was tested over a three-year period after the completion of therapy. The study found correlations between higher oxidative stress and lower executive functioning at the two year post-treatment point of the study. In addition, there was a significant correlation between younger age at diagnosis, higher oxidative stress levels, and lower executive functioning ability. How oxidative stress levels might impact the brain is unclear, but the findings overall indicate that children with ALL must cope with an array of physiological changes that are detrimental to their cognitive functioning.

In contrast to an MRI of the brain, which is a static image, functional MRIs (fMRI) provide images of the brain in an active state. Using fMRI, in conjunction with an executive functioning cognitive rehabilitation curriculum, Kesler, Lacayo, and Jo (2011) conducted a study with 23 post therapy children with ALL. This study concluded that the cognitive rehabilitation curriculum improved executive function and memory skills, based on neuropsychological test changes (processing speed, sort test, verbal and picture memory) as well as brain activation as noted in the fMRI (increases in dorsal lateral prefrontal cortex activation).

Robinson et al. (2010) utilized fMRIs to examine working memory and executive functioning in children with ALL who had received systemic and intrathecal chemotherapy between the ages of 10 to 16 years old ( $n = 8$ ). Controls included age and gender matched healthy peers ( $n = 7$ ). The study found that children with ALL did more poorly on tasks of working memory accuracy and had greater brain activity when focusing on working memory tasks. The dorsolateral and ventrolateral prefrontal cortex showed substantial activation during these tasks. In addition, the dorsal and ventral anterior cingulate cortex (involved in problem solving, motivation, and assessing emotional information) demonstrated larger activation on error monitoring tasks. Both of these findings suggest that compensatory activation was needed in these brain regions to complete executive functioning tasks.

In summary, many of the imaging studies of children who had been treated for ALL relate their changes in brain state and function to decrements in neuropsychological functioning. These decrements are associated with physiological effects from treatment. Taken together, the imaging and neurocognitive research has provided stakeholders with a more complete understanding of the cognitive challenges faced by post therapy children with ALL on a daily basis. Potential difficulties in academic performance (math and reading), intellectual functioning, processing difficulties (visual-motor, fine-motor, and processing speed), short-term and working memory, and difficulties with executive functioning skills (planning and organization, attention, and multistep problem solving) are possible effects of chemotherapy treatment. More research is necessary to better predict which children with ALL are likely to struggle and when. Exploring ways to minimize negative effects and predict those children at greatest risk, without compromising treatment efficacy, is an important task. These findings offer areas ripe for

research on how to support children's ability to develop compensatory neural processes that might mitigate some of the negative physiological effects of treatment.

### **Summary of Childhood ALL Neurocognitive and Achievement Research**

Lifesaving treatment for childhood acute lymphocytic leukemia has been ongoing since the 1970s. The success rates and reduction of long-term effects for children with ALL have increased dramatically over the past 50 years as treatment protocols shifted from including cranial-spinal radiation, intrathecal, and systemic chemotherapies, to less toxic intrathecal and systemic chemotherapy only protocols. Factors such as 1) a younger age at diagnosis and initial treatment (with females being more susceptible than males), 2) time off therapy with neurocognitive late effects presenting at approximately five or more years off therapy, but sometimes sooner, and 3) higher cumulative doses and numbers of intrathecal chemotherapy treatments often have been associated with negative neurocognitive effects. However the majority of the findings from these studies demonstrate that children with ALL typically perform in the average range, albeit significantly lower than their comparison groups (Ashford et al., 2010; Brown et al., 1996; Buizer et al., 2005; Cheang & Krull 2015; Espy et al., 2001; Essing et al., 2014; Jansen et al., 2008; Kaemingk et al., 2004; Kanellopoulos et al., 2016; Lyer et al., 2016; Reddick et al., 2006; Waber et al., 2007). Although recent research has become more specific regarding the effects of chemotherapy, more studies are needed to better understand these cognitive, educational, and neuropsychological outcomes in children treated for ALL.

In pursuing this line of research, adequate control groups are essential. Some studies have had no controls, some do match on several variables, and others use mixed control groups of friends, siblings or convenience samples of healthy peers. It is common to simply compare the performance of children with ALL to standardized test norms. Thus far, siblings have been used

sparingly as a healthy control group in childhood cancer research. A review of the literature reveals that only six empirical studies of SC + IT treatment effects since the 1980s have included siblings of children with ALL (Jansen et al., 2008; Kaemingk et al., 2004; Mitby et al., 2003; Reddick et al., 2006; Reeves et al., 2007; Rodgers, Marckus, Kearns, & Windebank, 2003). Of these six, three used a battery of neurocognitive tests, including intelligence, achievement, and executive functioning assessment (Jansen et al. 2008; Reddick et al., 2006; Reeves et al., 2007). All three of these studies were whole-group comparisons and used a smaller number of siblings than the number of children with ALL in the studies, primarily for the purpose of ensuring that basic demographic and intellectual functioning was controlled. The use of healthy sibling controls, one-to-one matches, has the advantage of controlling for SES, race/ethnicity, parent education, genetics, home climate, and the shared crisis experience. Ideally, this research would be best suited to a twin study, but finding sets of twins where one is diagnosed with leukemia and one is not is almost unheard of.

Taken as a whole, studies of the neurocognitive and achievement effects of childhood ALL treatments leave little room for questioning the general phenomenon of long-term effects. Using a range of methodological approaches, these studies established that many children who undergo treatment for ALL face later learning challenges, even though they may score in the average range on many of the neuropsychological and achievement measures.

Although childhood cancer treatment has made great strides in increasing life expectancy and reducing overall neurocognitive deficits due to treatment, intellectual, academic and neuropsychological relative delays remain. These delays are milder than treatments that include cranial radiation, but they nevertheless remain persistent, subtle, and varied. Because of the set of findings around the late-term neurocognitive effects for children with ALL, it is critical that we

continue to deepen our understanding of the consequences of various combinations of treatments. This understanding can lead to revising treatment protocols and a greater focus on early intervention for predictable cognitive, achievement, and neuropsychological weaknesses.

### **Current Study**

The primary research question in the current study was how high vs. low numbers of intrathecal treatments, and high vs. low time off therapy relate to specific cognitive, achievement, and neuropsychological outcomes for children who had been treated for ALL, when compared with their siblings. This study examined the effects of ALL treatment by creating high and low IT groups based on the number of intrathecal chemotherapies ( $< 20$  or  $\geq 20$ ). High and low time off therapy groups also were created based on five or more, vs. below five, years off therapy. The IT and TOT group cut offs were based on research showing more neurocognitive late effects with 20 or more ITs, or at 5 or more years off treatment.

The current study used a healthy sibling control group in order to better control for the family's cancer experience, as well as for demographics, such as SES and parent educational level. These factors have seldom been considered when studying late effects among children with ALL. Previous research comparing post therapy children with ALL to their healthy sibling counterparts has found differences in intellectual, achievement, processing speed, memory, fine-motor, visual-motor and attention domains (Janson et al., 2008; Kaemingk et al., 2004; Reddick et al., 2006; Reeves et al., 2007; Rodgers et al., 1999). The current study explored these domains but also added some measures seldom used in ALL studies: Executive Functioning Scale, Reading Comprehension, Phonemic Awareness, Math Reasoning, and Writing Sample.



Knowing that neurocognitive late effects can appear as early as two years off therapy and become even more evident at five or more years off therapy, this study examined how weaknesses would manifest in children with ALL with high vs. low time off therapy and with high vs. low numbers of intrathecal treatments. It was predicted that children with ALL who were classified as high IT or high TOT would show greater weaknesses on the study's measures than those in the low IT or low TOT groups, when compared with their healthy siblings.

## **Chapter 3: Method**

### **Rationale for the Method**

This study has taken advantage of the controls inherent in sibling controlled research designs. The primary advantage of this design is the ability to vary one aspect of the environment (childhood cancer treatment based on number of intrathecal chemotherapies or time off therapy) while keeping much of the environment similar (home life, school, SES, and partial genetic control) (Donovan and Susser, 2011). This study design allows for exploration of whether analyzing sibling difference scores is helpful to statistical analysis when sample size is small. To date, no studies of children with ALL have used sibling difference scores for the data analysis. This study divided participants into a high and low group based on number of intrathecal chemotherapy treatments, and a high and low group based on time off therapy, in order to explore late effects on intelligence, academic achievement, and neuropsychological functioning among children treated for ALL. In addition to using measures common in late effect research (intelligence, verbal memory, executive functioning, attention, processing speed), this study also added measures of prose writing, math reasoning, pseudoword reading, reading comprehension, and parent rating of executive functioning.

### **Participants**

Post therapy children with ALL and their healthy siblings were recruited from Tomorrows Children's Institute. Sixteen families agreed to have both the child with ALL and a healthy sibling participate. Thirteen of the sixteen families were from Northern New Jersey and from either middle-class (average household income of \$60,000 – \$90,000) or upper middle-class towns (average household income of \$91,000 or more). All but one family identified as white. In total, 32 participants between the ages of 8 - 14 participated in this study. Children

with ALL ranged in age from 8 years – 5 months to 14 years - 9-months, with a mean age of 11 years -6 months. Healthy siblings ranged in age from 8 years - 0-months to 14 years - 7-months with a mean age of 11 years – 3 months. The average age for the children with ALL in this study was 142 months, while the average age for the healthy siblings participating in this study was 138 months. Healthy siblings with any documented attention, learning, or cognitive disability were not permitted to participate in this study. The children with ALL had been diagnosed, treated, and/or were currently followed by the Department of Pediatrics at the Joseph M. Sanzari Children’s Hospital at Hackensack University Medical Center. All of the participants with ALL received both intrathecal and systemic chemotherapy treatments that included methotrexate chemotherapy, using one of four different childhood cancer protocols. All four protocols used intrathecal methotrexate, but three included two additional intrathecal medications. Four potentially toxic systemic drugs were common to all protocols. One protocol added a 5<sup>th</sup> drug, another added a 6<sup>th</sup> drug, and one added a 7<sup>th</sup> and 8<sup>th</sup> drug.

This study included children with ALL between the ages of eight- and fourteen-years-old who were treated with systemic (SC) and intrathecal (IT) chemotherapy (no radiation therapy), and who had been off treatment for at least two years with no relapse. This combination of SC and IT is the most commonly used therapy for childhood ALL and research has consistently demonstrated that IT chemotherapy is linked to intellectual, cognitive, and information processing delays (Anderson et al., 2009; Brown et al., 1998; Copeland et al., 1996; Lansky et al., 1984).

This study used 20 and above as the high IT group requirement, and five or more years off therapy as the high time off therapy group requirement. Because of the small sample size and use of four different treatment protocols, the cumulative dosage approach to classifying high vs.

low IT was not possible. Therefore, this study took an approach used in two prior studies, estimating high and low dosage levels from the number of ITs. Pui et al. (2003) extrapolated from their meta-analysis that 20 ITs is a likely threshold for increased risk of long-term cognitive effects. In addition, Ashford et al., (2010) conducted a study which grouped participants based on biological factors on MRI scans, number of intrathecal treatments, and cumulative dosage of chemotherapies. Participants in Ashford et al.'s high risk group (16-25 ITs and greater cumulative dosage) performed more poorly on working memory tasks than participants who received lower numbers of IT (13-18) and lower cumulative dosage. In the current study, using the 20 IT cut off resulted in seven children with ALL being in the high IT group and nine being in the low IT group, with a sample mean for ITs of 18.81 ( $SD = 2.56$ ). This study compared post therapy children with ALL with 20 or above ITs to those with 19 and fewer ITs. The field of childhood ALL research has been moving toward decreasing the amount of toxicity children receive, by decreasing both total number of ITs and cumulative dosage of chemotherapies. This is reflected in the study's sample, where younger children with ALL were more prevalent in the low IT groups. This study excluded children with ALL who had received cranial-spinal radiation as part of their ALL treatment. Children with ALL also were excluded if they had any relapse or any secondary cancer. Finally, no children who had been off treatment for ALL for less than 24 months were permitted to participate, as prior studies found that it is around age two that some late effects of treatment begin to appear.

Based on literature showing that five years off therapy reveals more marked late effects on neurocognition than fewer years off therapy (Espy et al., 2001; Kingma et al., 2002; Nathan et al., 2007), five years or more off therapy was set as the high TOT group requirement. Children

off therapy for less than five years were categorized in the low TOT group. This resulted in nine children in the high TOT group and seven in the low TOT group.

Healthy siblings of the children with ALL who were between the ages of eight and fourteen and who had no history of cancer were included in the study. The healthy sibling control group allowed the researchers to control for potential co-varying factors such as socioeconomic status (SES), parent education, race/ethnicity, the effects of the family crisis, and genetic propensity toward certain temperamental traits and abilities that impact cognitive and educational performance. Table 1 provides a list of sibling pair demographic data (see Appendix A for tables).

### **Recruitment**

According to hospital records, 64 childhood cancer survivors met the criteria for this study. A chart review of these 64 survivors was conducted and 24 families were identified that had one or more siblings who also met the age and health criteria for this study. Potential participants were contacted via first class mail and invited to participate in the study. Approximately one week after receiving the letter, each family that had not already contacted the researcher received a phone call from the researcher inquiring about their interest. Of the 24 families, 16 agreed to participate (participation rate of 67%). Four families did not respond to the letter or to the follow-up call, and four more families refused participation. Of the 16 families that agreed to participate, 14 families had a childhood cancer survivor who was male and two who were female, thus gender could not be analyzed as a factor in this study. Families that indicated interest were given opportunities to ask questions about the research during the phone call. Upon verbal agreement to participate, an appointment for the testing sessions was scheduled. Prior to the beginning of the testing session, the researcher gave the child (ages 9 to

14) an assent form and the parent/guardian the study consent form to read and review. The researchers verbally reviewed the assent form with 8-year-old participants as per hospital policy.

## **Measures**

### **Intelligence.**

#### ***Intelligence Composite-Wechsler Intelligence Scale for Children–Fourth Edition.***

The Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler, 2003) was used in this study as a benchmark of intellectual performance. For analysis, the current study drew from procedures used by Kadan-Lottick et al. (2009), who used the Full Scale Intelligence score. By using the Full Scale score on the WISC-IV, the intelligence quotient is comprised of subtests that measure verbal comprehension, perceptual-reasoning, processing speed, and working memory.

The WISC-IV is a clinical instrument for measuring the intellectual capacity of children. The test comprises ten core subtests: Vocabulary, Similarities, Comprehension, Block Design, Picture Concepts, Matrix Reasoning, Digit Span, Letter-Number Sequencing, Coding, and Symbol Search. These subtests generate a Full Scale score (FSIQ), as well as four composite indices: Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Processing Speed (PSI), and Working Memory (WMI). This instrument takes approximately one and a half hours for the child to complete. Inter-rater-reliability coefficients (how much agreement there is in the test scoring by different testers) for the Verbal Scale are .92 to .96 (average .95); Performance Scale are .89 to .94 (average .91); and Full-Scale are .94 to .97 (average .96). Criterion validity compares the WISC-IV to previous versions of the WISC battery as well as other standardized cognitive measures, such as the Stanford-Binet and the Kaufman Assessment Battery for Children. The norm sample included 2,200 cases from across the nation, including 200 children in each of the

11 age groups (ranging from 6 to 16 years). Norming data also included representative percentages by socio-economic status, gender, and urban, suburban, and rural locations.

**Verbal memory.**

***California Verbal Learning Test for Children.***

The California Verbal Learning Test for Children (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994) was used as the primary measure of verbal memory performance. To create a memory composite score, this study drew from procedures in Anderson et al. (2009) and Reddick et al. (2003) when using the CVLT-C. In both of these childhood cancer studies, the researchers used the List A Total Trials 1-5 score as the general measure of overall verbal memory performance. The CVLT-C assesses short-term and long-term memory in children ages five to sixteen. A list of 15 words that can be organized into three categories (e.g., fruits, clothing, and toys) is dictated to the child over five consecutive trials. The list of words is always read in the same order. The child is asked to verbally recall the words immediately following each trial. This instrument takes approximately 20 minutes for the child to complete, plus an additional 20-minute delay to assess long-term free and cued recall. Internal consistency on the test ranges from .81 to .91 across ages. Between trial consistency ranges from .84 to .91, and the semantic categories reliability coefficient ranges from .64 to .80. Word consistency ranges from .67 to .86. The CVLT shows moderate construct and content validity with the Wechsler Intelligence Scale for Children - Revised Vocabulary subtest, with correlations ranging from .32 to .40. The norming sample consisted of 920 typically functioning children between the ages of five and sixteen, and controlled for location within the United States, socio-economic status, gender, and urban, suburban, and rural locations.

## **Executive functioning.**

### ***The Rey-Osterrieth Complex Figure Test.***

The Rey-Osterrieth Complex Figure Test (RCFT) (Osterrieth, 1944) was used as a measure of visual spatial organization and planning. This study drew procedures from Campbell et al. (2009) and Waber et al. (2007) for selection of subtests to examine planning and organization skills. The rationale for this choice is rooted in Waber's long history of use of the RCFT with children with ALL, dating to the mid-1980s. Waber and Bernstein (1995) created the developmental scoring system for the RCFT. The RCFT is a tool designed to measure a child's visual perceptual ability and organization of complex material by copying a figure and one minute later drawing it from memory. The child is given five markers to use to complete the copying task. The examiner asks the child to change markers upon request in order to better assess the child's organizational approach to the task. Based on Campbell et al. (2009) and Waber et al.'s (2007) precedent, the current study used the RCFT Copy score, which scores the quality of copying rather than the child's organizational approach. Because of the complexity of the figure, most children fail to reproduce it correctly. Production failure provides insight into the preferred problem solving and organizational approach of the learner (Meyers & Myers, 1995). Inter-rater reliability was randomly performed on 52 protocols with a reliability coefficient of .95 for the Copy-Organization score. Inter-rater reliability coefficient for the Style (copy) score was .88). Raters' ability to identify critical features ranged from .91 to .96 (Meyers & Meyers, 1995). Test-retest reliability was not calculated due to clinical considerations that would make this invalid (*i.e.*, once a child has the experience of drawing the figure s/he is no longer naive to drawing it). This test was normed on 450 children ages 6 to 14. The RCFT norming data used in the current study was drawn from Myers & Meyers (1995) and consisted of 505 typically



functioning children between the ages of 6-years-0-months and 17-years-11-months from the Midwestern United States. In this norming sample the authors controlled for gender and socioeconomic status.

***Behavior Rating Inventory of Executive Functioning - Parent Form.***

The Behavior Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, & Guy, 2001) was used in the current study as a measure of perceived executive functioning. A composite score to measure perceived executive functioning was necessary in order to maximize statistical power level and still analyze this domain. In order to create a composite score from the parent rating measure, the current study used the procedures in Sullivan and Riccio (2006), in which significant inter-correlations supported creating a Global Executive Composite from the BRIEF Inhibit, Initiate, and Monitor subscales. It is important to note that the BRIEF is missing data from two sibling pairs whose parents chose not to complete these forms. Therefore, analysis was conducted with an  $n = 28$  (14 sibling pair difference scores) instead of  $n = 32$  (16 sibling pair difference scores).

The BRIEF is a questionnaire for parents of school-aged children five-to-eighteen-years old. This measure is normed on 1,419 parent and 740 teacher reports balanced for socioeconomic status, gender, and urban, suburban, and rural locations. The BRIEF has eight scales that focus on different aspects of executive function (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor). Parents are asked to respond to the 86 items on a 3-point Likert scale ranging from *Never*, *Sometimes*, to *Always*. This instrument takes approximately 20 minutes to complete. The BRIEF's internal consistency coefficients range from .80 to .98 on the Parent Form, and test-retest correlations range from .76 to .88. Construct validity was determined by comparing the BRIEF to more general measures of

behavior such as the ADHD Rating Scale-IV, the Child Behavior Checklist Parent and Teacher Form, the Behavior Assessment System for Children, and the Connors' Rating Scale. Through correlations and factor analysis, the BRIEF was found to correlate strongly with measures of general behavioral functioning, and to correlate less strongly with measures of emotional functioning.

### **Attention.**

#### *Test of Variable Attention.*

The TOVA was used in the current study to measure both inattentiveness and impulsivity. The current study drew from procedures used in Aijaz et al. (2006). In their study of medically fragile children, Aijaz et al. used attention composite scores to measure various aspects of attentional performance. Similarly, this study used the TOVA omission and commission scores to create two separate composite scores, one for inattention (omission) and one for impulsivity (commission) to analyze attention. Composite scores were necessary to maximize statistical power level for analysis of these domains. The composite scores were created by combining the four quartile error scores separately for omission and commission errors.

The TOVA is a measure of sustained attention and examines the participant's errors of omission (inattentiveness), commission (impulsivity), response speed, and variability of response rate. The child completes the task on the computer and is told to click a finger-button switch when a black box appears on top of the screen, and to not respond when the black box appears on the bottom. This instrument takes approximately 25 minutes for the child to complete. The test developers computed Pearson R correlations for all variables. Condition 1 (Quarters 1 and 2, stimulus infrequent) reported correlations across quarters ranging from .69 to .92. Condition 2

(Quarters 3 and 4, stimulus frequent) reported correlations ranging from .70 to .92. Cronbach alpha, split-half, and Kuder-Richardson reliability coefficients, traditionally reported as a measure of test consistency, are not appropriate for timed tasks such as the TOVA (Anastasi, 1988). Norming data consisted of 1,590 children and adults ranging from ages 4 to 80 from across the United States. The majority of those tested were from either rural or suburban Midwestern communities. The norming data controls for gender, but does not control for socioeconomic status.

### **Processing speed.**

#### ***Test of Variable Attention.***

The Test of Variable Attention (TOVA; Greenberg, Kindschi, & Corman, 2000) was used in the current study as a measure of processing speed. Response time is the amount of time it took the subject to press the mouse button when the target was presented. The current study created a composite Response Time score drawing from Aijaz et al. (2006), who combined the four response time quartiles (Q1, Q2, Q3, and Q4) to create a composite score.

### **Academic achievement.**

#### ***Wechsler Individual Achievement Test Second Edition.***

The Wechsler Individual Achievement Test - Second Edition (WIAT-II; Wechsler, 2003) was used in the current study to measure academic performance in reading and math. Reading and math deficits for post therapy children with ALL are well documented (Armstrong et al., 1999; Brown et al., 1998; Reddick et al., 2006). The current study created a composite score for reading (Reading Comprehension and Pseudoword subtests), based on the inter-correlation for these subtests reported by Wechsler (.48 - .65) on the Reading Comprehension and Pseudoword subtests. The WIAT-II Reading Comprehension requires students to read several passages

within a grade-appropriate item set and answer questions. Questions about the passages involve detecting the main idea and supporting details, making inferences, and defining vocabulary. The participants chose the best of four possible multiple-choice answers. The Pseudoword task required decoding phonemic nonsense words.

The Math Reasoning task included counting, identifying shapes, and solving math word problems. Participants were presented a series of math problems, both verbally and by visual display, to assess their ability to reason mathematically. This test is not timed and participants could use scrap paper if requested. This test takes approximately 40 minutes to administer.

Inter-rater reliability coefficients of WIAT-II subtests range from .71 to .99. Test-retest reliability for subtests range from .81 to .99. Construct validity with the Math Reasoning subtest and the WRAT3 Arithmetic Subtest is .77; WIAT-II Reading Comprehension subtest with WRAT3 Reading is .73. Norming data consisted of a national sample of 2,950 participants ranging in age from 4 to 19-years-11-months. Norming data also included variables such as socio-economic status, gender, and urban, suburban, and rural locations.

### **Writing.**

#### ***Three-Minute Writing Sample.***

A three-minute writing sample was used to assess written expression abilities of the participants. There is no known research regarding written expression and skills of post therapy children with ALL. This task is not a nationally norm-referenced measure. The current study utilized the three-minute writing task procedures described by Malecki and Jewell (2003) as inter-correlations between total words written and the five other writing indices range from .56 to .99. Total words written is a standard measure in response to intervention writing assessment (Gansle, Noell, van der Heyden, Naquin, & Slider, 2002).

The Three-Minute Writing task was scored using an original data set analyzed across gender and grade level in the central United States (Malecki & Jewell, 2003). The participants in that study were 946 first- through eighth-grade students from three schools in rural and suburban northern Illinois. The sample consisted of 48% males and 51% females, but no other demographic data was reported. The participants consisted of 133 (14.1%) first-graders, 200 (21.1%) second-graders, 168 (17.8%) third-graders, 192 (20.3%) fourth-graders, 127 (13.4%) fifth-graders, 57 (6.0%) sixth-graders, 44 (4.7%) seventh graders, and 25 (2.6%) eighth-graders. The original 3-minute writing task tested for Total Words Written, Words Spelled Correctly, Correct Spelling Sequences, and Percentage of Words Spelled Correctly. Reliability and validity data was not gathered. Studies find that three-minute writing samples correlate well with standardized writing achievement scores (Amato & Watkins, 2011; Fewster & Macmillan, 2002).

### **Procedures**

Participants were asked to complete approximately four hours of testing consisting of cognitive, academic, executive functioning, and information processing assessments across two 2-hour sessions on the same day (*e.g.*, 10:00 am to 12:00 pm, and 1:30 pm to 3:30 pm). Whenever possible, two participants were tested on the same day. This investigator was responsible for administering all of the executive functioning, memory, and achievement measures. A pediatric neuropsychologist administered all intelligence, attention, and processing speed measures.

Testing was conducted at the Cure and Beyond Office (a cancer survivorship program) within Hackensack University Medical Center. While the child was completing the evaluation, the parent(s) were asked to complete two forms for further background information, along with the BRIEF, which measures their perceptions of their child's executive functioning abilities.

Children with ALL and healthy siblings alternated between the two test administrators in the AM or PM to control for time of day. The measures administered to the participants were evenly split between AM and PM. One child in each family pair was administered the intelligence and achievement measures in the AM, while the other child was administered the executive functioning and information processing measures. The children switched measures for the PM assessment session. In four instances families were unable to commit to completing testing in one day and came back within two weeks to complete the testing. Within six weeks of completing testing, the investigator and neuropsychologist scored tests and provided a brief written report to the family describing their children's functioning in each of the areas. Families also were given the opportunity to meet with the researcher to discuss findings further upon request. Upon completion of the testing, each participant received a \$20.00 gift certificate to Barnes and Noble or Toys R Us. In addition, each family was provided \$20.00 to cover travel expenses.

### **Confidentiality**

The participants' identities in this study remained confidential. Each participant was identified by a number code system created by the investigator and employed after testing was completed. This code was destroyed at the completion of this study and will not appear in any publications or presentations of this material. The investigator reviewed participants' health and academic records. These records are maintained using the confidentiality rules set forth by Hackensack University Medical Center and the Health Information Personal Privacy Act (HIPPA) standards for medical, hospital, or psychiatric treatment records and are kept in a locked cabinet in a locked office.

## Research Design and Statistical Analysis

The current study was designed to study the effects of high vs. low IT and TOT on the cognitive, academic, and neuropsychological functioning of post therapy children with ALL, using healthy siblings as the control. By using healthy siblings as the control, the data provide an estimate of developmental capabilities while also controlling for the family experience and demographics. Gender analysis was not possible, as only two of the 16 children with ALL were female.

The current study assessed the neurocognitive late effects for high vs. low number of intrathecal chemotherapy sessions. Typically, the more IT chemotherapy a patient receives, the higher the likelihood for cognitive late effects (Espy et al. 2001; Heukrodt et al., 1988). Based on findings in the research literature, participants were grouped either into the high IT group (20 or more ITs) or the low IT group (19 or fewer ITs).

The current study also measured the effects of time off therapy (a variable often associated with cognitive late effects) by creating a categorical time off therapy factor: each participant was categorized as less than 5 years post treatment ( $TOT > 5$  years), or 5 or more years post treatment ( $TOT \leq 5$  years). All of the current study's children with ALL were two or more years off therapy. The low TOT group's ages ranged from 8 years – 5 months to 12 years – 6 months. The high TOT group's ages ranged from 10 years – 4 months to 14 years – 9 months. The design is in line with previous childhood cancer research showing that some cognitive effects may present by two years off therapy, with even more late effects becoming apparent at five or more years off therapy (Brown et al., 1998; Copeland et al., 1996; Espy et al., 2001; Kingma et al., 2002; Nathan et al., 2007).

All of the measures used in this study, with the exception of the writing task, are nationally normed, age-based, standardized measures. The writing test is age-normed, but is based on norming data from one school district in the Midwest. Due to limited sample size, composite scores for measures were used when possible, rather than subtest analysis. When composite scores were unavailable, either a combined subtest score or individual subtest scores were used based on the practice in previous studies in the field of childhood ALL neurocognition and childhood illness. While information was requested from teachers on student achievement, there was a low response rate from teachers (4 out of the 16 children with ALL), and only 3 of the 16 healthy siblings. This information was not used as the majority of the data was incomplete.

Initially, the analysis plan was to conduct eight 2x2 ANOVAs and one MANOVA on difference scores between children with ALL and healthy siblings. Inopportunistically, for the 2x2 ANOVAs, one of the cells ( $\leq 19$  ITs and  $> 5$  years TOT) had a  $n = 0$ , as children treated over five years ago typically received greater ITs (see Table 2: Scatter Plot). More recent protocols prescribe fewer ITs, in an effort to reduce the number of neurocognitive late effects, while keeping survivor levels at a high percentage. Therefore, the data were dealt with as two independent factors, one studying the effects of IT and one studying the effects of TOT. Thus, two analyses, with 10 one-tailed  $t$ -tests each, were conducted. For the  $t$ -tests, the factors were low and high number of intrathecal chemotherapies (IT), and low and high time off therapy (TOT). These  $t$ -tests were conducted on the sibling pair difference scores for each of the measures administered. Difference scores permitted analysis of data in a way that maximized power with a small sample size.



A Cohen's *d* score was also calculated to analyze effect size of high vs. low IT and high vs. low TOT difference scores for each measure. The Cohen's *d* measures the ratio of difference between the means of two groups in relation to the size of their standard deviations (Sullivan & Feinn., 2012). Effect size can be useful in studies with small sample sizes, where there is a greater likelihood of Type II error. According to Cohen (1992), typically 0.20 is considered a small effect size, 0.50 is considered a moderate effect size, and 0.80 is considered a large effect size. Unlike the Pearson *r* effect size, a Cohen's *d* cannot account for a specific amount of variance; it can only be used in the context of identifying a small, moderate, or large effect size.

### **Assessment of Violation of Assumptions**

*T*-tests were conducted on the following domains using the measures indicated: intelligence (WISC-IV full scale intelligence quotient), verbal memory (CVLT-C List A Trials 1-5 score), executive functioning (RCFT Copy score), executive functioning – parent report (BRIEF Global Executive Composite score), processing speed (TOVA response time composite score), inattention (TOVA omission composite score), impulsivity (TOVA commission composite score), reading (WIAT-II Reading Comprehension and Pseudoword composite score), math concepts (WIAT-II Math Reasoning score), and writing (three minute writing sample – total words written score).

This study used sibling pair difference scores to compare ALL children to a proximal representation (their siblings) of what their neurological function might have been without ALL treatment. The *t*-tests allow one to test the significance of the difference between children treated for ALL who have high or low numbers of intrathecal treatments and high or low time off therapy, and their siblings. The study protected against Type I error by using the Holmes-Bonferroni a priori correction of the Alpha level to .005.

Given the small sample size in this study, it is not surprising that testing of violation of assumptions finds the study underpowered. A power analysis was conducted for an independent sample *t*-test to determine a sufficient sample size using an alpha of 0.005, a power of 0.8, a large effect size ( $d = 0.8$ ), and one tail (Kock, 2015). Based on the aforementioned assumptions, the desired sample size was 39 pairs.

Levene's Tests for homogeneity of variance found homogeneity for eight of the ten IT analyses and eight of the ten TOT analyses. For IT, the homogeneity assumption was violated for inattention ( $p = .008$ ) and impulsivity ( $p = .015$ ). When analyzing TOT, the homogeneity assumption was violated for inattention ( $p = .033$ ) and Executive Functioning Parent Rating ( $p = .051$ ).

A significant negative skew was found for: the high IT children with ALL on Reading (-2.06) and Processing Speed (-1.13); the low IT children with ALL on Processing Speed (-1.06) and Executive Functioning Copy (-1.03). For the high IT siblings, a negative skew was found on Total Words Written (-1.16) and Executive Functioning Copy task (-1.21), and a positive skew on Reading (1.12). Platykurtic kurtosis was found for: high IT children with ALL on Executive Function Copy (-2.63) and the Executive Function Parent Rating (-2.23); the high IT siblings on inattention (-2.01) and impulsivity (-2.29). Leptokurtic kurtosis was found on Reading for the high IT children with ALL (4.59) and the high IT siblings (2.03).

A significant negative skew was found for: the high TOT children with ALL on Reading (-1.39); the high TOT siblings on IQ (-1.12), Reading (-1.02), Processing Speed (-1.52), and Verbal Memory (-1.40). Reading had a significant negative skew for low TOT siblings (-1.35). Platykurtic kurtosis was found for the high TOT ALL children for Executive Function Copy

(-2.44), as well as for the high TOT siblings for Processing Speed (-2.22). A leptokurtic kurtosis was found for the high TOT children with ALL for Verbal Memory (2.25).

Given that this study was underpowered and that a number of the samples were not normally distributed, the findings must be interpreted with caution. In addition, interpretation of findings was complicated as all high IT children happened to also be high TOT, and all low IT children happened to also be low TOT; but two children crossed groups because they were low IT and High TOT. To assure the most conservative interpretation of findings, post hoc t-tests deleted the two “mixed” sibling pairs. The resulting comparison of only high IT and high TOT (n=7) vs. low IT and low TOT (n=7) sibling pairs, prevented the two mixed sibling pairs from exerting a disproportionate effect on this study’s findings.

## Chapter 4: Results

### Descriptive Statistics

This study used paired sibling difference scores on intelligence, achievement, and neuropsychological measures to assess the effects of high and low number of intrathecal chemotherapy treatments and high and low number of years off therapy on performance of children who had been treated for ALL. Group descriptive statistics indicate that mean scores for both the children with ALL and siblings are in the average ranges for the domains studied, with the exception of below average inattention among siblings (see Table 3). Descriptive statistics for the IT and TOT ALL groups are presented in Table 4. Descriptive statistics for the sibling IT and TOT groups are presented in Table 5. Scores on the measures with significant *t*-test findings, and large or moderate effect sizes, are found in Table 6 for children with ALL and Table 7 for healthy siblings.

Sibling pair difference score groupings consisted of a high intrathecal (IT) group of  $\geq 20$  IT ( $n = 7$ ), a low intrathecal group of  $\leq 19$  IT ( $n = 9$ ), high time off therapy (TOT) group of  $\geq 5$  years ( $n = 9$ ) and a low time off therapy group of  $< 5$  years ( $n = 7$ ). The sibling pair difference score analyses for high and low number of intrathecal chemotherapy groups (IT) are presented in Table 8. The sibling pair difference score analyses for high and low time off therapy groups (TOT) are presented in Table 9. Negative difference scores indicate that the children with ALL performed more poorly than their healthy siblings. Positive difference scores indicate that the children performed better than their healthy siblings.

### Intelligence

Participants scored within the average to high average range on the Wechsler Intelligence Scale for Children – Fourth Edition Full Scale IQ, with ten of the 16 children with ALL

performing more poorly than their healthy sibling. The subscale group means and standard deviations for children with ALL and their healthy siblings are presented in Table 10. The Full Scale WISC-IV scores of individuals with ALL ranged from 87 to 116 ( $M = 103.25$ ,  $SD = 8.73$ ) (see Table 11). Full Scale WISC-IV scores for the healthy siblings ranged from 85 to 121 ( $M = 107.31$ ,  $SD = 8.70$ ) (see Table 12).

#### **Number of intrathecal chemotherapies (ITs).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being intelligence as operationalized by the WISC-IV Full Scale IQ. The Full Scale IQ score combines the scores from all 10 subtests that assess intellectual functioning related to verbal comprehension, perceptual reasoning, working memory, and processing speed. A positive difference score indicates that the child with ALL performed better than his or her healthy sibling, while a negative difference score indicates the child with ALL performed more poorly than his or her healthy sibling. The  $t$ -test  $p$ -value for the factor IT was set at .005 (see Table 8) and fell short of significance when applying the Holmes-Bonferroni Correction,  $t(14) = 1.798$ ;  $p = .047$ , although the effect size was large ( $d = .89$ ). The mean IQ difference score between children with ALL who received high IT and their healthy siblings was approximately minus nine points ( $M = -8.71$ ,  $SD = 10.22$ ), whereas the mean difference score between children with ALL who received low IT and their healthy siblings was negligible ( $M = -0.44$ ,  $SD = 8.20$ ). Mean IQ for children with ALL who received high IT was 102.00 ( $SD = 9.39$ ), vs. 110.71 ( $SD = 6.34$ ) for their healthy siblings.

### **Time off therapy (TOT).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being time off therapy high (TOT  $\geq 5$ ) and low (TOT  $< 5$ ), and the dependent variable being intelligence as operationalized by the WISC-IV Full Scale IQ (see Table 9). The *t*-test indicated no significant intelligence effects for the factor TOT,  $t(14) = .525, p = .304$ . The mean difference score between high TOT children with ALL and their healthy siblings ( $M = -5.22, SD = 11.51$ ), versus the mean difference score between low TOT children with ALL and their healthy siblings ( $M = -2.57, SD = 7.59$ ), indicated that IQ scores of children with ALL who were off therapy for varying periods of time were equivalent.

### **Reading Composite**

The scores on the Wechsler Individual Achievement Test - Second Edition subtests (WIAT-II) measuring reading comprehension and pseudoword reading ranged from low average to high average. Children with ALL had reading composite scores ranging from 92 to 114 ( $M = 107.96, SD = 9.76$ ). Scores for the healthy sibling group ranged from 92 to 123 ( $M = 108.96, SD = 10.35$ ). See Tables 6 and 7 for participants' individual scores for Reading Composite.

### **Number of intrathecal chemotherapy (ITs).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high (IT  $\geq 20$ ) and low (IT  $\leq 19$ ), and the dependent variable being reading as operationalized by the Reading Composite score of the WIAT-II. The reading composite score represents participants' combined performance on the WIAT-II Reading Comprehension and Pseudoword subtests. The *t*-test indicated a significant reading effect for the factor IT,  $t(14) = 3.633, p < .001$ , and a large effect size ( $d=1.81$ ) was noted (see Table 8). The mean difference score between children with ALL who received high IT was seven points lower

than their healthy siblings ( $M = -7.36, SD = 6.54$ ), while the mean difference score for the children with ALL who received low IT was about four points higher than their siblings ( $M = 3.94, SD = 5.89$ ). Using the Holmes-Bonferroni Correction, these findings reach statistical significance.

### **Time off therapy (TOT).**

A one-tailed t-test on sibling pair difference scores was conducted with the factor being time off therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), and the dependent variable being reading as operationalized by the Reading Composite score of the WIAT-II. The reading composite score represents subjects' combined performance on the WIAT-II Reading Comprehension and Pseudoword subtests. The *t*-test indicated no significant reading effects for the factor TOT,  $t(14) = 2.077, p = .028$ , although the effect size was large ( $d=1.06$ ) (see Table 9). The mean difference score between children with ALL and their healthy siblings ( $M = -4.44, SD = 8.16$ ) indicated that children with ALL who were off therapy longer performed four points lower than their healthy siblings on the reading composite measure. Low TOT children with ALL scored three points above their healthy siblings ( $M = 3.43, SD = 6.56$ ).

### **Math Reasoning**

The scores on the Wechsler Individual Achievement Test - Second Edition (WIAT-II) testing math reasoning ranged from low average to superior. The scores of children with ALL ranged from 89 to 125 ( $M = 108.43, SD = 9.40$ ) on math reasoning. Scores for the healthy sibling group ranged from 85 to 132 ( $M = 109.12, SD = 12.70$ ). See Table 6 (children with ALL) and Table 7 (healthy siblings) for participants' individual scores for math reasoning.

**Number of intrathecal chemotherapies (ITs).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being math reasoning as operationalized by the Math Reasoning Score of the WIAT-II. The *t*-test indicated significant math reasoning effects for the factor IT,  $t(14) = 3.079, p = .004$ , and a large effect size ( $d=1.61$ ) was noted (see Table 8). The mean difference score between children with ALL who received high IT was about nine points below their healthy siblings ( $M = -8.85, SD = 6.04$ ), while children with ALL who received low IT performed five points higher than their healthy siblings ( $M = 5.22, SD = 11.46$ ). Using the Holmes-Bonferroni Correction, these findings reach statistical significance.

**Time off therapy (TOT).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being time off therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), and the dependent variable being math reasoning as operationalized by the Math Reasoning Score of the WIAT-II. The *t*-test was not significant between the two groups for the factor TOT,  $t(14) = 2.791, p = .007$ , although the effect size was large ( $d=1.30$ ) (see Table 9). The high TOT mean difference score indicated that children with ALL who were off therapy longer performed about seven points lower on the math measure than their healthy siblings ( $M = -6.67, SD = 6.09$ ). The mean difference score of the low TOT children with ALL indicates they performed six points higher than their healthy siblings ( $M = -6.43, SD = 12.83$ ).



### **Three-Minute Writing Sample**

The scores for the three-minute writing task ranged from borderline to high average. The scores of children with ALL ranged from 65 to 112 ( $M = 93.62$ ,  $SD = 13.83$ ) on the writing task. Scores for the sibling group ranged from 72 to 120 ( $M = 96.83$ ,  $SD = 19.93$ ).

### **Number of Intrathecal chemotherapies (ITs).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being writing as operationalized by the total words written. The  $t$ -test indicated no significant writing effects for the factor IT,  $t(14) = .406$ ,  $p = .345$  (see Table 8).

### **Time off therapy (TOT).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being time off therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), and the dependent variable being writing as operationalized by the total words written. The  $t$ -test indicated no significant writing effects for the factor TOT,  $t(14) = -.185$ ,  $p = .527$  (see Table 9).

### **Inattention**

The Test of Variable Attention – Omission composite scores (inattention) ranged from well below average to the average range for the participants in this study. The scores of children with ALL ranged from 83 to 110 ( $M = 97.01$ ,  $SD = 14.08$ ). Scores for the healthy sibling group ranged from well below average to the average range 41 to 105 ( $M = 83.31$ ,  $SD = 22.87$ ). See Table 6 (children with ALL) and Table 7 (healthy siblings) for participants' individual scores for inattention.

### **Number of intrathecal chemotherapies (ITs).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being inattention as operationalized by the *TOVA* – Omission composite score (inattention). The *t*-test indicated no significant inattention effects for the factor IT,  $t(14) = 1.198, p = .125$ , although the effect size was moderate ( $d = .62$ ) (see Table 8). The mean difference score between children with ALL who received high IT and their healthy siblings indicated that the siblings performed six points lower on this measure of inattention ( $M = 6.21, SD = 16.06$ ). The mean difference score between children with ALL who received low IT and their healthy siblings was about 20 points lower for the siblings ( $M = 19.52, SD = 25.65$ ).

### **Time off therapy (TOT).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being time off therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), and the dependent variable being inattention as operationalized by the *TOVA*– Omission composite score. The *t*-test indicated no significant inattention effects for the factor TOT,  $t(14) = .707, p = .246$  (see Table 9). The mean difference score of high TOT children with ALL from their siblings indicated that children with ALL who were off therapy longer performed over one standard deviation better than their healthy siblings on the measure of inattention ( $M = 17.25, SD = 26.75$ ). In contrast, the mean difference score of low TOT children with ALL was nine points higher than their healthy siblings ( $M = 9.14, SD = 15.92$ ).

### **Impulsivity**

The Test of Variable Attention Commission composite scores, which tested impulsivity, ranged from well below average to high average. The scores of children with ALL ranged from

60 to 111 ( $M = 92.31$ ,  $SD = 17.84$ ). Scores for the healthy siblings ranged from 52 to 111 ( $M = 87.32$ ,  $SD = 20.21$ ). See Table 6 (children with ALL) and Table 7 (healthy siblings) for participants' individual scores for impulsivity.

#### **Number of Intrathecal chemotherapies (ITs).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being impulsivity as operationalized by the TOVA Commission composite score. The  $t$ -test indicated no significant impulsivity effects for the factor IT,  $t(14) = 1.304$ ,  $p = .107$ , although the effect size was moderate ( $d = .64$ ) (see Table 8). The mean difference score between children with ALL who received high IT and their healthy siblings indicated that they performed similarly to their healthy siblings ( $M = -3.61$ ,  $SD = 20.87$ ). Low IT children with ALL outperformed their healthy siblings by approximately 12 points ( $M = 11.67$ ,  $SD = 24.86$ ).

#### **Time off therapy (TOT).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being time off therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), and the dependent variable being impulsivity as operationalized by the TOVA Commission composite score (impulsivity). The  $t$ -test indicated no significant impulsivity effects for the factor TOT,  $t(14) = -.415$ ,  $p = .342$  (see Table 9). The mean difference score of the high TOT group was seven points ( $M = 7.22$ ,  $SD = 28.20$ ), and the mean difference score of the low TOT group was two points ( $M = 2.11$ ,  $SD = 18.30$ ), when compared to their healthy siblings.

#### **Processing Speed**

Scores for the Test of Variable Attention Response Time composite (TOVA) ranged from well below average to the superior range. The scores of children with ALL ranged from 48 to

121 ( $M = 95.37$ ,  $SD = 24.07$ ). Scores for the healthy siblings ranged from 56 to 117 ( $M = 92.40$ ,  $SD = 20.19$ ).

**Number of intrathecal chemotherapies (ITs).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being processing speed as operationalized by the TOVA. The  $t$ -test indicated no significant processing speed differences for the factor IT,  $t(14) = .504$ ,  $p = .311$  (see Table 8).

**Time off therapy (TOT).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being Time Off Therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), and the dependent variable being processing speed as operationalized by the TOVA Response Time Score. The  $t$ -test indicated no significant processing speed effects for the factor TOT,  $t(14) = .960$ ,  $p = .177$  (see Table 9).

**Verbal Memory**

Participant's scores ranged from below average to above average on the Combined List A 1-5 of the California Verbal Learning Test for Children (CVLT). The scores of children with ALL ranged from 73 to 121 ( $M = 102.62$ ,  $SD = 12.46$ ). Scores for the healthy siblings ranged from 76 to 121 ( $M = 99.86$ ,  $SD = 12.66$ ).

**Number of intrathecal chemotherapies (ITs).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being verbal memory as operationalized by the CVLT combined List A 1-5. The  $t$ -test indicated no significant verbal memory effects for the factor IT,  $t(14) = .046$ ;  $p = .481$  (see Table 8).

### **Time off therapy (TOT).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being Time Off Therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), the dependent variable being verbal memory as operationalized by the CVLT Lists A 1-5. The *t*-test indicated no significant verbal memory effects for the factor TOT,  $t(14) = -.018, p = .507$  (see Table 9).

### **Executive Functioning**

All but one subject's scores were within average ranges on the Rey Osterrieth Complex Figure Test (RCFT) Copy Measure. Scores of children with ALL ranged from 90 to 104 ( $M = 99.98, SD = 4.29$ ). Scores for the healthy siblings ranged from 82 to 108 ( $M = 98.69, SD = 6.30$ ).

### **Number of intrathecal chemotherapies (ITs).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being executive functioning as operationalized by the RCFT Initial copy score. The *t*-test indicated no significant executive function effects for the factor IT,  $t(14) = .582; p = .285$  (see Table 8).

### **Time off therapy (TOT).**

A one-tailed *t*-test on sibling pair difference scores was conducted with the factor being Time Off Therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), and the dependent variable being executive functioning as operationalized by the RCFT Initial copy score. The *t*-test indicated no significant executive functioning effects for the factor TOT,  $t(14) = .601, p = .279$  (see Table 9).

### **Parent Perception of Executive Functioning**

Participants' scores ranged from below average to high average on the Behavioral Rating Index of Executive Functioning - Global Executive Composite (BRIEF). The scores of children

with ALL ranged from 84 to 130, ( $M = 100.32$ ,  $SD = 17.10$ ). Scores for the siblings ranged from 84 to 133, ( $M = 103$ ,  $SD = 17.20$ ).

#### **Number of intrathecal chemotherapies (ITs).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being number of intrathecal chemotherapies, high ( $IT \geq 20$ ) and low ( $IT \leq 19$ ), and the dependent variable being parent perspective of executive functioning as operationalized by the *BRIEF* - Global Executive Function Composite, which consists of the BRIEF Inhibit, Initiate, and Monitor scores. The  $t$ -test for the factor IT indicated no significant executive functioning effects based on parent perspectives,  $t(12) = .392$ ;  $p = .278$  (see Table 8).

#### **Time off therapy (TOT).**

A one-tailed  $t$ -test on sibling pair difference scores was conducted with the factor being Time Off Therapy, high ( $TOT \geq 5$ ) and low ( $TOT < 5$ ), and the dependent variable being parent perspective of executive functioning as operationalized by the BRIEF. The  $t$ -test indicated no significant executive functioning effects of TOT, based on parent perspective,  $t(12) = .370$ ,  $p = .337$  (see Table 9).

#### **Post Hoc Analysis**

There are many limitations that threaten both the internal and external validity of this study. Many of the issues stem from the small sample size. Despite best efforts to obtain a larger cohort, the sample size issue that is common with single site pediatric cancer studies occurred in this study as well. Therefore, interpretation of the findings need to be cautious and conservative.

Moreover, interpretation of findings was hampered due to the artificial division of participants into high and low groups. To help understand the findings a post hoc correlation analysis examined the relationship between number of intrathecal chemotherapies and the

amount of time off therapy for the children with ALL. Results indicated a positive relationship between IT and TOT  $r(16) = .72$ .

In addition it was noted that seven participants in the high IT group also were in the high TOT group, and seven in the low IT group also were in the low TOT group; this meant that data for these students were identical when analyzing high vs. low IT or TOT. In contrast, the remaining two participants contributed unique variance in the analyses because they were “mixed”: in the low IT group but high TOT, These two *mixed* children may have disproportionately affected the findings as either their IT or TOT was unlike that of their other group members. It could be argued that the analysis might have been done best by excluding these two families. In this case, the groups in all domains would be  $n = 7$  for high IT and high TOT, and  $n = 7$  for low IT and low TOT.

To explore this point, post hoc analyses was conducted, without the two *mixed* pairs, for all domains that had a significant finding or moderate to large effect size in the original analyses. As in the original analysis, the  $t$ -test ( $n = 14$ ) found significantly poorer reading composite ( $p = .005$ ) and large effect size ( $d = 1.65$ ) for the high IT (and high TOT) group, than for the low IT (and low TOT) group, when compared with their healthy siblings ( $p = .005$ ). Unlike the original analysis, the math reasoning effect for children with ALL missed significance ( $p = .007$ ), though the effect size remained large ( $d = 1.52$ ). The original analysis reported a large effect size for FSIQ, which in the post hoc analysis became a moderate effect size ( $d = .68$ ). The moderate effect sizes for inattention and impulsivity in the initial analysis did not hold up in the post hoc analyses. Given these post hoc results, a conservative and cautious approach to interpretation of the results is warranted.

## Summary

This study examined the intellectual, academic, and neuropsychological outcomes of ALL treatment using a sibling-controlled design. Overall, the post therapy children with ALL and their healthy siblings performed in the average range for all the domains studied. The only exception was for both inattention and impulsivity, where the healthy siblings in the low IT and high TOT groups scored below average.

Despite the overall average performance of the children with ALL, children who had received high numbers of intrathecal chemotherapy treatments had significantly lower reading composite and math performance than the low IT ALL group, relative to their healthy siblings. The children with ALL in the high IT and high TOT groups demonstrated a large effect size for both the reading composite and math reasoning domains. Intelligence quotient showed a large effect size for high IT children with ALL, who scored lower than low IT children with ALL, when compared to their healthy siblings. Moderate effect size for inattention and impulsivity also related to the factor number of ITs, where low IT children with ALL outperformed their healthy siblings. Given that several of these findings did not hold up in the post hoc analyses, they should be interpreted with caution.



## Chapter 5: Discussion

### Major Findings

The current study's findings replicate prior research demonstrating delays in IQ, reading, and math achievement for children who had been treated for ALL, although their performance was in the average range. The study supports findings (Brown et al., 1996; Brown et al., 1998; Espy et al., 2001; Lyer et al., 2016; Peterson et al., 2008; Reddick et al., 2006) that the relative delay experienced by children with ALL in these areas is related to high IT. There also is evidence in this study that the relative delay on reading composite and math reasoning is influenced by high TOT. In this study, low IT (19 or fewer ITs) and low TOT (under 5 years off therapy) were not related to any harmful effects on the participants' cognitive, academic, or neuropsychological development.

In summary, when compared to their siblings, children who received 20 or more ITs performed poorer on intelligence, reading, and math measures than those who received 19 or fewer intrathecal treatments. In addition those with five or more years off therapy were more discrepant from their siblings in reading and math reasoning than children with ALL who were off therapy fewer than five years. Because there was no baseline data available, it is impossible to know if the losses experienced by children with ALL are minor or major losses. These findings suggest that future research should explore in greater depth the particular elements of intelligence, reading, and math that are affected by ALL treatment, in order to take preventive and remedial action. Despite treatment effects noted in this study, it is heartening that, after two and a half years of therapy that includes systemic chemotherapy, intrathecal chemotherapy, and a host of other treatments, post therapy children with ALL generally performed at expected levels for their ages on the study's measures.

This study did not replicate findings of prior research that showed weaknesses in verbal memory, processing speed, attention, and executive functioning in children who had been treated for ALL. In addition, no weaknesses were found on factors that have seldom been explored in the ALL literature: writing prose, parent rating of executive functioning, and the role of impulsivity in poor attention.

The findings of this study suggest that, where sample size is low, sibling difference scores might be a valuable method of analyzing the effects of treatment on post therapy children with ALL, and possibly other types of rare childhood medical conditions. Analyzing difference scores, one factor at a time, provides an alternative to the ANOVA when cell size is small, as is common in single site studies.

The findings of this study also suggest that comparing the number of IT chemotherapies, and how these affect intelligence, achievement, and neuropsychological outcomes, is valuable in studying long term effects of ALL treatment where matching of treatment protocols is not possible. The current study adopted Ashford et al.'s (2010) and Pui et al.'s (2003) method of using number of ITs to study the impact of high vs. low IT on children with ALL.

Only six known studies (in addition to the current study) have used sibling control groups (Jansen et al., 2008; Kaemingk et al., 2004; Mitby et al., 2003; Reddick et al., 2006; Reeves et al., 2007; Rodgers et al., 2003). Of these studies, Jansen et al., Reddick et al., and Reeves et al. used a neurocognitive battery similar to that in the current study. The use of healthy sibling controls allowed this study to control for the family's cancer experience, family genetics, and for demographics, such as SES and parental education level. It could not control, however, for age, gender and undiagnosed medical or psychosocial conditions. Due to this and other methodological issues in this study, any conclusions must be interpreted cautiously.

## Domain Specific Findings

Research has indicated that general IQ may be affected by higher cumulative doses of IT chemotherapy (Kingma et al., 2002; Ochs et al., 1991; Reddick et al., 2006). The current study found a similar impact on intellectual functioning when receiving 20 or more ITs. The current study did not find any effect on IQ when analyzing the number of years off therapy.

Recent studies have found moderate reading decoding delays among children who have been treated for ALL (Campbell et al., 2007; Peterson et al., 2008; Reddick et al., 2006; Spiegler et al., 2006). Some studies have found reading comprehension delays as well, while others have not (Brown et al., 1998; Campbell et al., 2007; Espy et al., 2001; Waber et al., 2007). The findings from the current study support previous research demonstrating that a relative reading weakness, when compared to their healthy siblings, is not unusual for children with ALL who were treated with high IT and were five or more years off therapy. Perusal of the group means indicated that pseudoword reading was comparable across all groups, and that the significant findings for reading composite likely were due to weaker reading comprehension in high IT children with ALL; these children scored 12 points lower on the Reading Comprehension subtest than their healthy siblings. Similarly, the high TOT children with ALL underperformed their healthy siblings by about eight points. Low IT and low TOT children with ALL performed on both tasks very much like their healthy siblings. Future research needs to explore which of these aspects of reading skill are most at risk, as both are critical to reading success.

Similar to reading, the majority of studies of math achievement have shown math calculation delays in children treated for ALL (Brown et al., 1996; Carey et al., 2008; Espy et al., 2001; Kaemingk et al., 2004; Reddick et al., 2006; Waber et al., 2007). The current study is one of only a few that utilized math reasoning rather than math calculations in the assessment battery.

The analyses demonstrated a relative weakness in math reasoning, when compared to their healthy siblings, for both the high IT and high TOT groups; children with ALL scored approximately one-half *SD* below their healthy siblings in both cases. In contrast, the low IT and low TOT ALL groups performed somewhat stronger than their siblings. It is suggested that further research consider a mathematics-specific study that compares math calculation versus conceptual math ability, relative to number of ITs and time off therapy for survivors of childhood ALL.

There were unexpected moderate effect size findings for inattention and impulsivity in the original analyses, with healthy siblings scoring worse than the children with ALL. When the post hoc analysis was conducted, however, these findings changed to a small effect size. The effect of the two *mixed* families that switched in the analysis between the high and low groups, exemplifies the concern that with a small sample size even two family pairs can disproportionately affect findings. Table 13 illustrates the number of times that individual families showed large variability in performance between the two siblings, again calling for a conservative approach to conclusions drawn from this study. In addition to the above concerns, it should be noted that some of the sibling data in this small N study was not normal, therefore complicating interpretation.

Despite caution in interpreting this study's findings, the question of how the cancer experience affects siblings remains. Reddick et al. (2006), one of three known studies of ALL chemotherapy effects to use a matched sibling control group to study attention, found attentional issues with the healthy siblings.

The researcher contacted Dr. Reddick from St. Jude's Hospital to request unpublished data from his study regarding healthy sibling attention. In an email correspondence, Dr. Reddick

(2/18/2010) shared unpublished healthy sibling data, which demonstrated attention issues on the Conner's Continuous Performance Test (CPT) (see Table 14). According to the Connors CPT, *T*-scores in the low 60s are mildly atypical and *T*-scores of 70 or higher are considered markedly atypical. Reddick et al. reported extremely atypical omission scores for sibling controls on the Conner's CPT ( $t = 80.75 \pm 19.199$ ), while performance of children with ALL was "at risk" ( $t = 62.9 \pm 8.7$ ).

A review of Sharpe and Rossiter's (2002) meta-analysis of 51 studies across different childhood medical conditions found that cognitive development scores were lower for siblings who had a brother or sister with a chronic medical condition than for siblings who had healthy brothers or sisters. Research on siblings of children with cancer almost always focuses on social or emotional aspects of having a sibling with a life-threatening illness (e.g., post-traumatic stress disorder symptoms) and not on cognitive consequences (Alderfer, Labay, & Kazak, 2003; Campbell et al., 2009; Kazak et al., 2004). For example, Alderfer et al. (2003) found that 49% of siblings exhibited mild post-traumatic stress disorders (PTSD), and an additional 32% exhibited moderate to severe levels of PTSD. This data suggests that a sizable percentage of siblings of childhood ALL survivors may be at risk for experiencing emotional and/or other disorders related to the shared childhood cancer experience and that this should continue to be explored.

### **Limitations**

The small, self-selected convenience sample, coupled with the large number of dependent variables measured and the artificial grouping into high or low IT and TOT groups caused analysis concerns in this study. Control for sex, age, SES, age at diagnosis of ALL, treatment protocol, and other factors in this study was not possible. Moreover, this was an underpowered study that also had issues of normality on some of the measures. Despite findings

that replicate other, (e.g., Brown et al., 1996, Brown et al., 1998; Kaemingk et al., 2004), this study's results need to be interpreted cautiously due to the many methodological constraints.

As is the case with many single-site research studies of children with cancer, the small sample size left the current study vulnerable to Type II error: failing to find significance due to limits with power (Campbell et al. 2007). Sample size required this study to utilize composite scores, which then limited the ability to distinguish patterns across the composites' subtests. For example, although reading composite results were significant, performance on the pseudoword (decoding) task could not be compared statistically with reading comprehension performance. The current study's limited sample size prevented a more processing-focused approach to understanding intelligence, achievement, and neuropsychological functioning with this population of learners.

Unfortunately, the present study had only two female participants with ALL. Numerous studies have found females with ALL to be more susceptible to cognitive late effects of treatment (Brown et al., 1998; Butler et al., 2002; Mulhern et al., 2004), but this couldn't be explored further in this study.

Another limitation is that this study focused on math reasoning only. Most previous research has focused on math calculation. Studies with post therapy children with ALL that focus on both math concepts and math calculations would be essential to better understand the impact of the cancer experience on math skills.

Design issues are common in this field of work, as so few children are diagnosed with childhood cancer (Moore, 2005). Children at a single hospital will typically be treated on different protocols and a number of variables will impact the amount of treatment they receive (e.g., age, weight, gender, disease progression at time of diagnosis). All of these factors influence

the treatment regimen and ultimately potential outcomes. For example, all participants with ALL in the current study received methotrexate via IT, which puts them into a higher risk category for late effects than had non-methotrexate protocols been followed. However, the sample size prevented analysis of the data by age, chemotherapy protocol, and the other relevant variables mentioned above.

Grouping participants into high and low IT groups also brings up the issue of how much the significant findings for high vs. low IT were related to the anesthesia necessary to administer treatment, rather than to the chemotherapy itself. At each IT treatment, the patient with ALL receives general anesthesia. Although the effects of anesthesia in children are not well known, Wilder et al. (2009) found that when children under the age of four are exposed to multiple anesthetics (two or more), there is a statistically significant increase in learning disabilities later in life. Similarly, Flick et al. (2011) found that multiple anesthetics increased the likelihood for learning disabilities, even when the analysis ruled out confounding health related issues that may themselves negatively impact learning. Ing et al. (2012) found that children under the age of three who were exposed to anesthesia were more likely than their healthy peers to experience significant delays in receptive language, expressive language, and cognition. This raises the question of whether some portion of detrimental effects typically experienced by children with ALL may be due to factors related not just to the intrathecal treatment but to other aspects of the treatment experience as well, such as anesthesia effects.

Another factor this study was unable to account for was the effect of direct instructional time and number of days absent from school, both of which could affect the performance of children with ALL. Also, considering this was a single-site study at a treating institution with a robust educational intervention program, it is unclear how these educational services influenced

the outcome of this study. It is estimated that approximately 60 of the 230 children's hospitals in the U.S. have some level of dedicated educational support staff, making this treatment center somewhat unusual with its high level of support (two full-time educational liaisons). Much still needs to be learned about the impact of these programs, and whether participants, such as in this study, experience fewer academic and cognitive late effects of treatment due to the intensive educational and emotional support they receive during- and post-treatment.

Seven children with ALL (44%) in this study took advantage of hospital educational outreach services, and nine of the children with (56%) agreed to have the hospital set up a 504 Plan or Individual Educational Program (IEP) while on treatment. Students with 504 Plans received extra time on tests, extra time passing in the hall, and other accommodations, such as note-takers when absent from school. Students with IEPs were given the same accommodations, but also benefitted from additional direct instruction by educators at home or in the hospital. This support may have mitigated the development of more serious delays. Unfortunately, a record review did not reveal any further information that could be used to interpret the relative strengths and weaknesses of the children treated for ALL.

### **Implications of Findings**

This study has five important findings to contribute to the study of effects of treatments on children with ALL:

- 1) In general, post therapy children with ALL are performing within average ranges in every domain assessed, which implies that treatment protocols are causing less harm in the realms of cognition, learning, and information processing than in the past. In fact, the average performance of children with ALL in the low IT group surpassed their healthy siblings in reading



composite, math reasoning, attention measures, processing speed, verbal memory, and executive functioning (copying task).

2) This study's findings replicated neurocognitive relative weaknesses for post therapy children with ALL who received high IT on intelligence, reading composite, and mathematics reasoning tasks.

3) This study explored the impact of a five-year time off therapy split to investigate if and when declines in skills such as reading and math reasoning become evident. The results from this study show that late effects in reading and math reasoning are particularly problematic five or more years off therapy.

4) This study demonstrated that number of ITs may be a possible substitute when cumulative dosage information is not a practical option, due to small sample size and multiple treatment protocols.

5) This study utilized sibling difference scores as the data for analysis when studying childhood ALL. The use of difference scores proved promising for maximizing power, given the small sample size.

Continued study of the cognitive, academic, and neuropsychological effects of childhood ALL treatments is important in order to identify and find ways to mitigate delays that become apparent over time. With more knowledge about the treatment factors that are particularly deleterious, treatment protocols can be modified and educational interventions introduced to prevent predicted neurocognitive weaknesses.

### **Suggestions for Future Research**

The findings of this study suggest there is still much to learn and understand about the cognitive, academic, and neuropsychological characteristics and needs of children treated for

acute lymphocytic leukemia. The continued participation of healthy sibling cohorts in neurocognitive studies also is useful in shedding light on the needs of healthy siblings who have lived through the cancer experience. Of course, the use of a healthy sibling has its limitations as each sibling and each home experience is unique. Therefore, in addition to healthy sibling groups, researchers should continue to use other comparison groups of children with chronic conditions or survivors of childhood cancers that do not require cognitively threatening therapy. These controls allow the researcher to differentiate the psychosocial issues, as well as treatment protocol and disease effects, on learning and development. The need for larger sample sizes when possible is evident.

When possible, future researchers should consider gathering samples from multiple childhood cancer treatment institutions in order to obtain an adequate number of subjects to control for the variables that could not be controlled in this study. When small sample sizes are unavoidable, it is recommended that researchers choose a more narrow focus of study so that specific areas of cognitive functioning may be evaluated in more depth. This study suggests that the many aspects of reading decoding, comprehension, math calculation and math reasoning be explored in depth by using diagnostic assessment batteries. The more researchers can discover about the weaknesses contributing to academic delays, the more able educators will be to design interventions that target the weaknesses and accelerate success. When there are no diagnostic batteries to measure a certain skill, it is recommended that multiple measures of the same construct be administered (e.g., executive functioning, attention) to tap its multiple components to the fullest extent possible. In addition, more research is needed to better understand what impact there is on affective functioning such as resilience and risk taking, and how these factors impact the academic functioning of children with ALL. Finally, while it is difficult to do,

research in the field would be clearer if baseline data could be collected at the time of ALL diagnosis, or as soon after treatment begins as is practical.

Given recent MRI results pointing to structural brain differences associated with ALL treatment, future childhood ALL research may find it useful to use fMRI to compare brain activation during specific tasks. Studies also could consider including in the assessment battery a computerized continuous processing test (CPT) to measure attentional issues.

While a high amount of IT chemotherapy is typically considered a negative predictor in reading and math areas, so is more time off therapy. In addition to accounting for the number of ITs and cumulative dosage that a child receives, future studies should continue to explore the role of TOT, which suggests that relatively negative effects become more apparent with time, especially five or more years post-treatment. What remains unexplored is if the relationship between longer time off therapy and difficulty in learning tasks relates to the more challenging academic expectations in the upper elementary grades or to the loss of instructional time when basic skills were being developed. Given the high inter-correlation between IT and TOT among post therapy children with ALL, future research should attempt to tease out how much of the treatment effects reported in the literature are accounted for by IT, and how much by the more difficult school curriculum as TOT increases. Specifically, studies with larger sample sizes could examine the interaction between time off therapy and ITs in relation to task demands that get harder. In larger studies, control for the age when the child became ill also is recommended.

The cancer experience stretches a family's time, emotional, and financial resources (Labay & Walco, 2004; Steinglass, 1998). Prior research has documented the social-emotional effect of cancer treatment on patients, and recent research has begun to focus on long-term psychosocial effects on healthy siblings without cancer, primarily in the form of PTSD issues.

Alderfer et al. (2003; 2010), Campbell et al. (2009), Kazak et al. (2004), and Long, Marsland, and Alderfer (2013) have found that the cancer experience has a considerable emotional and social toll on the healthy siblings as well as the child with ALL. This body of work emphasizes the need to provide increased support early on, not only to children with cancer, but also to their families in general, and to the siblings specifically. The need to more systematically measure whether early psychoeducational support helps to minimize relatively negative effects on the healthy siblings is very important.

Future studies at a national level also should compare the outcomes from treating hospitals that have educational services for children with ALL vs. those that do not. Canada recently moved to standardizing psychosocial care at all 17 of the pediatric cancer centers throughout the country. Therefore, if a child in Canada is diagnosed with cancer, the child will receive the same level of educational service regardless of SES, geography, or treating institution. This includes standardizing the educational supports childhood cancer patients receive while on treatment and after treatment is completed. This allows Canada to conduct national studies focused on various aspects of psychosocial and educational care, including educational and cognitive effects of childhood cancers. This type of national study is not possible in the U.S. at this time.

Peterson et al. (2008) concluded that a national standardized neuropsychological battery needs to be created and implemented across studies of ALL outcomes in hopes of being able to better track outcomes and impediments in the educational experience of children with ALL. This in turn would allow educators to be more proactive regarding the learning needs of children with ALL, even after treatment has terminated. There is a move among hospital-based educators in the U.S. to begin to address these concerns (Irwin & Elam, 2011).

The current study indicates that high numbers of IT treatments appear to be problematic for reading and mathematics skills, and affect intellectual functioning. In addition, late effects of ALL treatment are more evident five years or more off therapy, than fewer years off therapy. Much more research needs to be conducted on the issues discussed above. Fortunately for children with ALL, lower number of IT treatments continues to be the trend in treating the disease, which seems to result in fewer decrements in achievement. Moreover, the TOT literature implies the need to take preventive educational measures, in the hopes of stemming predictable late effects of treatment.

## Appendices

**List of Tables, Consent, and Institutional Review Board Forms**

**Appendix A**

**Tables**

**Table 1**

*Sibling Pair Demographic Data*

Sibling Pair No.	Age at Time of Testing	Number of ITs	Time Off Therapy Years -Months-Days	Gender	SES	Race
Family 1 Survivor Sibling	10-7 12-10	19	4 -10 -19	Male Male	Upper Middle	White
Family 2 Survivor Sibling	9-4 10-10	16	3 - 3-22	Male Female	Middle	White
Family 3 Survivor Sibling	10-9 13-3	15	4 - 2 -27	Male Female	Upper Middle	White
Family 4 Survivor Sibling	11-0 13-11	16	4 - 1 – 28	Male Female	Upper Middle	White
Family 5 Survivor Sibling	10-7 8-5	18	3 - 10 – 16	Male Male	Upper Middle	White
Family 6 Survivor Sibling	12-6 10-8	16	2 - 10 - 11	Male Female	Upper Middle	White
Family 7 Survivor Sibling	11-7 8-0	16	2 - 9 - 8	Male Female	Middle	White
Family 8 Survivor Sibling	11-10 13-3	19	5 - 9 - 0	Male Male	Lower Middle	White

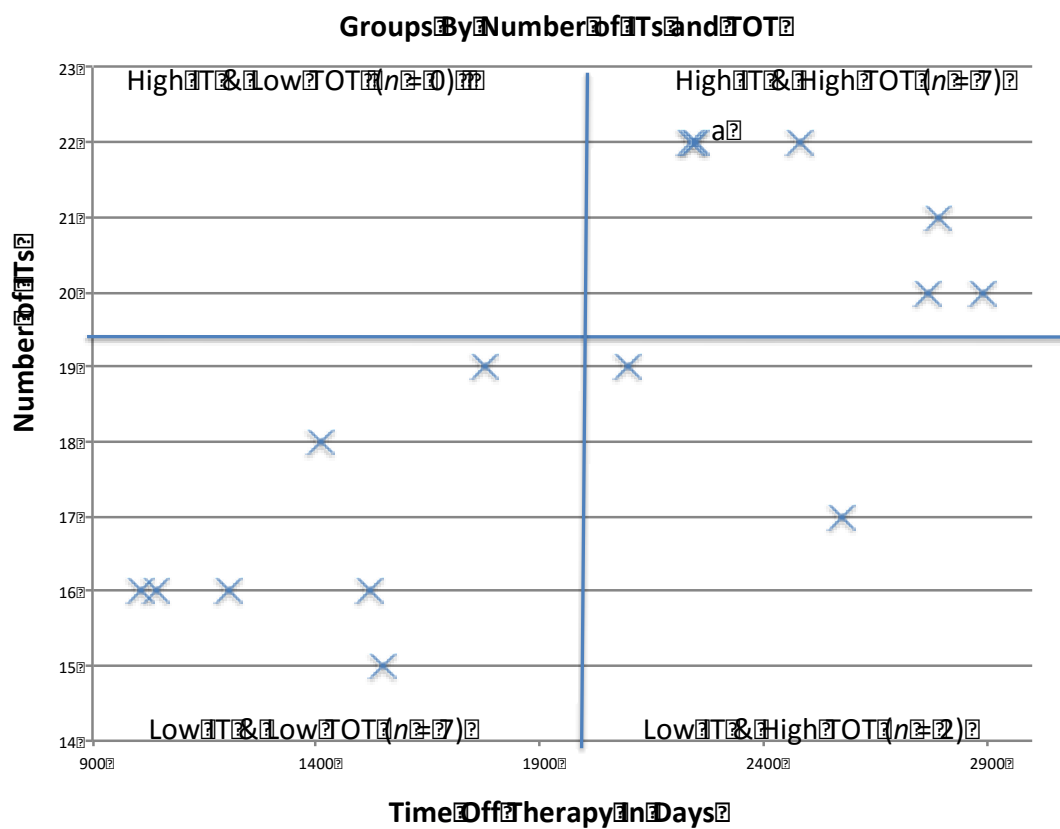
Sibling Pair No.	Age at Time of Testing	Number of ITs	Time Off Therapy Years -Months-Days	Gender	SES	Race
Family 9 Survivor Sibling	10-4 8-0	17	7 - 0 - 21	Male Female	Lower Middle	White
Family 10 Survivor Sibling	14-9 11-9	20	7 - 11 - 3	Male Female	Upper Middle	White
Family 11 Survivor Sibling	12-8 11-0	22	6 - 1 - 25	Female Male	Middle	Hispanic
Family 12 Survivor Sibling	13-9 12-0	22	6 - 9 - 19	Male Female	Middle	White
Family 13 Survivor Sibling	14-0 12-2	20	7 - 7 - 0	Male Female	Upper Middle	White
Family 14 Survivor Sibling	12-7 11-0	22	6 - 1 - 15	Male Female	Upper Middle	White
Family 15 Survivor Sibling	14-4 11-7	22	6 - 1 - 26	Female Male	Low Middle	White
Family 16 Survivor Sibling	12-6 14-7	21	8 - 1 - 20	Male Male	Middle	White

*Note.* SES = Socioeconomic Status; ITs = Number of Intrathecal chemotherapies.



Table 2

## Scatter Plot of Participant IT and TOT Groups



Note. ITs = number of intrathecal chemotherapies; TOT=time off therapy; a = 3 subject data points (all completed therapy within three days of each other).

**Table 3***Descriptive Statistics for Children with ALL and Healthy Sibling Groups*

Domain & Measure	Children with ALL <i>n</i> = 16 <i>M</i> ( <i>SD</i> )	Siblings <i>n</i> = 16 <i>M</i> ( <i>SD</i> )
Intelligence Quotient: <i>WISC-IV Full Scale IQ</i>	103.25(8.73)	107.31(8.70)
Reading Composite: <i>WIAT-II</i>	107.96(9.76)	108.96(10.35)
Mathematics: <i>Math Reasoning</i>	108.43(9.40)	109.12(12.70)
Writing: <i>Three-Minute Writing Sample</i>	93.62(13.83)	96.83(19.93)
Inattention: <i>TOVA Omission</i>	97.01(14.08)	83.31(22.87)
Impulsivity: <i>TOVA Commission</i>	92.31(17.84)	87.32(20.21)
Processing Speed: <i>TOVA Response Time Composite</i>	95.37(24.07)	92.40(20.19)
Verbal Memory: <i>CVLT List A 1-5</i>	102.62(12.46)	99.86(12.66)
Executive Function: <i>RCFT – Copy</i>	99.98(4.29)	98.69(6.30)
Executive Function: <i>BRIEF – Global Executive Composite</i>	100.32(17.10) <i>n</i> =14	103.00(17.20) <i>n</i> =14

*Note.* *M* = mean; *SD* = standard deviation; *n* = sample size; WISC-IV = Wechsler Intelligence Scale for Children - Fourth Edition; IQ = intelligence quotient; WIAT-II = Wechsler Individual Achievement Test - Second Addition; TOVA = Test of Variable Attention; CVLT = California Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; BRIEF = Behavior Rating Inventory of Executive Functioning.

**Table 4*****Descriptive Statistics for High/Low IT and High/Low TOT Groups of Post Treatment for Children with ALL***

Domain & Measure	High IT ( $\geq 20$ ) <i>n</i> = 7	Low IT ( $\leq 19$ ) <i>n</i> = 9	High TOT ( $\geq 5$ years) <i>n</i> = 9	Low TOT ( $< 5$ years) <i>n</i> = 7
	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )
Intelligence Quotient: WISC-IV Full Scale IQ	102.00(9.39)	104.22(8.61)	101.66(10.59)	105.28(5.67)
Reading Composite: WIAT-II	107.85(8.92)	108.05(6.72)	107.00(6.76)	109.21(9.33)
Mathematics: Math Reasoning	106.57(10.32)	109.44(8.96)	105.33(9.60)	112.42(8.05)
Writing: Three-Minute Writing Sample	95.81(16.56)	93.07(16.11)	95.04(10.08)	91.79(18.31)
Inattention: TOVA Omission	95.71(9.25)	98.02(9.15)	98.41(9.70)	95.21(8.28)
Impulsivity: TOVA Commission	88.92(18.42)	94.94(12.03)	91.55(17.40)	93.28(12.18)
Processing Speed: TOVA Response Time Composite	97.25(24.49)	93.91(22.80)	100.22(22.02)	89.14(23.93)
Verbal Memory: CVLT List A 1-5	105.28(8.15)	101.44(15.29)	102.88(13.71)	103.42(11.74)
Executive Function: RCFT – Copy	101.46(1.83)	98.82(5.35)	101.51(1.89)	98.01(5.77)
Executive Function: BRIEF – Global Executive Composite	106.99(28.85) ( <i>n</i> = 6)	95.77(22.98) ( <i>n</i> = 8)	109.04(20.67) ( <i>n</i> = 8)	92.12(22.18) ( <i>n</i> = 6)

*Note.* IT = Intrathecal chemotherapies; TOT = Time off therapy; *M* = mean; *SD* = standard deviation; *n* = sample size; WISC-IV = Wechsler Intelligence Scale for Children - Fourth Edition; IQ = intelligence quotient; WIAT-II = Wechsler Individual Achievement Test - Second Addition; TOVA = Test of Variable Attention; CVLT = California Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; BRIEF = Behavior Rating Inventory of Executive Functioning.

**Table 5***Descriptive Statistics for High/Low IT and High/Low TOT Groups of Healthy Siblings*

Domain & Measure	<i>High IT</i> (>20) <i>n = 7</i> <i>M (SD)</i>	<i>Low IT</i> (<19) <i>n = 9</i> <i>M (SD)</i>	<i>High TOT</i> (>5 years) <i>n = 9</i> <i>M (SD)</i>	<i>Low TOT</i> (<5 years) <i>n = 7</i> <i>M (SD)</i>
Intelligence Quotient: WISC-IV Full Scale IQ	110.71(6.34)	104.66(9.68)	106.88(10.28)	107.85(6.89)
Reading Composite: WIAT-II	115.21(4.09)	104.11(9.80)	111.44(8.46)	105.78(10.42)
Mathematics: Math Reasoning	115.42(9.08)	104.22(13.35)	112.00(10.45)	105.99(15.13)
Writing: <i>Three-Minute</i> Writing Sample	94.33(11.43)	97.63(12.52)	97.60(14.78)	95.85(13.86)
Inattention: TOVA Omission	89.50(14.12)	78.50(20.21)	81.16(21.29)	86.07(14.26)
Impulsivity: TOVA Commission	92.53(8.36)	83.27(21.81)	84.33(17.93)	91.17(17.34)
Processing Speed: TOVA Response Time Composite	91.25(24.99)	93.30(11.25)	92.86(22.02)	91.82(12.20)
Verbal Memory: CVLT List A 1-5	101.85(8.82)	98.44(15.37)	98.77(9.78)	101.42(16.38)
Executive Function: RCFT – Copy	100.94(3.73)	96.95(7.55)	100.51(5.47)	96.36(7.01)
Executive Function: BRIEF – Global Executive Composite	106.83(14.85)  ( <i>n = 6</i> )	100.12(15.03)  ( <i>n = 8</i> )	109.85(15.74)  ( <i>n = 8</i> )	96.14(10.76)  ( <i>n = 6</i> )

*Note.* IT = Intrathecal chemotherapies; TOT = Time off therapy; *M* = mean; *SD* = standard deviation; *n* = sample size; WISC-IV = Wechsler Intelligence Scale for Children - Fourth Edition; IQ = intelligence quotient; WIAT-II = Wechsler Individual Achievement Test - Second Edition; TOVA = Test of Variable Attention; CVLT = California Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; BRIEF = Behavior Rating Inventory of Executive Functioning.

**Table 6***Children with ALL: Mean Scores on Significant, Large, and Medium Effect Size Measures*

Family No.: (Groups)	FSIQ	Reading Composite	Math Reasoning	Inattention	Impulsivity
1 (Low IT Low TOT)	105	99.5	100	97	97
2 (High IT High TOT)	112	112	113	83	94
3 (Low IT High TOT)	87	98	96	110	60
4 (High IT High TOT)	98	112	103	97	101
5 (Low IT Low TOT)	108	113.5	125	96	108
6 (High IT High TOT)	116	113	123	103	94
7 (Low IT High TOT)	106	110	106	106	91
8 (Low IT Low TOT)	105	116	109	84	81
9 (Low IT Low TOT)	105	112.5	111	100	98
10 (High IT High TOT)	92	106.5	104	101	70
11 (Low IT Low TOT)	115	116	118	99	80
12 (High IT High TOT)	92	93.5	107	100	108
13 (Low IT Low TOT)	96	92.5	108	85	84
14 (Low IT Low TOT)	103	114.5	116	107	108
15 (High IT High TOT)	99	109	107	83	71

Family No.: (Groups)	FSIQ	Reading Composite	Math Reasoning	Inattention	Impulsivity
T6 (High IT High TOT)	105	109	89	105	111

---

*Note.* FSIQ = Full Scale Intelligence Quotient; IT = Intrathecal chemotherapies; TOT = Time off therapy.

**Table 7***Healthy Siblings: Mean Scores on Significant, Large, and Medium Effect Size Measures*

Family No.: (Groups)	FSIQ	Reading Composite	Math Reasoning	Inattention	Impulsivity
1 (Low IT Low TOT)	96	95	85	93	79
2 (High IT High TOT)	108	114	115	71	94
3 (Low IT High TOT)	85	94.5	98	41	60
4 (High IT High TOT)	110	115	116	97	70
5 (Low IT Low TOT)	116	122	123	97	96
6 (High IT High TOT)	121	123	132	105	82
7 (Low IT High TOT)	102	102	102	63	52
8 (Low IT Low TOT)	114	110.5	110	71	62
9 (Low IT Low TOT)	112	111.5	126	63	82
10 (High IT High TOT)	112	113.5	106	99	86
11 (Low IT Low TOT)	108	107.5	96	103	104
12 (High IT High TOT)	110	113.5	112	82	85
13 (Low IT Low TOT)	104	91.5	95	95	104
14 (Low IT Low TOT)	105	102.5	103	87	111
15 (High IT High TOT)	114	110	121	101	98

Family No.: (Groups)	FSIQ	Reading Composite	Math Reasoning	Inattention	Impulsivity
16 (High IT High TOT)	1	117.5	106	73	103

---

*Note.* FSIQ = Full Scale Intelligence Quotient; IT = Intrathecal chemotherapies; TOT=Time off therapy.



**Table 8*****Difference Score Statistical Analyses for Numbers of Intrathecal Chemotherapy Treatments***

Domain & Measure	High IT ( $\geq 20$ ) $n = 7$	Low IT ( $\leq 19$ ) $n = 9$	<i>t</i> -test	<i>p</i> value	Cohen's <i>d</i>
	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )			
Intelligence Quotient: WISC-IV Full Scale IQ	-8.71(10.22)	-.44(8.20)	1.798	.047	d=.89
Reading Composite: WIAT-II	-7.36(6.54)	3.94(5.89)	3.633	.001*	d=1.81
Mathematics: Math Reasoning	-8.85(6.04)	5.22(11.46)	3.079	.004*	d=1.61
Writing: Three-Minute Writing Sample	1.48(16.72)	-4.56(17.35)	.406	.345	d=.21
Inattention: TOVA Omission	6.21(16.06)	19.52(25.65)	1.198	.125	d=.62
Impulsivity: TOVA Commission	-3.61(20.87)	11.67(24.86)	1.304	.107	d=.64
Processing Speed: TOVA Response Time Composite	6.00(16.54)	.61(24.17)	.504	.311	d=.26
Verbal Memory: CVLT List A 1-5	3.43(11.98)	3.00(22.02)	.046	.481	d=.02
Executive Function: RCFT – Copy	0.52(3.73)	1.87(10.94)	.582	.285	d=.29
Executive Function: BRIEF – Global Executive Composite	0.16(10.51) ( $n = 6$ )	-4.35(15.79) ( $n = 8$ )	.392	.278	d=.15

*Note.* *M* = mean difference score between sibling pairs based on a *M* of 100; *SD* = standard deviation; a *SD* of 15; *n* = sample size; IT = Intrathecal chemotherapies; WISC-IV = Wechsler Intelligence Scale for Children - Fourth Edition; IQ = intelligence quotient; WIAT-II = Wechsler Individual Achievement Test - Second Addition; TOVA = Test of Variable Attention; CVLT = California Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; BRIEF = Behavior Rating Inventory of Executive Functioning. \* *p* = .005, one tailed *t*-test.

**Table 9*****Difference Score Statistical Analyses for Time off Therapy***

Domain: Measure	High TOT (>5 years) <u>n = 9</u>	Low TOT (<5 years) <u>n = 7</u>	t-test	p value	Cohen's d
Intelligence Quotient: WISC-IV Full Scale IQ	-5.22(11.51)	-2.57(7.59)	.525	.304	d=.27
Reading Composite: WIAT-II	-4.44(8.16)	3.43(6.56)	2.077	.028	d=1.06
Mathematics: Math Reasoning	-6.67(6.09)	6.43(12.83)	2.791	.007	d=1.30
Writing: Three-Minute Writing Sample	-2.56(10.02)	-4.06(19.91)	-.185	.572	d=.09
Inattentiveness: TOVA Omission	17.25(26.75)	9.14 (15.92)	.707	.246	d=.37
Impulsivity: TOVA Commission	7.22(28.20)	2.11(18.30)	-.415	.342	d=.22
Processing Speed: TOVA Response Time Composite	7.36(14.89)	-2.68(26.63)	.960	.177	d=.47
Verbal Memory: CVLT List A 1-5	4.11(15.00)	2.00(22.06)	-.018	.507	d=.11
Executive Function: RCFT – Copy	1.00(6.32)	1.65(10.99)	.601	.279	d=.30
Executive Function: BRIEF – Global Executive Composite	-0.81(9.94) (n = 8)	-4.02(17.02) (n = 6)	.370	.337	d=.10

*Note.* *M* = mean difference score between sibling pairs based on a *M* of 100; *SD* = standard deviation; a *SD* of 15; *n* = sample size; IT = Intrathecal chemotherapies; WISC-IV = Wechsler Intelligence Scale for Children - Fourth Edition; IQ = intelligence quotient; WIAT-II = Wechsler Individual Achievement Test - Second Addition; TOVA = Test of Variable Attention; CVLT = California Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; BRIEF = Behavior Rating Inventory of Executive Functioning. \**p* = .005, one tailed *t*-test.

**Table 10*****Wechsler Intelligence Scale for Children - Fourth Edition Subscale Scores***

	High IT (>20) <i>n</i> = 7	Low IT (<19) <i>n</i> = 9	High TOT (>5 years) <i>n</i> = 9	Low TOT (<5 years) <i>n</i> = 7
Intelligence Quotient Subscale	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )
<b>Children with ALL</b>				
Verbal Comprehension Index	105(13.85)	103.11(14.78)	104.11(17.93)	103.71(12.49)
Perceptual Reasoning Index	103.71(11.14)	106.66(8.17)	103.33(9.97)	108(8.22)
Working Memory Index	100.42(4.75)	103.22(10.98)	103.57(12.66)	106.28(7.93)
Processing Speed Index	93.28(8.15)	98(12.88)	93.88(8.84)	98.57(12.77)
<b>Siblings</b>				
Verbal Comprehension Index	114.28(7.06)	107.33(12.40)	111.44(9.34)	109(12.90)
Perceptual Reasoning Index	108.57(4.96)	105.55(7.87)	106(6.83)	108(6.95)
Working Memory Index	106.28(7.93)	101.44(14.54)	102.77(11.88)	104.57(13.03)
Processing Speed Index	100.57(20.18)	96.11(9.30)	97.11(18.77)	99.28(7.91)

*Note.* *M* = mean; *SD* = standard deviation; *n* = sample size.

**Table 11***Children with ALL: WISC-IV Subscale Individual Scores*

Family No.	WISC-IV V.C	WISC-IV P.R	WISC-IV W.M	WISC IV P.S.	WISC IV FSIQ
1	95	100	120	106	105
2	110	117	102	103	112
3	81	96	102	83	87
4	106	98	102	80	98
5	112	117	91	94	108
6	124	121	102	94	116
7	121	108	102	109	114
8	124	110	94	75	105
9	102	104	102	106	105
10	98	94	94	88	92
11	110	121	120	91	115
12	87	92	107	94	92
13	87	102	91	112	96
14	96	102	107	106	103
15	91	102	102	103	99
16	119	102	94	91	105

*Note.* WISC IV V.C. = Wechsler Intelligence Scale for Children - Fourth Edition, Verbal Comprehension Index; WISC P.R. = Wechsler Intelligence Scale for Children - Fourth Edition, Perceptual Reasoning Index; WISC W.M. = Wechsler Intelligence Scale for Children - Fourth Edition, Working Memory Index; WISC P.S. = Wechsler Intelligence Scale for Children - Fourth Edition, Processing Speed Index; WISC FSIQ = Wechsler Intelligence Scale for Children - Fourth Edition, Full Scale Intelligence Quotient.

**Table 12***Healthy Siblings: WISC-IV Subscale Individual Scores*

Family No.	WISC-IV	WISC-IV	WISC-IV	WISC-IV	WISC-IV
	V.C.	P.R.	W.M.	P.S.	FSIQ
IV1	96	102	88	100	96
2	112	115	94	97	108
3	93	94	77	85	85
4	114	104	107	103	110
5	128	112	102	100	116
6	124	115	116	109	121
7	110	100	104	85	102
8	119	115	107	97	114
9	119	106	126	83	112
10	106	108	107	115	112
11	104	98	116	106	108
12	110	104	116	100	110
13	95	117	94	106	104
14	102	106	99	103	105
15	110	110	102	121	114
16	124	104	102	59	100

*Note.* WISC IV V.C. = Wechsler Intelligence Scale for Children - Fourth Edition, Verbal Comprehension Index; WISC P.R. = Wechsler Intelligence Scale for Children - Fourth Edition, Perceptual Reasoning Index; WISC W.M. = Wechsler Intelligence Scale for Children - Fourth Edition, Working Memory Index; WISC P.S. = Wechsler Intelligence Scale for Children - Fourth Edition, Processing Speed Index; WISC FSIQ = Wechsler Intelligence Scale for Children - Fourth Edition, Full Scale Intelligence Quotient.

**Table 13*****Sibling Pair Large Variability Data***

Dependent Variable:	Family Pair Number Child with ALL Negative Skew			Family Pair Number Child with ALL Positive Skew		
Full Scale IQ	(#13) -20	high IT & high TOT	(#9) 12	low IT & high TOT		
	(#14) -18	high IT & high TOT				
	(#15) -15	high IT & high TOT				
Reading Composite	(#14) -20	high IT & high TOT	(#15) 12	high IT & high TOT		
Math Reasoning	(#3) -15	low IT & low TOT	(#1) 15	low IT & low TOT		
	(#16) -17	high IT & high TOT	(#4) 22	low IT & low TOT		
Total Words Written	(#1) -21	low IT & low TOT	(#6) 20	high IT & high TOT		
	(#13) -19	high IT & high TOT				
	(#4) -36	low IT & low TOT				
TOVA Inattention	(#16) -18	high IT & high TOT	(#8) 69	low IT & high TOT		
			(#9) 43	low IT & high TOT		
			(#14) 18	high IT & high TOT		
			(#15) 20	high IT & high TOT		
TOVA Impulsivity	(#11) -31	high IT & high TOT	(#1) 17	low IT & low TOT		
	(#13) -16	high IT & high TOT	(#8) 50	low IT & high TOT		
	(#4) -25	low IT & low TOT	(#9) 40	low IT & high TOT		
	(#5) -20	low IT & low TOT	(#7) 18	low IT & low TOT		
	(#15) -26	high IT & high TOT	(#3) 15	low IT & low TOT		
			(#14) 23	high IT & low TOT		
TOVA Response Time	(#1) -22	low IT & low TOT	(#10) 35	high IT & high TOT		
	(#2) -34	low IT & low TOT	(#9) 18	low IT & high TOT		
	(#7) -31	low IT & low TOT	(#4) 35	low IT & low TOT		
			(#14) 19	high IT & high TOT		
			(#5) 17	low IT & low TOT		
CVLT List A	(#7) -13	low IT & low TOT	(#9) 19	low IT & high TOT		
			(#3) 15	low IT & low TOT		
			(#5) 23	low IT & low TOT		

Dependent Variable:	Family Pair Number	Survivor Negative Skew	Family Pair Number	Survivor Positive Skew		
RCFT – Copy	(#11)	-25	high IT & high TOT	(#1)	20	low IT & low TOT
	(#9)	-24	low IT & high TOT	(#8)	22	low IT & high TOT
	(#7)	-30	low IT & low TOT	(#3)	29	low IT & low TOT
	(#13)	-16	high IT & high TOT	(#15)	34	high IT & low TOT
	(#16)	-20	high IT & high TOT			
BRIEF Parent Report	(#11)	-13	high IT & high TOT	(#15)	51	high IT & high TOT

*Note.* IT = Intrathecal chemotherapies; TOT = Time off therapy.

**Table 14*****Healthy Sibling and Post Therapy Children with ALL Attention Data: Reddick (2006)***

Attention	<u>Siblings (n = 33)</u> T Score	<u>Survivors (n = 84)</u> T Score
Omissions (percentile)	80.75 ± 19.199*	62.9 ± 8.7b*
D (attentiveness) <sup>a</sup>	57.47 ± 9.06	57.6 ± 10.4b

*a*=attentiveness was measured as the time difference between the stimulus and non-stimulus item on the screen (how often and how quickly the participant clicks the response button, when the target is not on the screen)

*b*=Statistically significant differences from test norms superscript symbols ( $P < 0.01$ ) as analyzed in the 2006 study

\*Scores of 60 or above indicate abnormally high inattention or impulsivity



## Appendix B

## Consent Forms Hackensack University Medical Center

Consent Approved Expedited Review

Date: 6/9/05Date Exp.: 6/14/06

30 Prospect Avenue  
Hackensack, N.J. 07601  
201.996.2000

Affiliated with the  
University of Medicine and  
Dentistry of New Jersey

Member of the  
University Health System  
of New Jersey

**HACKENSACK UNIVERSITY MEDICAL CENTER****Consent Form****Title of Protocol**

Profiles of Executive Functioning with Survivors of Childhood Acute Lymphocytic Leukemia and Children with Attention Deficit Hyperactivity Disorder, Inattentive Type.

**Who is conducting this study?**

Anne R. Farrar-Anton, Ph.D., Neuropsychology Fellow, ICD  
David S. Gordon, M.S., Coordinator of Educational Services, TCI & CAB  
Carol A. Friedman, Ph.D., Coordinator of Psychological Services, ICD  
Larissa Labay, Psy.D., Psychologist, TCI & CAB

**Why have I been asked to take part in this research study?**

You have been asked to take part in this study because your child has been previously diagnosed with Acute Lymphocytic Leukemia (ALL), Attention Deficit Hyperactivity Disorder, Inattentive Type (ADHD), or you have a child with no known or diagnosed attentional or executive functioning difficulties. It is up to you to decide whether or not to take part in this study. Please read this entire consent form. This consent form may contain words that you do not understand. Please ask Dr. Farrar-Anton or Mr. Gordon to explain any words or information that you do not clearly understand. You may want to think about or discuss this with family or friends before making your decision.

**Why is this study being conducted?**

Previous research indicates that both childhood survivors of ALL and children with ADHD can experience difficulties in both the school and home environments. One theory of this is that executive functioning (attention, planning, organization, working memory, and ability to monitor one's own behavior) can play a primary role in these difficulties. The primary goal of this research is to distinguish neuropsychological profiles of children with ADHD and survivors of ALL and compare them to a group of children with no known attentional and/or executive functioning difficulties. The results of this study can help medical staff, clinicians, educators, and parents gain a better understanding of how to best meet children's needs.

**How many people will participate in this study?**

It is expected that approximately 40 survivors of childhood ALL, 40 children with ADHD, and 40 children with no history of attentional problems or childhood cancer will participate in this study. The ages will range from 8 to 14. All children recruited will have been diagnosed with

and/or are patients within the Department of Pediatrics within the Joseph M. Sanzari Children's Hospital at Hackensack University Medical Center. The control group will consist of 40 siblings to the survivors of ALL.

#### **What is involved in this study?**

Your child will be asked to attend approximately 4 hours of testing across 2 2-hour sessions. This time may vary depending on the child's work pace. Prior to your child's participation in the study you will be asked to complete 3 forms for further background information along with some questions regarding your perceptions of your child's executive functioning abilities and any concerns you may have about their emotional and behavioral difficulties. These forms will take approximately one hour for you to complete. You will be also asked to give a copy of the executive functioning instrument to your child's previous or current teacher for their input. The teacher form will take approximately 20 minutes to complete. We also ask for the parent's to bring in a copy of your child's most recent report card along with their end of the year standardized test score.

If your child is currently prescribed any medication, the investigators will ask you about which medications prior to the evaluation process as some medications are prescribed to improve attention and others such as asthma medication and antihistamines can impact attention. Please inform the investigator about your child's medication use within the last month.

#### **How long will I be in the study?**

This study consists of either one or two days of testing for your child in order to gather an accurate assessment of their executive functioning. It is anticipated that the total testing time will be approximately 4 hours, as noted earlier this is dependent on your child's work pace. Parent's participation will require approximately one hour and the child's teacher will require approximately 20 minutes.

#### **What are the risks involved in this study?**

It is expected that the majority of children will have no adverse reactions or effects to the testing process. At times, children can become anxious and worried about their test performance. Therefore, time will be allotted time in the beginning as well as the end of the testing to help acclimate the child to the testing process along with debriefing the experience upon completion. Also, breaks will be given when needed. In the unlikely event that a child remains considerably anxious, testing will be postponed or concluded.

#### **Are there benefits to taking part in the study?**

You may have no direct benefit for participating in this study. However, your child's participation in this study will hopefully lead to increased knowledge of attention and executive functioning of children who are survivors of childhood ALL and children with ADHD for medical staff, clinicians, educators, and parents. Within 30 days of child's testing, a written summary will be provided to the families.

### **What other treatment options are there?**

This study is voluntary, deciding to not participate will in no way impede your child's therapy and/or medical treatment at this facility. The other option would be not to participate.

### **How will information about me be kept private?**

Your identity and participation are confidential to the extent permitted by law. In addition, the investigators of the research and/or the Institutional Review Board will be granted direct access to your child's original medical records for verification purposes. Records identifying you and your child will be kept confidential to the extent permitted by applicable law. If the results of the research are published and/or presented your identity will remain confidential.

### **What are the costs?**

There are no costs to you or your child. Participants will not be reimbursed for their time, though they will be given \$20.00 per child for travel expenses. Children who participate in the study will be given a \$20.00 gift certificate to Toys 'R Us or Barnes and Noble. Parents will also be provided with a brief copy of the results of their child's testing approximately one month upon completion of the study.

### **What are my rights as a research participant?**

Your decision to take part in this study is voluntary. If you decide not to participate or if you choose to withdraw after beginning the study, you will not lose any benefits associated with your medical care. You are encouraged to ask questions before deciding whether you wish to participate and at any time during the course of the project. Your participation may be terminated by the investigators without regard to your consent.

You will be told of any new findings that may influence your decision to continue to participate in this research project. If information becomes available that may influence your decision to take part in this study you will be asked to sign a revised consent or consent addendum. This will be at the discretion of the Institutional Review Board.

In the case of physical injury resulting from participation in the study, treatment determined by a physician will be made available to you. This care will be billed to you/your insurance company in the usual and customary manner. There will be no monetary compensation by Hackensack University Medical Center.

### **Who can I call if I have questions or problems?**

For questions concerning this research project and/or research subjects' rights, you should call Dr. Ramazzotto at 201-996-2725 or The Institutional Review Board Office at 201-996-2255. In the event that assistance is required, you are instructed to call Dr. Farrar-Anton at 201-996-5255 or Mr. Gordon at 201-996-5358.

IRB # 04.01.056B

## HACKENSACK UNIVERSITY MEDICAL CENTER

AUTHORIZATION TO USE OR DISCLOSE PROTECTED HEALTH INFORMATION  
FOR A RESEARCH STUDY

I hereby authorize use or disclosure of the named individual's health information as described below.

Patient Name	Date of Birth	Social Security Number
Address (Street, City, State, Zip Code)		Telephone Number
The following individual or organization is authorized to make the disclosure: Hackensack University Medical Center, Dr. Anne R. Farrar-Anton, David S. Gordon, and their associates on this research study.		
<u>Title of Protocol:</u> Profiles of Executive Functioning with Survivors of Childhood Acute Lymphocytic Leukemia and Children with Attention Deficit Hyperactivity Disorder, Inattentive Type		
This information may be disclosed to and used by the following individual or organization: FDA (Food and Drug Administration), and other government agencies, The IRB staff, and the Department of Research staff		
Treatment dates: Past, Present, and Future Medical Records	Purpose of Request: The primary objective of this research is to determine whether or not children diagnosed with ADHD, Inattentive Type as well as survivors of childhood ALL exhibit significant executive dysfunction.	
The following information is to be disclosed:  Completion of the Behavior Rating Inventory of Executive Functioning (BRIEF). Demographics: (such as sex, age, race, date of birth, zip code, Social Security #, Medical Record #) Name of child's classroom teacher, school name, city, state, phone number Personal Health Information including Medical History, Disease process and Treatment History		
<b>Sensitive Information:</b> I understand that the information in my record may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or infection with the Human Immunodeficiency Virus (HIV). It may also include information about behavioral or mental health services or treatment for alcohol and drug abuse.		
<b>Right to Revoke:</b> I understand that I have the right to revoke this authorization at any time. I understand if I revoke this authorization I must do so in writing. I understand that the revocation will not apply to information that has already been released based on this authorization.		
<b>Expiration:</b> Unless otherwise revoked, this authorization will expire at the end of the research study.		
<b>Redisclosure:</b> I understand that any disclosure of information carries with it the potential for redisclosure and the information may not be protected by federal confidentiality rules.		
<b>Other Rights:</b> I understand that authorizing the disclosure of this health information is voluntary. I can refuse to sign this authorization. I do not need to sign this form to assure treatment. However, since this authorization is needed for participation in a research study, my enrollment in the research study may be denied.		
I understand that I may inspect or obtain a copy of the information to be used or disclosed, as provided in CFR 164.524.		
If I have any questions about disclosure of my health information, I can contact Anne R. Farrar-Anton at 201-996-5255 or David Gordon at 201-996-5358.		
Signature of Research Subject or Legally Authorized Representative		Date
If Signed by Legally Authorized Representative, Relationship to Research Subject		

### Consent

- I have read or it has been explained to me and I understand the information in this consent form. All my questions have been answered to my satisfaction. I consent to participate in this study.
- I understand that I will receive a signed and dated copy of this consent form for my records.
- By signing this consent form I have not waived any of the legal rights which I otherwise would have as a participant in a research study.

I hereby consent (to have my child/ward consent) to participate.

\_\_\_\_\_  
 Person Obtaining Consent

\_\_\_\_\_  
 Signature of Person Obtaining Consent

\_\_\_\_\_  
 Date

\_\_\_\_\_  
 Subject's Name or Legally Authorized Representative

\_\_\_\_\_  
 Signature of Subject (If participant is 9 years old or older)  
 Or Signature of Legally Authorized Representative

\_\_\_\_\_  
 Date

\_\_\_\_\_  
 Parent/Guardian's Name if Participant is a Minor

\_\_\_\_\_  
 Signature

\_\_\_\_\_  
 Date

*A witness is someone who has no connection with the clinical trial. A witness is only required in cases where the subject cannot read or is not able to understand the consent document. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to and apparently understood by the subject or the subjects legally acceptable representative and that the informed consent was freely given by the subject or the subjects acceptable representative. In cases where this does not apply N/A should be placed in the witness section.*

*Witness (someone not connected to this research project):* \_\_\_\_\_ *Date:* \_\_\_\_\_

*Witness Identification: (nurse, friend, receptionist, etc.)* \_\_\_\_\_

*If the assent of the child, age 9 or older is not obtained, the reason should be stated below or attached to this consent form.*

### Financial Disclosure

The Principal Investigator is not receiving payment for this study. If you have questions about this disclosure please ask the principal investigator or call Louis Ramazzotto, Ph.D., Director of Research at (201) 996-2725.

## Appendix C

## Consent Forms Syracuse University



## SYRACUSE UNIVERSITY

SCHOOL OF EDUCATION  
TEACHING & LEADERSHIP PROGRAMS

**ASSENT BY MINOR SUBJECT NINE YEARS OF AGE OR OLDER**

You are being asked to agree to participate in this research study. You have the right to find out what is involved for you if you participate, and to tell your parent(s) whether you do or do not want to participate.

Your parents will also be asked to give permission for you to participate in this study.

Any child who states that he/she does not want to participate will be excused from participation in this study. In addition, all procedures, risks, and discomforts have been explained to the child.

Dr. Anne R. Farrar-Anton or Mr. David S. Gordon and your parent(s) have explained to you the procedures that are involved, and if you do not understand them please ask for clarification.

Dr. Anne R. Farrar-Anton or Mr. David S. Gordon and your parent(s) have also explained to you potential discomforts, risks or inconveniences that may be involved if you participate.

At this time, you have asked any questions you have, and all your questions have been answered. You understand everything that has been told to you and that your participation is voluntary.

Check one:

I agree to participate in this study.

I do not agree to participate in this study.

\_\_\_\_\_  
Child's Name

\_\_\_\_\_  
Child's Age

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness

\_\_\_\_\_  
Relationship of Witness to Child

\_\_\_\_\_  
Principal Investigator

Art Education, Educational Leadership, Elementary Education, Inclusive Education, Mathematics Education  
Music Education, Science Education, Social Studies Education, Special Education, Teaching and Curriculum

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## SYRACUSE UNIVERSITY

SCHOOL OF EDUCATION  
TEACHING & LEADERSHIP PROGRAMS

### Consent Form

#### Title of Protocol

Achievement and Executive Functioning of Survivors of Childhood Acute Lymphocytic Leukemia (ALL).

#### Who is conducting this study?

Anne R. Farrar-Anton, Ph.D., Neuropsychology Fellow, ICD  
David S. Gordon, M.S., Coordinator of Educational Services, TCI  
Carol A. Friedman, Ph.D., Coordinator of Psychological Services, ICD  
Larissa Labay, Psy.D., Psychologist, TCI

#### Why have I been asked to take part in this research study?

You have been asked to take part in this study because you have a child that has a sibling that has previously diagnosed with Acute Lymphocytic Leukemia (ALL). It is up to you to decide whether or not to take part in this study. Please read this entire consent form. This consent form may contain words that you do not understand. Please ask Mr. Gordon to explain any words or information that you do not clearly understand. You may want to think about or discuss with family or friends before making your decision.

#### Why is this study being conducted?

Previous research indicates that childhood survivors of ALL can experience difficulties in both the school and home environments. One theory of this is that executive functioning (attention, planning, organization, working memory, and ability to monitor one's own behavior) can play a primary role in these difficulties. The primary goal of this research is to investigate the neuropsychological profiles of survivors of ALL and compare them to a group of their siblings. The results of this study can help medical staff, clinicians, educators, and parents gain a better understanding of how to best meet the child's needs.

#### How many people will participate in this study?

It is expected that approximately 30 survivors of childhood ALL, and 30 children with no history of attentional problems or childhood cancer will participate in this study. The ages will range from 8 to 14. All children recruited will have been diagnosed with and/or patients within the Department of Pediatrics within the Joseph M. Sanzari Children's

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Hospital at Hackensack University Medical Center. The control group will consist of 30 siblings to the survivors of ALL.

**What is involved in this study?**

Your child will be asked to attend approximately 4 hours of testing across 2 half day sessions. This time may vary depending on the child's work pace. Prior to your child's participation in the study you will be asked to complete 3 forms for further background information along with some questions regarding your perceptions of your child's executive functioning abilities and any concerns you may have about their emotional and behavioral difficulties. These forms will take approximately one hour for you to complete. You will be also asked to give a copy of the executive functioning instrument to your child's previous or current teacher for their input. The teacher form will take approximately 20 minutes to complete. We also ask for the parents to bring in a copy of your child's most recent report card along with their end of the year standardized test score.

**How long will I be in the study?**

This study consists of 2 half days of testing for your child in order to gather an accurate assessment of his/her executive functioning. It is anticipated that the total testing time will be approximately 4 hours, as noted earlier. This is dependant on your child's working pace. Parent's participation will require approximately one hour and the child's teacher will require approximately 20 minutes.

**What are the risks involved in this study?**

It is expected that the majority of children will have no adverse reactions or effects to the testing process. At times, children can become anxious and worried about their test performance. Therefore, time will be allotted time in the beginning as well as the end of the testing to help acclimate the child to the testing process along with debriefing the experience upon completion. Also, breaks will be given when needed. In the unlikely event that a child remains considerably anxious, testing will be postponed or concluded.

**Are there benefits to taking part in the study?**

Your child's participation in this study will hopefully lead to increased knowledge of attention and executive functioning of children who are survivors of childhood ALL for medical staff, clinicians, educators, and parents. In addition this study will provide participants and their families with helpful information that can be used for educational planning.

**What other treatment options are there?**

This study is voluntary. Deciding to not participate will in no way impede your child's therapy and/or medical treatment at this facility.

**How will information about me be kept private?**

Your identity and participation are confidential to the extent permitted by law. In addition, the investigators of the research and/or the Institutional Review Board will be granted direct access to your child's original medical records for verification purposes. Records identifying you and your child will be kept confidential to the extent permitted by applicable law. If the results of the research are published and/or presented your identity will remain confidential.

**What are the costs?**

There are no costs to you or your child. Participants will not be reimbursed for their time, though they will be given \$20.00 per child for travel expenses. Children who participate in the study will be given a \$20.00 gift certificate to Toys 'R Us or Barnes and Noble. Parents will also be provided with a brief copy of the results of their child's testing approximately one month after completion of the study.

**What are my rights as a research participant?**

Your decision to take part in this study is voluntary. If you decide not to participate or if you choose to withdraw after beginning the study, you will not lose any benefits associated with your medical care. You are encouraged to ask questions before deciding whether you wish to participate and at any time during the course of the project. Your participation may be terminated by the investigators without regard to your consent.

You will be told of any new findings that may influence your decision to continue to participate in this research project. If information becomes available that may influence your decision to take part in this study you will be asked to sign a revised consent or consent addendum. This will be at the discretion of the Institutional Review Board.

In the case of physical injury resulting from participation in the study, treatment determined by a physician will be made available to you. This care will be billed to you/your insurance company in the usual and customary manner. There will be no monetary compensation by Hackensack University Medical Center.

**Who can I call if I have questions or problems?**

For questions concerning this research project and/or research subjects' rights, you should call Dr. Ramazzotto at 201-996-2725 or The Hackensack Institutional Review Board Office at 201-996-2255. In the event that assistance is required, you are

instructed to call Dr. Farrar-Anton at 201-996-5255 or Mr. David Gordon at 201-996-5358. You may also contact Syracuse University Institutional Review Board at 113 Bowne Hall, Syracuse University Syracuse, NY 13244-1200, Tel: 315-443-3013.

**Financial Disclosure:** The Principal investigator is not receiving payment for this study. If you have questions about this disclosure please ask the principal investigator or call Louis Ramazzotto, Ph.D., Director of Research at (201) 996-2725.

### Consent

Through discussing this study with the investigators and reading this consent, I believe that I have enough knowledge concerning participation in this study in order to willingly participate. Any questions I had have been answered and any aspects of this study that I did not understand have been thoroughly explained to my satisfaction.

I have read or it has been explained to me and I understand the information in this consent form. All my questions have been answered to my satisfaction. I consent to participate in this study.

I understand that I will receive a signed and dated copy of this consent form for my records.

By signing this consent form I have not waived any of the legal rights which I otherwise would have as a participant in a research study.

I hereby consent (to have my child/ward consent) to participate.

\_\_\_\_\_  
Person Obtaining Consent

\_\_\_\_\_  
Signature of Person Obtaining Consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Subject's Name or Legally Authorized Representative

\_\_\_\_\_  
Signature of Subject (If participant is 9 years old or older)  
Or Signature of Legally Authorized Representative

\_\_\_\_\_  
Date

\_\_\_\_\_  
Parent/Guardian's Name if Participant is a Minor

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

A witness is someone who has no connection with the clinical trial. A witness is only required in cases where the subject cannot read or is not able to understand the consent document. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to and apparently understood by the subject or the subjects legally acceptable representative and that the informed consent was freely given by the subject or the subjects acceptable representative. In cases where this does not apply N/A should be placed in the witness section.

Witness (someone not connected to this research project), \_\_\_\_\_ Date: \_\_\_\_\_

*Witness Identification: (nurse, friend, receptionist, etc.)*

If the assent of the child, age 9 or older is not obtained, the reason should be stated below or attached to this consent form.

## Appendix D

## Institutional Review Board Hackensack University Medical Center



THE DAVID JOSEPH JURIST RESEARCH BUILDING

30 Prospect Avenue  
Hackensack, N.J. 07601  
201.996.2255  
201.968.0536 Fax

Affiliated with the  
University of Medicine and  
Dentistry of New Jersey -  
New Jersey Medical School

*Institutional  
Review Board*

May 9, 2005

Anne R. Farrar-Anton, Ph.D.  
Institute for Child Development  
30 Prospect Avenue  
Hackensack, NJ 07601

Dear Dr. Farrar-Anton:

**Meeting Date:** 06/15/05  
**RE: Our Study:** 04.01.056B  
**Protocol Title:** Profiles of Executive Functioning with Survivors of Acute Childhood Lymphatic Leukemia and Attention Deficit Hyperactivity Disorder, Inattentive Type.

The above referenced study has been reviewed via expedited review and will be presented to the full board on the date identified above, and the following actions taken subject to the conditions and explanation provided below.

Please be reminded that all modifications to the approved projects must be reviewed and approved by the Institutional Review Board below before they may be implemented. Any changes to this protocol must be suited for IRB approval before initiated.

All serious adverse events and unexpected adverse events must be reported to the Institutional Review Board.

Please do not make any changes to the IRB approved consent without approval of the IRB. Only the IRB stamped approved consent should be used.

It is necessary that you utilize the assigned protocol number in any and all communication submitted to the IRB Office, i.e., amendments, audits, etc.

**DOCUMENT AND CORRESPONDENCE RECEIVED INCOMPLETE OR WITHOUT THE PROTOCOL NUMBER WILL BE RETURNED.**

**Internal #:** 5147  
**Expiration Date:** 06/14/06  
**On Agenda For:** Expedited  
**Reason 1:** Progress Report      **Reason 2:** Expedited Continuing Review

RE: IRB Study # 04.01.056B

Page 2

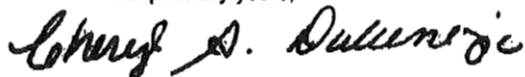
**Description:** This study is open to enrollment and there are 8 patients currently enrolled in the study.

**IRB ACTION:** RENEWED

**Action**

**Explanation:** This study was reviewed and approved via Expedited Review by Jerome Levine, MD on May 9, 2005.

Respectfully yours,



Cheryl Dubenezic, RN, CIM  
IRB Manager

## Appendix E

## Institutional Review Board Syracuse University



**SYRACUSE UNIVERSITY**  
**Institutional Review Board**  
**MEMORANDUM**

**TO:** Corinne Smith  
**DATE:** June 24, 2009  
**SUBJECT:** Full Board Protocol Renewal Review-Modifications Required  
**IRB #:** 05-127  
**TITLE:** Achievement and Executive Functioning of Survivors of Childhood Acute Lymphocytic Leukemia (ALL)

The above referenced protocol renewal was reviewed at the ~~June 15, 2009~~ convened meeting of the Institutional Review Board (IRB) and has been evaluated for the following:

1. the rights and welfare of the individual(s) under investigation;
2. appropriate methods to secure informed consent; and
3. risks and potential benefits of the investigation.

Following discussion, the IRB determined that this protocol renewal should receive provisional approval and requires the following changes:

1. Please complete the part of the renewal application that asks for the number of consent and assent documents (page 5).

Please be aware that your protocol is set to expire on **August 17, 2009** and federal regulations do not permit the IRB to waive this requirement or to grant an extension. The required modifications listed above need to be submitted to our office before the expiration date in order to process your renewal before it expires. These required modifications should be addressed in a memorandum outlining changes, including highlighted changes to the application or consent form(s) as indicated. If changes to your consent form(s) are necessary, a clean copy of the consent form(s) should be included with your response. The Board needs only one copy of the revisions.

Thank you for your cooperation in our shared efforts to assure that the rights and welfare of people participating in research are protected.

Diane S. Young, Ph.D.  
 Chair

*Note to Faculty Advisor: This notice is only mailed to faculty. If a student is conducting this study, please forward this information to the student researcher.*

DEPT: School of Education, 136 Huntington Hall

STUDENT: David S. Gordon

**Office of Research Integrity and Protections**  
 121 Bowen Hall, Syracuse, New York 13244-1200  
 (Phone) 315.443.3013 • (Fax) 315.443.9889  
 orip@ syr.edu • www.orip.syr.edu



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Williams, J. M., Ochs, J., Davis, K. S., & Daniel, M. (1986). The subacute effects of CNS prophylaxis for acute lymphoblastic leukemia on neuropsychological performance: A comparison of four protocols. *Archives of Clinical Neuropsychology*, *1*, 183–192.

## David Gordon

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Staten Island, NY

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### Education

**Ph.D.** May 9, 2016. Syracuse University, Syracuse, New York,  
Committee: Corinne Smith (Chair), Benita Blachman, Larry Lewendowski  
Dissertation: *The Cognitive, Academic, and Neuropsychological Effects of Treatment On Survivors of Childhood Acute Lymphocytic Leukemia*

**M.S.** Southern Connecticut State University, New Haven, Connecticut.  
*Master of Science*, Special Education: Learning Disabilities. December 1992.

**B.A.** Southern Connecticut State University, New Haven, Connecticut.  
*Bachelor of Arts*, Secondary Education: Social Studies. December 1991.

**Other:** Richmond the American International University in London, United Kingdom. January-June 1989.

### PROFESSIONAL EXPERIENCE

Staten Island Academy, Director of the Patrick Academic Resource Center, Staten Island, NY	2016 - Present
Wagner College, Assistant Professor Education Department	2011 - 2016
Living Through Learning Foundation, Executive Director, Iselin, NJ	2008 - 2015
Tomorrows Children's Institute, Coordinator of Educational Services, Hackensack, New Jersey	2000 - 2008
Exceptional Family Resources, Educational Advocate, Syracuse, NY	1999 - 2000
LeMoyne College, Adjunct Professor, Syracuse, NY	1999 - 1999
Seneca Army Depot, Employment & Training Specialist, Romulus, NY	1996 - 1997
State University of New York, Learning Disabilities Specialist, Norwich Campus, Norwich, NY	1994 - 1996
Landmark College, Educator, Putney, VT	1993 - 1994
Southern Connecticut State University, International Programs Coordinator, New Haven, CT	1990 - 1993

### TEACHING

*Wagner College Undergraduate Education Program*

- ED 312/412 - Strategies for Teaching Inclusive Education
- ED 335 - Assessment & Evaluation in Inclusive Settings
- ED 414 - Inclusive Methods & Curriculum for Middle Children

*Wagner College Learning Communities*

- ED 291 - Framing Disabilities (ILC, Fall 2013)

- MDS291 - Civil Liberties, Human Rights, and Disability Studies (ILC, Spring 2014)
- MDS 106 - Ways of Knowing (FYP, Fall 2011)
- LC 21 - Connecting with Gotham through Literature, Learning, and Knowing the Community (FYP, Fall 2011)
- LC 21 - The Education, Law and Politics of Disability (FYP, Fall 2012)
- LC 19: Views From the Fringe: RFT (FYP, Fall 2014)

*Wagner College Graduate Education Program*

- ED 601 - Learning Environments for Students with Exceptionalities
- ED 699 - Thesis Seminar

*Other Colleges & Universities*

- SPE 600 - Perspectives in Disabilities: Syracuse University
- SPE 670 - Internship in Special Education: Syracuse University
- SPE 311 - Perspectives in Disabilities: Syracuse University
- SPE 312 - Practicum in Disabilities: Syracuse University
- SPE 612 - Introduction to Learning Disabilities: LeMoyne College
- CLS 101 - College Learning Strategies: Syracuse University
- GNED 110 - College Transfer & Career Planning: GNED SUNY Morrisville
- GNED 102 - Practical Study Skills: SUNY Morrisville
- GNED 100 - Freshman Experience: SUNY Morrisville

## **SCHOLARSHIP**

### **PUBLICATIONS**

Refereed Articles and Submissions

Gordon, D. & Fitzgerald, J.C. (under review 2014). Fostering democratic engagement: A case analysis of two professors promoting civic engagement. *Journal of Public Deliberation*.

Love, A. G., Dietrich, A., Fitzgerald, J., & Gordon, D. (2014). Integrating Collaborative Learning Inside and Outside of the Classroom. *Journal on Excellence in College Teaching*, 25(3/4) 177-196.

Gordon, D. S., & Ghosh, C. (2013). Building Community Partnerships with Adults with Disabilities: A Case Study Using Narrative Literacy as a Conduit for Shared Learning. *Learning Communities Research and Practice*, 1(3), Article 8. Available at <http://washingtoncenter.evergreen.edu/lcrjournal/vol1/iss3/8>

### **Book Chapter**

Gordon, D.S. (under review 2015). *Using Civil Rights and Disability Rights History to Encourage Social Equity*. In the forthcoming book: *Beyond Bystanders: Educational Leadership for a Humane Culture in a Globalizing Reality*.



Gordon, D.S. (2009). Case study: Online learning as a way to access and involve new communities. In W. B. Crow and H. Din, *Unbound By Place or Time: Museums and Online Learning*, American Association of Museums Press, 109-113.

#### Other Selected Reports and Publications

Gordon, D.S. and Armstrong, D. Pediatric Cancer - Insights, Challenges, Strategies & Resources (2011). Educational materials development for the Leukemia and Lymphoma Society's continuing education training programs for oncology nurses and social workers. Available at [http://www.lls.org/researchershealthcareprofessionals/ce/cepast/051911\\_pediatric](http://www.lls.org/researchershealthcareprofessionals/ce/cepast/051911_pediatric).

Gordon, D.S., contributor and reviewer (2013). *Learning and Living with Cancer: Advocating for Your Child's Educational Needs*. Leukemia and Lymphoma Society. Training and resource material for the Society's continuing education program, "Staying Connected: Facilitating the Learning Experiences During & After Cancer Treatment." Available at <http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/childhoodbloodcancer/pdf/learninglivingwithcancer.pdf>.

Labay, L, and Gordon, D.S. (2007). The Use of Genetic Technology in Pediatric Oncology. *The Research Connection*. The Joint Psychosocial and Nursing Advisory Group to the New Jersey Commission on Cancer Research. 1, 4-6. Available at <http://www.state.nj.us/health/ccr/documents/2007number1.pdf>.

Donnangelo, S. & Gordon, D. (2007). Robot connects high school "teachers" with hospitalized learners. The NYIT Educational Enterprise Zone Videoconferencing News, 18.

Donnangelo, S. & Gordon, D. (2007). Student with chronic illness stays connected with classmates. The NYIT Educational Enterprise Zone Videoconferencing News, 19.

Gordon, D.S. and Finley, S.M. (2002). Advocacy through education: Tomorrows Children's Institute *Educational Outreach Service*. New Jersey Commission on Cancer Research *The Research Connection*, Spring 2002, 4-6.

**(December 1, 2020)** WABC News NYC  
["Using Video conferencing to keep youth connected to learning"](#)

#### PRESENTATIONS

Refereed National and International Conferences

Gordon, D., (April 10, 2015). Bringing the Museum to You: Utilizing Virtual Technology to Increase Motivation and Educational Engagement Council for Exceptional Children International Conference. San Diego, CA.

Gordon, D., (2014). Bone Marrow Transplant Information Network International Conference. "Managing Learning & School Issues After a Pediatric Transplant." East Rutherford, NJ September 12, 2014.

Grimmet, K., and Gordon, D.S., (2014). Counsel for Exceptional Children. "Experiencing Willowbrook: Using Virtual Faculty to Connect Educators to the Past and the NEW Present." Philadelphia, PA. April 11, 2014

- Lemke, R., Gordon, D.S., and Griffin, K., (2014). Association for Pediatric Hematology Oncology Educational Specialists. “Models of Hospital Education: Next Steps for improving Quality and Sustainability” Columbus, OH May 2, 2014
- Gordon, D.S., (2012). Association of Pediatric Hematology Oncology Educational Specialists (APHOES). “The Sibling Perspective: Possible Attentional Effects on siblings of Childhood Cancer Survivors”. Akron, OH. May 2, 2012.
- The Technology Haystack: How to Know Which Technology to Use When with Children with Chronic Health Conditions. Association for the Education of Children with Medical Needs (AECMN) National Conference Portland, OR. November 9, 2012.
- Gordon, D.S., (2011). Association for the Education of Children with Medical Needs (AECMN) National Convention. “Educational Outcomes of Digital Based Learning for Children with Cancer.”. Atlanta, GA, October 18, 2011.
- Fitting a Square Peg in a Round Hole: An Acquired Learning Disability February, 2002 Learning Disabilities Association International Conference. Denver, CO.
- Complex Issues Courageous Lives: Living and Learning at College with Asperger’s Syndrome March 3-6, 2001 American College Personnel Association (ACPA) Conference. Boston, MA.
- Academic and Social Effects for Survivors of Childhood Cancer at College, March 3-6, 2001 American College Personnel Association (ACPA) Conference. Boston, MA.

### **Invited National Presentations**

- Gordon, D.S., (2014). Keynote: *Bringing the Museum to You: Utilizing Virtual Technology to Increase Motivation and Educational Engagement*. At the Empowering Students with Physical & Health Impairments conference, California Association for Physical and Health Impairments. San Diego, CA, February 14-15.
- Gordon, D.S., (2012). Keynote: *I Deal to Ideal: An Inside Out Approach to Education*. MSTI Education Conference St. Luke’s Hospital, Boise, ID, September 22, 2011.
- Gordon, D.S., (2012). Keynote: *Transition, Access, and Equity: Avoiding Transitional Pitfalls to Achieve Life’s Goals*. MSTI Education Conference. St. Luke’s Hospital, Boise, ID September 22, 2011.

### **Regional Presentations**

#### **Leukemia and Lymphoma Society Psychosocial Trainer/Speaker:**

- Gordon, D.S. (2014). *Staying Connected: Facilitating the Learning Experiences During & After Cancer Treatment*. Training for the Leukemia and Lymphoma Society, West Chester, NY, April 24.
- Gordon, D.S. (2014). *Staying Connected: Facilitating the Learning Experiences During & After Cancer Treatment*. Training for the Leukemia and Lymphoma Society, NY, NY, May 22.

Gordon, D.S. (2012). *Staying Connected: Facilitating the Learning Experiences During & After Cancer Treatment*. Training for the Leukemia and Lymphoma Society, West Chester, NY, February 16.

Gordon, D.S. (2012). *Choosing the Right College: An Educational Program for Survivors of Childhood Cancer*. Training for the Leukemia and Lymphoma Society, West Islip, NY March 30.

Gordon, D.S. (2002-2010). *Welcome Back: Facilitating the Return to School for Children with Cancer*. Multiple presentations, typically 2-6 times a year, for Leukemia Lymphoma Society, Make A Wish Foundation, New Jersey's School Counselor's Conference, New Jersey Commission on Cancer Research (NJCCR), and the New Jersey Office of Cancer Control regarding the educational needs of children with life threatening illnesses.

#### Additional Regional Presentations:

Gordon, D.S. (2014). *Supporting Special Needs Students*. The Staten Island Reading Association Annual Literacy Symposium, Staten Island, NY, October 28.

Gordon, D.S. (2012). *How to Incorporate Technology as a Home Instruction Teacher in NYC*. NYC DOE Hospital & Home Instruction Inservice Day. May 5. Staten Island Home Instruction.

DeMoss, K, Fitzgerald, J., Gordon, D.S., and Preskill, S. (2012). *The Right to Education*. Panel presentation as part of Constitution Day. Wagner College, Staten Island, NY, September 17.

Gordon, D.S. (2012). *Building Strong Community Partnerships in the FYP*. Faculty Presentation at Wagner College, Staten Island, NY, November 14.

Gordon, D.S. (2008). Grand Rounds, *Educating Students with Chronic Health Conditions: Old Problems New Solutions*. Newark Beth Israel Hospital, Newark, NJ, October 17.

Gordon, D.S. (2002). *From Classrooms to Cafeterias: A School Re-entry Program for Children with Chronic Illness*. Presentation for the National Association of School Psychologists National Conference. Chicago, IL, March 1.

Gordon, D.S. (2001). *School and Work: What the Primary Physician Should Know*. Sickle Cell Disease in 2001: Insights for Pediatric Health Care Providers. Conference. Hackensack, NJ, June 6

Gordon, D.S. (2001). *Navigating the Educational System*. Children with Cancer Go Back to School. Stony Brook University Hospital and Medical Center, NY, NY April 5.

Gordon, D.S. (2000). *Working with Preservice Teachers with Disabilities* Panel discussion member to the New York State Department of Education committee on Teacher Preparation and Preservice Teacher Standards. Albany, NY, March 31

## **RESEARCH PROJECTS AND GRANTS**

### **Wagner College 2014**

New York Community Trust (\$10,000). Reaching Learners with Special Needs through 21<sup>st</sup> Century Technology Skills. This program provides a series of learning goals that allow special

needs students to take risks, socialize, and engage in collaborative conversations to strengthen their digital media skills. In a format of three modules structured with technology teaching time and socialization time to promote social and emotional learning, Wagner College undergraduate and graduate students will assist in implementing the workshops.

Robinson Fellowship (\$2,500). An Investigation of the Implicit and Explicit Components of Democratic Engagement Taught Through Not-for-profit Educational Programs.

Virtual Visits Science Labs with New York Hall of science (\$100,000). The goal of this pilot program is to allow these students to get the science lab experiences they need virtually and still graduate on time with a Regents Diploma. Wagner College Portion (\$10,000).

HIVE NYC Grant with New York Hall of Science (\$150,000). Air Casting for Middle School Students. Wagner College portion (\$9,000).

Silverman Family Foundation Grant with New York Hall of Science for virtual educational programming for hospital and homebound children (\$10,000). Through work with Living Through Learning Foundation.

### **Wagner College 2013**

HIVE NYC Grant with Parsons New School for Design (\$100,000). gadgITERATION is a series of hands-on, entry-level design workshops that encourage students' creative and artistic engagement with technology. Wagner College portion (\$6,200).

HIVE NYC Grant with New York Hall of Science (\$150,000). Air Casting for Middle School Students. Wagner College portion (\$9,000).

Silverman Family Foundation Grant with New York Hall of Science for virtual educational programming for hospital and homebound children (\$10,000). Through work with Living Through Learning Foundation

Survivor Vision Foundation Research Grant for educational technology use by hospital teachers Pilot study to direct creation of a phone application for hospital and home instruction teachers (\$10,000).

### ***MEDIA REPORTS***

Lore, D. (2014, April 27). Wagner partners with Lifestyles for the Disabled. *Staten Island Advance*. Available at [http://www.silive.com/news/index.ssf/2014/04/in\\_our\\_schools\\_wagner\\_college.html](http://www.silive.com/news/index.ssf/2014/04/in_our_schools_wagner_college.html).

Lore, D. (2014, July 22) Wagner College hosts scholars from Obama's Young African Leaders initiative. *Staten Island Advance*. Available at [http://www.silive.com/northshore/index.ssf/2014/07/wagner\\_college\\_hosts\\_group\\_fro.html](http://www.silive.com/northshore/index.ssf/2014/07/wagner_college_hosts_group_fro.html).

## **SERVICE**

### **National**

Founder and Executive Director, The Living Through Learning Foundation. 2008 – Present.  
[www.livingthroughlearning.org](http://www.livingthroughlearning.org),

Reviewer & Advisory Board Member, 2014-15. *Handbook of Research on Effective Communication in Culturally Diverse Classrooms*, Frumkin, R. and Gonzalez, K, eds. Advances in Higher Education and Professional Development (AHEPD). Forthcoming 2015-16.

President Elect, Division for Physical Health and Multiple Disabilities, Council for Exceptional Children (CEC), 2013-14.

- Review and approve all presentation for national CEC conference
- Organize and run all Executive board meetings
- Set national division agenda for 2015
- Collaborate with all committee chairs including journal editor, newsletter editor, membership committee, by-laws committee, and special topics committees

Past President of Association of Pediatric Hematology Oncology Educational Specialists, (2009 – 2012)

- Chaired Nominating Committee
- Provided counsel to current president and other board members
- Continue to provide leadership during national conference

Joint Committee member for Association of Pediatric Hematology Oncology Educational Specialists and Association for the Education of Children with Medical Needs (2014 – Present)

- One of seven individuals selected to provide recommendations to both organizations around complex and sensitive issues such as joint conferences, joint legislative agendas, and possible merger of the two organizations

Reviewer & Advisory Board Member, 2011. *Controlling Complexities: Understanding the Structures of Questions*. Hardt, M. eds. Skill Plan. 2011.

### **Regional/Local**

Provided test design & item design theory in-services for New World Prep Charter School

Co-ran the Collect, Construct, Change (C3) project with New World Prep Charter School which aimed to: (1) equip youth with skills, knowledge, and tools to record, interpret, and communicate air quality information; (2) furnish youth with learning experiences that encourage them to engage with their environment, participate in community life, and understand why science is important in solving real-world problems; and (3) provide meaningful air quality information to the public and policy makers.

**College**

- Academic Review Committee (2012 – 2014)
- Intermediate Learning Community Member (2013 – 2014)
- First Year Program Member (2011, 2012, & 2014)
- Advisor for new student organization, Exceeding the Expectations, focused on raising disability awareness. (2014)
- Lead Educator for one week in the Young African Leaders Institute (Summer, 2014)
- 2014 Diversity Action Council Award recipient

**Department**

- Member, NCATE accreditation preparation team (2011-2012)
- Lead, Council for Exceptional Children (CEC) Specialty Program Association Accreditation Reports, grades 1-6 & 7-12 (2011-12)
- Lead, Council for Exceptional Children (CEC) Specialty Program Association Accreditation Reports, grades birth through 2 (2013-14)
- Lead, student support, both individual and group, for certification exam preparation for the Students with Disabilities CST Exam (2011-present)
- Departmental advisement beyond assigned advisees (2011-present). Entrance and exit interviews for undergraduate and graduate students, non-education students with an interest in psychosocial employment (psychology, social work, child life therapy, educational specialists) in hospital settings.

**Professional Associations**

- Association of Pediatric Hematology Oncology Educational Specialists (APHOES). President (2009 – 2012) & Founding Member (2005 – Present)
- Association for the Education of Children with Medical Needs (AECMN). Member, Advocacy Committee (2008 – Present)
- Council For Exceptional Children (CEC) (2006-present)