Neurocognitive Effects of Treatment of Pediatric Acute Lymphocytic Leukemia: A Neuroimaging Analysis

Child Development Honors Thesis

April 4, 2008

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Abstract

Acute Lymphocytic Leukemia (ALL) is the most prevalent form of cancer diagnosed in children. The current survival rate is approximately 85% and has been rising over the last two decades. The standard treatment regimen involves intrathecal chemotherapy in addition to corticosteroid drugs. Intrathecal chemotherapy has been shown to cause neurocognitive effects in executive function and IQ. The current study investigates differences in brain activation patterns that could account for the differences in neurocognitive function observed between ALL survivors and healthy controls. In this study, neurocognitive function of ALL survivors was assessed using a test battery that consisted of the Wechsler Intelligence Test for Children-Fourth Edition (WISC-IV) and the Delis-Kaplan Executive Function System (D-KEFS). ALL survivors showed significant deficits on these tests compared to matched, healthy controls. Survivors demonstrating the poorest performance on this battery participated in the neuroimaging component of the study in which brain activation during an inhibitory control task, the Simon task, was measured using functional magnetic resonance imaging (fMRI). ALL survivors demonstrated a compensatory mechanism of cortical recruitment during the Simon task, while performing worse than their matched, healthy controls. There was a significant difference in activation between survivors and healthy controls in the anterior cingulate cortex (BA 24), as predicted, although no differences were found between groups in the prefrontal cortex.

Introduction

As the survival rates for pediatric cancer continue to increase, researchers are becoming more interested in the quality of life of pediatric cancer patients after the completion of treatment. The most common type of pediatric cancer is Acute Lymphocytic Leukemia (ALL), which has a survival rate around 85% (NCI, 2004). A diagnosis of cancer and its treatment have become less fatal in the past few years; however, they are not without their side effects. Cancer and its treatment can cause social, intellectual, emotional, developmental, and financial stress. This stress not only affects the child receiving the diagnosis, but also the parents and siblings of the child in both positive and negative ways. During treatment, children show a decrease in social interactions and stimulation, demonstrate impaired emotional development, and often miss school resulting in falling behind academically.

Children's risks when receiving cancer treatment differ from adults because they are in their prime developmental stages. The developing brain in early childhood is characterized by both increases and decreases in gray matter and an increase in white matter. The gray matter increases as neurons grows, new synapses form, and dendrites mature. The growth is followed by a gray matter decrease, or pruning, when neurons and synaptic connections that are unnecessary are eliminated through apoptosis (Moore, 2005). The process of apoptosis increases the efficiency of the brain and its functioning. An increase in white matter, more specifically myelin, occurs in the developing brain in early childhood. Myelination, which increases the speed and efficiency of communication between neurons in the brain, begins in the third or fourth month of gestation and continues until the age of 20 (Moore, 2005). Myelination is completed last in the frontal and prefrontal lobes, which are responsible for higher order cognitive processes referred to as executive functions. Executive functions include planning,

organizing behaviors, controlling attention, and working memory (Mulhern et al., 2003). Moore (2005) points out that deficits in processing speed, memory, and executive functions are associated with white matter lesions in the brain. Certain drugs used for cancer treatment have been shown to damage myelin-producing glial cells; therefore, children are at risk for brain functioning deficits due to the disruption of myelination by cancer fighting medications (citation).

Acute Lymphoblastic Leukemia (ALL)

Cancer in children is not a common disease; only 1 or 2 children per 10,000 in the United States are diagnosed each year (Moore, 2005). ALL is the most commonly diagnosed cancer in children under the age of 20 (Mulhern et al., 2003) and the chance for long term survival is around 85% (Moore 2005). As the survivorship rate is increasing, the number of pediatric ALL survivors will also increase. ALL is a disease in which lymphoid cells found in bone marrow migrate to the central nervous system and other organs infecting the entire body by means of the circulatory system. Although the cause of ALL is uncertain, symptoms of the disease occur because accumulation of immature white blood cells in the bone marrow prevents the normal production of red blood cells, white blood cells, and platelets. These symptoms include bruising, pallor, fatigue, fever, bone pain, and anorexia (Mulhern et al., 2003). The symptoms listed can be common symptoms in other nonmalignant diseases; therefore, diagnosis of ALL is sometimes postponed.

Treatment for ALL

When diagnosed with pediatric ALL, a child's risk is assessed based on age, white blood cell count at diagnosis, and presence of specific cytogenic abnormalities to determine the specific course of treatment for the individual (NCI, 2004). This risk-based method of determining treatment maximizes each child's likelihood of survival. Treatment for ALL is divided into the following stages: remission induction, consolidation (also called intensification), and maintenance therapy. Remission induction involves the use of chemotherapy to eliminate leukemia cells from the bone marrow. Complete remission is when less than 5% of cancer cells remain in the marrow and the patient's blood count returns to normal. During remission induction children receive intrathecal chemotherapy, during which chemotherapy is injected into their cerebrospinal fluid to kill any cancer cells that may have spread to the CNS, and also receive corticosteroid drugs (usually dexamethasone) as anti-inflammatory treatment and to kill leukemia cells (ACS, 2008). For high-risk ALL additional drugs may be administered.

Once remission induction is achieved, the patient will undergo a period of consolidation aimed to reduce the number of remaining leukemia cells in the body. This period is the most intensive and usually lasts 4 to 8 months. Children with high risk factors will receive more intense chemotherapy in this phase. Upon completion of consolidation, maintenance therapy begins. Most children are given methatrexate and 6-mercaptopurine in the form of pills during this stage. In addition, vincristine, administered intravenously is also given along with a common steroid, typically dexamethasone. The entire course of treatment for patients ranges from 2 to 3 years. (ACS, 2008)

Neurocognitive Effects

Neurocognitive effects of chemotherapy and cranial radiation therapy (CRT) have become increasingly interesting to researchers. A recent meta-analysis (Campbell et al., 2006) combined 28 studies of children survivors of ALL who had received CRT, intrathecal chemotherapy, or both. Childhood ALL survivors showed clinically significant deficits in attention, speed of information processing, and executive functioning. Campbell et al. (2006) noted that all mean effect sizes, which spanned nine neurocognitive domains, were in the negative direction (g = -.034 to -.71) indicating consistent deficits in the overall neurocognitive functioning of ALL survivors. Of particular interest were 15 studies that evaluated attention in ALL survivors. The effect size (calculated at Hedge's g) was -.57 with a 95% confidence interval of -.71 to -.42 and $p<.001$. This demonstrates an overall deficit of attention in ALL survivors compared to control groups of siblings and healthy controls.

As an example of studies of the neurocognitive effects of ALL treatment, Mulhern et al. (2003) report on a group of 24 patients at the Children's Hospital of Los Angeles. Children's IQs were tested prior to treatment, 1 year post treatment, and 4 years post treatment. At the one year follow up no significant difference was observed in the children who received treatment; however, at four years post treatment, declines were observed in full scale, verbal, and performance IQ. Mulhern et al. (2003) also report on a between-groups study that took place at St. Jude's Research Hospital. Researchers examined groups of patients who received different doses of cranial radiation therapy (CRT) to determine if the magnitude of dosage made a difference in the child's neurocognitive outcome. It was reported (Mulhern et al., 2003) that higher does of CRT were associated with clinically larger significant declines in IQ and scores on arithmetic tests.

Moore (2005) revealed similar findings in a review of studies. He too found that ALL survivors who had received intrathecal chemotherapy and/or radiation therapy did significantly poorer on attention tests. Moore (2005) suggests a multitude of factors such as patient sex, age at treatment, elapsed time since therapy, preoperative evens, and cancer severity that could all contribute to a patient's neurocognitive function upon completion of treatment. Similarly, other researchers have begun to look at different mechanisms to explain the observed neurocognitive deficits in ALL survivors.

One possible mechanism that could explain the observed neurocognitive deficits deals with less white matter in the brains of ALL survivors. Intrathecal injection of methatrexate is thought to disrupt the natural myelination process by damaging myelin-producing glial cells (citation). Therefore, deficits in volume of white matter (myelin) could be reflected in deficits in children's' processing speed and efficiency. Another possible mechanism could result from corticosteroid treatment, specifically administration of dexamethasone, which is believed to have direct effects on neurons and neural connections (gray matter). Thus, there are inherent risks involved in the administration of drugs that could disturb the natural course of gray and white matter development in children.

Imaging Research

As discussed, chemotherapy and CRT effectively destroy cancer cells, but not without side effects to the brain. To examine possible mechanisms of neurocognitive damage of these therapies on developing cells in the brain, Reddick et al. (2003) looked at the association between full scale scores on intelligence tests (FSIQ) and normal-appearing white matter (NAWM). Specifically, Reddick et al. (2003) used magnetic resonance imaging (MRI) and

neurocognitive assessments to obtain data from 40 adolescent brain tumor survivors. Treatment for brain tumors, usually involving cranial radiation therapy and chemotherapy, is comparable to treatment for ALL. By comparing cancer survivors to healthy controls, they found that attentional deficits can explain a significant portion of the association between FSIQ and NAWM. Therefore, Reddick et al. (2003) suggest that chemotherapy leads to a decrease in NAWM and the deficit in white matter causes decreased attention and FSIQ scores.

Mulhern et al. (2004) found similar results in a sample of 37 long term survivors of malignant brain tumors in children. These children were treated with cranial radiation therapy with or without chemotherapy and were tested using the Conners' Continuous Performance Test (CCPT) in conjunction with MRI scans. When looking at CCPT performance and NAWM, lower volumes of NAWM were always associated with worse CCPT performance (Mulhern et al., 2004). On the overall attention index of the CCPT, scores of brain tumor survivors compared to age and gender normative data was significantly different ($p < .001$). Deficits on the CCPT were also correlated with decreased white matter volume in the frontal lobe, prefrontal lobe, and the cingulate gyrus. This study suggests that the long term attention deficits observed in brain tumor survivors may be contributed to a decrease in NAWM. The prefrontal, frontal, and cingulate regions that showed decreased white matter are the last to become myelinated in the developing brain, thus, are more susceptible to damage during chemotherapy and CRT treatment.

Similar relations between white matter and executive functions have been found in other populations of patients suffering from chronic conditions. In a study of Multiple Sclerosis patients, Sweet et al. (2006) used the n-back task to examine the relationship in task demand, task performance, and brain function. This study demonstrated that MS patients performed on the same level as healthy controls, although they responded slower. However, MS patients did

demonstrate different brain activity in response to the task as compared to healthy controls. The MS patients showed increased activation in clusters in the primary motor cortex, somatosensory cortex, right dorsolateral prefrontal cortex, right premotor cortex, and left insula on the 1-back task. This suggests a compensatory mechanism in brain activation and cortical recruitment when performing an executive function task.

Georgiou-Karistianis et al. (2007) observed increased cortical recruitment in patients with Huntington's disease during the Simon task, a measure of inhibitory control. As they expected, Huntington's' disease patients showed similar behavioral performance on the task as healthy controls. Nonetheless, the Huntington's patients showed increased blood recruitment to the anterior cingulate cortex (ACC), the right inferior frontal cortex, the parietal-temporal cortices (both left and right), the left dorsal premotor cortex, and the right precuneus/superior parietal region compared to the healthy controls; the healthy controls did not have significantly more activation in any region compared to the Huntington's patients. Georgiou-Karistianis et al. (2007), like Sweet et al. (2006), suggest a compensatory mechanism for patients, in which they recruit more blood to the regions of interest to perform equally as well as the controls on a task.

In a comparison of Stroop and Simon tasks (two similar measures of inhibitory control), Petersen et al. (2002) used fMRI to determine which brain regions are utilized during these tasks. They concluded that both interference tasks activated similar brain regions which include the supplementary motor (Brodmann's Area 6), visual spatial (BA 19), anterior cingulate (BA 24), interior temporal (BA 37), inferior parietal (BA 40), inferior frontal (BA 44), and dorsal prefrontal (BA 46). In addition, Petersen et al. (2002) showed that the supplementary motor (BA 6), superior parietal (BA 19), and superior temporal (BA 21) regions activated more strongly for the Simon task that for the Stroop.

In a recent report, Cacioppo et al. (2007) summarize research involving the anterior cingulate cortex (ACC). They report that the ACC is one of the circuits, in addition to the dorsolateral prefrontal cortex and ventromedial/orbitofrontral cortex, which is involved with self-regulation. More specifically, Cacioppo et al. (2007) suggest that the ACC is involved in decision making and monitoring, detection and processing of response conflict, action monitoring, and error detection.

Current Study and Hypotheses

A goal of this study is to examine the difference in brain activation patterns between pediatric ALL survivors and healthy controls during a measure of inhibitory control, the Simon task. It is believed that the Simon task will be a good indication of how cancer survivors are performing on executive function tasks. To determine if attentional and inhibitory control is impaired in children who undergo chemotherapy as treatment for ALL, fMRIs were acquired while children performed the Simon task.. If children receive chemotherapy during the period of natural brain development, natural brain development could have been disrupted. Therefore, we hypothesize, that ALL survivors will show deficits in their ability to demonstrate inhibitory control.

In addition, Georgiou-Karistianis et al. (2007) demonstrated that Huntington's disease patients show increased cortical recruitment during the Simon task, suggesting a compensatory mechanism compared with healthy controls. Based on this previous finding, we hypothesize that pediatric ALL survivors will also show a compensatory mechanism and will have increased cortical recruitment, as measured by number of activated volumes of interest (VOI) while performing the Simon task compared to their matched healthy controls.

Finally, there are many brain regions generally associated with executive function, attention, and inhibitory control. Based on previous findings, several of these areas include Brodmann's area (BA) 6 (supplementary motor cortex), 44 (inferior frontal cortex), and 46 (dorsal prefrontal cortex) (Petersen et al., 2002) as well as the Anterior Cingulate Cortex (ACC) (Cacioppo et al., 2007). Therefore, we hypothesize that the increase in activated volumes of interest will occur in BA 9, BA 44, BA 46, and the ACC.

Methods

Participants

ALL survivors who were treated with intrathecal methatrexate (but not cranial radiation therapy) at the Vanderbilt Medical Center were recruited for phase one of the study. For phase two of this study, the focus of the analyses reported here, we recruited those ALL survivors from phase one who demonstrated the greatest neurocognitive deficits. This included 8 survivors (4 girls and 4 boys), between the ages of 10 and 19 (mean=14.07 years old). In addition 7 healthy controls were recruited and were also between the ages of 10 and 19 (mean=14.54 years old). Healthy controls were matched as best as possible by age, gender, and socioeconomic status. Of the recruited ALL survivors, 75% identified themselves as Caucasian and 25% as African American. Of the healthy controls, 100% identified themselves as Caucasian. ALL survivors were initially contacted if they had completed treatment for a diagnosis of high-risk ALL, they had not received cranial radiation therapy during the course of treatment, and they were in remission (and had not experienced a previous relapse). Healthy controls were required to have no serious medical illness or history of cancer. Children were excluded from the study if they had low birth weight, known premorbid neurodevelopmental problems, or learning problems.

Measures

Phase I: In part 1 of the study, we administered the Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV), six subtests of the Delis-Kaplan Executive Function System (D-KEFS), including the Color-Word Interference, Tower, Sorting, Trail Making, Verbal Fluency, and Design Fluency tests. The full version of the WISC-IV was used to generate information on intelligence. The Color-Word Interference test (D-KEFS), much like the Stroop test, assesses the ability of children to inhibit automatic responses and also has a condition that measures mental flexibility. In the Tower test (D-KEFS) participants are required to build towers on a board with three pegs in the fewest number of moves possible. This task measures planning, rule learning, inhibition to impulsive responding, inhibition to perseveration, and establishing and maintaining an instructional set. The Sorting test (D-KEFS) requires participants to sort cards in different concepts or rules and tests problem solving and conceptual reasoning skills. In the Trail Making test (D-KEFS), participants are asked to draw through patterns of numbers in different conditions, such as numerical order, alphabetically, or switching between numbers and letters in order. This measures primary executive functioning. The Verbal Fluency test (D-KEFS) requires participants to think of as many words as possible that start with a certain letter, assessing the verbal fluency of the participant. Finally, the Design Fluency test (D-KEFS) has participants connect arrays of dots in different conditions (e.g. connect the shaded dots, connect the empty dots).

In addition to the WISC-IV and the D-KEFS participants were asked to fill out the Responses to Stress Questionnaire-Pediatric Cancer Version (RSQ) and the Youth Self Report (YSR), which assess anxiety and depressive symptoms. Also, parents were asked to complete the Responses to Stress Questionnaire-Pediatric Cancer Version (RSQ) about their child, the

Child Behavior Checklist (CBCL) regarding their child's anxiety and depressive symptoms, and the Behavior Rating Inventory of Executive Function (BRIEF) about their child.

Phase II: Three tasks were completed in phase II. First, an N-back task was used to elicit the brain regions responsible for working memory; results of this task are reported elsewhere. The next task in the scanner was the Simon task, which is an interference task and it is the focus of the current study. Finally, a film clip was shown to assess participants' emotional regulation and coping (results reported elsewhere).

Simon Task: In this task, a white arrow was presented on a black computer screen and two variables were manipulated. The arrow was presented on either the right or left side of the screen, this was considered the location variable. In addition the arrow would be pointed either to the left or right. Participants were asked to respond to the direction of the arrow while inhibiting where it was presented on the screen. If the arrow pointed in the same direction as the side of the screen it was presented on (i.e. an arrow was presented on the left and was pointing left) it was considered a congruent trial. If the arrow pointed in the opposite direction as the side of screen it was presented on (i.e. an arrow was presented on the left and pointed right) it was considered an incongruent trial. There were 2 blocks of the task, each containing 140 trials, for a total of 280 trials per participant. Of the 280 trials, an incongruent trial occurred every 7-13 trials, totaling 22-30 incongruent trials per participant. Participants had two seconds to respond on each trial.

Image Acquisition: Imaging consisted of a 3-plane localizer (5 slices per plane, 22s scan time) from which 20 oblique axial slices (parallel to the AC-PC line) were prescribed. High resolution 3D anatomical images were acquired using an inversion-prepared spoiled gradient recalled echo sequence (IR-SPGR), with an inversion time TI of 400ms, a TR of 15ms, minimum

TE (3ms), a matrix size 256x192x128 for a FOV of 200x200x154mm^3 with near isotropic resolution, for use in volumetric analysis. All functional images were acquired with a gradient echo EPI pulse sequence, with TE 30ms (optimized for T2* at 3T), flip angle of 70°, TR 2s, 20 slices 5mm thick and 1mm skip, and a matrix size of 64x64 sampled at +/-62.5kHz. The first 6 image volumes of the functional image dataset were discarded to allow magnetization to reach equilibrium**.**

Procedure

Phase I: Letters were sent describing the study to ALL survivors who were eligible to participate. Dr. Susan Alisanski, a former Pediatric Oncology/Hematology Fellow at Vanderbilt Children's Hospital, contacted eligible participants to obtain consent for the research assistants to contact interested families. Control families were contacted and consented by a member of our research team. A research assistant called all families to explain the study in detail and to schedule a visit to Vanderbilt. Informed written consent from a parent and assent from the child was obtained at the family's first visit to Vanderbilt. Also during this visit, each participant completed the neurocognitive battery. The tests were administered in a private room in the Jesup Laboratory or at Vanderbilt Children's Hospital.

Phase II: Phase II of the study (neuroimaging) was explained to families during their visit in phase I. Appropriate written consent and assent were obtained, and later, families who assented and consented to phase II scheduled an appointment at the Vanderbilt University Institute of Imaging Science (VUIIS). During this visit, each participant laid in a mock scanner to emulate the environment of the actual scanner and ensure comfort. In addition, participants practiced the neurocognitive tasks that were presented during the fMRI portion of the scan.

Neurocognitive tasks were presented in E-Prime and projected onto a screen in front of the participants face while they were in the scanner. Participants responded during tasks using a key pad that was attached to each hand. Neuroimaging was conducted by a technician who works for VUIIS. Anatomical, functional, and diffusion images were obtained to provide measures of tissue volume, brain function, and brain structure. Each participant spent approximately one and a half hours in the scanner to complete this phase of the study.

Results

Demographics

In order to control for possible confounds in comparisons between ALL survivors and healthy controls, participants were matched based on age, race, and socioeconomic status (SES). An independent samples t-test demonstrated that there was no difference in the age of participants between the groups (M_{ALL}= 14.07 years, SD_{ALL}= 2.23, M_{HC}= 14.54, SD_{HC}= 2.47). (See Table 1). Additionally, a chi-square test for significance showed that the groups were similar in race ($\chi^2 = 2.02$, $p = .27$). (See Table 1). Finally, socioeconomic status was determined by family income, which was reported in ranges of $10,000. A chi-square test for significance proved that the groups did not significantly differ in reported family income ($\chi^2 = 7.47$, $p = .11$). (See Table 1).

Questionnaire Measures

Survivors and healthy controls did not show significant differences on child reports of internalizing behavior, externalizing behavior, and overall competence (p=.74, p=.24 , and p=.10 respectively) obtained from the Youth Self Report (YSR) (see Table 1). Parent reports of

children's internalizing behavior, externalizing behavior, and overall competence from the Child Behavior Checklist (CBCL) also showed no significant differences between groups (p=.18, p=.57 , and p=.71 respectively) (see Table 1). Finally, parent reports of children's executive function obtained from the Behavior Rating Inventory of Executive Function (BRIEF) had no significant differences between ALL survivors and healthy controls (p= .34) (see Table 1).

Neurocognitive Assessment

To ensure that selected ALL survivors demonstrated significant neurocognitive deficits, independent samples t-tests were run on executive function performance, assessed by the Delis-Kaplan Executive Function Scale (D-KEFS), and overall cognitive assessment, determined by the Weschler Intelligence Scale for Children (WISC) (see Table 1). ALL survivors compared to healthy controls demonstrated significant deficits in verbal comprehension (WISC VCI t=-4.25, p= <.01), working memory (WISC WMI t=-2.76, p= .02), processing speed (WISC PSI t=-3.30, p= <.01), and overall cognitive ability (WISC FSIQ t=-3.98, p= <.01). In addition, ALL survivors performed more poorly on the D-KEFS color-word association task (t= -2.27, p= .04) and the D-KEFS sorting task (t= -2.63, p= .02). These differences verified that the selected ALL survivors demonstrate executive function and overall cognitive deficits compared to their matched healthy controls.

Neuroimaging

Task Performance. Independent samples t-tests were run to compare performance on the Simon task during fMRI between ALL survivors and matched, healthy controls (see Table 2). Effect sizes were also calculated for each condition. Although t-tests show that ALL survivors

and healthy controls do not significantly differ in response accuracy in three of the conditions (incongruent right, incongruent left, congruent right, and congruent left), it is noted that the differences approach significance in the expected direction, and reached significance in the incongruent left condition (see Table 2). Additionally, the mean accuracy for the overall task between groups did significantly differ ($p < .0001$). (See Table 2). The incongruent right ($p = .09$), incongruent left ($p = .05$), and congruent left ($p = .08$) conditions all show large effect sizes ($d = -.98$, $d = -1.11$, and $d = -1.03$ respectively), while the congruent right condition and overall mean for accuracy both have a medium effects ($d = -.78$ and $d = -.64$, respectively), with respect to Cohen's standards for effect size. Negative effects for response accuracy indicate poorer performance by ALL survivors than healthy controls.

Independents samples t-tests for differences in reaction time between ALL survivors and healthy controls show no significant differences. In addition, the effect sizes for the incongruent right, incongruent left, congruent left, and overall mean reaction time conditions are all small ($d = .41$, $d = .21$, $d = -.01$, and $d = .12$ respectively), while group has a medium effect on reaction time in the congruent right condition ($d = .59$). Positive effects for reaction time indicate longer reaction time for ALL survivors than healthy controls.

Brain Area Activation. *Between Group Analysis*. Between groups analyses were conducted to examine the differences in brain activation between ALL survivors and healthy controls while they performed the Simon task. Congruent trials of the task were used as a baseline measure; therefore, the areas of activation indicate when ALL survivors showed significantly more activation during incongruent trials compared to healthy controls. Eleven clusters, composed of at least 50 contiguous voxels of activation, showed significantly more activation during incongruent trials for ALL survivors than for healthy controls (see Table 3).

One of these clusters was in an a priori region of interest, the anterior cingulate cortex (BA 24). Other areas that showed significantly more activation for ALL survivors than controls are Brodmann's areas 4, 19, 31, 37, and 42. (See Table 3). Brodmann area 4 is involved in motor control, 19 and 37 are part of the visual cortex, 31 exhibits somatosensory control, and 42 is part of the auditory cortex. Significantly more activation indicates that ALL survivors recruited more oxygenated blood to these areas during incongruent trials of the Simon task.

Discussion

The current pediatric ALL survival rate is approximately 85% (NCI, 2004) and has been increasing for the past 20 to 30 years. With this increase, researchers have gained interest in the quality of life of survivors after the completion of treatment. Brain development begins in utero and continues into late adolescence and adulthood; thus, when children receive chemotherapy as treatment for ALL their brains are still in the midst of the natural developmental process. Therefore, chemotherapy poses a threat to the normal progression of brain developmental and the late effects associated with this threat are of particular interest in this study. In a meta-analysis of previous research, Campbell et al. (2006) demonstrated that ALL survivors performed worse than siblings or healthy controls in all neurocognitive areas assessed, which ranged from IQ to executive functioning. The current study replicates and extends those findings. The participants in this study showed deficits in verbal comprehension, processing speed, working memory, and overall cognitive ability as well as poorer performance on a sorting task and color-word association task. With clear evidence of decreased neurocognitive functioning in ALL survivors compared to healthy controls, this study examined the underlying mechanisms associated with these deficits.

Participants for the imaging portion of this study were selected based on their performance on a neurocognitive test battery. From a larger group of ALL survivors, the 8 survivors recruited demonstrated the poorest performance on the phase I assessment. Therefore, the deficits observed in this study may represent a subgroup of the larger population of ALL survivors. Nonetheless, the survivors in this study may reflect a subgroup of ALL survivors who are experiencing significant late effects in executive functioning. The healthy controls were recruited from the Vanderbilt University Medical Center email database, and thus may also present a somewhat biased group of participants. It should also be noted that parents' decisions to have their children included in the study may have been influenced by their children's poor performance in school, children's demonstration of gifted abilities, or desire to have their children tested. This is not an exhaustive list of factors that may have contributed to a child's inclusion in the study but should be taken into account when considering the outcomes of the study. These limitations notwithstanding, the findings of this study add to the literature on neurocognitive effects in pediatric cancer survivors.

Interestingly, although ALL survivors demonstrated significant deficits in performance on measures of the WISC and D-KEFS, they did not display significant differences in response accuracy in individual conditions on the Simon task during the fMRI. Nonetheless, survivors showed significantly poorer performance on the overall task. The effect sizes for response accuracy between the two groups were medium and large for all conditions and the p-values obtained from the independent samples t-tests, if not significant, approached significance. Therefore, although the differences were not all statistically significant between groups, it is clear that the ALL survivors showed poorer performance on the Simon task with respect to performance accuracy. In addition, there were no significant differences between survivors and

healthy controls in their reaction time. The effect sizes for the differences in reaction time between the groups were small in all conditions, with the exception of the congruent right condition which showed a medium effect.

The performance deficits observed during the Simon task mimic the results observed in the neurocognitive battery. Since ALL survivors and their matched, healthy controls had similar reaction times during the Simon task, the observed differences in accuracy cannot be attributed to impulsivity in responding. From this observation, we hypothesize that the accuracy difference between ALL survivors and healthy controls is a matter of their cognitive ability to perform the task and not an issue of an inability to inhibit an impulsive response. Concurrent with previous findings (Campbell et al., 2006), parent observations from the BRIEF (Behavior Rating Inventory of Executive Function), and the Simon task performance data, it is clear that there are meaningful late effects on children's executive function after receiving intrathecal chemotherapy as treatment for ALL.

Since the prefrontal cortex and anterior cingulate cortex are areas that have been shown to be associated with executive function, they were a focus in this study. In particular, Brodmann's areas 6, 44, and 46 in the prefrontal cortex were selected as regions of interest, in addition to the anterior cingulate cortex (BA 24). The significant activation found in BA 24 is consistent with previous studies (Petersen et al. 2002; Cacioppo et al. 2007). As participants perform the Simon task, they must override the tendency to respond to the latent variable (location of the arrow on the screen) that is interfering with processing the variable of interest, direction of the arrow. BA 24 is responsible for error detection and monitoring, performance monitoring, and decision making, thus, it is not surprising that it is involved in performing the Simon task.

Consistent with prior research, ALL survivors demonstrate a compensatory mechanism of cortical recruitment during executive functions. Robinson et al. (2008) demonstrated that ALL survivors perform equally well on measure of working memory as their matched, healthy controls, but show increased cortical recruitment and activation in brain regions involved. These results indicate that ALL survivors worked harder to achieve similar results to their healthy peers. Staffen et al. (2002) suggest that this type of compensation is carried out to preserve overall functioning on executive function tasks.

Interestingly, in this study ALL survivors showed significantly greater activation in BA 24 than their matched healthy controls, but performed less accurately. Greater activation in BA 24 indicates that ALL survivors worked harder to perform the Simon task. Furthermore, with a greater amount of activation and more recruited blood to BA 24, ALL survivors still could not obtain equal achievement on the task as the control group. This finding indicates less efficiency in this particular brain region than their healthy peers suggesting a maximum level of cortical compensation for ALL survivors. Therefore, ALL survivors not only demonstrate meaningful late effects on tasks of executive function, but are also having to work harder to perform such tasks.

Overall, ALL survivors are demonstrating clear deficits on executive function and cognitive tasks. These deficits have the potential to interfere with everyday functioning of survivors in social, intellectual, and behavioral domains. The underlying neural mechanisms observed in this study show that survivors are recruiting more oxygenated blood to the brain during the tasks. These two observations taken together imply that as ALL survivors work harder to perform a task (by recruiting more blood to the brain) they still are incapable of achieving equal performance with their peers.

Although the sample size of this study was small and may have contributed to our inability to obtain statistically significant differences in performance in certain conditions of the Simon task, it is a comparable sample size to other imaging studies. Interestingly, we did not observe significant differences in BA 6, 44, and 46, which were selected as a priori regions of interest since they have been shown to be involved in executive function tasks (Robinson et al., 2008; Petersen et al. 2002). Since the prefrontal region of the brain is one of the last to undergo myelination, it was proposed that chemotherapy would pose the greatest developmental threat to this region. However, ALL survivors did not engage the prefrontal cortex, specifically BA 6, 44, and 46, differently than healthy controls on the Simon task. The specific means of why there was no difference is unclear and could be investigated further in future studies.

Subsequent research could examine how executive function tasks overflow into everyday functioning ability. More specifically, further research could look at the ability of ALL survivors to cope with a socially stressful situation while obtaining functional brain images in order to observe the brain activation patterns during such task. In addition, to further understand the cause of poorer neurocognitive performance and increased cortical recruitment, diffusion tensor imaging (DTI) or functional connectivity magnetic resonance imaging (fcMRI) could examine white matter in the brain or the neural connections in the brain, respectively. Finally, the effects of corticosteroids, besides dexamethasone, should be examined and their late effects should be evaluated in comparison to the late effects from the current treatment protocol for ALL. Additional research based evidence regarding brain deficits of ALL survivors will provide researchers and physicians with useful knowledge and will enable them to seek methods of treatment or interventions to minimize such deficits.

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Table 1
Group Comparisons on Demographics, Emotional and Executive Functioning, and Cognitive Ability

	Survivors (*n = 8)*	Healthy Controls (*n = 7)*	*T*	*p*	Cohen's *d*
Demographics					
Child Age	14.07 (2.23)	14.54 (2.47)	-0.39	.70	0.20
Family Income	8.00 (2.07)	6.57 (2.30)	1.27	.23	0.65
Questionnaire Measures					
YSR Internalizing	50.50 (8.33)	49.17 (8.11)	0.34	.74	0.16
YSR Externalizing	46.88 (8.18)	52.33 (9.03)	-1.23	.24	0.63
YSR Total Competence	42.38 (8.19)	51.17 (9.28)	-1.77	.10	1.00
CBCL Internalizing	58.38 (9.99)	54.00 (8.44)	1.41	.18	0.47
CBCL Externalizing	55.75 (9.63)	51.67 (12.79)	0.59	.57	0.30
CBCL Total Competence	41.75 (10.94)	50.50 (14.90)	-0.38	.71	0.67
BRIEF Composite	129.00 (42.71)	111.00 (22.29)	1.00	.34	0.53
Cognitive Assessment					
WISC VCI	99.43 (13.28)	128.14 (11.95)	-4.25	<.01	2.27
WISC PRI	94.75 (18.24)	110.86 (11.98)	-1.99	.07	1.04
WISC WMI	84.67 (18.48)	112.00 (17.18)	-2.76	.02	1.53
WISC PSI	81.25 (12.33)	107.14 (17.89)	-3.30	<.01	1.69
WISC FSIQ	88.86 (17.73)	119.86 (10.53)	-3.98	<.01	2.13
D-KEFS Color-Word	8.25 (2.66)	11.00 (1.92)	-2.27	.04	1.19
D-KEFS Tower	9.88 (2.42)	11.43 (2.07)	-1.33	.21	0.69
D-KEFS Sorting	7.63 (3.58)	11.43 (1.40)	-2.63	.02	1.40

Note. YSR = Youth Self Report; CBCL = Child Behavior Checklist; BRIEF = Brief Rating Inventory of Executive Function; WISC VCI = Wechsler Intelligence Scale for Children (4th Edition) Verbal Comprehension Index; WISC PRI = Wechsler Intelligence Scale for Children (4th Edition) Perceptual Reasoning Index; WISC WMI = Wechsler Intelligence Scale for Children (4th Edition) Working Memory Index; WISC PSI = Wechsler Intelligence Scale for Children (4th Edition) Processing Speed Index; WISC FSIQ = Wechsler Intelligence Scale for Children (4th Edition) Full Scale IQ; D-KEFS = Delis-Kaplan Executive Function System. Scores for the YSR and CBCL are normalized *T* scores. Scores for the WISC are standardized scores (M = 100, SD = 15).
[a]Values in parentheses indicate standard deviation.

Table 2

Group Comparisons on Simon Task Performance

Simon Task **Accuracy Rates**	Survivors	Healthy Controls	*t*	*p*	Cohen's *d*
Incongruent Right	0.63 (.19)	0.78 (.10)	-1.85	0.09	-0.98
Incongruent Left	0.59 (.35)	0.89 (.18)	-2.19	0.05	-1.11
Congruent Right	0.85 (.25)	.99 (.02)	-1.43	0.18	-0.77
Congruent Left	0.74 (.34)	.99 (.02)	-2.06	0.08	-1.03
Total Accuracy	0.78 (.41)	0.98 (.15)	7.6656	<.0001	-0.65
Reaction Time (ms)					
Incongruent Right	780.95 (141.47)	735.27 (69.59)	0.77	0.45	0.41
Incongruent Left	787.27 (196.78)	752.60 (126.31)	0.40	0.70	0.21
Congruent Right	647.00 (109.28)	589.34 (86.14)	1.12	0.28	0.59
Congruent Left	595.89 (178.48)	596.96 (80.24)	-0.02	0.99	-0.01
Mean Reaction Time	640.95 (309.30)	610.21 (186.35)	1.42	0.16	0.12

Table 3

Significant Between Group Differences in BOLD Responses, for Survivors and Controls, by contrast on the Simon Task.

	Region	BA		Talairach Coordinates		*T*	*p*	# Voxels
ALL > Control			x	y	z			
Incongruent-Congruent	Parahippocampal Gyrus	37	36	-37	-5.1	5.14	0.000189	66
	Posterior Cingulate	31	7.8	-64	15	3.24	0.006418	66
	Cingulate Gyrus	24	-0.37	-4.8	26	2.27	0.040951	52
	Lentiform Nucleus	*	-9.5	-0.13	1.9	6.96	0.00001	229
	Caudate	*	-14	-19	27	4.72	0.0004	87
	Fusiform Gyrus	19	-23	-84	-11	4.91	0.000287	69
	Culmen	*	-24	-38	-18	3.93	0.001722	93
	Fusiform Gyrus	19	-27	-68	-8.3	4.47	0.00063	183
	Claustrum	*	-34	11	-1.8	5.15	0.000186	233
	Precentral Gyrus	4	-48	-9.2	44	4.71	0.000408	239
	Superior Temporal Gyrus	42	-56	-27	15	2.15	0.051416	97