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# LATE COGNITIVE, ACADEMIC, AND BEHAVIORAL FUNCTIONING IN CHILDHOOD CANCER SURVIVORS TREATED BEFORE AGE FIVE WITH NON-CNS-DIRECTED THERAPY

A Thesis in

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## Abstract

Children who have been treated for cancer are at risk for experiencing cognitive, academic, and behavioral difficulties which may not appear until long after treatment has ended. These difficulties, known as neurocognitive late effects, are believed to result in part from damage to the central nervous system (CNS) caused by the cancer and by neurotoxic treatment methods. Until recently, children whose cancer and treatment protocols did not target the CNS were believed to be protected from such damage. However, research suggests that these cancer survivors may indeed experience some degree of neurocognitive impairment following treatment. Cognitive, academic, and behavioral functioning were examined in a group of 18 long-term cancer survivors treated prior to school-age with only non-CNS-directed chemotherapy and radiation. Survivors' scores were compared to their healthy siblings and to the normative population. Although the differences were not statistically significant, the healthy siblings outperformed survivors on all measures, including IQ, reading, math fluency, working and auditory memory, and processing speed. Furthermore, survivors were much more likely to be receiving special education services than their siblings. Cancer survivors demonstrated higher levels of parent-reported problems with attention and executive functioning, compared to both siblings and the normative population. Medium to large effect sizes were associated with the differences between survivors' and siblings' auditory memory scores and small to medium effects were found between survivors and the normative group in math fluency. In spite of the differences, survivors' mean scores on all of the measures fell within the average range, and both survivors' and siblings' IQs were slightly above average. Exploratory regression analyses suggested that parent education was the only significant predictor of attention and executive functioning, while time since diagnosis was the only significant predictor of survivors' scores on the auditory memory composite. The small *n* was a significant limitation in terms of

statistical power and the ability to generalize the findings. Nevertheless, results from the study do support the need for future large-scale research with this population of cancer survivors to determine whether they are at risk for later neurocognitive deficits, and if so, which areas of functioning are likely to be affected.

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# Acknowledgements

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A chronic health condition is one that lasts, or is expected to last, more than 3 months, often involves extended medical treatment, and may lead to physical, cognitive, or psychosocial limitations or disabilities (Perrin et al., 1993; Phelps, 2006). The prevalence of children with chronic health conditions has increased significantly over the last few decades (Tarnowski & Brown, 2000) and ranges from 6.5% up to 31%, depending upon how the term *chronic illness* is defined (Newacheck & Halfon, 1998; Perrin et al.). The rise in prevalence has been attributed to the fact that more children are surviving acute medical illness due to early diagnosis and improved treatment methods (Olson, Seidler, Goodman, Gaelic, & Nordgren, 2004; Thompson & Gustafson, 1996). In recent years, childhood cancer has shifted from an acute to a chronic condition, since most children now survive the disease but may face long term effects from the cancer or its treatment (Katz, Dolgin, & Varni, 1990). Thus, worries about whether a child will survive have evolved into concerns related to quality of life following diagnosis and treatment (Cruce & Stinnett, 2006).

A significant number of children experience a medical condition that affects their quality of life by limiting daily activities, such as school functioning (Power, DuPaul, Shapiro, & Parrish, 1995). Children with a chronic heath condition are at an increased risk for school performance problems (Eiser & Vance, 2002; Thompson & Gustafson, 1996). The risk for problems with school adjustment and performance is especially high if the illness affects the brain or if there is an accompanying physical disability (Howe, Feinstein, Reiss, Molock, & Berger, 1993; Thompson & Gustafson). In the case of childhood cancer, tumors of the brain or spinal cord are generally acknowledged to have the potential to result in cognitive changes in some survivors (Duffner, 2004; Espy et al., 2001; Kadan-Lottick & Neglia, 2005; Mulhern, Phipps, & White, 2004; Reddick et al., 2003). Extensive research has shown that children treated for brain tumors are at high risk for experiencing brain damage and subsequent changes in intelligence, behavior, and social-emotional functioning as a

result of the tumor itself and the treatment process (Armstrong, 2003; Moore, 2005). When cognitive changes occur in cancer survivors, they are often accompanied by problems with academic achievement and school functioning (Kadan-Lottick & Neglia; Kingma et al., 2001; Haupt et al., 1994), and may not be apparent for months or years after treatment has ended (Mulhern & Palmer, 2003a; Twaddle, Britton, Craft, Noble, & Kernahan, 1983; Wissler & Proukou, 1999). In some cases, cognitive problems may not be noticed until a child begins to struggle in school. Leukemia, a cancer of the blood, is not known to have any direct effects on the brain; nevertheless, central nervous system (CNS) involvement can occur through prophylactic treatments that target the brain and spinal cord (Armstrong; Mulhern & Palmer, 2003a). Hence, current knowledge suggests that both CNS tumors and CNS-directed cancer therapies have the potential to negatively affect a child's educational development and functioning (Mitby et al., 2003; Oeffinger & Hudson, 2004; Peckham, 1991).

Other less common childhood cancers occur outside the central nervous system, and until recently they were not believed to be associated with damage to the CNS. Because of this belief, few studies have been designed to directly examine long-term cognitive and behavioral outcomes among childhood cancer survivors whose disease did not directly involve the brain or spinal cord. However, information from the available studies, combined with clinical observations, suggest that some of these children may also be vulnerable to cognitive damage and learning difficulties.

The current study examines survivors of childhood cancer, diagnosed and treated prior to school age, whose disease and treatment have not traditionally been associated with adverse effects on the CNS. The study is designed to enhance knowledge about survivors of these less common childhood cancers by determining whether they are at an increased risk

for later cognitive, academic, or behavioral difficulties, and if so, which areas of functioning are most likely to be affected.

## Chronic Illness and School Performance

Advances in medicine and technology have led to greater numbers of children with chronic health conditions who are able to attend school, rather than to be confined to their home or a hospital (Olson et al., 2004; Thies & McAllister, 2001). When they return to school following hospitalization or treatment, children with chronic conditions may experience difficulties adapting to the school environment (Power et al., 1995) and the exacerbation of pre-existing learning difficulties or newly acquired problems (Lee & Janik, 2006; Sexon & Madan-Swain, 1993). Studies have found that although their scores fall within the average range, children with chronic health conditions tend to perform significantly below their healthy peers on standardized academic achievement tests (Fowler, Johnson & Atkinson, 1985; Howe et al., 1993). Furthermore, research has consistently shown that these children are at higher risk for special education placement and repeating a grade than are healthy children (Brown & Madan-Swain, 1993; Fowler et al.; Gortmaker, Walker, Weitzman, & Sobol, 1990; Mulhern et al., 1992a).

School adjustment and performance problems in childhood cancer survivors may be a consequence of brain damage caused by a tumor. Alternatively, these difficulties may be related to other aspects of the cancer experience as well as individual and family characteristics. In particular, school performance can be affected by (1) psychological stress and parenting behaviors, (2) missed school, and (3) socioeconomic factors (Kazak & Rourke, 2003; Thompson & Gustafson, 1996).

First, childhood chronic illness is a potential stressor for the individual and his or her family. Many children experience some symptoms of posttraumatic stress, which may include health-related worries or fears that make it difficult to concentrate in school (Kazak

& Rourke, 2003). In some cases, parents exhibit even more symptoms of stress than the cancer survivors themselves (Kazak & Rourke). It has been shown that parental stress affects parenting behaviors which, in turn, influence children's cognitive and social development (Thompson & Gustafson, 1996).

Second, children with cancer and other chronic conditions miss more days of school each year than their healthy peers (Fowler et al., 1985; Keene, 2003). When a child is of school age during cancer diagnosis and treatment, he or she might miss school for a variety of reasons, such as medical appointments, hospitalizations, and illness due to the disease or side-effects of treatment. Some children with cancer miss additional days of school due to parents' fear for the child's safety or health, distress over separation from the parent, school avoidance or phobia following prolonged absences, changes in physical appearance, or suspected learning problems (Armstrong, 2003). In studies of healthy children, there is typically a significant relationship between the number of school absences and academic achievement (Fowler et al.). Butler, Hill, Steinherz, Meyers, and Finlay (1994) evaluated 120 childhood cancer survivors post-treatment and found that the amount of school missed significantly predicted later reading and spelling achievement, global and verbal intelligence quotients (IQ), and nonverbal memory scores.

Third, socioeconomic status (SES) is positively correlated with academic achievement and IQ in healthy children (Sattler, 2001), as well as those with cancer (Copeland, Moore, Francis, Jaffe, & Culbert, 1996) and other chronic illnesses (Fowler et al., 1985). Indeed, Fowler et al. found that for children with a chronic illness, academic achievement was associated with socioeconomic factors and specific health conditions, but not with the amount of missed school. One indicator of socioeconomic status, years of maternal education, was significantly related to developmental performance and IQ in a group of premature infants who were assessed at 24 months and again at 5 years of age

(Cohen & Parmelee, 1983). In that study, maternal education was the single best predictor of a child's IQ at age 5. Understanding how factors like SES affect IQ is important because most experts agree that a person's global IQ is the best available single predictor of future academic achievement (Reschly, 1997; Sattler). In addition to socioeconomic factors, IQ is also influenced by genetics, home environment, and the quality of a child's school (Sattler).

## Childhood Cancer

Cancer refers to a group of diseases that are characterized by uncontrolled cell growth and the spread of abnormal cells throughout the body (Cruce & Stinnett, 2006). The cancer cells can invade tissues that are nearby or settle in other places in the body by traveling in bodily fluids (Keene, 2003). The aberrant cancer cells may form a tumor and lead to organ damage or malfunction, or cancers like leukemia may affect the blood and cause problems in multiple organs. The American Cancer Society (2006) estimates that during 2006, about 9,500 children between birth and 14 years old will be diagnosed with cancer. Although the incidence of childhood cancer is rare, it is the second leading cause of death in children, and over 1,500 will die from cancer this year. Leukemia is the most common cancer found in children, accounting for 30% of cases, followed by brain and other nervous system cancers which account for approximately 22% of cases. Other cancers diagnosed in children include neuroblastoma (7.3%), Wilms' tumor (5.6%), Hodgkin (3.5%) and non-Hodgkin lymphomas (4.5%), rhabdomyosarcoma (3.1%), retinoblastoma (2.8%), osteosarcoma (2.4%), and Ewing Sarcoma (1.4%; American Cancer Society).

Gains have been made over the past 30 years and the mortality rate due to cancer in children has decreased significantly. Depending upon the type of cancer, the five-year survival rate for children is nearly 80%, compared to only 57% in the mid-1970s (Ries et al., 2006). The increase in the number of survivors of childhood cancer has been linked to improvements in treatment protocols and earlier detection (Brown & Madan-Swain, 1993;

Peckham, 1991; Robison et al., 2002). Unfortunately, the optimism regarding more effective treatment methods has been tempered by the fact that even if the cancer is successfully removed, survivors may experience significantly diminished quality of life following the course of treatment (Brown & Madan-Swain; Mulhern et al., 2004). Survivors can struggle with medical complications including secondary cancers (Neglia et al., 2001), poor stamina, fatigue, weight gain, hair loss, vision or hearing loss, seizures, stroke, organ damage, and physical disabilities that involve gross- or fine-motor impairment (Friedman, 2003; Oeffinger & Hudson, 2004). They may also experience indirect effects such as depression and anxiety, learning difficulties, and poor social development (Kazak & Rourke, 2003; Mulhern & Palmer, 2003a; Peckham).

*Treatment Methods*

The methods that are most often used to treat childhood cancer are surgical resection, chemotherapy, radiation, and stem cell transplantation (Keene, 2003). One or more of these methods may be employed in a particular case depending upon characteristics of the patient, the type of cancer, and its location and size. Radiation involves using high-energy x-rays to kill cancer cells (Keene), and the amount of absorbed radiation is measured in Grays (Gy) or centigrays (cGy). Cranial radiation therapy (CRT) refers to when these x-rays are directed at areas of the brain or brain stem. Chemotherapy involves the use of a variety of toxic drugs to destroy or disrupt the growth of cancer cells (Keene). Intrathecal chemotherapy (ITC) refers to a procedure whereby the drugs are injected into the space surrounding, or directly into, the spinal cord instead of intravenously (IV; also referred to as systemic chemotherapy).

Most of the studies that have investigated potential adverse treatment effects have focused on patients who received CNS-directed therapies, which are routinely included in treatment protocols for the most common childhood cancers. The potential for negative effects following surgical removal of a tumor depends upon the location and extent of the

surgery. When brain tumors are removed surgically, the opportunity exists for a wide range of complications and problems to occur (Keene, 2003; Moore, 2005). In the case of leukemia, the CNS can harbor occult cancer cells and consequently, the CNS often receives prophylactic treatment (Balis & Poplack, 1989). The CNS is targeted via treatment with CRT or ITC, or both. Though highly effective in killing cancer cells, CRT and ITC can also cause physical changes in the brain and nervous system, such as focal necrosis, leukoencephalopathy (damage to white matter), decreased brain volume, cerebral calcifications, large-vessel stroke, myelitis, ototoxicity, and nerve damage leading to blindness (Freidman, 2003; Iuvone et al., 2002; Mulhern & Palmer, 2003a; Ober, Beaverson, & Abramson, 2004; Shearer, 2004). Depending upon the degree of severity, a child who experiences such damage to the brain or loss of vision or hearing may have difficulties learning and functioning in school. In fact, the most common neurocognitive complications observed in cancer survivors are learning difficulties caused by late effects of combined CNS-directed therapies (Kadan-Lottick & Neglia, 2005). In general, survivors treated with ITC and CRT demonstrate poorer long-term cognitive and academic outcomes when compared to survivors treated with surgery alone (Mulhern et al., 1999; Reimers et al., 2003) and children with other chronic illnesses (Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000). Cognitive changes that result from damage to the brain are often called *neurocognitive* or *neurobehavioral* late effects (Kadan-Lottick & Neglia).

*Late Effects of Cancer*

Late effects refer to damage to healthy tissue that results from chemotherapy, radiation, or the disease process. Mulhern and colleagues (2004) explain that late effects are "temporally defined as occurring after the successful completion of medical therapy, usually two or more years from the time of diagnosis, and it is generally assumed that late effects are chronic, if not progressive in their course" (p. 18). Late effects can be distinguished from the

acute or temporary effects of treatment, such as nausea and vomiting from chemotherapy, which typically subside following treatment or resolve in a time-limited manner (Mulhern et al.). Due to the nature of late effects, they may not be noticed for years after treatment has ended (Mulhern & Palmer, 2003a; Wissler & Proukou, 1999). Current information on late effects of cancer comes primarily from research on children who have been treated for acute lymphoblastic leukemia (ALL) or brain tumors, the two most common forms of childhood cancer (Mulhern et al.). Late effects may affect physiology, as well as psychological and neurocognitive functioning (Wissler & Proukou).

Brain imaging techniques, such as MRI, can be used to evaluate physical changes in the brain (Mulhern & Palmer, 2003a). For example, studies of patients treated with cranial radiation, chemotherapy, or both, have found changes in brain structure, such as reduced white matter volume (Khong et al., 2006; Kingma et al., 2001; Mulhern et al., 1999), blood vessel damage, brain shrinkage and enlarged ventricles (Kingma et al.; Mulhern & Palmer, 2003b). The severity of white matter loss correlates with age at cranial radiation and cranial radiation dose, with young age and higher doses associated with greater loss (Khong et al.). White matter abnormalities have also been linked with poor performance on measures of visual-motor integration (Iuvone et al., 2002). Alternatively, Kingma et al. did not find significant relationships between brain image abnormalities and neurocognitive test scores, placement in special education, or level of educational attainment in a Dutch sample ($n$ = 45) treated with or without cranial radiation.

Neurocognitive late effects are generally characterized by problems with thinking, learning, and remembering (Mulhern & Palmer, 2003b). Reviews of the literature reveal that indicators of potential neurocognitive problems in cancer survivors include difficulties with basic reading, reading comprehension, and arithmetic; deficits in receptive and expressive language; decreased speed of mental processing; memory and attention deficits; behavior

problems; poor school attendance; poor hand-eye coordination; poor organization skills; difficulty following directions; and poor performance under stress (Brown & Madan-Swain, 1993; Peckham, 1991; Schwartz, Hobbie, & Constine, 2005). Neurocognitive effects are typically measured through assessment of the abilities and behaviors that are believed to be associated with, or dependent upon, the functioning of certain areas of the brain. Traditionally, IQ and academic achievement tests have been the primary measures used to determine whether deficits are present, and such tests continue to be used in many studies of neurocognitive late effects (see Espy et al., 2001; Mulhern & Palmer, 2003a, 2003b; Palmer et al., 2001; Precourt et al., 2002).

Recently, some authors have hypothesized that global declines in IQ and academic performance are merely symptoms of changes in children's ability to attend to and process new information (Reddick et al., 2003). In fact, Mulhern and Palmer (2003b) identified a phenomenon called the "neurocognitive phenotype" (p. 181), which has been observed in some childhood cancer survivors. The term refers to a set of primary deficits in attention, memory, and processing speed, and secondary deficits in IQ and academic achievement. Findings from a longitudinal study of childhood cancer survivors seem to support the existence of such a phenomenon (Palmer et al., 2001). Results revealed that the observed decline in survivors' IQ scores over time was due to a failure to acquire new information at a rate similar to peers, rather than a loss of previously acquired information. Furthermore, in a study with ALL survivors, Schatz, Kramer, Ablin, and Matthay (2000) showed that IQ differences between the CRT and control groups were mediated by differences in working memory. In addition, processing speed was found to be an important moderator of working memory. The authors proposed a model of cognitive deficits related to processing speed, which they believe might inhibit working memory.

*Neurocognitive late effects of cranial radiation therapy (CRT).* The fact that radiation directed at the CNS can damage the brain and nervous system and result in neurocognitive deficits has been well-established in the literature (Duffner, 2004; Espy et al., 2001; Kadan-Lottick & Neglia, 2005; Mulhern et al., 1999; Mulhern et al., 2004; Ober et al., 2004; Raymond-Speden et al., 2000; Reddick et al., 2003; Shearer, 2004). Some studies have found dose-dependent results, with higher doses of CRT leading to more severe impairment (Silber et al., 1992; Waber et al., 2001). In one study, participants received 1800 cGy, 2400 cGy, or 3600 cGy of CRT as part of their treatment protocol (Silber et al.). Results showed that participants' global IQ scores decreased significantly as radiation dose increased. Other studies have not found significant differences associated with increased radiation dose, but instead, demonstrated that doses of 1800 cGy and higher resulted in similar degrees of damage (Butler et al., 1994).

The most common neurobehavioral impairments associated with CRT involve short term (working) memory, decreased processing speed, distractibility, fine-motor coordination, visual-spatial ability, and somatosensory functioning (Kadan-Lottick & Neglia, 2005). The cognitive and academic consequences of CRT include lower IQ, academic failure, increased likelihood of referral for special education, and lower final secondary educational attainment when compared to healthy siblings (Kadan-Lottick & Neglia; Kingma et al., 2001; Haupt et al., 1994).

*Neurocognitive late effects of CNS-directed chemotherapy.* Damage to the CNS was previously thought to be limited to children treated with cranial radiation, but more recent studies have shown that children treated only with CNS-directed chemotherapy (ITC) are also at risk for neurocognitive deficits (Ochs et al., 1991; Kadan-Lottick & Neglia, 2005; Kingma et al., 2001), although probably to a lesser degree (Precourt et al., 2002). To date, the findings related to adverse neurocognitive outcomes caused by ITC are mixed. Ochs et al.

showed that cognitive deficits were observed not only following radiation treatment, but were also independently associated with ITC. Specifically, global IQ, verbal IQ, and arithmetic scores declined significantly in the ITC-only group. A recent study by Buizer and colleagues compared ALL survivors who were treated with a combination of ITC and systemic chemotherapy with Wilms' tumor survivors (systemic chemotherapy only), sibling controls, and a healthy control group (Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2006). Results showed significant difficulties with attention, behavior problems, and weaker academic performance when ALL survivors were compared to controls. Although the mean score for parent- and teacher-rated attention problems fell within the average range, the mean was significantly higher for children treated for ALL than for controls and a higher percentage fell outside of the normal range.

Past research has shown that steroid treatment can be associated with negative neurocognitive and behavioral changes in cancer patients (Drigan, Spirito, & Gelber, 1992; Waber et al., 2000) and in non-cancer populations (Stuart, Segal, & Keady, 2005; Wolkowitz, 1994). Glucocorticoids (steroids) are often included in cancer treatment protocols and have been shown to cause damage to an area of the brain known as the hippocampus (Sapolsky, 1993), injury to which has been related to memory decline (Rosenzweig, Leiman, & Breedlove, 1996). Waber et al. (2000) found that patients treated with the steroid dexamethasone evidenced working memory deficits, significantly lower academic achievement scores, and difficulties with visual-motor integration. Kingma et al. (2001) reported similar results when young cancer patients were treated with dexamethasone and high doses of chemotherapy. Those patients demonstrated significantly poorer auditory memory and fine-motor functioning when compared to healthy controls. Two separate reviews of the literature have reported declines in cognitive performance and increased hyperactivity, aggressiveness, and psychosis following steroid treatment (Stuart et al.;

Wolkowitz). When steroids are used to treat asthma and other diseases, some patients do experience damage to the hippocampus and memory impairment (Bender, Lerner, & Poland, 1991; Keenan et al., 1996). Fortunately, it appears that most negative effects generally subside once the steroids are discontinued (Stuart et al.).

CNS-directed chemotherapy (ITC) may not inevitably lead to significant neurocognitive deficits. For example, a longitudinal study by Copeland et al. (1996) examined ALL survivors treated only with ITC. They compared the group of patients treated with ITC to a group treated with systemic chemotherapy, 3 years post-treatment. The study failed to find significant differences between the two groups on a battery of neurocognitive tests, suggesting that those who received ITC were no worse than those who received systemic chemotherapy. Furthermore, neither group evidenced significant decreases in IQ, memory, language, or executive/planning skills. Although the investigators observed declines in academic achievement in both groups over time, the changes were not statistically significant and the mean scores remained within the average range. A notable limitation of this study was that it did not include a non-cancer control group. Butler et al. (1994) also reported no significant deficits in patients treated with ITC methotrexate (a chemotherapeutic drug) alone, but the investigators concluded that the ITC may have enhanced the negative effects of CRT in patients who received both treatments. Others have not found evidence to support these apparent synergistic effects of ITC and CRT (Dowell, Copeland, Francis, Fletcher, & Stovall, 1991).

*Intelligence*

Many studies have demonstrated post-treatment changes in the intellectual abilities of childhood cancer survivors or deficits when compared to healthy controls or the normative population (Butler et al., 1994; Cousens, Waters, Said, & Stevens, 1988; Espy et al., 2001; Mulhern et al., 1992a; 1999; Ochs et al., 1991; Palmer et al., 2001; Precourt et al., 2002;

Silber et al., 1992). In these studies, intelligence is routinely assessed using standardized, norm-referenced IQ tests, with the well-known Wechsler scales being most popular. The most extreme changes or deficits in global IQ have been associated with CRT, with study effect sizes of up to 1.7 (i.e., a 22-point difference in IQ score) reported between patients and controls (Cousens et al.). Significant changes or deficits in global IQ have also been observed in survivors who received a combination of CRT and ITC (Butler et al., 1994; Mulhern et al., 1992a, 1999; Ochs et al.; Palmer et al.; Precourt et al.; Raymond-Speden et al., 2000; Silber et al.) as well as those who received ITC alone (Ochs et al.; Precourt et al.; Raymond-Speden et al.).

The negative effects on global IQ seem to be more apparent among girls (Iuvone et al., 2002; Waber, Tarbell, Kahn, Gelber, & Sallan, 1992), those treated with higher doses of CRT (Palmer et al., 2001; Silber et al., 1992; Waber et al., 2001) or ITC (Waber et al., 1992), and those treated at younger ages, especially under 5 years of age (Mulhern et al., 1992a, 2004; Palmer et al., 2001; Silber et al.). Intellectual deficits have been observed in both CNS and non-CNS treated patients, but deficits are consistently more evident in patients who have received treatment of the CNS (Twaddle et al., 1983).

A number of studies have also revealed specific deficits or decreases in survivors' performances on measures of verbal IQ (Ochs et al., 1991; Precourt et al., 2002; Raymond-Speden et al., 2000), non-verbal or performance IQ (Butler et al., 1994; Iuvone et al., 2002; Mulhern et al., 1999; Raymond-Speden et al.), and processing speed (Butler et al.; Khong et al., 2006; Schatz et al., 2000; Waber et al., 1992).

*Academic Achievement*

Tests of academic achievement given to childhood cancer survivors have revealed the presence of deficits or declines in the areas of reading, writing, and mathematics (Reddick et al., 2003). Significant declines in arithmetic performance have been demonstrated in many

studies, and this seems to be the academic area most often affected following cancer treatment (Espy et al., 2001; Mulhern et al., 1992a; Ochs et al., 1991; Raymond-Speden et al., 2000; Reddick et al.; Waber et al., 1992). Ochs et al. found arithmetic deficits in survivors treated with CRT and ITC, as well as those treated with ITC alone. Espy and colleagues observed a significant decline in ALL survivors' arithmetic scores over time that did not appear to be related to receiving CNS prophylaxis, but rather to pre-treatment characteristics like maternal education. However, when maternal education was included in the model, the decline in arithmetic remained significant. Unfortunately, this study did not include measures of attention and concentration, so it could not examine their potential impact on arithmetic performance.

Reading and writing performances may also be negatively affected following cancer treatment (Precourt et al., 2002; Reddick et al., 2003). Precourt et al. found significantly lower reading comprehension scores for female survivors treated for ALL with either ITC alone or with a combination of ITC and CRT, as compared to healthy controls. Reddick et al. found significantly lower reading and spelling scores in a group of brain tumor survivors when their scores were compared to the age-adjusted test norms. In a study by Brown et al. (1996), survivors who received ITC experienced greater negative effects on academic functioning than those treated without ITC. The differences in academic achievement between the groups were not immediately evident; however, 3 years after diagnosis the children who received ITC earned lower scores on academic tests of reading, spelling, and arithmetic than the children without CNS treatment.

*Executive Function*

According to Mulhern et al. (2004), "the contemporary focus [of late effects research] is on the assessment of executive functions, such as working memory, and other cognitive processes that affect learning for ALL survivors, but are not apparent until later captured by

declining IQ and academic achievement test scores" (p. 24). Memory and attention are recognized as being essential to the process of learning new information (Dennis, Hetherington, & Spiegler, 1998). In addition, Schatz et al. (2000) have asserted that 45% of the variance in IQ is accounted for by working memory and processing speed. Assessing these functions may provide more information about the basis for cognitive deficits and how they might be treated (Keene, 2003).

Newer studies have begun to examine some of the underlying cognitive processes that might lead to deficits in IQ or achievement. Most of those processes fall under the broad heading of executive functions, which are thought to be primarily mediated by control mechanisms in the frontal cortex (Mulhern et al., 2004). Specific examples of these cognitive processes include shifting and sustaining attention, regulating emotions, initiating and inhibiting behavior, utilizing working memory, planning, organizing, and self-monitoring (Gioia, Isquith, Guy, & Kenworthy, 2000; Mulhern et al., 2004)

*Attention.* Many of the recent investigations of late effects have examined potential effects on attention. Cranial radiation therapy is associated with deficits on measures of attention and concentration, and with increased distractibility (Brown & Madan-Swain, 1993; Butler et al., 1994; Iuvone et al., 2002; Langer et al., 2002; Rodgers, Horrocks, Britton, & Kernahan, 1999; Said, Waters, Cousens, & Stevens, 1989). However, survivors treated with all forms of CNS-directed therapy have demonstrated significant deficits in attention compared to test norms or control groups (Reddick et al., 2003; Rodgers et al.; Said et al.). Declines in attention scores have also been observed in childhood cancer survivors when evaluated over time (Langer et al., 2002). In studies involving cancer survivors, attention has been assessed in several ways. Some investigators have used parent or teacher ratings (see Buizer et al., 2006), while others administered continuous performance tests (see Reddick et al.; Rodgers et al.), attention-related subtests (e.g., Wechsler scale subtests such as Coding,

Arithmetic, and Digit Span), or used index scores such as the Freedom from Distractibility Index (see Langer et al.; Rodgers et al.; Said et al.). As is the case with most of the other neurocognitive areas, the findings regarding negative effects of cancer treatment on attention are not yet conclusive. At least one study reported that survivors of leukemia treated without CRT did not exhibit deficits in attention and performed at comparable levels to their healthy siblings (Rodgers, Marckus, Kearns, & Windebank, 2003).

A noteworthy finding in recent literature is that the ability to sustain attention seems to be significantly related to survivors' performances on math tests. For instance, Reddick et al. (2003) demonstrated that after controlling for IQ, survivors' attention scores were significantly and positively associated with their performance on a math achievement test. In another study, low scores on sustained attention were associated with poorer mathematics performance (Buizer et al., 2006).

*Memory.* Studies of neurocognitive late effects have also examined the domain of memory. Often, investigators distinguish between different types of memory when presenting their hypotheses and describing assessment measures. Working memory is the type most frequently assessed and the tests administered are usually categorized as either auditory/verbal or visual/non-verbal memory tasks. A solid base of literature has established support for the presence of deficits and declines in both verbal and non-verbal memory among childhood cancer survivors (Copeland et al., 1996; Kingma et al., 2001; Mulhern, Wasserman, Fairclough, & Ochs, 1988; Mulhern et al., 1992a; Precourt et al., 2002; Reddick et al., 2003; Waber et al., 2000). Memory problems have been found in patients treated with a combination of CRT and ITC (Butler et al., 1994; Mulhern et al., 1988; Precourt et al.; Schatz et al., 2000), as well as with ITC alone (Kingma et al.; Mulhern et al., 1988). Conversely, others have found that the performance of survivors treated with ITC alone was similar to healthy control groups (Precourt et al.; Schatz et al.).

Nagel et al. (2006) utilized the California Verbal Learning Test–Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994), a word-list memory task, to evaluate memory function in medulloblastoma (brain tumor) patients who had received a combination of CRT and ITC. Survivors obtained significantly lower scores than healthy controls in the areas of auditory attention span, immediate recall and initial learning, and delayed recall. The authors concluded that the medulloblastoma group demonstrated significant difficulties with both retrieval and encoding of auditory information. Notably, the Nagel et al. study was not a late effects study, as it was conducted while some patients were still receiving treatment. However, no difference was found between the patients being treated and those who had completed treatment on any performance variable.

On a similar auditory/verbal memory test, Mulhern et al. (1992a) found ALL survivors performed significantly worse than Wilms' tumor survivors on immediate, short-term, and long-term recall. Visual/non-verbal memory appeared to be less affected in that study, with the only significant difference between groups found in the area of immediate recall.

*Visual-Motor Performance*

Results from several studies suggest that visual-motor skills may be especially vulnerable following CNS treatment (Buizer, de Sonneville, van den Heuvel-Eibrink, Njiokiktjien, & Veerman, 2005; Butler et al., 1994; Copeland et al., 1996; Espy et al., 2001; Iuvone et al., 2002; Waber et al., 2000). For example, children treated with a combination of ITC and systemic chemotherapy showed significant declines in visual-motor integration, and the effects were even more dramatic in those children who also received CRT (Espy et al.). Copeland et al. reported declines in perceptual-motor skills in ALL survivors treated only with ITC. Similarly, Buizer et al. found visual-motor deficits in a group of ALL survivors

treated with ITC only, but no deficits in a non-CNS treated (Wilms' tumor) comparison group, when the groups were assessed at least 1 year after the end of treatment.

*Risk Factors for Neurocognitive Deficits*

Many factors are believed to influence an individual's risk of experiencing neurocognitive damage and subsequent late effects. These potential risk or protective factors fall into two broad categories: individual characteristics and treatment-related characteristics.

*Individual characteristics.* Individual characteristics include socioeconomic status (Grill, Kieffer, & Kalifa, 2004; Butler et al., 1994), baseline intelligence (Ahles & Saykin, 2002; Silber et al., 1992), tumor location (Kadan-Lottick & Neglia, 2005; Mulhern et al., 2004; Reimers et al., 2003), psychological factors (Ahles & Saykin), and gender (Kadan-Lottick & Neglia; von der Weid et al., 2003).

Socioeconomic status (SES) is believed to be a risk factor for cognitive impairment in children treated for brain tumors (Grill et al., 2004) and leukemia (Butler et al., 1994; Copeland et al., 1996; Oeffinger & Hudson, 2004). In one study, SES (estimated using a combination of parental education and occupation) significantly predicted post-treatment full scale or global IQ, verbal memory, receptive vocabulary, and reading and spelling achievement scores in childhood leukemia survivors (Butler et al.). In a study of French cancer survivors, the mean IQ of children from families with a high standard of living was 82.1 ($n$ = 12; $SD$ = 16.7) versus 71.8 ($n$ = 19; $SD$ = 16.5) in children from less affluent families, when paternal occupation was used to estimate standard of living (Grill et al., 1999). Although the difference in IQ scores was not statistically significant, the power of the study to detect such a difference was probably low, given the small sample. The authors strongly recommended including SES in any analysis of neurocognitive effects following cancer treatment (Grill et al., 2004).

Intelligence is moderately to highly correlated with performance on other tests of cognitive functions and academic achievement (Roid, Prifitera, & Weiss, 1993; Sattler, 2001). Some authors have suggested that higher pre-morbid intelligence may serve as a protective factor, enabling a person to suffer some degree of damage while maintaining average functioning; a phenomenon referred to as *cognitive reserve* (Ahles & Saykin, 2002). In addition to intelligence, psychological factors, like fatigue, depression, and anxiety, are often related to observed cognitive decline and poor performance on neurocognitive tests (Ahles & Saykin).

Several studies have explored gender differences, and have found that female cancer survivors tend to experience late neurocognitive deficits more often, and to a greater degree, than males (Buizer et al., 2005; Kadan-Lottick & Neglia; Mulhern et al., 2004; von der Weid et al., 2003; Waber et al., 1992). Specific areas of functioning that seem to be more affected in girls are global IQ (Waber et al.), verbal IQ and learning (Precourt et al., 2002), and visual-motor integration (Buizer et al.). In Waber and colleagues' study of children treated for ALL, an increased dose intensity of systemic chemotherapy was associated with lower global IQ scores, but only in females. Results showed that 80% of females who were treated with high-dose chemotherapy exhibited a low IQ (defined as a standard score lower than 90), versus only 25% of females who received low-dose chemotherapy. Overall, approximately 50% of the females exhibited a low IQ compared to 14% of male participants (Waber et al.).

*Treatment-related characteristics.* Combinations of treatment methods, dosage, intensity, and length of treatment may predict neurocognitive outcomes (Brown & Madan-Swain, 1993; Mulhern et al., 2004). Some studies have shown that when certain chemotherapy drugs, including steroids, are administered with CRT, the late effects appear to intensify (Butler et al., 1994; Oeffinger & Hudson, 2004). Other studies have found that higher doses of radiation or chemotherapy are associated with more severe deficits (Silber et

al., 1992; Waber et al., 1992). However, the research findings are mixed, and not all studies have found greater effects with CRT (Mulhern et al., 1988), combined treatments, or higher doses (Brown & Madan-Swain; Palmer et al., 2001; Waber et al., 1992). Route of administration may be another risk factor, since chemotherapy delivered intrathecally has been found to result in greater deficits than when delivered systemically (Brown et al., 1996; Buizer et al., 2005; Oeffinger & Hudson). In summary, the risk for treatment-related neurocognitive deficits has been associated most strongly with ITC, high dose systemic chemotherapy, CRT (> 1800 cGy), and surgery to remove a CNS tumor (Schwartz et al., 2005).

A risk factor that has gained significant attention and is particularly relevant to the current study is the age of a child at diagnosis and treatment (Brown & Madan-Swain, 1993; Cousens et al., 1988; Oeffinger & Hudson, 2004; Palmer et al., 2001). Older age at diagnosis has been shown to be protective in children and adolescents receiving CNS-directed therapy for ALL and brain tumors (Copeland et al., 1996; Jannoun & Bloom, 1990; Mulhern et al., 1992a; Silber et al., 1992; von der Weid et al., 2003; Waber et al., 2001). Silber et al. showed that global IQ was significantly predicted by age at treatment with CRT. In that study, the predicted decline in IQ for 10-year-olds was 11.9 points less than in 3-year-olds with equivalent doses. Furthermore, Mulhern et al. (1992a) found that CRT, administered between the ages of 0 and 24 months, led to greater deficits in both IQ and memory than when the same treatment was given to older patients.

A meta-analysis by Cousens et al. (1988) examined effect sizes (ES) in 27 studies that measured IQ decreases in ALL survivors. The results showed that age at diagnosis or irradiation was significantly correlated with ES, with a larger mean ES associated with younger mean age at treatment. The studies confirmed that negative effects were particularly apparent in survivors treated at age 4 or younger (Cousens et al.). Although there have been

studies that have not found age effects (Mulhern et al., 1988), the prevailing opinion is that children under the age of 4 who are treated for brain tumors are especially at risk because they are exposed to potentially neurotoxic agents during a period of rapid development of the brain and nervous system (Mulhern et al., 2004).

Nervous systems of infants and young children are generally believed to be more vulnerable to toxins due to their immaturity, though it has been argued that they may also be protected by a higher degree of neural plasticity (Robaey et al., 2000). Many experts believe that infancy is a critical period of development when the brain is sensitive to damage (Taylor & Alden, 1997). Over the course of development, cognitive functions that are not yet well-established are believed to be more vulnerable to the effects of a brain injury. On the other hand, young children's brains may have a greater capacity to recover from certain types of injury than is seen later in development (Robaey et al.). Early intervention may lead to greater recovery of function in young children (Robinson, 1998); however, other studies have contradicted those findings, showing poorer cognitive outcomes among children who suffer injuries at younger ages (Webb, Monk, & Nelson, 2001). The extent that either vulnerability or plasticity moderates the adverse effects of cancer and treatment methods is not yet clear.

## Neurocognitive Late Effects of Non-CNS-Directed Therapies

Due to the strong evidence for treatment-related late effects that now exists in the literature, children who have received CNS-directed therapies are considered to be at risk for cognitive changes by follow-up care providers (Peckham, 1991; Wissler & Proukou, 1999). Unfortunately, less is known about the risks associated with less common childhood cancers, specifically, those that do not include CNS-directed therapies as part of the treatment plan.

In a study by Espy et al. (2001), ALL survivors who had received either ITC alone or in combination with systemic chemotherapy were compared on a battery of neurocognitive tests. The results showed that both groups evidenced significant declines in verbal fluency

and arithmetic performance. However, the patients treated with ITC and systemic chemotherapy demonstrated significantly greater declines in visual-motor skills, and a more rapid rate of decline over a 4-year period, compared to the patients treated with ITC alone. This suggests that systemic chemotherapy may exert its own negative effects.

A study by Waber et al. (1992) found that girls treated with a combination of CRT, ITC, and high-dose systemic chemotherapy had significantly lower global IQ scores than those who received low-dose systemic chemotherapy, which implies that high-dose systemic chemotherapy may increase the negative effects seen in some survivors. Similar dose-related effects were observed by Copeland et al. (1996). Survivors who received a treatment protocol that included small doses of ITC and larger doses of systemic chemotherapy demonstrated lower memory performances during two annual follow-up assessments than the group that received higher doses of ITC and lower doses of systemic chemotherapy. Notably, the trends were non-significant and no gender differences were evident. Nonetheless, these results point to the need for more information on the effects of non-CNS-directed (systemic) chemotherapy. Since the patients in these studies received treatment to the CNS in addition to systemic chemotherapy, none of the adverse effects can be specifically attributed to the systemic treatment.

*Evidence from Adult Cancer Studies*

One advantage of conducting research on long-term neurocognitive functioning with adult cancer survivors is that the results are generally not confounded by missed school or side-effects of treatment which adversely affect school functioning. Short- and long-term changes in neurocognitive functioning have been observed in studies of adult women who received only systemic chemotherapy for breast cancer (Ahles & Saykin, 2002; Phillips & Bernhard, 2003; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006). Furthermore, after controlling for potential confounds like depression, anxiety, and fatigue, some long-

term cognitive deficits in adult breast cancer survivors appear to be directly related to treatment with systemic chemotherapy (Ahles & Saykin). The women in these studies experienced difficulties on several cognitive tests, including attention, memory, and executive functions.

In one longitudinal study of breast cancer survivors, Schagen et al. (2006) compared women in the Netherlands who were randomly assigned to receive either high-dose systemic chemotherapy, standard dose chemotherapy, or no chemotherapy, to a healthy control group. Participants were given a battery of cognitive tests prior to receiving any treatment and then were tested again 6 months after treatment. Analyses of cognitive change were corrected to account the effects of repeated testing (i.e., practice effects). A significant decline in cognitive performance was observed in the women who had received the high-dose chemotherapy, with the greatest effect seen in the test scores that were sensitive to executive functions. In the presence of other potentially influential factors such as fatigue, stress, anemia, pre-existing deficits, and hormones, determining whether chemotherapy agents are detrimental to cognitive functioning in adults can be a difficult task (Ahles & Saykin, 2002). Schagen et al. made attempts to address this problem by controlling for pre-existing cognitive deficits and assessing participants' psychological and physiological symptoms. They found that neither baseline cognitive performance, nor post-treatment cognitive change, was associated with participants' reports of anxiety, depression, fatigue, or menopausal status.

Late effects of adjuvant treatment for breast cancer were also the focus of a study by van Dam and colleagues in 1998. Their results showed that women who received high-dose systemic chemotherapy were 8.2 times more likely to evidence cognitive impairment compared to healthy controls, and 3.5 times more likely than women who received low-dose chemotherapy. Although other studies also showed that the scores obtained by the chemotherapy groups were lower than the scores of comparison groups, the scores usually

fell within the average range when compared to the published test norms (Ahles & Saykin, 2002).

*Evidence from Childhood Cancer Studies*

Compared to the abundance of literature on children whose cancer and treatment directly involved the CNS, very few studies have examined survivors of cancer without direct CNS involvement. The need for a mechanism to study survivors of these less common childhood malignancies has recently been acknowledged (Robison et al., 2002). A review of the literature yielded 10 published studies that investigated neurocognitive late effects in childhood cancer survivors and included a non-CNS-treated cancer group. Table 1 presents the key characteristics, methodologies, and outcomes of the 10 previous studies.

In general, non-CNS cancer survivors have been used as a cancer comparison group, but have not been the primary focus of these investigations. The non-CNS group has typically been composed of childhood survivors of solid or non-solid tumors, outside the CNS, who were treated with systemic chemotherapy, with or without radiation to an area of the body (excluding the cranium). These studies report varied findings regarding the presence of late neurocognitive and academic-related effects in non-CNS cancer survivors.

For example, Twaddle and colleagues (1983) looked at a small sample whose primary diagnoses included Wilms' tumor, rhabdomyosarcoma, Ewing sarcoma, neuroblastoma, and four other rare tumors. Changes in estimated pre-treatment and actual post-treatment global IQ scores of the solid tumor group were compared with a group of ALL survivors and healthy siblings. Results showed that the survivors of solid tumors demonstrated intellectual deficits post-treatment, yet not to the extent seen in the ALL group (Twaddle et al.). Furthermore, age at radiation was not found to be a significant factor in predicting neurocognitive sequelae in the solid tumor group, and unlike the ALL group, intellectual deficits in the solid tumor group appeared to decrease as time since treatment increased. The

main limitation of the study is that the authors attempted to obtain an estimate of pre-treatment IQ using a statistical formula and the known average correlation of sibling IQ scores. They should be commended for this effort; however, their findings would clearly have been strengthened by the use of actual pre-treatment scores. Only two studies were found that included both a non-CNS treatment group and a pre-treatment assessment (Brown et al., 1996; Copeland et al., 1996). Results showed that the non-CNS group's IQ and academic achievement scores actually increased over time, while executive functions decreased (Copeland et al.). Unfortunately, neither of those studies included a healthy control group for comparison. In addition, Brown et al. did not appear to adequately address the issue of practice effects due to repeated measures, which might account for the observed score increases.

According to Mulhern et al. (1992a), patients treated during infancy for Wilms' tumor had a lower incidence of special education, and higher mean global IQ, verbal and auditory memory, and arithmetic achievement than ALL patients treated at similar ages with CRT. Although the mean IQ and academic achievement scores obtained by Wilms' survivors fell within the average range, they were about .33 *SD* below the means of the normative population. Furthermore, it was reported that 27% of the Wilms' tumor group had repeated a grade in school. That percentage is almost triple the overall rate of school children, aged 16 to 19, who were ever retained in the United States (13% for boys, 6% for girls, $M = 10\%$; National Center for Education Statistics, 2006). Importantly, Mulhern and colleagues tried to minimize the effect of missed school days by limiting participation to survivors who were treated prior to school age.

Table 1

*Characteristics, Methodology, and Outcomes in Studies of Neurocognitive Late Effects in Childhood Cancer Survivors Treated without CNS Therapies*

| Study | *N* | | Design | Pre-treatment assessment | Outcomes | Variables controlled[a] | Strengths & limitations |
|---|---|---|---|---|---|---|---|
| | Treatment | Control | | | | | |
| Brown et al. (1996) (Australia) | 38 ITC<br><br>25 Non-CNS | None | Longitudinal; Non-random assignment | Yes (Baseline evaluation at a mean of 5 weeks from diagnosis) | Differences in the mean IQ scores of the Non-CNS and ITC groups did not vary over time. The Non-CNS group academic achievement scores increased over time, while the ITC group scores decreased, though the changes were not statistically significant. Differences between the two groups' mean scores in reading, spelling, and arithmetic showed moderate to large effect sizes (ranging from .79 to 1.65) 3 years post-diagnosis. In the ITC group, the number of missed school days was inversely related to reading scores at 2 years post-diagnosis. | 1, 2, 3, 4, 7, 8, 9, 11, 13, 15, 17 | Strengths: Consecutively referred at diagnosis (decreases selection bias due to learning/school problems); included a pre-treatment assessment and detailed inclusion criteria; included a measure of SES; collected data on number of school days missed for 4 years; used Bonferroni correction; reported effect sizes.<br><br>Limits: No HC; used WISC-R American norms because there were no Australian norms, thus, score comparisons could only be made relative to the other treatment group; attrition and test age limits restricted sample sizes in analyses; low power; did not address potential effect of repeated measures; reported several trends due to low power. |
| Buizer et al. (2005) (Netherlands) | 34 ITC<br><br>38 Non-CNS | 20 ITC sibs<br><br>23 Non-CNS siblings<br><br>108 HC | Cross-sectional; Non-random assignment | No | The Non-CNS group did not differ from siblings/controls in visual-motor performance. The ITC group evidenced visual-motor deficits when compared to siblings/controls. Risk factors for poor performance were female gender and shorter time since treatment. | 1, 2, 3, 4, 6, 7, 8, 12 | Strengths: 81% participation; included control groups; included a measure of SES; no differences in demographic or illness characteristics between participants and non-participants; groups matched by age and gender; used Bonferroni correction for univariate tests; reported effect sizes.<br><br>Limits: Survivors assessed as little as 1 year post-treatment; ITC group differed by treatment |

| Study | *N* Treatment | *N* Control | Design | Pre-treatment assessment | Outcomes | Variables controlled[a] | Strengths & limitations |
|---|---|---|---|---|---|---|---|
| | | | | | | | (standard dose versus high dose); less detailed inclusion criteria; ITC and Non-CNS groups differed by age at diagnosis and time since treatment. |
| Buizer et al. (2006) (Netherlands) | 28 ITC<br><br>36 Non-CNS | 37 siblings<br><br>98 HC | Cross-sectional; Non-random assignment | No | The Non-CNS group did not differ from siblings/controls on any outcome measure. The ITC group had greater problems with attention, behavior, social/ emotional problems, and was more likely to repeat a grade compared to siblings/controls. ITC showed lower teacher-rated academic performance compared to siblings/controls. | 1, 2, 3, 7, 8, 9, 11, 15 | Strengths: 85% participation; included control groups; measure of SES; no differences in demographic or illness characteristics between participants and non-participants.<br><br>Limits: Survivors assessed as little as 1 year post-treatment; ITC group differed by treatment (standard dose versus high dose); ITC and Non-CNS groups differed significantly by age at diagnosis and time since treatment; less detailed inclusion criteria. |
| Butler et al. (1994) (United States) | 38 Combined<br><br>22 ITC<br><br>34 Surgery only or pre-treatment<br><br>26 Non-CNS | None | Cross-sectional; Non-random assignment | No | Non CNS-treatment predicted fine-motor speed and coordination in the non-dominant hand. Combined CNS treatment was associated with decreased NVIQ, arithmetic, visual-motor skills, susceptibility to distraction, and auditory language comprehension. Reading and spelling were related to SES & missed school. Global IQ was predicted by CRT, SES, & missed school. | 1, 2, 4, 8, 18, 7, 9, 11, 13, 15, 17 | Strengths: Three of the groups were referred for the study per standard protocol (no selection bias), used Scheffe's procedure to control for family-wise error rates; included power analysis; assessed the impact of missed school by parent estimate of months missed.<br><br>Limits: No HC; four participants had treatment-related neurological conditions; selection bias possible in Non-CNS group who volunteered for study; different tests given at different ages; no effect sizes reported. |

| Study | *N* | | Design | Pre-treatment assessment | Outcomes | Variables controlled[a] | Strengths & limitations |
|---|---|---|---|---|---|---|---|
| | Treatment | Control | | | | | |
| Copeland et al. (1996) (United States) | 51 ITC<br><br>48 Non-CNS<br><br>-diagnosed from 32 to 191 months of age | None | Longitudinal; Non-random assignment | Yes (Baseline assessment conducted 1-3 months from diagnosis) | At 3 years post-diagnosis, there were no group differences on any neuropsychological measures and mean scores of both groups were well within normal range. At the long-term follow-up (5 to 11 years), both groups had increased in PIQ but declined in tactile-spatial and executive skills. The Non-CNS group also performed higher on memory tests. ITC group scores remained stable over time while Non-CNS group scores improved. ITC group showed decreased perceptual-motor skills. Within ITC group, observed a trend toward lower performance in those who received higher-dose systemic chemotherapy and lower-dose ITC. | 1, 4, 8, 9, 10, 12, 15, 14, 17, 18 | Strengths: Included pre-treatment assessment; examined effects of SES, gender, age at diagnosis, time since diagnosis, and ethnicity; attempted to reduce practice effects when possible; created domain scores by taking mean of several tests to reduce the overall number of comparisons; used Bonferroni correction.<br><br>Limits: No HC; age at diagnosis differed between groups; attrition due to death, non-compliance, moving away and relapse, different tests given at different ages; no effect sizes reported; reported results that approached significance and trends. |
| Dowell et al. (1991) (United States) | 25 Combined<br><br>11 CRT, no ITC<br><br>24 ITC, no CRT<br><br>25 Non-CNS | None | Cross-sectional; Non-random assignment | No | The Non-CNS group had IQ and achievement scores within the average range. Combined treatment group had the lowest scores and showed weaknesses in visual-motor integration, fine-motor, nonverbal memory and arithmetic. The non-irradiated groups tended to score higher than CRT groups on all measures. Main effects of CRT were found for IQ, verbal, fine-motor, attention, and school achievement domains. | 4, 7, 8, 10, 12, 17, | Strengths: 90% participation; consecutively invited at follow-up appointment (decreases selection bias due to learning/school problems); used Bonferroni correction; created domain scores by taking mean of several tests to reduce the overall number of comparisons.<br><br>Limits: No HC; deviated from standardization to some degree on WISC-R; small ($n < 20$) and disproportionate CRT only group. |

| Study | *N* | | Design | Pre-treatment assessment | Outcomes | Variables controlled[a] | Strengths & limitations |
|---|---|---|---|---|---|---|---|
| | Treatment | Control | | | | | |
| Mulhern et al. (1992a) (United States) | 26 Combined<br><br>26 Non-CNS<br><br>- diagnosed in infancy, 0 to 24 months of age | None | Cross-sectional; Non-random assignment | No | In the Non-CNS group, 27% had repeated a grade, but only 4% received SPLED services. The Non-CNS group's mean IQ and achievement scores were within average range. Combined group had lower global IQ, memory, arithmetic, and higher rate of SPLED compared to Non-CNS group. Combined group showed inverse relationship between IQ and time since treatment, but this relationship was not seen in Non-CNS group. | 1, 2, 4, 9, 11, 12, 17 | Strengths: 85% participation; inclusion criteria controlled for missed school; detailed inclusion criteria; included measure of SES; included power analysis; compared results using parametric and non-parametric statistics and results were the same.<br><br>Limits: No HC; Combined and Non-CNS groups differed by age at diagnosis and time since treatment; 36% of Combined group had history of seizures and some had high doses of CRT while others had none; did not address multiple comparisons. |
| Twaddle et al. (1983) (Great Britain) | 23 Combined<br><br>19 Non-CNS<br><br>- diagnosed from 9 to 180 months of age | 23 Combined siblings<br><br>19 Non-CNS siblings | Cross-sectional; Non-random assignment | Yes (Estimated pre-treatment IQ scores using sibling IQ and McNemar method) | There was no difference between estimated pre- and post-treatment IQ scores in the Non-CNS group. IQ scores in both groups fell within the average range, for the pre-treatment estimate and at post-treatment measurement. Combined group showed decline between estimated pre- and post-treatment IQ scores. Time since treatment effect observed only in the Combined group. | 4, 17 | Strengths: Equal group sizes; included control groups; attempted to obtain a pre-treatment estimate of IQ.<br><br>Limits: Less detailed inclusion criteria; different test batteries given at different ages; estimated IQ score was used to evaluate change in IQ post-treatment; reported non-significant trends; only 15 (Combined) and 8 (Non-CNS) pairs used in analyses due to age limits of tests administered; small ($n < 20$) Non-CNS group. |
| von der Weid et al. (2003) (Switzerland) | 132 ITC<br><br>100 Non-CNS<br><br>- diagnosed from 0.6 to | None | Cross-sectional; Non-random assignment | No | No difference in IQ between ITC and Non-CNS groups. Mean IQ scores fell within the average range ($M = 104.6$ for both groups). Age at diagnosis, testing, gender and SES had no | 1, 3, 4, 8, 9, 11, 12, 13, 15, 18 | Strengths: Large sample size; included measure of SES; detailed inclusion criteria; examined effects of age at diagnosis, age at testing, gender, & SES; used corrected alpha level for multiple |

| Study | *N* Treatment | *N* Control | Design | Pre-treatment assessment | Outcomes | Variables controlled[a] | Strengths & limitations |
|---|---|---|---|---|---|---|---|
| | 14.5 years of age | | | | effect on IQ in the Non-CNS group. In the ITC group, age at diagnosis was positively related to IQ and females scored lower than males. | | comparisons.<br><br>Limits: No HC; used adapted versions of WISC-R in German and French, not clear whether appropriate norms exist in these languages. |
| Waber et al. (1990) (United States) | 51 Combined<br><br>15 Non-CNS | None | Cross sectional; Non-random assignment | No | The Non-CNS group performed higher than normative population and had higher global IQ, reading, and spelling than Combined group. Combined group performed lower than normative population on all tests (IQ, reading, spelling, arithmetic). Males in both groups had higher scores than females on several tests. In the Combined group, 73% ($n$ = 37) evidenced learning problems, compared to 26% ($n$ = 4) of the Non-CNS group, who all happened to be females. | 1, 2, 3, 4, 6, 7, 8, 9, 17 | Strengths: 61% participation; included measure of SES; in-depth examination of gender differences.<br><br>Limits: No HC; used one-tailed tests; no experiment-wise $p$ value stated; reported marginally significant results; small ($n$ < 20) and disproportionate Non-CNS group; examined interaction effects in a small sample. |

*Note.* ITC = intrathecal chemotherapy, with or without systemic chemotherapy; CRT = cranial radiation therapy; Combined = CRT + ITC; Non-CNS = systemic chemotherapy with or without non-cranial radiation; HC = healthy control group, never diagnosed with cancer or other chronic illness; Illness = chronic illness comparison group; PIQ = performance IQ; NVIQ = non-verbal IQ; SPLED = special education.

[a]No significant difference was found between groups prior to analyses or the variable was controlled statistically or by design. 1 = previously identified mental deficiency or traumatic brain injury (TBI); 2 = previously diagnosed attention-deficit hyperactivity disorder or learning disability; 3 = other previously identified neurological/psychological diagnosis; 4 = cancer experience; 5 = other chronic illness experience; 6 = current medical illness or complications; 7 = age; 8 = gender; 9 = socioeconomic status (SES); 10 = race/ethnicity; 11 = age at diagnosis; 12 = minimum time since end of treatment; 13 = missed school (separately from cancer/illness experience); 14 = treatment exposures (dose, volume, length, method, drugs); 15 = time from diagnosis or treatment to testing; 16 = practice effects for repeated measures; 17 = presence/type of CNS cancer; 18 = spoken language.

In another investigation, Buizer et al. (2006) found no differences in attention, behavior, or academic performance between Wilms' tumor survivors and their siblings or a healthy control group. School absences were not a large contributor to the results of this study, as over 70% of the survivors had completed treatment prior to entering primary school. Another study that utilized Wilms' tumor survivors as a cancer comparison group also did not reveal deficits for the group as a whole, although 26% of the group was significantly delayed on at least one measure of cognitive function (Waber et al., 1990).

Several studies have found that non-CNS cancer survivors scored within the average range (Buizer et al., 2005, 2006; Copeland et al., 1996; Dowell et al., 1991; Mulhern et al., 1992a; Twaddle et al., 1983; von der Weid et al., 2003), or higher (Waber et al., 1990), compared to test norms. Unfortunately, only three of the studies included a sibling or healthy control group (Twaddle et al., 1983; Buizer et al., 2005, 2006), and those studies are not without their own limitations.

Investigators have made attempts to uncover the potential mechanisms behind neurocognitive impairments following treatment with systemic chemotherapy. One possible explanation is that chemotherapeutic agents do cross the blood-brain barrier to some extent (Balis & Poplack, 1989). In fact, certain chemotherapeutic agents are selected for treatment protocols specifically because they are more cytotoxic and may penetrate the CNS more readily (Waber et al., 2000). Other scientists have suggested that chemotherapeutic agents and their metabolites may generate autoimmune responses, inflammation, direct injury to neurons, and damage to blood vessels (Barton & Loprinzi, 2002). The result may be damage to the blood-brain barrier which allows potentially neurotoxic agents to enter the brain. Research studies have found support for some of these mechanisms (Mirkes, 1985; Okeda et al., 1990; Sood & O'Brien, 1996).

*Challenges Involved in the Study of Late Effects*

A large body of research clearly demonstrates that certain cancers and treatment protocols used with children and adults are associated with adverse neurocognitive outcomes. Still, many questions remain regarding which treatments have the potential to cause neurocognitive damage, and which patients are most vulnerable to that damage (Eiser & Vance, 2002; Robison et al., 2002). Existing evidence leaves open the possibility that some survivors of childhood cancer treated with non-CNS-directed therapies may experience neurocognitive deficits, though probably to a lesser degree than CNS-treated patients (Kadan-Lottick & Neglia, 2005). However, these findings should not be interpreted without taking into account the limitations present in much of the childhood cancer literature.

Practical and methodological challenges are numerous when conducting research with survivors of childhood cancer (Butler & Copeland, 1993). Although some challenges are unavoidable, many can be remedied or minimized through careful planning and research design. According to Brown and Madan-Swain (1993), studies often fail to control for demographic variables, medical complications, and the effect of having a chronic illness in general. Others lack appropriate control groups, do not use consistent measures across participants, utilize questionable statistical analyses, or fail to report potential confounds. Butler and Copeland identified some of the common methodological issues that are found in studies of the neuropsychological effects of CNS-directed treatments in long-term cancer survivors. According to the authors, the issues fall into one of four categories: measurement, research design, extraneous variables, and statistical analyses. A brief discussion of the methodological limitations identified in existing studies is followed by an explanation of how those issues have been addressed in the current study.

*Measurement.* The measurement of neurocognitive and behavioral functioning in long-term cancer survivors can be a complex task. One of the largest long-term survivor

studies, the Childhood Cancer Survivor Study (CCSS), relied solely on self-report questionnaire data to assess outcomes (Buizer et al., 2006). Self-report data is highly susceptible to bias based upon the characteristics of non-responders and the potential for socially desirable responses (Cozby, 1997). Furthermore, the nature and depth of information that can be obtained via a rating scale or questionnaire is limited. For instance, a valid estimate of a person's IQ score cannot be obtained from a self-report measure. One alternative to self-report measures, standardized tests, can provide information that is not readily available via self-report and is less prone to be biased by socially desirable responses or the subjectivity of individuals' perceptions.

For the most part, neurocognitive functioning in childhood cancer research has been assessed using norm-referenced, standardized tests. However, these measures pose their own unique set of challenges. Age-limits sometimes prevent the same test from being used across all ages, so participants are given different tests based upon their age (Butler et al., 1994; Copeland et al., 1996; Twaddle et al., 1983). This can pose a problem when attempting to compare the scores of individuals who took different tests, as well as when trying to examine changes in functioning over time (Mulhern, Ochs, & Fairclough, 1992b). Another concern is that longitudinal studies do not always adequately address the potential effect of repeated measures, which can make the findings difficult to interpret.

Standardized tests can also be used in ways that might be considered inappropriate. This happens when the tests administered were not normed on the population under investigation (Brown et al., 1996; von der Weid et al., 2003) or when the norms are outdated (Kingma et al., 2002). Such practices inhibit investigators from drawing meaningful conclusions about differences in performance between the treatment group and the normative population. In other cases, it appears that standardized test administration procedures were not rigorously adhered to (Dowell et al., 1991), which diminishes the validity of the results.

Furthermore, since significant time and resources are needed to administer a comprehensive battery of neurocognitive tests, many investigators draw conclusions about a particular area of functioning based upon a single subtest or a shortened version of a test (Brown et al.; Buizer et al., 2005; Mulhern et al., 1992a; von der Weid et al.; Waber et al., 1990). Unfortunately, subtests and abbreviated forms are usually less reliable than index or composite scores. One notable limitation found in the existing studies is that most do not provide sufficient discussion of the reliability and validity of the tests administered.

*Research design.* Research design challenges can limit the ability to draw definitive conclusions from existing studies and might discourage investigators from initiating new studies. A true experimental design is not possible because it would require that children be randomly selected to experience cancer, and that all participants, including a healthy control group, be given neurocognitive tests prior to receiving any cancer treatment (Butler & Copeland, 1993). Although children cannot be randomly selected, the ability to draw conclusions regarding treatment effects would be greatly enhanced by evaluating survivors' cognitive and academic skills prior to the start of treatment. With sufficient planning, pre-treatment assessments can be obtained fairly easily with school-aged children. However, this task poses a much greater challenge with a younger population, since it is particularly difficult to assess specific cognitive abilities in infants and toddlers in a reliable and valid manner, and essentially impossible to assess academic skills, which have not yet been taught.

Cross-sectional studies examine the relationship between variables in different individuals at a single point in time (Cozby, 1997). This design is less expensive than a longitudinal study and it provides immediate results, but it cannot determine cause and effect or uncover changes in a group over time. Without pre-treatment assessment of neurocognitive functioning, it is not possible to ascertain whether post-treatment scores represent a decline in functioning or a pre-existing cognitive deficit, nor can deficits be

attributed to a specific cause, such as treatment method. In spite of these significant drawbacks, most of the investigations of the long-term neurocognitive effects of non-CNS cancers and treatments are cross-sectional, post-treatment-only designs.

In longitudinal studies, the same individuals are assessed repeatedly over time (Cozby, 1997). Longitudinal designs are more expensive and time consuming, and they are more susceptible to attrition, but they have the advantages of reducing the effects of individual differences and allowing an examination of the temporal relationships between variables. Two separate longitudinal studies that included non-CNS treated childhood cancer survivors assessed participants' neurocognitive functioning shortly after diagnosis, but before treatment, allowing the evaluation of cognitive changes over time (Brown et al., 1996; Copeland et al., 1996). Unfortunately, both of these studies were limited by attrition and the lack of a healthy control group. Even if pre-treatment test scores are obtained, bias can be introduced when groups that received different treatment regimens are compared, since patients are not randomly assigned to treatments, but are treated based upon the nature of their disease and other risk factors.

A feasible and frequently used alternative to pre-testing is to compare the target group to a control or comparison group with certain shared attributes, other than the variable of interest. This allows one to compare the target group's actual scores with their expected scores, which theoretically, should be similar to those of the control group. Comparing survivors' test scores with normative population data alone is unwise, due to the possibility of cohort effects and the fact that a nationally representative sample is not necessarily comparable to the target group in terms of gender, race, socioeconomic status, and education. For health-related studies, Mertens and Yasui (2005) recommend that a comparison group should represent a population with the potential to develop the disease or condition being studied. The Childhood Cancer Survivor Study, a large, retrospective study of cancer

survivors, used survivors' siblings as comparisons based on the assumption that they share many of the same genetic and environmental factors, with the exception of disease and treatment exposures, and as a result, their risk for developing the disease is comparable to that of the sibling who had cancer (Robison et al., 2002). Siblings typically share characteristics like home environment, parental education, and genetic potential which are believed to contribute to intellectual functioning and school performance (Sattler, 2001). On the other hand, because the siblings of cancer survivors also share other characteristics, such as family dysfunction and quality of schooling, their scores might not be comparable to the general population. If time and resources allow, studies should include a sibling group and a healthy, non-related control group, and also compare results to the normative population. Unfortunately, many pediatric cancer facilities lack the resources to conduct comprehensive research studies with childhood cancer survivors, especially longitudinal designs and those that include multiple comparison groups (Butler & Copeland, 1993).

*Extraneous variables.* Extraneous variables, also known as confounds, are a significant concern in studies of non-CNS treated childhood cancer survivors. A common problem when studying late effects involves sorting out the effects of the cancer and various treatment methods from other factors that may influence a child's educational and cognitive performance (Brown & Madan-Swain, 1993). Virtually all existing studies fail to control for the effects of experiencing a chronic illness in general. A single study of neurocognitive functioning in long-term childhood cancer survivors utilized an illness control group to account for the effect of having a chronic illness on cognitive and academic functioning (Raymond-Speden et al., 2000). The inclusion of an illness control group was not found in any existing studies of neurocognitive late effects in *non-CNS* childhood cancer survivors.

Currently, non-CNS tumors themselves are not believed to cause damage to the CNS, so it is plausible that toxic treatment methods might contribute to the long-term

neurocognitive changes observed in some survivors. Isolating the effects of specific treatments means gaining access to a large number of survivors with the same type of cancer and treatment protocol, which usually requires being part of a multi-center clinical-trial cooperative group (Armstrong & Reaman, 2005). Childhood cancer is rare, so individual medical centers have a limited population of survivors from which to draw participants (Moore, 2005). As a result, the samples that are obtained often include children with different types of cancer who received various combinations of surgery, chemotherapy, and radiation.

Selection bias can occur in samples of childhood cancer survivors in several ways. Longitudinal studies are especially subject to attrition and missing data (Moore, 2005). Patients who experienced a relapse or who died following cancer treatment are not included in these studies, creating a potential bias toward participants whose medical outcomes were more positive. On the other hand, patients who have maintained contact with a long-term follow-up clinic are more easily located for study recruitment, but they may also have had ongoing medical issues, creating a potential bias toward more negative outcomes.

Age-related factors, mainly age at diagnosis and treatment, appear to be important variables in childhood cancer research. Problems arise when investigators do not control or examine the influence of these variables through their inclusion criteria and statistical analyses. For example, all but one of the studies in Table 1 included participants who were diagnosed and/or treated at school age, and those children may have missed a significant amount of school during their illness. They may also have experienced side effects, such as fatigue and malaise, which negatively affected their school performance (Armstrong, 2003; Friedman, 2003). The potential impact of those factors makes it difficult to isolate the effects of the cancer, treatment, school attendance, and psychological or behavioral barriers to learning. Attempts have been made to assess group differences with regard to missed school and evaluate its potential effect on outcomes by collecting information on the number of

absences (Brown et al., 1996; Butler et al., 1994; von der Weid et al., 2003). Yet, only one study is known to have actually controlled this variable by restricting participation to children who were diagnosed and treated prior to school age (Mulhern et al., 1992a).

Previous research has shown that the length of time since the end of treatment is a factor that should not be ignored. Some studies that appear to examine *late* effects actually measured cognitive and academic functioning during or shortly after the end of treatment, making it difficult to determine whether the observed adverse outcomes were temporary or would persist over time. If a minimum length of time since treatment is not specified as part of inclusion criteria, then it is likely that some participants might have just recently completed treatment while others finished treatment years earlier. Considering that deficits seem to become more apparent as time since treatment increases, combining these two populations as a single group in analyses is not recommended.

The groups being compared should not differ significantly by gender, SES, or missed school. To address concerns regarding the influence of extraneous variables, investigators should provide detailed information and rationale regarding the criteria for inclusion and exclusion, recruitment methods, participation rates, and whether significant demographic or health-related differences exist between participants and non-participants.

*Statistical analysis.* The statistical analyses selected for a study can be problematic for several reasons. Examples of questionable practices found in the existing literature include using statistical procedures that are inappropriate for very small samples, such as examining interaction effects following regression (Precourt et al., 2002; Schatz et al., 2000; Waber et al., 1990). One of the most widespread limitations in childhood cancer studies is inadequate statistical power to detect effects due to small sample size (Armstrong & Reaman, 2005). When a study has a small sample and low power is a concern, effect sizes should be reported along with results of significance tests, yet this is rarely done. Another statistical

matter that is sometimes neglected involves alpha and experiment-wise error rates. For example, some authors do not state the predetermined experiment-wise alpha level (Waber et al., 1990) nor do they adequately address the issue of multiple comparisons (Mulhern et al., 1992a; Precourt et al.; Schatz et al.). In contrast, some investigators do use adjusted alpha levels (e.g., Bonferroni correction) or attempt to decrease Type I error rates by reducing the overall number of comparisons. This can be accomplished by creating domain scores that combine scores from multiple tests of the same area.

Many studies rely solely on statistical significance when evaluating the results, and do not take advantage of measures of clinical significance, such as effect size. Possibly in an effort to compensate for low power, some investigators choose to report "borderline" or "nearly" statistically significant results (Copeland et al., 1996; Evans et al., 1991; Waber et al., 1990) and non-significant trends (Brown et al., 1996; Copeland et al., 1996; Twaddle et al., 1983), or use one-tailed tests of significance (Evans et al.; Kingma et al., 2001, 2002; Waber et al., 1990). Positively, most investigators appear to make appropriate decisions regarding the use of nonparametric or parametric statistics, and occasionally, authors will use both methods and compare the results (Iuvone et al., 2002; Kingma et al 2001; Mulhern et al., 1992a; Precourt et al).

## The Current Study

The current study aimed to contribute to the knowledge base while avoiding some of the common limitations found in the existing childhood cancer literature. The study utilized a cross-sectional, non-randomized research design. A battery of norm-referenced, standardized tests was used to examine participants' neurocognitive and academic functioning. In addition, parents completed rating scales to assess participants' behavioral functioning. The evaluation instruments provided measures of intellectual functioning and academic achievement, as well as attention, memory, and executive functions, since these are the

cognitive areas that appear to be most affected by CNS-directed therapies. The previously established reliability and validity of all measures are discussed in detail. Analysis of individual subtests was minimized and composite scores were used whenever possible to maximize the reliability and validity of scores. Furthermore, efforts were made to ensure that the tests included in the battery contained up-to-date norms that were appropriate for the population being assessed. The neurocognitive test battery was consistent across all participants, unless age-appropriate norms did not exist. In those situations, an equivalent or highly comparable standardized test was administered. Given the target group's young age at diagnosis, often at birth or shortly thereafter, no pre-treatment assessment information could be obtained. Thus, cancer survivors' neurocognitive, academic, and behavioral functioning were compared to that of their healthy siblings. In addition, since the sample size was likely to be small, and siblings of cancer survivors are not necessarily comparable to the general population, survivors' test scores were also compared to test normative data.

In the current study, attempts were made through both study design and statistical procedures to identify potential sources of bias and control them when possible. Study inclusion and exclusion criteria are described in detail. The potential effects of missed school and illness-related side effects on school functioning were minimized by limiting participation to children who were diagnosed and treated prior to school age. Therefore, all participants in the study have been in remission and off treatment for a minimum of 2 years to reduce the influence of the acute effects that are often associated with cancer and its treatment. Finally, only survivors of non-CNS tumors were invited to participate in the current study. Since the current study was conducted at a single institution with an already rare population of cancer survivors, a small sample size was anticipated. For that reason, significant efforts were made to recruit all eligible survivors and their siblings by inviting those who moved away from the treatment facility and by using hospital records, internet-

based tracking, and telephone white pages to locate those survivors whose contact information was no longer current. It was not expected that the current study would have difficulties with attrition, as participants only attended one appointment. However, because participation was voluntary, the sample could be biased in terms of gender, age, SES, and other characteristics. To control for confounds such as home environment, genetic potential, SES, and school quality, a sibling closest in age to the patient with no history of malignancy was invited to participate in a comparison group.

This study is designed to improve upon existing studies through careful selection of appropriate statistical procedures with consideration given to the sample size and the assumptions of the tests. The issues of experiment-wise error, criterion alpha levels, and correction for multiple comparisons are discussed. All statistical tests are two-tailed, and the results are reported along with effect sizes to aid in interpreting the clinical significance of findings (Kraemer et al., 2003). The study has the potential to grant insight into the long-term consequences of non-CNS cancers and treatments in young children, by reducing the influence of missed school, the short-term side effects of the disease and treatment on school functioning, and by controlling for confounding variables that are shared by siblings.

*Rationale*

Prior research suggests that children, adolescents, and young adults treated for cancer before the age of 5 with systemic chemotherapy and radiation may be at risk for subsequent neurocognitive deficits with a similar pattern to that of patients who receive CNS-directed therapy. This study answers the call for “research on the psychological and educational difficulties of childhood cancer survivors which is needed to add to the understanding of the challenges they face in response to the disease and its psychological and educational effects” (Cruce & Stinnett, 2006, p. 52). The extent to which any adverse psychological and educational effects are related to childhood cancer treatment methods is unknown. Although

improved methods have been credited with saving many lives, to date, few studies have evaluated the long-term neurocognitive functioning of childhood cancer survivors who have received only non-CNS-directed therapies. Kadan-Lottick and Neglia (2005) caution that "new treatment approaches, including therapies that eliminate radiation, must not be assumed to be non-toxic; late toxicities must be investigated with rigor" (p. 47).

*Purpose*

The primary purpose of the current study is to determine whether these childhood cancer survivors are indeed at an increased risk for neurocognitive late effects, and to determine which areas of functioning are most likely to be affected. First, it is hypothesized that childhood cancer survivors who received non-CNS therapies before the age of 5 will evidence lower scores on tests of cognitive and academic skills, and higher levels of parent-reported behavior problems, when compared to healthy siblings who were never treated for cancer. Specifically, the cancer survivors will demonstrate statistically significant differences in mean scores of global intelligence, working and auditory memory, processing speed, attention, and academic achievement than their healthy siblings. Furthermore, mean parent ratings will reveal greater difficulties with attention and executive functions for the non-CNS-treated cancer survivors when compared to their siblings. Second, it is hypothesized that the cancer survivors will demonstrate significantly lower scores on tests of cognitive and academic skills, and higher levels of parent-reported behavior problems when compared to the normative population. Third, it is predicted that the cancer survivors will be more likely to be receiving special education services and to have repeated a grade in school than their siblings. Finally, SES, age at diagnosis, treatment intensity, and time since diagnosis will be examined to determine whether they predict scores on selected neurocognitive, academic, or behavior measures in this group of childhood cancer survivors.

# Method

The procedures for the research study were reviewed and approved by the University's Research Subjects Review Board (RSRB) prior to beginning recruitment, and approval was renewed on a yearly basis through the end of active enrollment. Since the study involved the collection of treatment-related information and valid health-related outcomes, thus requiring access to patient records, written permission was obtained from participants or their parents using a Health Insurance Portability and Accountability Act (HIPAA; 1996) authorization document, which was part of the informed consent form.

## *Participants*

*Survivors*. Patients were identified from the long-term survivor cohort in the Division of Pediatric Hematology/Oncology at a large university medical center in the northeastern United States. A trained research assistant reviewed patient medical records using a detailed list of criteria to determine whether a survivor was eligible to participate. To be considered eligible, a survivor must have been (a) diagnosed with a malignancy prior to his or her fifth birthday, (b) treated without central nervous system therapy, defined as intrathecal chemotherapy or cranial radiation therapy, (c) currently between the ages of 6 and 21 years, and (d) at least two years off treatment, which is a time frame that has been used in similar studies of late effects (Anderson, Smibert, Ekert, & Godber, 1994). Any participants with identified pre-morbid neuropsychological impairment were not considered eligible (e.g., previous diagnosis of ADHD, head injury, seizure disorder, mental retardation, etc.). The age limits were selected to allow for the use of the same battery of assessment measures across participants. To maximize recruitment from this already small population and to minimize potential selection bias, all eligible survivors were invited to participate in the study, including those who had moved out of state since the end of treatment. One sibling who was closest in age to the survivor and had no history of malignancy was also invited to participate

as a comparison. Therefore, study participants were long-term survivors of childhood cancer between the ages of 6 and 21 years and their healthy siblings of a similar age.

Survivor participants included 19 children treated without CRT or ITC, and the sample included 9 males (47%) and 10 females (53%). All of the participants identified their race as White, non-Hispanic. Survivors ranged in age from 6 years 4 months to 19 years 3 months (*M* = 12 years 8 months; *Mdn* = 13 years 1 month). Of those identified as eligible, 41% (*n* = 25) did not respond to the invitation letter or telephone call, or they had missing or outdated contact information and were considered lost to follow-up. Twenty-eight percent (*n* = 17) were contacted but declined to participate. Reasons for declining included, “No reason” (*n* = 9), “Not interested” (*n* = 5), and “Do not have time” (*n* = 3). The survivor group was composed of survivors of Wilms’ tumor (*n* = 7), neuroblastoma (*n* = 7), hepatoblastoma (*n* = 2), rhabdomyosarcoma (*n* = 2), and retinoblastoma (*n* = 1). The earliest diagnosis occurred with a survivor at the time of their birth, and the latest occurred at 53 months of age. Survivors were diagnosed at a mean age of 15 months (*Mdn* = 12 months). Sixty-eight percent (*n* = 13) received systemic chemotherapy alone and 32% (*n* = 6) received both systemic chemotherapy and non-cranial irradiation. The survivors who were treated with chemotherapy received between two and eight different chemotherapeutic drugs. Total radiation dose was measured in centigrays (cGy). Of the survivors who received irradiation, three received cumulative doses of 1000-1990 cGy, two received 2000–2990 cGy, and one received 5000–5990 cGy. Table 2 shows the illness and treatment characteristics of the survivor group.

Table 2

*Illness and Treatment Characteristics of Survivor Participants*

| Characteristic | *N* (%) |
|---|---|
| Gender | |
| Male | 8 (44) |
| Female | 10 (56) |
| Diagnosis | |
| Neuroblastoma | 7 (39) |
| Wilms Tumor | 7 (39) |
| Rhabdomyosarcoma (non-head/neck) | 2 (11) |
| Hepatoblastoma | 1 (6) |
| Retinoblastoma | 1 (6) |
| Other | 0 (0) |
| Treatment | |
| Chemotherapy only | 12 (67) |
| Radiation only | 0 (0) |
| Combination | 6 (33) |
| Radiation cumulative dose (cGy) | |
| Less than 1000 | 0 (0) |
| 1000 – 1990 | 3 (17) |
| 2000 – 2990 | 2 (11) |
| 3000 – 3990 | 0 (0) |
| 4000 – 4990 | 0 (0) |
| 5000 – 5990 | 1 (6) |
| 6000 + | 0 (0) |
| Chemotherapy | |
| Number of unique drugs administered | |
| Two | 8 (44) |
| Three | 5 (28) |
| Four | 3 (17) |
| Five | 1 (6) |
| Eight | 1 (6) |
| Drugs administered | |
| Vincristine (VCR) | 13 (72) |
| Doxorubicin, Adriamycin (ADR) | 10 (56) |
| Dactinomycin, Actinomycin-D (AMD) | 9 (50) |
| Cyclophosphamide (CTX) | 8 (44) |
| Cisplatin (CDDP) | 5 (28) |
| Etoposide (VP16) | 5 (28) |
| Carboplatin | 3 (17) |
| Flourouracil (5-FU) | 1 (6) |
| Ifosfamide (IFOS) | 1 (6) |
| Other | 1 (6) |

*Siblings.* Eleven siblings responded that they were interested in participating in the study. However, one sibling exceeded the study's age limit and another was adopted, so each was deemed ineligible to participate. In all, approximately 50% ($n$ = 9) of the siblings

eventually participated in the study. Sibling participants included four males (44%) and five females (56%). All of the siblings identified their race as White, non-Hispanic. Siblings ranged in age from 6 years 6 months to 19 years 1 month (*M* = 12 years 3 months; *Mdn* = 11 years 10 months). Reasons that siblings declined included “Not eligible/other” (*n* = 5), “No reason given” (*n* = 3), “Do not have time” (*n* = 1), and “Not interested” (*n* = 1).

One survivor-sibling pair was unable to complete the assessment battery using standardized administration procedures due to significant cognitive, physical, and behavioral impairments experienced by the cancer survivor. Thus, only those participants with usable scores (18 survivors and 8 siblings) were included in the subsequent tables and analyses. Table 3 provides a summary of demographic characteristics for all study participants.

Table 3

*Demographic Characteristics of All Study Participants*

| Characteristic | Cancer survivors (%) | Siblings (%) |
|---|---|---|
| Gender | | |
| Male | 8 (44) | 3 (38) |
| Female | 10 (56) | 5 (62) |
| Age at testing[a] | | |
| Range | 76-231 | 78-229 |
| *M* | 157 | 155 |
| *Mdn* | 159 | 155 |
| *SD* | 44.4 | 52.4 |
| Father's education | | |
| 8th grade or below | 0 | 0 |
| 9th–12th grade | 1 (6) | 1 (13) |
| High school diploma/ GED | 4 (22) | 1 (13) |
| Some college (<1–4 years) | 6 (33) | 2 (25) |
| Associate's degree | 1 (6) | 1 (13) |
| Bachelor's degree | 3 (17) | 2 (25) |
| Master's degree | 2 (11) | 0 |
| Doctoral degree | 1 (6) | 1 (13) |
| Post-doctoral study | 0 | 0 |
| *Mode* | Some college (<1-4 yrs) | Some college (<1-4 yrs); Bachelor's degree[b] |
| Mother's education | | |
| 8th grade or below | 0 | 0 |
| 9th–12th grade | 1 (6) | 1 (13) |
| High school diploma/ GED | 6 (33) | 1 (13) |
| Some college (<1–4 years) | 2 (11) | 2 (25) |
| Associate's degree | 4 (22) | 2 (25) |
| Bachelor's degree | 2 (11) | 1 (13) |
| Master's degree | 3 (17) | 1 (13) |
| Doctoral degree | 0 | 0 |
| Post-doctoral study | 0 | 0 |
| *Mode* | High school diploma/ GED | Some college (<1-4 yrs); Associate's degree[b] |

[a]Reported in months. [b] Distribution was multi-modal.

## *Measures*

The neuropsychological battery was designed to measure a wide range of cognitive functions, including intelligence, academic achievement, attention, memory, and executive functions. All of the tests that were included in the battery are listed in Table 4. Although most tests were appropriate for participants aged 6 to 21, not all tests could be administered to all participants. When a test's normative age limit prevented its use with older participants,

a very similar alternative test was administered, if available. For example, for participants aged 17 and above, the corresponding subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997) were substituted for subtests from the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler, 2003). Similarly, for participants aged 17 and above, the California Verbal Learning Test – Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) was substituted for the California Verbal Learning Test for Children (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994). The Conners' Parent Rating Scales – Revised (CPRS-R; Conners, 1997) only applies to participants aged 17 and under, and use of the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) is limited to participants aged 18 and under; however, no alternative forms for those scales exist, so the measures were not administered to the older participants.

Table 4

*Neurocognitive Test Battery*

| Domain | Test | Subtest(s) or score(s) |
|---|---|---|
| Intelligence | Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) | Full Scale IQ (2 subtests) |
| Academic achievement | Woodcock-Johnson: Tests of Achievement-Third Edition (Woodcock, McGrew, & Mather, 2001) | Letter-Word Identification and Math Fluency subtests |
| Executive function | Behavior Rating Inventory of Executive Function (Gioia, Isquith, Guy, & Kenworthy, 2000) | General Executive Composite |
| Attention | Conners' Parent Rating Scales–Revised: Long form (Conners, 1997) | Cognitive Problems/Inattention scale |
| Memory | California Verbal Learning Test for Children (Delis, Kramer, Kaplan, & Ober, 1994) or California Verbal Learning Test–Second Edition (Delis, Kramer, Kaplan, & Ober, 2000) | List A Trials 1-5, Long-delay free recall, Long-delay cued recall |
| | Wechsler Intelligence Scale for Children–Fourth Edition (Wechsler, 2003) or Wechsler Adult Intelligence Scale–Third Edition (Wechsler, 1997) | Working Memory Index (Digit Span and Letter-Number Sequencing subtests) |
| Processing speed | Wechsler Intelligence Scale for Children–Fourth Edition or Wechsler Adult Intelligence Scale–Third Edition | Coding subtest |

*Note*. Table lists the tests, subtests, or scores selected for inclusion in the current study prior to analysis. Some tests and subtests that were part of the battery are not listed here.

*Intelligence.* The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) is an individually-administered, brief measure of intelligence which can be used with children and adults aged 6 to 89 years. The WASI was standardized on a national sample of 2,245 children and adults that represented the U.S. population in terms of gender, race and ethnicity, education level, and geographic region.

The WASI is designed to provide an estimate of intelligence when a full evaluation is not possible. The complete test includes four subtests (Vocabulary, Similarities, Matrix Reasoning, and Block Design) and yields the Full Scale IQ (FSIQ) and two indices, a Verbal

IQ and a Performance IQ. The short form includes two subtests (Vocabulary and Matrix Reasoning) and only yields the FSIQ score. To maximize participation, efforts were made to keep the assessment battery as brief as possible while maintaining adequate reliability and obtaining the desired information. Therefore, the short form of the WASI was used in the current study. The Vocabulary (VO) subtest includes 38 vocabulary words presented orally and visually, which the examinee is asked to define. The first four items on the Vocabulary subtest are presented as pictures to be named by the examinee. Matrix Reasoning (MR) uses a progressive matrix design in which the examinee inspects a set of figures with a missing part and then he or she selects the missing piece from an array of five possible choices to complete the original set. The WASI short form can be administered in approximately 15 minutes.

The subtests contained in the WASI are based on research from the WISC-III and WAIS-III. Although the subtests are very similar to the other Wechsler scales, new items were developed for the WASI. The reliability of scores on the WASI is supported by Spearman-Brown corrected split-half reliabilities of .81 to .98 for the subtests, and .92 to .98 for the IQs, all of which are considered adequate or better. Test-retest reliabilities also appear to be acceptable, as almost all are above .85. The stability coefficient for the FSIQ (two-subtest version) is .83 for children aged 6 to 11 years. Validity evidence for the WASI scores includes correlations with the corresponding scales on the WISC-III and WAIS-III that are moderate to high, ranging from .66 to .88 for the subtests, and .76 to .92 for IQs. The WASI IQs are also good predictors of achievement as measured by the Wechsler Individual Achievement Test (WIAT; see Wechsler, 2001). Exploratory and confirmatory factor analyses were used to demonstrate that the structure of the WASI is consistent with the constructs it purports to measure.

*Academic achievement.* The Woodcock-Johnson III: Tests of Achievement (WJ-III: ACH; Woodcock, McGrew, & Mather, 2001) are a battery of individually-administered tests designed to assess an individual's academic strengths and weaknesses. The WJ-III: ACH is composed of 12 standard subtests and an extended battery with 10 additional subtests. The WJ-III: ACH can be used with children and adults aged 2 to 90 years. To keep the study's assessment battery to a reasonable length, only two subtests were selected from the WJ-III: ACH to provide estimates of academic achievement. Letter-Word Identification (LWID) measures a person's ability to recognize letters of the alphabet and to read a list of increasingly difficult words. Math Fluency (MF) measures a person's skill at correctly solving simple arithmetic problems within a time limit. The WJ-III: ACH was normed using a sample of 8,818 participants, including 4,783 school-aged children, who matched the characteristics of the U.S. in the late-1990s in the areas of geographic region, community size, gender, race, Hispanic origin, and type of school or college. The median split-half reliability for LWID is .91 (ages 5 to 19) and the reliability of MF using Rasch analysis is .89 (ages 7 to 19). Evidence for the content validity of the WJ-III: ACH comes from the validity of previous versions of the test, and comparisons with other achievement tests and established practices in schools. However, specific evidence of the test's relation to curriculum used in schools is not provided. Factor analyses and internal correlations between areas of achievement support the battery's construct validity. Furthermore, scores on the WJ-III: ACH have medium to high correlations with other well-known achievement tests, demonstrating concurrent validity.

*Executive function.* The Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000) is an individual- or group-administered questionnaire designed to assess impairment of executive function behaviors in the home and school environments. The 86-item questionnaire can be used for children aged 5 to 18 years, and there are separate forms

for parents and teachers. The BRIEF takes approximately 10 to 15 minutes to complete. Only the Parent Form was used for the current study. On the BRIEF, parents are asked rate their child's functioning on various executive function tasks based upon the past 6 months. Raters use a 3-point scale (e.g., *Never*, *Sometimes*, or *Often*) to rate the frequency of the behavior. The BRIEF yields eight clinical scales, two broader indexes, and an overall composite. The eight clinical scales measure aspects of executive functioning including the abilities to switch to a new task or activity, modulate emotional responses, initiate tasks and activities, manipulate information in memory, manage task demands, maintain orderliness of work and play areas, perform self-assessments, and demonstrate inhibitory control. The first index, the Behavioral Regulation Index (BRI), is composed of the Inhibit, Shift, and Emotional Control scales. The second index, the Metacognition Index (MI), is composed of the Initiate, Working Memory, Plan-Organize, Organization of Materials, and Monitor scales. The overall score, a sum of the two indexes, is called the Global Executive Composite (GEC). The questionnaire also includes indicators of inconsistent responses and overly negative ratings. Scores can be derived based upon the combined norm group or by gender within the norm group.

The standardization sample for the Parent Form included parents' ratings for 1,419 youth from the state of Maryland. Weighting was used to make the sample match the U.S. population with respect to gender and ethnicity. The internal consistency reliability of the BRIEF scores is satisfactory, with Cronbach's alpha coefficients ranging from .80 to .98. The composites are more reliable than the scales, with most coefficient alphas in the mid to upper .90s. Test-retest reliabilities for the composites were evaluated with an average of two weeks between administrations. The test-retest correlations for the BRI, MI, and GEC were .84, .88, and .86, respectively (Baron, 2000). Evidence for content, construct, convergent and divergent validity is presented in the BRIEF professional manual. The authors cite the review

of relevant literature, clinical experience, and information gathered through clinical interviews as support for the scale's content validity. The item content was also compared to other well-known behavior rating scales, such as the Conners' Rating Scales and the Child Behavior Checklist, to ensure that the BRIEF primarily captured elements of executive functions and not general behavior problems or attention. Pilot ratings obtained prior to standardization were used to refine the scales, and statistical techniques were employed to ensure a reasonable number of items per scale, while maintaining maximum internal consistency. The scale structure of the BRIEF is supported by results from factor analyses, demonstrating evidence of its construct validity. Convergent and divergent validity were examined by correlating the BRIEF with four other well-known teacher rating scales, and both were found to be satisfactory. Initial support for the predictive validity of the BRIEF was demonstrated when logistic regression was used to examine diagnostic group membership for children with ADHD. Results showed that specific BRIEF subscales were able to distinguish between children with and without ADHD, and between subtypes of ADHD (Baron). Finally, the validity of scores is supported by the presence of high interrater reliability between several pediatric neuropsychologists and the authors, although the exclusion of parent ratings for interrater reliability estimates is noted as a weakness.

*Attention.* The Conners' Parent Rating Scale–Revised (CPRS-R; Conners, 1997) is an individually-administered rating scale designed to assess psychopathology and problem behaviors in children and adolescents aged 3 to 17 years. The main focus of the CPRS-R is the assessment of Attention-Deficit Hyperactivity Disorder (ADHD). The CPRS-R includes both long- and short-forms, and ratings are provided by the parents. The current study utilized the 80-item CPRS-R: Long form to assess participants' behaviors at home and in the community. On the CPRS-R: L, parents are asked to rate their child's behavioral, social, and emotional functioning based upon the past 6 months. There are seven clinical subscales in the

CPRS-R: L including Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious-Shy, Perfectionism, Social Problems, and Psychosomatic. Two Global Indices (Emotional Lability and Restless-Impulsive), an ADHD Index, and a DSM-IV Total symptoms subscale (Inattentive and Hyperactive-Impulsive) can also be derived. Based upon previous findings of cognitive and attention problems in cancer survivors, the Cognitive Problems/Inattention subscale was selected for inclusion in the current study. The standardization sample for the CPRS-R: L was drawn from ratings of 2,482 children from the U.S. and Canada. The normative scores are split into five age groups. Demographic information indicates that 83% of the parent respondents in the normative sample were identified as Caucasian/White, while only 4.8% were African American/Black. However, little additional data are available regarding the normative sample (e.g., age, gender, education level).

The reliability of the CPRS-R: L is supported by low standard errors of measurement, which indicate that the scales provide stable scores for individual assessment. Overall, internal reliability coefficients are adequate, ranging from .72 to .95. Cronbach's alpha coefficients for the Cognitive Problems/Inattention subscale are very good, and are .92 and .93 for females and males, respectively. Test-retest reliability coefficients ($n$ = 49), across a six-to eight-week interval were .69 for Cognitive Problems/Inattention. A limitation of the CPRS-R is that no interrater reliability estimates have been reported. The CPRS-R demonstrates excellent face validity. The technical manual indicates that all CPRS-R scales were derived using factor analytic data from a pilot study that included parent ratings of 2,200 youth. The intercorrelations between the subscales appear to be acceptable, and the factor structures provide evidence of construct validity. Finally, the technical manual addresses convergent and divergent validity. Correlations between different respondents (i.e., parents, teachers, and adolescents) were found to vary widely between subscales, and included some low or non-significant correlations. Evidence for the scale's discriminant

validity is found in the reports of significant differences in the expected directions across all subscales when used to distinguish between ADHD, emotional problems, and normative group samples.

*Auditory memory and learning.* The California Verbal Learning Test for Children (CVLT-C; Delis et al., 1994) is an individually-administered measure of a person's ability to learn and remember verbally presented information in the form of items on a shopping list. The list is composed of 15 items that fall into one of three semantic categories. The examiner begins by reading List A and asking the child to recall as many of the items from the list as he or she can. This procedure is repeated four more times. Next an interference list, List B, is read aloud and the child is asked to recall as many List B words as he or she can. For the next two trials, the child is again asked to recall the words from List A (short-delay free recall) and then to recall words from List A that fall into the three semantic categories (short-delay cued recall). After a 20-minute delay, the child is asked to repeat the last two trials (long-delay free and long-delay cued recall). Finally, the child is read a list of 45 items and asked to state whether or not each item was on List A (recognition trial). Normative data are provided for children aged 5 to 16 years, with scores split into 12 age groups of similar size. The standardization sample included 920 children who closely matched the 1988 U.S. Census in terms of race-ethnicity, parental education, and geographic region. The technical characteristics of the CVLT-C are good. Split-half reliability coefficients range from .84 to .91 with an average of .88, and coefficient alphas range from .81 to .88 with an average of .85, across the age spans. Test-retest reliabilities are adequate given the nature of the test. Evidence for content, criterion-related, and construct validity is presented in the examiner's manual. The authors cite a strong research base as support for the scale's content validity. Criterion-related validity was demonstrated through moderate (.32 to .40) correlations with the WISC-R vocabulary scores, suggesting that the CVLT-C measures an area of cognition

that is distinct from a measure of verbal ability. Factor analyses revealed a theoretically meaningful six-factor structure, which lends support to the CVLT-Cs construct validity. One notable drawback of the CVLT-C is the lack of concurrent validity studies reported.

The content and administration of the California Verbal Learning Test–Second Edition (CVLT-II; Delis et al., 2000) are very similar to the CVLT-C, except that its shopping list is composed of 16 items that fall into one of four semantic categories. Normative data are provided separately for males and females, aged 16 to 89 years, and divided into seven age groups. The standardization sample included 1,087 adults who closely matched the 1999 U.S. Census in terms of race-ethnicity, education level, and geographic region. Internal consistency was assessed using the split-half method with Spearman-Brown correction. The reliability coefficients were generally above .90 across various age groups, with a reliability coefficient of .94 for the entire sample. When reliability was calculated using other forms of split-half reliability, the estimates were good and all above .80. Test-retest reliability from one study ($N$ = 78) yielded an uncorrected correlation of .82; however, the retest interval varied widely across participants, ranging from 9 to 49 days ($Mdn$ = 21 days). Validity evidence for the CVLT-II is drawn primarily from the significant research base of its predecessor the CVLT, and the authors cite moderate to high correlations between the two tests. Nonetheless, independent evidence for the construct validity of the CVLT-II needs to be established. Additional validity evidence provided in the manual includes factor structures with clinical and non-clinical samples and expected correlations with age, education, and IQ scores. In general, the technical characteristics of the CVLT-II appear to be good.

*Working memory and processing speed.* The Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV; Wechsler, 2003) is an individually-administered test of a child's cognitive ability. The scale is comprised of 10 core subtests which provide a Full

Scale Intelligence Quotient (FSIQ) and four index scores: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. Three WISC-IV subtests were selected for the current study to allow the assessment of auditory working memory and processing speed. Digit Span (DS) and Letter-Number Sequencing (LNS) combine to provide the Working Memory Index (WMI) score, and Coding (CD) provides an estimate of processing speed. Normative data are provided for children aged 6 years 0 months to 16 years 11 months. The standardization sample included 2,200 children, divided into 11 age groups, who closely matched the 2000 U.S. Census in terms of age, gender, race-ethnicity, parental education, and geographic region. Overall, the technical characteristics of the WISC-IV are excellent. Although reliabilities are higher for the FSIQ and Index scores, subtest score reliabilities are also quite high. The split-half reliability coefficient with Spearman-Brown correction for the WMI is at least .90, and coefficients for the three subtests are .87 (DS), .90 (LNS), and .85 (CD). Test-retest reliabilities for the three selected subtests range from .83 to .84, and were corrected for restriction of range. The test-retest reliability for the WMI is .84 or higher for all age groups. Evidence for the scales' criterion-related and construct validity is presented in the form of correlation coefficients with the WISC-III, WAIS-III, WIAT-II, Children's Memory Scale (CMS), and the Adaptive Behavior Assessment System - Second Edition (ABAS-II), and factor analyses that indicate the best fitting model contains four factors that correspond to the WISC-IV Index scores. The examiner's manual refers to extensive literature reviews and the input of consultants, expert panels, and psychologists as support for the scales' content validity.

The content and administration of the corresponding Wechsler Adult Intelligence Scale–Third Edition (WAIS-III; Wechsler, 1997) subtests are very similar to the WISC-IV. Normative data are provided for adults aged 16 to 89 years, and divided into 13 age groups. The standardization sample included 2,450 adults who closely matched the 1995 U.S. Census

in terms of gender, socioeconomic status, race-ethnicity, educational level, and geographic region. The WAIS-III has excellent reliability. The internal consistencies of the DS, LNS, and CD subtests are .90, .82, and .84, respectively (Sattler, 2001). Test-retest coefficients, assessed over a five-week interval on average, for DS, LNS, and CD are .73, .71, and .91, respectively (Sattler). Evidence in the form of input from expert panels, literature reviews, correlations between WAIS subtests and scales, correlations with the WASI, WISC-III, and Wechsler Individual Achievement Test (WIAT), and factor analyses suggests adequate content, concurrent (criterion-related), and construct (convergent and discriminant) validity of the WAIS-III (Sattler).

*Procedure*

The study utilized a cross-sectional design, which assessed the neurocognitive functioning of cancer survivors and untreated siblings on a single occasion. Outcomes were measured through a combination of self-report and individually-administered, standardized, neurocognitive tests. A major limitation of using a battery of standardized neuropsychological tests involves the time and resources needed to administer the battery to every participant. In the case of the current study, that factor may have prohibited the enrollment of a large number of participants. Additional demographic and educational background information was gathered through a questionnaire completed by a parent or guardian.

A written invitation was sent from the cancer survivor's oncologist at the treating hospital to the parent/guardian or to the survivor, if he or she was at least 18 years of age. Patients who were seen in the long-term follow-up clinic during the enrollment period were also given the invitation letter at the time of their visit. The letter introduced the study and briefly explained its purpose. Parents or survivors who were interested in participating, or had questions regarding the study, were provided with a telephone number and instructed to

contact the research coordinator. If a response was not received within 2 weeks from the date the letter was mailed, a follow-up phone call was made to the parent or survivor to verify that the invitation had been received and to answer any questions related to participation in the study. When letters were returned due to an incorrect or outdated mailing address, patient records, telephone directories, and internet white pages were searched in an attempt to locate an updated address. If a current address was found, then the invitation letter was mailed again. If an updated address could not be located using any of the methods above, the survivor was classified as lost to follow-up.

Two separate enrollment periods were utilized during this study, with a span of 7 months between the first and the second enrollments. At the end of the first enrollment period, a second invitation was sent to those survivors who had not responded to the first letter or the follow-up telephone call. In addition, an initial invitation was sent to survivors who had since become eligible (e.g., those who recently turned 6 years old or reached 2 years off treatment). Again, if a response was not received within 2 weeks of the mailing, the research assistant made a follow-up telephone call. Recruitment efforts targeted 61 eligible patients from the long-term survivor database. Overall, 31% ($n$ = 19) of the eligible survivors participated in the study; however, for those survivors with confirmed contact via mail or telephone, participation was 53%. Although the participation rate was lower than expected, it was comparable to other long-term follow-up studies of childhood cancer survivors that reported participation rates of about 30% (Schatz et al., 2000; Tercyak, Donze, Prahlad, Mosher, & Shad, 2006). Waber et al. (2001) obtained a slightly higher participation rate of 42% in their study of ALL survivors who were recruited at a median of 7 years from diagnosis.

Patients and siblings who agreed to participate attended a single appointment. Individual appointments were scheduled in 3-hour blocks, and siblings who wished to be

scheduled together were given a 5-hour block. Once the appointments were made, an appointment confirmation letter that contained the date and time of their appointment and directions to the testing location was sent to the family or participant. On the day of the appointment, the research assistant met the family and participants in a large waiting room where introductions were made. Then the participant was taken to the testing room to complete preliminary paperwork. If the participant was a minor, a parent also accompanied the child to the testing room. The research assistant answered any remaining questions that the survivor, sibling, or parents had related to the study's purpose, procedures, or use of the results. Informed consent or assent, and parental permission for minors, were obtained prior to enrollment. Additional information was gathered from the parent and participant, including demographic data, treatment details, school performance, and current medical status. Once the necessary paperwork was completed, the parent and sibling were directed back to the waiting room and a nearby play area. Testing was conducted in a quiet room located on the pediatric floor of the hospital where the survivor had received treatment.

The battery of neurocognitive measures was administered to each participant in a standardized order by a single examiner. Typically, an evaluation took between 90 and 120 minutes to complete. Following completion of the test battery, each participant received a copy of the signed consent or assent and a small incentive for their participation. Raw scores on each of the neurocognitive measures were then calculated. Standard scores were obtained from the appropriate normative tables. Approximately 2 weeks after completing the evaluation, participants or their parents received a brief report describing the child's performance on all measures administered.

*Analyses*

Data were entered into a spreadsheet and analyses were conducted using *SPSS for Windows (SPSS)*, Version 11.0.1. Prior to analysis, the dependent variables were examined

for accuracy of data entry, missing values, and fit between their distributions and the assumptions of univariate analyses. Descriptive statistics, histograms, and boxplots were generated and examined to assess the data for normality, homogeneity of variance, and for the presence of outliers. Non-parametric statistics were chosen for most analyses due to the small sample size, occasional violations of the assumptions of normality and homogeneity of variance, and because some comparisons involved unequal groups. Compared to parametric statistics, non-parametric statistics are less likely to result in bias when distributional assumptions are violated, but they also result in the loss of some power to detect differences. Frequencies were compared using the chi-square test of independence ($\chi^2$) or Fisher's exact probability test when cell sizes were less than 10. Pearson product-moment ($r$) or Spearman rank order correlations ($r_s$) were used to assess the relationships between variables. Spearman rank order correlation may be used when the data do not meet the assumptions required for Pearson's $r$ (Thorne & Slane, 1997), which is more likely to occur in a small sample. Differences between survivors' and siblings' test scores were assessed using the Wilcoxon signed-rank test, which is the non-parametric alternative to a paired samples *t*-test. Survivor group means were compared with test normative population means using a series of one-sample *t*-tests.

Childhood cancer survivors who were eligible but did not participate in the study fell into two groups. First, there were eligible survivors who were contacted but declined participation (Declined). Second, there were eligible survivors who did not respond to the invitation or were lost to follow-up (LTF). The two groups were evaluated separately for all variables, with the exception of race. In that case, due to very small cell sizes, the two non-participant groups (Declined and LTF) were combined and race was changed to a binary variable (i.e., White versus non-White), creating a 2 x 2 table with cell sizes sufficient for analysis. Preliminary assumption testing was conducted to check for normality, linearity,

univariate outliers, homogeneity of variances, and multicollinearity. Due to the presence of small, unequal groups and non-normal distributions of age at diagnosis and treatment intensity, only non-parametric statistical tests were used. Differences between participants and the two non-participant groups were assessed using the chi-square test of independence ($\chi^2$) or Fisher's exact probability test for the binary variables and Kruskal-Wallis one-way analysis of variance tests were used for the three continuous variables.

Finally, the relationships between selected neurocognitive test scores and SES (parent education), treatment intensity, age at diagnosis, and time since diagnosis were examined using multiple linear regression. During the regression analysis, all four predictor variables were entered in a backward stepwise fashion, and iterations continued until only those variables that significantly predicted the dependent variable at an alpha criterion of $p < .05$ remained. Fathers' and mothers' levels of completed education were initially coded as ordered, categorical variables, that ranged from 1 = 8$^{th}$ grade or below to 9 = post-doctoral study. Because of the small sample sizes in some of the educational categories, level of education was dichotomized based upon whether or not the parent had completed a bachelor's degree or higher. Then for the sake of analysis and to minimize the total number of significance tests, fathers' education and mothers' education were combined to create a binary measure of parent education. The family was considered lower SES (scored as 1) if both parents reported completing associate's degrees or below, and higher SES (scored as 2) if at least one parent reported completing a bachelor's degree or above. Treatment intensity, in the current study, was roughly defined as a combination of the chemotherapy and radiation administered over the course of a child's cancer treatment. To create the treatment intensity variable, cumulative radiation received was converted to an ordered, categorical variable (e.g., 0 = no radiation, 1 = less than 1000 cGy, 2 = 1000 – 1990 cGy, 3 = 2000 – 2990 cGy, 4 = 3000 – 3990 cGy, 5 = 4000 – 4990 cGy, 6 = 5000 – 5990 cGy, 7 = 6000 cGy and higher)

and added to the number of unique chemotherapy drugs administered, which ranged from two to eight. Time since diagnosis was calculated by subtracting a participant's age (in months) at diagnosis from his or her age at the time of the study. To permit comparisons between participants and non-participants, a standard date (12/31/2005) was used for the time of the study rather than the actual evaluation date, since the non-participants were not evaluated. Prior to analysis, the variables were evaluated for multicollinearity, outliers, normality, linearity, homoscedasticity, and independence of residuals, with no major violations noted.

Suggested sample sizes for regression analyses range from 15 (Stevens, 1996) to 40 participants per predictor for stepwise analyses (Tabachnick & Fidell, 2001). Given the small sample here, the regression analyses were conducted purely for exploratory purposes, with the understanding that it would not be possible to draw definitive conclusions nor extend the results beyond the current sample. Furthermore, regression was only applied to the measures that showed significant differences or large effect sizes when survivors' scores were compared to their siblings.

*Alpha*. Since previous research with this particular subgroup of cancer survivors is limited and has produced mixed findings, all significance tests in the current study were two-tailed. When working with small samples, some statisticians suggest the use of a less stringent alpha level such as .10 to increase power (Stevens, 1996). Clearly, adjusting the alpha level solely to increase power is an undesirable practice. However, in the case of the current study, the consequences of a small increase in the probability of a Type I error are potentially less harmful than increasing Type II error (i.e., the probability of not detecting a difference between the groups when a true difference exists), so a less rigorous experiment-wise alpha level (.10) was employed. All of the statistics used to test one of the study's hypotheses were evaluated for significance using Bonferroni-corrected alpha levels based

upon the number of individual tests per family of analyses. Tests of statistical significance that were not directly related to the study's hypotheses (e.g., tests of statistical and distributional assumptions) were conducted using alpha = .05.

*Clinical significance*. Statistical significance alone does not assist in determining the strength of a relationship, or whether the relationship, if one exists, is meaningful (Kraemer et al., 2003). Hence, knowing the effect size is essential, since the presence or absence of statistical significance does not give information about the size or importance of the outcome (Kraemer et al.). Therefore, effect sizes were calculated to evaluate clinical significance by dividing the mean differences by the pooled standard deviations (Cohen, 1988), and then adjusting the statistic based upon the small sample size (Hedges & Olkin, 1985). Effect sizes are reported in the form of Hedge's unbiased *d*, which adjusts *d* for small samples (Hedges & Olkin, 1985). The criteria for evaluating effect sizes was based upon Cohen's (1988) standards where .20 represents a small effect, .50 represents a medium effect, and .80 or higher represents a large effect. Effect sizes were calculated using the *Effect Size Calculator* computer program (Watkins, 2003) and correlations (*r*) were converted to Hedge's unbiased *d* by manual calculation.

*Power*. Power analyses were performed prior to data collection using *Java Applets for Power and Sample Size* (Lenth, 2006). The original target sample sizes of 30 survivors and 30 sibling controls would have yielded ample power to detect a .40 *SD* difference in means between the survivor and sibling groups (power = .80, alpha = .10, two-tailed). That effect size was deemed reasonable based on a meta-analysis of 20 studies (with a total of 30 comparisons) of ALL survivors treated with cranial radiation that found a mean global IQ effect size of -.67 *SD* when measured over time or compared to control groups (Cousens et al., 1988). Furthermore, mean differences in neurocognitive test scores of 1.0 *SD* or larger have been found between treatment groups in previous research (Ochs et al., 1991).

Unfortunately, enrollment for the current study yielded approximately one-half to one-third of the number of desired participants in each group. Given 8 survivor and sibling pairs, the power to detect a .65 *SD* difference between groups was less than desired, and equal to .51 (alpha = .10). The study possessed adequate power to detect a .98 *SD* difference between the survivor and sibling groups (power = .80, alpha = .10). Statistical power was sufficient to detect a .61 *SD* difference in the mean scores of the of the 18 cancer survivors with the normative population (power = .80, alpha = .10, two-tailed).

# Results

## *Sample Characteristics*

*Survivor participants and non-participants*. Survivors who participated in the study were compared to eligible non-participants to determine whether they differed by gender, race, age-related factors, and treatment intensity (Tables 5 and 6). A Bonferroni-corrected alpha of .02 (.10/5) was used to determine if the differences between participants and non-participants were statistically significant.

Results showed that non-participants were significantly more likely than participants to be of a non-White racial background ($p = .006$, Fisher's Exact Test). The three groups did not differ according to gender, $\chi^2$ (2, $N = 61$) = .789, $p = .674$. Three Kruskal-Wallis one-way analysis of variance tests were performed to investigate group differences in age-related factors and treatment intensity. The three dependent variables that were examined included age at diagnosis, time since diagnosis, and treatment intensity. A fourth variable, age at study (age in months at the time of the study), was considered for inclusion, but it was found to be highly correlated with time since diagnosis ($r = .94$, $p < .000$), so the decision was made to exclude age at study from the analysis. Table 6 shows the ranges, means, and standard deviations for age at study, age at diagnosis, time since diagnosis, and treatment intensity for the three groups of eligible cancer survivors

Table 5

*Demographic and Treatment Characteristics of Eligible Cancer Survivors*

| | | Non-participants | |
|---|---|---|---|
| Characteristic | Participants (*n* = 19) | Declined (*n* = 17) | No response/ LTF (*n* = 25) |
| Gender | | | |
| Male | 9 (47) | 10 (59) | 15 (60) |
| Female | 10 (53) | 7 (41) | 10 (40) |
| Race | | | |
| White, non-Hispanic | 19 (100) | 15 (88) | 14 (56) |
| Black, non-Hispanic | 0 (0) | 2 (12) | 7 (28) |
| Hispanic | 0 (0) | 0 (0) | 3 (12) |
| Asian/Pacific Island | 0 (0) | 0 (0) | 1 (4) |
| Other | 0 (0) | 0 (0) | 0 (0) |
| Treatment protocol[a] | | | |
| Chemotherapy only | 13 (68) | 12 (71) | 12 (48) |
| Chemotherapy and Radiation | 6 (32) | 5 (29) | 12 (48) |
| Chemotherapy drugs[b] | | | |
| Two | 8 (42) | 8 (47) | 8 (32) |
| Three | 5 (26) | 4 (24) | 8 (32) |
| Four | 3 (16) | 2 (12) | 4 (16) |
| Five | 2 (11) | 2 (12) | 3 (12) |
| Eight | 1 (5) | 1 (6) | 0 (0) |
| Radiation cumulative dose (cGy)[c] | | | |
| Less than 1000 | 0 (0) | 0 (0) | 0 (0) |
| 1000 – 1990 | 3 (16) | 2 (12) | 6 (24) |
| 2000 – 2990 | 2 (11) | 1 (6) | 1 (4) |
| 3000 – 3990 | 0 (0) | 1 (6) | 2 (8) |
| 4000 – 4990 | 0 (0) | 0 (0) | 2 (8) |
| 5000 – 5990 | 1 (5) | 0 (0) | 0 (0) |
| 6000 + | 0 (0) | 1 (6) | 0 (0) |

*Note.* LTF = Lost to follow-up. Parentheses contain the corresponding percentage of each group [a]Treatment information missing for one non-participant in the No response/LTF group. [b]Cells represent the number of unique drugs administered during the course of treatment. [c]Radiation dose missing for two non-participants in the No response/LTF group.

Table 6

*Summary of Age at Diagnosis and Study, Time since Diagnosis, and Treatment Intensity in Eligible Cancer Survivors*

| Characteristic | Participants ($n$ = 19) | Non-participants | |
|---|---|---|---|
| | | Declined ($n$ = 17) | No response/LTF ($n$ = 25) |
| Age at study | | | |
| Low | 73 | 105 | 77 |
| High | 229 | 257 | 251 |
| *Mean (SD)* | 154.8 (45.9) | 198.1 (40.8) | 180.0 (47.7) |
| Age at diagnosis | | | |
| Low | 0 | 0 | 0 |
| High | 53 | 57 | 55 |
| *Mean (SD)* | 14.6 (13.7) | 27.2 (19.1) | 18.5 (15.8) |
| Time since diagnosis[a] | | | |
| Low | 58 | 74 | 71 |
| High | 224 | 248 | 242 |
| *Mean (SD)* | 140.2 (46.4) | 170.9 (46.6) | 161.5 (46.6) |
| Treatment intensity | | | |
| Low | 2 | 2 | 2 |
| High | 9 | 10 | 10 |
| *Mean (SD)* | 4.2 (2.4) | 4.1 (2.7) | 4.5 (2.3) |

*Note.* All data are reported in months, with the exception of treatment intensity. LTF = Lost to follow-up.

[a]Time since diagnosis was calculated by subtracting age (in months) at diagnosis from age at the time of the study, which was set at 12/31/2005.

There were no statistically significant differences between the groups for age at diagnosis (Kruskal-Wallis test, $H = 4.24$, $p = .120$), time since diagnosis (Kruskal-Wallis test, $H = 3.77$, $p = .152$), or treatment intensity (Kruskal-Wallis test, $H = .86$, $p = .649$), using the adjusted alpha level of .02. An inspection of means indicated that survivors who declined participation were somewhat older at diagnosis (Declined; $M = 27.2$, $SD = 19.1$, $n = 17$) than those who participated ($M = 14.6$, $SD = 13.7$, $n = 19$) and those who did not respond or were lost to follow-up (No response/LTF; $M = 18.6$, $SD = 16.4$, $n = 25$), though the difference was not statistically significant. Figure 3 shows the distribution of age at diagnosis for the three groups of eligible cancer survivors.

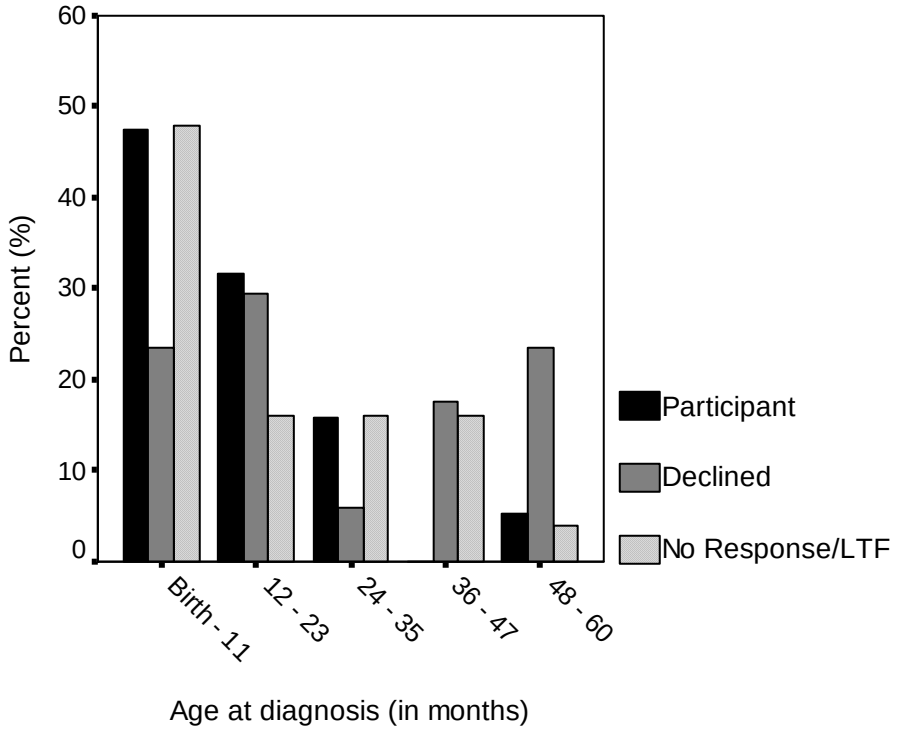


*Figure 1*. Age at diagnosis for all cancer survivors according to participation status: Participants (*n* = 19), Declined (*n* = 17), and No Response/LTF (*n* = 25). The figure shows the percentage of each group that was diagnosed at a given age, collapsed into 12-month intervals. LTF = lost to follow-up.

Survivors of several types of cancer were eligible to participate in the study, but the small sample size prevented statistical analyses of differences between groups based upon cancer type. Figure 2 shows the composition of the three groups in terms of cancer diagnosis.

In summary, the cancer survivors who participated in the study were similar in gender, age at diagnosis, and treatment intensity to both the non-participants who declined and those who did not respond or were lost to follow-up. Thus, the survivor participants appear to be representative of the larger survivor population, with the exception of race. In the current study, survivors with non-White racial backgrounds were significantly underrepresented.

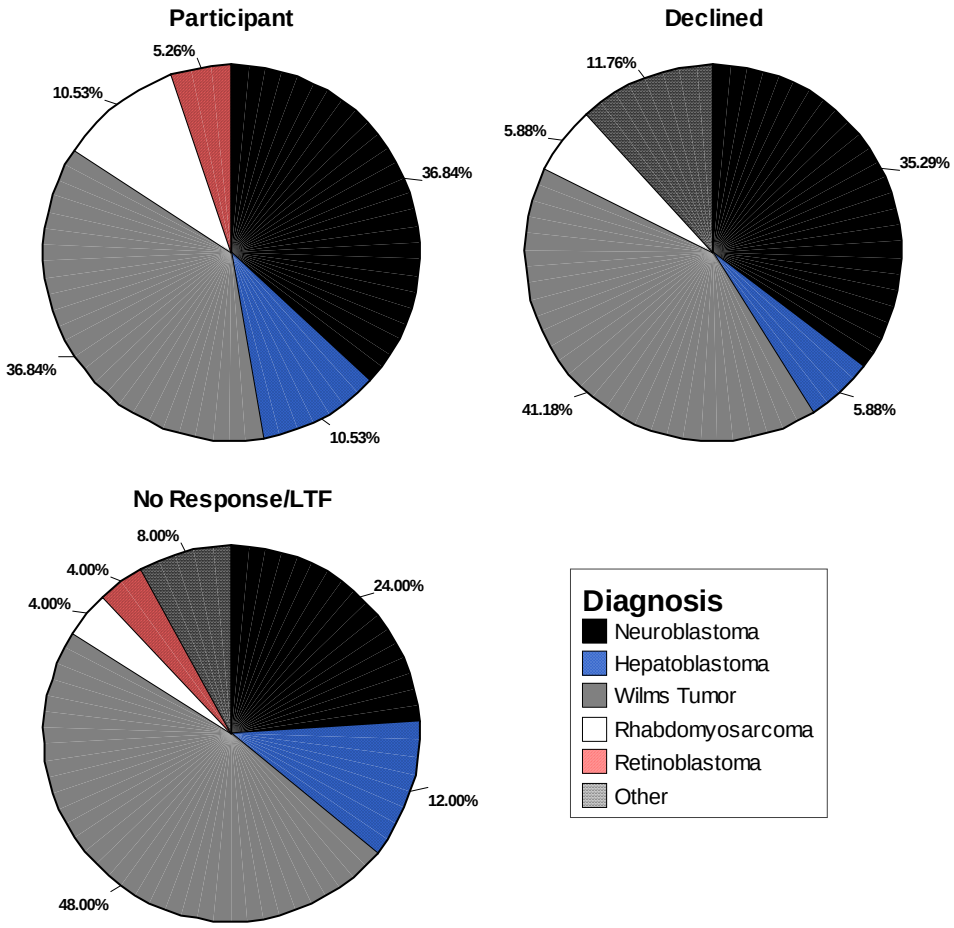


*Figure 2.* Types of cancer diagnosed in survivors according to participation status: Participants ($n$ = 19), Declined ($n$ = 17), and No Response/LTF ($n$ = 25). The figure shows the percentage of each group that experienced each type of cancer.

*Survivors and siblings.* Cancer survivor and sibling pairs were identical in terms of race and parent education. All of the pairs were identified as White, non-Hispanic ($n$ = 8). The levels of completed education reported by fathers and mothers are shown in Figure 3. The pairs were also similar with regard to gender ($p$ = .619, Fisher's Exact Test) and age at testing ($z$ = -.524, $p$ = .600). Thus, survivors and siblings were similar with regard to these primary demographic and socioeconomic factors.

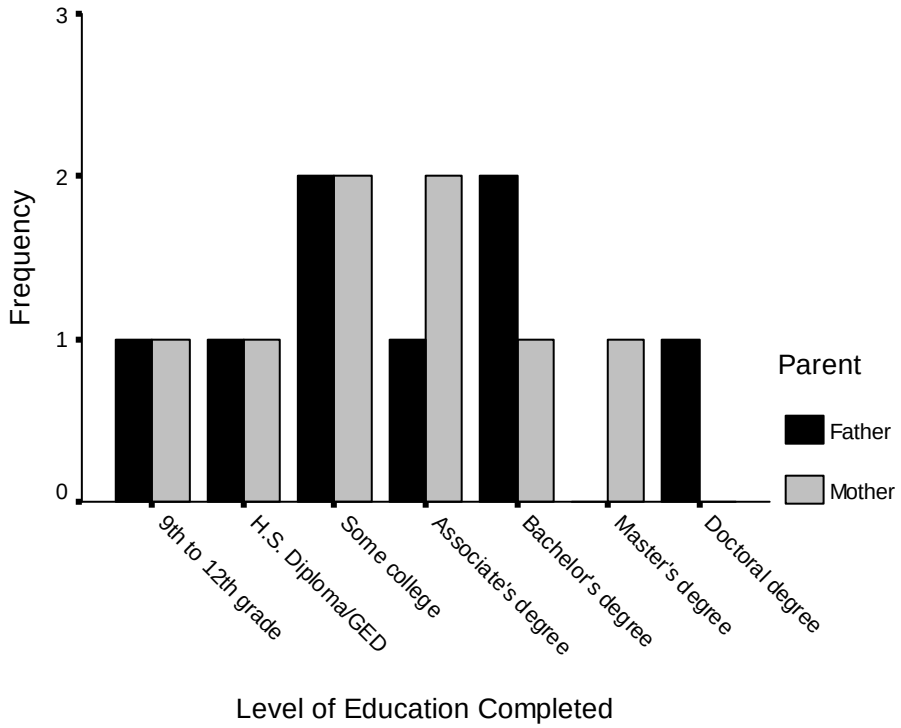


*Figure 3*. Fathers' and mothers' highest level of completed education for survivor-sibling pairs ($n$ = 8).

*Neurocognitive Test Performance*

*Survivors versus siblings*. First, the associations between the test scores of the survivor and sibling pairs were examined through correlation analysis. All of the Spearman Rank Order correlations have been provided in a table in the Appendix. A Bonferroni-corrected alpha of .01 (.10/10) was used to evaluate the statistical significance of the correlations between survivors' and siblings' test scores. Hedge's unbiased *d* was used to calculate all of the reported effect sizes. The correlation between survivors' and siblings' global IQ scores was small and negative ($r_s$ = -.11, $d$ = -.21). Survivors' and siblings' scores on all four of the tests that purport to assess memory skills showed large, negative correlations that ranged from -.61 to -.76 ($d$ ranged from -1.44 to -2.22). Correlations between both survivors' and siblings' reading scores (.76, $p$ = .031, $d$ = 2.18) and math scores (.83, $p$ = .011, $d$ = 2.77) were positive and large. Although none of the correlations

were statistically significant at $p < .01$, the effect sizes for memory, reading, and math scores are considered very large.

The associations between fathers' and mothers' education, age at testing, and global IQ scores were also examined via correlation. A Bonferroni-corrected alpha of .008 (.10/12) was used to evaluate the statistical significance of the correlations. For both the survivors and siblings, fathers' education and mothers' education were significantly and positively correlated with one another (both groups' $r_s = .91$, $p = .002$, Hedge's unbiased $d = 3.79$). Survivors showed a large, positive correlation between mother's education and survivors' global IQ ($r_s = .63$, $p = .100$, Hedge's unbiased $d = 1.40$), though it was not statistically significant. The relationship between the two variables was not as strong in the siblings ($r_s = .38$, $p = .351$, Hedge's unbiased $d = .72$). Fathers' education showed moderate to large correlations with global IQ scores in survivors' ($r_s = .46$, $p = .254$, Hedge's unbiased $d = .90$) and siblings' ($r_s = .57$, $p = .140$, Hedge's unbiased $d = 1.20$); however, here the relationship was stronger for the siblings. A moderate, negative association was found between age at testing and global IQ in survivors ($r_s = -.37$, $p = .365$, Hedge's unbiased $d = -.70$), while a moderate, but positive, association was observed in the siblings ($r_s = .30$, $p = .471$, Hedge's unbiased $d = .56$). Thus, among survivors, an older age at testing was associated with a lower global IQ score, whereas for the siblings, older age was associated with higher global IQ.

Table 7

*Mean Scores and Differences in Neurocognitive Test Performances in Survivor-Sibling Pairs*

| | Survivors | | | Direction of | Siblings | | | |
|---|---|---|---|---|---|---|---|---|
| Measure | *M* | *SD* | *n* | difference | *M* | *SD* | *n* | $z^b$ |
| WASI Full Scale IQ | 105.6 | 18.3 | 8 | < | 107.9 | 11.4 | 8 | -.169 |
| WJ-III | | | | | | | | |
| Letter-Word Identification | 101.4 | 14.3 | 8 | < | 103.5 | 8.9 | 8 | .000 |
| Math Fluency | 96.9 | 16.9 | 8 | < | 99.8 | 10.3 | 8 | -.561 |
| BRIEF General Executive Composite[a] | 56.8 | 13.1 | 6 | > | 43.0 | 7.0 | 6 | -1.782 |
| CPRS Cognitive Problems/Inattention[a] | 59.0 | 18.9 | 6 | > | 44.5 | 3.3 | 6 | -1.753 |
| WAIS-III/WISC-IV | | | | | | | | |
| Coding | 10.0 | 1.9 | 8 | < | 10.3 | 1.0 | 8 | -1.186 |
| Working Memory Index | 104.1 | 14.9 | 7 | < | 104.6 | 8.7 | 7 | .000 |
| CVLT-C/CVLT-II | | | | | | | | |
| List A Trials 1-5 | 47.1 | 12.0 | 8 | < | 57.6 | 2.9 | 8 | -2.103 |
| Long Delay Free Recall | 50.6 | 9.8 | 8 | < | 56.3 | 5.2 | 8 | -1.186 |
| Long Delay Cued Recall | 50.0 | 7.6 | 8 | < | 53.8 | 6.4 | 8 | -.710 |

*Note.* Table contains neurocognitive test scores of survivors and matched sibling pairs and results of Wilcoxon signed-ranks tests. WASI = Wechsler Abbreviated Scale of Intelligence, WJ-III = Woodcock Johnson: Tests of Achievement–Third Edition, BRIEF = Behavior Rating Inventory of Executive Function, CPRS = Conners' Parent Rating Scale-Revised, WAIS-III = Wechsler Adult Intelligence Scale–Third Edition, WISC-IV = Wechsler Intelligence Scale for Children–Fourth Edition, CVLT-C = California Verbal Learning Test for Children, CVLT-II = California Verbal Learning Test-Second Edition.

[a]Higher score indicates a greater level of perceived problematic behavior. [b]No *z* values met the $p < .009$ level required for statistical significance.

Differences in education-related outcomes and scores on the neurocognitive test battery were examined using non-parametric Wilcoxon matched-pairs signed-ranks tests (*z*-value reported) in which the significance level was adjusted based on the Bonferroni rationale to .009 (.10/11). The results of these paired tests are presented in Table 7. Overall, none of the tests of group differences achieved statistical significance. Cancer survivors and their healthy siblings demonstrated similar scores on global intelligence (WASI Full Scale IQ, $p = .866$), reading (WJ-III Letter-Word ID, $p = 1.000$), math fluency (WJ-III Math Fluency, $p = .575$), working memory (WISC-IV Working Memory Index, $p = 1.000$), processing speed (WISC-IV Coding, $p = .236$), auditory memory and learning (CVLT List A T1 to T5, $p = .035$), long delay free recall (CVLT long delay free recall, $p = .236$), and long delay cued recall (CVLT long delay cued recall, $p = .478$). Group differences in parent ratings of cognitive problems and inattention (CPRS Cognitive Problems/Inattention, $p = .080$) and ratings of overall executive functions (BRIEF General Executive Composite, $p =$

.075) were not statistically significant, though the cancer survivors were rated as having greater difficulties than their siblings. The differences between the survivor and sibling pairs were particularly noteworthy because they showed lower performance by the cancer survivors on all 8 tests and a higher level of perceived problematic behaviors on both rating scales.

In terms of clinical significance, large effect sizes were found for parent ratings of attention and executive functions (CPRS Cognitive Problems/Inattention, $d$ = .98, and BRIEF General Executive Composite, $d$ = 1.21). On these measures, the cancer survivors were rated as demonstrating greater difficulties with cognitive problems, inattention, and overall executive functioning than the sibling group, although the cancer group's mean scores remained within the average range when compared to same-age peers from the normative population. Medium to large effects were also observed for auditory learning and memory performance. The cancer survivors did not perform as well as the siblings on measures of auditory learning (CVLT List A T1 to T5, $d$ = -1.14), long-delay free recall ($d$ = -.69), and long-delay cued recall ($d$ = -.51).

Educationally, none of the survivors or siblings had ever repeated a grade in school. Four survivors were receiving special education services at the time of the study, compared to none of the siblings; however, the difference was not statistically significant ($p$ = .077, Fisher's Exact Test), since $p$ was not less than the Bonferroni-corrected alpha of .009. In terms of clinical significance, however, the risk difference was 50%, indicating that survivors were more likely than their siblings to be receiving special education services at the time of the study. The observed 50% risk difference corresponds to a large effect size (Kraemer et al., 2003). Of all 18 participating cancer survivors, 17% ($n$ = 3) had repeated a grade in school and 56% ($n$ = 10) were receiving special education services at the time of the study, based upon parent report.

*Survivors versus normative population.* To test the hypothesis that non-CNS treated cancer survivors would demonstrate deficits in IQ, reading, math, executive functions, attention, and memory when compared to the normative population, comparisons were made between the entire sample of cancer survivors ($n$ = 18) and the normative population using one-sample *t*-tests (two-tailed). Differences were considered statistically significant if the obtained *p*-value was less than the Bonferroni-corrected alpha of .01 (.10/10).

Results revealed no significant differences between the mean scores of the survivors and the normative population on any of the tests (Table 8). Although significant differences were not found in this sample, the mean scores of the cancer survivors revealed lower performances and more problematic behavior ratings compared to the normative population on 8 out of 10 measures. The only measure where the cancer survivors earned a higher mean score than the normative population was on the WASI Full Scale IQ. There, the survivor group's mean global IQ score was approximately 4 standard score points higher than the normative population.

Table 8

*Mean Scores and Differences in Neurocognitive Test Performances between Cancer Survivors and the Normative Population*

| | Survivors | | | Normative population | | | | |
|---|---|---|---|---|---|---|---|---|
| Measure | *M* | *SD* | Direction of difference | *M* | *SD* | *t* | *df* | *p* |
| WASI Full Scale IQ | 104.1 | 16.2 | > | 100 | 15 | 1.036 | 16 | .316 |
| WJ-III | | | | | | | | |
| Letter-Word ID | 98.9 | 15.2 | < | 100 | 15 | -.295 | 17 | .772 |
| Math fluency | 93.8 | 15.2 | < | 100 | 15 | -1.726 | 17 | .102 |
| BRIEF General Executive Composite [a] | 56.1 | 14.5 | > | 50 | 10 | 1.692 | 15 | .111 |
| CPRS Cognitive Problems/Inattention [a] | 55.9 | 15.9 | > | 50 | 10 | 1.482 | 15 | .159 |
| WAIS-III/WISC-IV | | | | | | | | |
| Coding | 9.9 | 2.7 | < | 10 | 3 | -.088 | 17 | .931 |
| Working Memory Index | 98.7 | 15.1 | < | 100 | 15 | -.369 | 16 | .717 |
| CVLT-C/CVLT-II | | | | | | | | |
| List A Trials 1-5 | 47.0 | 11.6 | < | 50 | 10 | -1.095 | 17 | .289 |
| Long Delay Free Recall | 50.0 | 10.4 | = | 50 | 10 | .114 | 17 | .911 |
| Long Delay Cued Recall | 49.4 | 10.4 | < | 50 | 10 | -.226 | 17 | .824 |

*Note.* Table contains neurocognitive test scores of survivors and normative population and the results of the one-sample *t*-tests.

[a]Higher score indicates a greater level of perceived problematic behavior.

In general, the effect sizes associated with the mean differences between the cancer survivors and the normative population were small, except for parent ratings of attention and executive functions, which both produced medium effect sizes (CPRS Cognitive Problems/Inattention, Hedges' unbiased *d* = .56 and BRIEF General Executive Composite, Hedges' unbiased *d* = .59). On those measures, survivors were rated as demonstrating greater difficulties with cognitive problems, inattention, and overall executive functioning than the normative population. In addition, the effect size for math fluency performance was small to medium (WJ-III Math Fluency, Hedges' unbiased *d* = -.41), suggesting that the survivors did not perform as well as the normative population in that area. It should be noted that the cancer survivors' mean scores remained within the average range on all three measures.

*Multiple Regression Analyses*

When differences between survivors and siblings were associated with large effect sizes, those outcome measures were further analyzed using stepwise regression. Therefore, regression analyses were conducted for parent ratings of survivors' executive functioning, cognitive problems/inattention, and for auditory learning and memory skills. The statistical significance of each regression model was evaluated based upon an alpha equal to .05. Table 9 shows the intercorrelations among the predictors and the correlations between predictors and the outcome measures.

Table 9

*Intercorrelations between Predictor Variables and Neuropsychological and Behavioral Outcomes in All Survivor Participants*

| Variable | Parent education | Age at diagnosis | Time since diagnosis | Treatment intensity |
|---|---|---|---|---|
| Parent education | -- | -.03 | -.14 | .35 |
| Age at diagnosis | | -- | -.27 | .21 |
| Time since diagnosis | | | -- | -.53** |
| Treatment intensity | | | | -- |
| WASI Full Scale IQ[a] | .47* | .21 | -.51** | .42* |
| WJ-III | | | | |
| Letter-Word Identification | .21 | .24 | -.40 | .15 |
| Math fluency | .37 | .15 | -.31 | .40* |
| BRIEF General Executive Composite[b] | -.65*** | -.33 | .17 | -.06 |
| CPRS Cognitive Problems/ Inattention[b] | -.54** | -.29 | .23 | -.09 |
| WAIS-III/WISC-IV | | | | |
| Coding | .28 | .09 | -.20 | .30 |
| Working Memory Index[a] | .06 | .06 | -.02 | .32 |
| CVLT-C/CVLT-II | | | | |
| List A Trials 1-5 | .04 | .24 | -.53** | .41* |
| Long Delay Free Recall | .09 | .41* | -.38 | .58** |
| Long Delay Cued Recall | .21 | .26 | -.37 | .59*** |

*Note.* $n$ = 18. Cells represent Pearson product-moment correlations. A positive correlation indicates that performance on an outcome measure improved as values of the predictor increased, except for the BRIEF and CPRS. A positive correlation with the BRIEF or CPRS indicates that levels of perceived problematic behavior increased as values of the predictor increased.

[a] $n$ = 17. [b] $n$ = 16.

*$p$ < .10. **$p$ < .05. ***$p$ < .01.

Results from backward stepwise regression showed that parent education was the only significant predictor of parent ratings of survivors' executive functioning ($p < .01$), as measured by the BRIEF General Executive Composite (Table 10). None of the illness- or treatment-related variables met the pre-determined statistical criteria for retention ($p < .10$), so they were automatically eliminated from the model. The final model, which contained only parent education, was significant ($R^2 = .43$, $p = .006$).

Table 10

*Summary of Stepwise Regression Analysis Predicting Ratings of Executive Functioning From Treatment Characteristics and Parent Education*

| Model and predictor variables | *B* | *SEB* | *β* | $R^2$ | $\triangle R^2$ |
|---|---|---|---|---|---|
| Model 1 | | | | .558** | .558 |
| Constant | 79.994 | 17.196 | | | |
| Age at diagnosis | -.294 | .221 | -.279 | | |
| Time since diagnosis | .013 | .082 | .036 | | |
| Treatment intensity | 1.900 | 1.406 | .325 | | |
| Parent education | -21.313 | 6.428 | -.736*** | | |
| Model 2 | | | | .557** | -.001 |
| Constant | 82.294 | 8.509 | | | |
| Age at diagnosis | -.301 | .207 | -.286 | | |
| Treatment intensity | 1.820 | 1.256 | .311 | | |
| Parent education | -21.405 | 6.135 | -.739*** | | |
| Model 3 | | | | .480** | -.078 |
| Constant | 84.574 | 8.710 | | | |
| Age at diagnosis | -.250 | .213 | -.237 | | |
| Parent education | -17.851 | 5.857 | -.617*** | | |
| Model 4 | | | | .425*** | -.055 |
| Constant | 82.067 | 8.557 | | | |
| Parent education | -18.867 | 5.870 | -.652*** | | |

*Note*. $n = 16$.
*$p < .10$. **$p < .05$. ***$p < .01$.

Parent education was also the only significant predictor of parent ratings of survivors' cognitive problems and inattention ($p < .05$), as measured by the CPRS Cognitive Problems/Inattention scale (Table 11). None of the illness- or treatment-related variables made significant unique contributions to the variance in cognitive problems/inattention ratings, so they were removed from the model. Again, the final model was significant with parent education as the only predictor ($R^2 = .29$, $p = .031$).

Table 11

*Summary of Stepwise Regression Analysis Predicting Ratings of Cognitive and Attention Problems from Treatment Characteristics and Parent Education*

| Model and predictor variables | *B* | *SEB* | *β* | $R^2$ | $\triangle R^2$ |
|---|---|---|---|---|---|
| Model 1 | | | | | |
| Constant | 71.857 | 22.200 | | .386 | .386 |
| Age at diagnosis | -.265 | .285 | -.230 | | |
| Time since diagnosis | .047 | .106 | .120 | | |
| Treatment intensity | 1.653 | 1.816 | .258 | | |
| Parent education | -18.430 | 8.298 | -.581** | | |
| Model 2 | | | | .375 | -.011 |
| Constant | 80.260 | 11.070 | | | |
| Age at diagnosis | -.290 | .270 | -.252 | | |
| Treatment intensity | 1.362 | 1.634 | .212 | | |
| Parent education | -18.766 | 7.981 | -.592** | | |
| Model 3 | | | | .339* | -.036 |
| Constant | 81.965 | 10.751 | | | |
| Age at diagnosis | -.252 | .263 | -.219 | | |
| Parent education | -16.107 | 7.229 | -.508** | | |
| Model 4 | | | | .292** | -.047 |
| Constant | 79.433 | 10.394 | | | |
| Parent education | -17.133 | 7.130 | -.540** | | |

*Note*. $n = 16$.
*$p < .10$. **$p < .05$. ***$p < .01$.

Survivors' auditory memory performances, measured by the CVLT List A Trials 1-5, were not significantly predicted by parent education, age at diagnosis, or treatment intensity (Table 12). Time since diagnosis was the only significant predictor ($p < .05$), and it accounted for approximately 28% of the variance in auditory memory scores. The final model was significant ($R^2 = .28$, $p = .023$). These results suggest that as the time since diagnosis increased, scores on the auditory memory task decreased.

Table 12

*Summary of Stepwise Regression Analysis Predicting Auditory Memory Performance from Treatment Characteristics and Parent Education*

| Model and predictor variables | *B* | *SEB* | *β* | $R^2$ | $\triangle R^2$ |
|---|---|---|---|---|---|
| Model 1 | | | | .321 | .321 |
| Constant | 59.630 | 15.356 | | | |
| Age at diagnosis | .080 | .204 | .094 | | |
| Time since diagnosis | -.104 | .069 | -.415 | | |
| Treatment intensity | .942 | 1.360 | .198 | | |
| Parent education | -2.061 | 5.660 | -.089 | | |
| Model 2 | | | | .314 | -.007 |
| Constant | 57.551 | 13.805 | | | |
| Age at diagnosis | .083 | .197 | .097 | | |
| Time since diagnosis | -.105 | .067 | -.420 | | |
| Treatment intensity | .781 | 1.246 | .164 | | |
| Model 3 | | | | .305* | -.009 |
| Constant | 59.418 | 12.713 | | | |
| Time since diagnosis | -.111 | .064 | -.441 | | |
| Treatment intensity | .823 | 1.207 | .173 | | |
| Model 4 | | | | .284** | -.022 |
| Constant | 66.100 | 7.954 | | | |
| Time since diagnosis | -.134 | .053 | -.533** | | |

*Note*. $n = 18$.
*$p < .10$. **$p < .05$. ***$p < .01$.

# Discussion

Children with chronic health conditions are at risk for experiencing impairments in cognitive, academic, or behavioral functioning that may be directly related to their illness or its treatment (Howe, Feinstein, Reiss, Molock, & Berger, 1993; Thompson & Gustafson, 1996). Their ability to learn can also be affected by via fatigue, psychological stress, socioeconomic factors, and missed school (Kazak & Rourke, 2003; Lee & Janik, 2006; Thompson & Gustafson). A substantial body of research has shown that some children exhibit deficits or declines in thinking, learning, and behavior following successful cancer treatment (Haupt et al., 1994; Kadan-Lottick & Neglia, 2005; Kingma et al., 2001). Investigators have reported that these difficulties may not be evident for months or even years after treatment (Mulhern & Palmer, 2003b; Twaddle, Britton, Craft, Noble, & Kernahan, 1983), so these effects are generally referred to as neurocognitive *late* effects.

Until recently, most studies of neurocognitive late effects of childhood cancer have focused on children who were treated for cancers of the brain and nervous system with CNS-directed therapies (Duffner, 2004; Espy et al., 2001; Mulhern et al., 2004). The emphasis on evaluating CNS cancers and therapies is logical since the brain and spinal cord are believed to be highly vulnerable to the effects of neurotoxic drugs and radiation (Iuvone et al., 2002; Mulhern & Palmer, 2003a). However, emerging evidence from children who were treated for cancers outside of the CNS with non-CNS-directed therapies has raised concerns about whether those survivors might also experience neurocognitive late effects (Butler et al., 1994; Copeland et al., 1996; Mulhern et al., 1992a, Twaddle et al., 1983). Specifically, the assumed safety of non-CNS-directed treatments has been questioned (Balis & Poplack, 1989, Waber et al., 2000). In fact, some findings do suggest that non-CNS-directed therapies may be associated with neurocognitive decline or deficit in adults (Ahles & Saykin, 2002; Schagen et

al., 2006) and in children (Copeland et al.; Espy et al., 2001; Mulhern et al., 1992a; Twaddle et al.).

To date, consensus has not been reached regarding the potential effects of systemic chemotherapy on the CNS. Some experts have concluded that "when not combined with CNS-directed chemotherapy or cranial radiation, the systemic administration of high doses of methotrexate [chemotherapy] has not been consistently associated with CNS sequelae" (Kadan-Lottick & Neglia, 2005, p. 40). However, others believe that more information about the consequences of non-CNS cancers and treatment methods is needed (Brown & Madan-Swain, 1993). A review of the current literature suggests that too little is known about the potential neurocognitive effects of systemic chemotherapy to draw firm conclusions about its safety. Thus, the purpose of the present study was to determine whether childhood cancer survivors, treated prior to school-age with only non-CNS-directed therapies, were at risk for late cognitive, academic, or behavioral difficulties.

First, this group of childhood cancer survivors was predicted to evidence significantly lower scores on tests of cognitive and academic skills, and higher levels of parent-reported behavior problems, when compared to healthy siblings who were never treated for cancer. Overall, the results do not support the presence of statistically significant differences in functioning between cancer survivors and their siblings. Survivors were outperformed by their healthy siblings on all of the measures selected for analysis, including IQ, reading, math fluency, processing speed, working memory, auditory memory, attention, and executive functioning, though none of the differences reached the level required for statistical significance. However, clinically significant differences were found in the areas of parent-rated attention and executive functioning, as evidenced by large effect sizes (ESs). These results suggest that cancer survivors are rated as demonstrating more problems with attention and difficulties with thinking, planning, organizing, and controlling their emotions than their

siblings. In addition, the medium to large ESs found for three measures of auditory memory and learning indicate that survivors do not perform as well as their siblings on these tasks. Survivors earned lower scores than siblings on tasks that first required them to remember a list of common household items that was read aloud over the course of 5 learning trials, and then to recall those items after a long delay, both with and without cues. Notably, the clinically significant differences between the groups do *not* necessarily mean that survivors experience observable problems in those areas, since both the survivors' and siblings' mean scores fell within the average range (calculated as *M* +/- 1 *SD*). The fact that the current sample earned scores that are considered average is consistent with what has been reported in previous studies of adults or children treated with chemotherapy (Ahles & Saykin, 2002; Copeland et al., 1996).

One interesting yet puzzling finding involved the observed correlation between the global IQ scores of the survivor-sibling pairs. In the 8 matched pairs, $r_{IQ}$ = -.11, revealing a small, negative association between their IQs. This correlation is much lower and in the opposite direction than would be expected based upon results from large-scale studies of intellectual abilities in siblings. For example, an analysis of over 26,000 pairs of biological siblings reared together revealed a mean correlation of .47 in their IQ scores (Sattler, 2001). According to Sattler, the association between IQ is even greater for fraternal ($r$ = .55) and identical twins ($r$ = .86), which makes the present findings more remarkable since the 8 pairs here included two sets of fraternal twins.

Examination of the fraternal twins' IQ scores reveals that the first pair earned scores of 118 (survivor) and 90 (sibling), and the second pair scored 116 (survivor) and 105 (sibling). The higher IQ scores obtained by the cancer survivors are expected to predict higher performances on the other measures, as well (Roid et al., 1993; Sattler, 2001). However, in both twin pairs, the survivors received lower scores than their siblings for math

fluency (scores differ by -.80 and -.25 *SD*, respectively), and their parent ratings indicated greater problems with attention (scores differ by 1.5 and 4.0 *SD*, respectively) and executive functioning (scores differ by 1.5 and 1.0 *SD*, respectively).

A third set of twins, who were identical, enrolled in the study but were not able to complete the neurocognitive testing in a standardized manner. Although the healthy twin completed several tests, the cancer surviving twin displayed significant difficulties that necessitated discontinuation of the testing. Parent report and clinical observations revealed that the survivor evidenced physical limitations, cognitive deficits, and anxiety, in addition to a hearing impairment. Thus, readers should note that the data reported in studies such as this may not reflect the functioning of the most severely impaired children, since standardized data collection is not always possible.

Second, the cancer survivors were predicted to obtain significantly lower mean scores on tests of cognitive and academic skills, and higher levels of parent-reported problems with attention and executive functioning, when compared to the normative population. Overall, the results of the current study do not reveal the presence of statistically significant differences in functioning between the cancer survivors and their same-age peers in the normative sample. However, like the healthy siblings, the normative population mean scores were higher than the survivors' mean scores on 8 of 10 measures selected for analysis, including reading, math fluency, processing speed, working memory, auditory memory, attention, and executive functioning, though none of the differences reached the level required for statistical significance. The only exception was found in the cancer survivors' mean global IQ score, which was four points higher than the normative mean of 100 (*SD* = 15).

Cancer survivors and siblings earned mean global IQ scores that were .40 and .53 *SD* higher than the normative population mean, respectively. Therefore, the groups' mean scores

on the tests of academic achievement and memory are predicted to be slightly above the population mean as well. Indeed, that was the case for reading and the WISC-IV/WAIS-III Working Memory Index, but not for math fluency and the CVLT auditory memory and learning tasks. There, the siblings continued to perform .40 to .80 *SD* above the normative mean, while the survivors performed in the average or slightly below average range on those tasks.

Clinically significant differences between survivors and the normative population were observed in the areas of parent-rated attention and executive functioning, as evidenced by medium ESs. Parents' ratings of cancer survivors seem to suggest more problems with attention and difficulties with thinking, planning, organizing, and controlling their emotions than parents' ratings of same-age peers from the normative sample. However, the higher levels of parent-perceived attention and executive functioning problems in survivors may have been influenced by factors other than true behavioral differences between survivors and siblings. For example, parents were not blind to the purpose of the study. When a family was invited to participate, they were informed that the investigators were interested in finding out whether children treated for cancer at a young age were at-risk for learning difficulties. Thus, parents' ratings may have reflected their desire to confirm the hypothesis, validate their own expectations, or cooperate with the investigators (Cozby, 1997). Parent ratings also appeared to differ depending upon parents' level of education. Since the ratings were based upon parents' individual experiences and perceptions, it is difficult to determine whether the results actually represented a lower incidence of problematic behaviors or if higher SES families perceived the behaviors as more manageable due to enhanced social support networks, parenting skills, or access to resources, for example. Another plausible explanation is that some parents were more apt to provide socially desirable responses which may have led to underestimates of behavior problems in certain groups.

In addition, a small to medium ES was found for math fluency, indicating that survivors did not perform as well as the normative population on this task. Again, the cancer survivors' mean scores on all measures are within the average range, normatively speaking, and it is unclear whether these scores are commensurate with their pre-morbid levels of performance.

Third, the cancer survivors were predicted to be more likely to receive special education services and to have repeated a grade in school than their siblings. In terms of special education services, the hypothesis was supported, since 50% of the survivors were receiving special education at the time of the study. Conversely, none of the healthy siblings were receiving special education, according to their parents. The risk difference, a measure of clinical significance, revealed that the survivors were much more likely to be in special education than siblings. Results from the complete survivor sample ($n$ = 18) were similar, as over half of the group reported receiving special education services at the time of the study. No statistically or clinically significant differences were found between cancer survivors and siblings in terms of having repeated a grade in school. However, whereas entry into special education is determined by law and relatively well-defined criteria (see Individuals with Disabilities Education Improvement Act of 2004 [IDEA], 2004), school districts generally define their own grade retention policies and practices. Thus, knowing whether a student has ever repeated a grade may not be a reliable way to assess whether that student has experienced academic difficulties.

The extent to which the differences in memory, math fluency, attention, and executive skills may have affected survivors' actual school performance, if at all, is difficult to judge. This is because, regrettably, only two brief academic achievement tests were administered and grades were not obtained from the child's school. However, the higher percentage of survivors receiving special education services at the time of the study implies

that they do experience more learning difficulties than their siblings. This finding is especially pertinent to the sample selected for this study, since all of the survivors were diagnosed before age 5 and their treatment ended before they began attending school or shortly thereafter. Therefore, the need for special education is unlikely to have arisen following an extended period of missed school or from impaired school functioning due to acute treatment-related side effects. In addition, race, SES, home environment, and school quality were controlled in the sibling pairs, which reduces the possibility that one or more of those factors was the source of the observed differences.

Intriguingly, the lower scores obtained on auditory memory, attention, and executive functions by this sample correspond to the same areas affected in survivors treated with CNS-directed chemotherapy and steroids, according to recent findings (Buizer et al., 2006; Kingma et al., 2001; Stuart et al., 2005). Although the differences were not statistically significant, the pattern of lower scores observed in the current sample also seems to fit with a model of primary and secondary deficits described by Mulhern and Palmer (2003b). In their model, primary deficits in attention, memory, and processing speed affect children's ability to attend to and process new information. Those difficulties then lead to secondary deficits in IQ and academic achievement. Indeed, in this sample, survivors received lower than expected scores and parent-ratings for auditory memory, attention, and overall executive skills, which encompass functions of attention, memory, regulation, and planning. Furthermore, survivors scored below the normative population mean on the math fluency subtest. This finding is relevant in the context of Mulhern and Palmer's model because it could be argued that the math fluency task was closer to a measure of processing speed than it was of math ability, since the problems were simple (single-digit) and the test was timed.

Finally, SES (parent education), age at diagnosis, treatment intensity, and time since diagnosis were examined to determine whether they were significant predictors of certain

neurocognitive and behavior measures in this group of childhood cancer survivors. Regression analyses were limited to only those measures that showed clinically significant differences between the cancer survivors and siblings, which included the BRIEF General Executive Composite, CPRS Cognitive Problems/Inattention, and the CVLT List A Trials 1 to 5. Results revealed that parent education was the only predictor that made a significant, unique contribution to parents' ratings of survivors' attention problems and executive functioning. The unstandardized regression coefficients show that when parent education is the only predictor ratings of cognitive and attention problems are approximately 17 points lower ($M$ = 50, $SD$ = 10) when one or both parents has completed a bachelor's degree or higher level of education (High SES). Similarly, when parent education is the only predictor ratings of problems with executive functioning are approximately 18 points lower ($M$ = 50, $SD$ = 10) when the family falls under the High SES category. This suggests that higher levels of parent education are associated with fewer parent-reported attention problems and executive skill deficits in this group of cancer survivors.

The results are consistent with studies showing that children from higher SES households tend to display lower rates of parent-reported behavior problems and higher levels of academic achievement and cognitive ability (Achenbach & Edelbrock, 1981; Dodge, Pettit, & Bates, 1994; McLoyd, 1998), although this does not explain the differences in parent-reported problems between the survivors and siblings. Studies of internalizing and externalizing symptoms in children with other chronic illnesses have found that parents report higher levels of symptoms in children with a chronic illness when compared to healthy controls (Lewis & Khaw, 1982) and that parent ratings are related to illness severity (Wamboldt, Fritz, Mansell, McQuaid, & Klein, 1998) and to characteristics of family functioning (Lewis & Khaw). Therefore, it is possible that parents' ratings in the current study were influenced by their child's cancer experience or by the severity of their illness,

resulting in differences between the pairs that are more pronounced than their actual behaviors might warrant.

In the area of auditory memory and learning, time since diagnosis was the only predictor that made a significant, unique contribution to performance on the CVLT List A Trials 1 to 5. The final regression model showed that survivors' norm-referenced, standardized scores on the auditory memory composite were .13 points lower ($M$ = 50, $SD$ = 10) for every month since diagnosis. In other words, when time since diagnosis is the only predictor, this model predicts that a survivor who was diagnosed 6 years ago would obtain an auditory memory composite score that is approximately 1 $SD$ (9.4 points) below that of a survivor diagnosed yesterday when compared to his or her same-age peers from the normative population.

To summarize, it appears that childhood cancer survivors treated at a young age with non-CNS-directed therapies may be at-risk for cognitive, academic, and behavioral difficulties following the end of their treatment. Although the survivors' mean scores in each of these areas remained within the average range, some of the differences between the groups were clinically significant, producing medium to large effect sizes. Results show that the survivors' scores on auditory memory and learning tasks were below expectations based upon the scores of their healthy siblings. Survivors also obtained lower scores on a math fluency task when compared to the normative population. Furthermore, this group of cancer survivors was rated as having more problems with attention and executive functioning, compared to both siblings and norms. Finally, the regression analyses suggested that parent education was the only significant predictor of parent-rated attention and executive functioning in cancer survivors. Time since diagnosis was the only significant predictor of survivors' scores on the auditory memory composite. However, the regression results must be interpreted with great caution due to the insufficient sample size and the tendencies of

stepwise procedures to overfit the model and capitalize on chance (Tabachnick & Fidell, 2001). Thus, though they may be useful in designing future studies, the results cannot be generalized beyond the current sample.

*Implications of the Current Study*

The findings from the current study add new information to what has been previously understood about late effects of childhood cancer on cognitive, academic, and behavioral functioning. The results are important for several reasons. First, this study points to the need for ongoing research to further investigate the presence of neurocognitive late effects in cancer survivors treated at a young age with non-CNS therapies.

*Implications for future research.* The present findings suggest that some non-CNS cancer survivors may experience late effects, though probably to a lesser degree than their CNS-treated counterparts. The question remains as to whether these underlying deficits will eventually lead to negative effects on standardized IQ and achievement scores. The high proportion of survivors receiving special education seems to suggest that some adverse effects on achievement are already evident. Larger scale studies will be required to obtain a sufficient number of participants and power to detect significant effects and group differences. Unfortunately, large-scale research projects are expensive and conducting research with children who are cancer survivors involves many challenges. For that reason, smaller-scale studies are essential to help justify, and determine the feasibility of, investing significant time and resources in multiple-institution studies. The need for future research with this population is clear, considering information from the existing literature and the results presented here. Moreover, the current study will assist future investigators in anticipating challenges and improving research design.

Tercyak et al. (2006) offer sound advice when it comes to planning and preparing for such an investigation. First, given that childhood cancer is rare, more than one recruitment

site is needed to obtain large numbers of participants (Tercyak et al.). Studies that recruit from single institutions generally suffer from small sample sizes and findings may be less generalizable (Mertens & Yasui, 2005). Second, intense recruitment and enrollment efforts are required to obtain valid, representative results. This process should include all available tracing methods to locate eligible participants with outdated contact information. Third, the study population must be defined in such a way that it is as representative as possible of the population of interest. Care must be exercised in selecting cases and controls to minimize the possibility of differential selection based on exposure. Strict criteria for inclusion and exclusion should be established to keep the disease and treatment methods well-defined. This will help to minimize the influence of confounding factors, such as pre-existing neurological disorders or brain injuries.

Mertens and Yasui (2005) emphasize the need to consider bias, confounding, and matching. Decisions about the use of specific control or comparison groups must be considered carefully. An important rule of thumb in selecting a comparison group is that it should represent a population with the potential to develop the disease or condition being studied (Robison et al. 2002). For example, siblings possess a similar risk of developmental disease, and share their genes and environment. However, since siblings can also experience adverse social, emotional, behavioral effects following a child's diagnosis of cancer, they may not be an optimal comparison group (Noll, Gerhardt, & Vannatta, 2003). Instead, Noll et al. suggest recruiting children without a chronic illness from the same community as the child with cancer. Another way to improve future studies would be to use a control group with a chronic illness other than cancer, who had spent similar amounts of time in the hospital and receiving treatment. Such a group provides a way to control for the effects of having a chronic illness in general. In order to draw more definitive conclusions about the role of specific cancer treatments, studies should also include a comparison group of cancer

survivors who did not receive chemotherapy or radiation. Realistically, obtaining a chemotherapy- and radiation-free control group may not be possible given that the vast majority of cancers are treated this way.

The goal for future research should be to conduct longitudinal studies with survivors of childhood cancer, since they permit the evaluation of changes in functioning over time. Furthermore, research designs must include a measure of pre-treatment functioning when at all possible. In an adult cancer study, 97% of the patients ($n$ = 29) reportedly evidenced some form of cognitive dysfunction *prior* to receiving cranial radiation (Komaki et al., 1995). This highlights the importance of obtaining a measure of baseline performance prior to the beginning of treatment.

Due to the sensitive nature of the research and the fact that children are the population of interest, additional challenges must be anticipated prior to initiating research with this group. One challenge is to make sure that participants understand the study and provide informed consent to participate. Investigators should be straightforward and honest with survivors and parents about the purpose and procedures of the study. If necessary, full explanations can be provided after data collection to prevent the influence of demand characteristics on the results. The importance of providing a thorough explanation about how results will be used and who will have access to them cannot be understated. Efforts should also be made to minimize the anxiety that survivors may experience upon returning to the hospital where they were treated and completing neurocognitive and academic testing.

*Prevention and intervention.* Second, this study also has implications for prevention and intervention efforts related to late effects in childhood cancer survivors. Evidence shows that many late effects can be minimized by prevention or early diagnosis and intervention (Oeffinger & Hudson, 2004). Three general prevention and intervention strategies that are recommended by Mulhern et al. (2004) include: (a) changing cancer treatment protocols, (b)

evaluating and monitoring neurocognitive functioning in at-risk children, and (c) treating and remediating neurocognitive and behavioral deficits. In this context, prevention usually refers to making changes in treatment protocols that reduce neurotoxicity (Oeffinger & Hudson). One of the main challenges in preventing negative CNS outcomes is to provide "alternative therapies that are less toxic but do not compromise cure" (Kadan-Lottick & Neglia, 2005, p. 43). According to Mulhern et al. (2004), such efforts are already being implemented with contemporary treatment protocols for CNS cancer which are now designed with consideration for the potential neurotoxicity of therapy. If findings from additional studies continue to suggest that non-CNS therapies have a degree of neurotoxicity, then similar consideration should be applied to treatment protocols for non-CNS cancer, as well. However, any attempts to limit treatment neurotoxicity clearly must not be at the expense of the effective treatment of the disease.

The study has implications for the evaluation and treatment of neurocognitive and academic deficits in childhood cancer survivors. Studies of cancer survivors with CNS-involvement have shown that neurocognitive deficits may appear gradually over time, or may not appear at all until months or years after the end of treatment (Mulhern & Palmer, 2003a; Palmer et al., 2001). Therefore, the risk for sustaining neurocognitive deficits does not end once treatment for cancer has ended. For that reason, cancer survivors should be evaluated immediately following the end of treatment -- or upon school re-entry -- and then monitored periodically for changes in neurocognitive functioning (Kadan-Lottick & Neglia, 2005; Peckham, 1991). Mulhern et al. (2004) recommend the development of a formal plan for evaluating and monitoring the neurocognitive status of each survivor which takes into account all known or suspected risk factors. Since changes may be subtle and early intervention is essential, neurocognitive evaluation plans should not be dependent on the presentation of symptoms (Kadan-Lottick & Neglia). This kind of evaluation and monitoring

program requires the expertise and supervision of a qualified psychologist. Psychologists conducting the neurocognitive evaluations should be aware of the physical impairments that may affect the standardized administration of tests. Physical problems can include hearing loss after treatment with certain chemotherapy drugs, blindness following retinoblastoma, and hemiplegia after a stroke. Whether the evaluation is conducted in a clinical setting or in the school, assessment results should be communicated directly to parents and teachers who can use the information to address the child's learning needs.

When the prevention of neurocognitive damage is not possible through changes to treatment protocols or when testing reveals the presence of neurocognitive or academic deficits, intervention may be the most appropriate alternative. Several different approaches have been suggested as ways to treat or remediate neurocognitive, academic, and behavioral problems following treatment for cancer. These approaches include cognitive remediation, pharmacotherapy, and environmental accommodations and modifications (Butler & Mulhern, 2005). According to Mulhern and Palmer (2003b), cognitive remediation or rehabilitation describes interventions designed "to restore lost cognitive functions or to teach skills to compensate for cognitive losses that cannot be restored" (p. 191). These interventions may involve repeated drill and practice (Butler & Mulhern) and cognitive behavior modification techniques like verbal self-instruction and utilization of problem-solving steps (Peckham, 1991). Pharmacotherapy involves the use of medication to treat neurocognitive or behavioral difficulties. Most of the pharmacologic recommendations pertain to the administration of psychostimulants, such as methylphenidate, to help improve symptoms of inattention and poor concentration (Mulhern & Palmer). In one study, cancer survivors with learning problems displayed significant improvements in their scores on a measure of sustained attention after treatment with methylphenidate, compared to those given a placebo (Thompson et al., 2001). Although they may improve attention in some cancer survivors,

existing evidence does not show that stimulants are effective in improving academic performance in cancer survivors (Butler & Mulhern). Finally, modifications and accommodations can be made within a students' environment to reduce the influence that neurocognitive deficits might have on their functional performance. Accommodations in the classroom may include preferential seating to minimize distractions, reducing the number of items on multiple choice tests, breaking assignments into several smaller steps, and allowing more time for the completion of exams (Butler & Mulhern).

*Teacher knowledge and preparation.* Finally, the study has implications for schools and the teachers who educate childhood cancer survivors. Many educators are not aware that childhood cancer survivors may experience long-term cognitive and learning difficulties as a result of their illness or treatment (Keene, 2003; Sexon & Madan-Swain, 1993). There are children with chronic conditions who do not show obvious signs of cognitive impairment, but who still fail to achieve at the level of their healthy peers (Sexon & Madan-Swain). This appears to be true in the current study, where although significant cognitive differences were not found, half of the cancer survivors were receiving special education services compared to none of the healthy siblings. As discussed earlier, other factors that can negatively affect academic performance include missed school, psychological stress, fears, parent attitudes and expectations, and side effects of the illness or treatment, such as fatigue, depression, difficulty concentrating, or physical limitations (Thompson & Gustafson, 1996). Therefore, it should not simply be assumed that children's functioning will return to normal following successful cancer treatment (Cruce & Stinnett, 2006). This study, and others like it, will help to inform educators about the potential learning difficulties and school performance problems that this group of childhood cancer survivors may experience, so that their needs can be appropriately addressed within the school setting.

Underscoring the need for more teacher education and training, a survey of teachers in New England revealed that school professionals perceived chronic health conditions to only have a modest impact in the classroom. The teachers perceived the greatest impact to be on themselves, requiring extra time and attention, and feeling personal liability or risk from potential medical issues during school hours. Teachers expressed the least amount of concern about children's academic limitations, and only one third thought that children with these conditions would have school difficulties and barriers to achievement (Olson et al., 2004). Positively, educators seem to recognize the need for information about health conditions and their impact on children's education. In a needs assessment conducted with over 300 teachers, 62% identified teacher knowledge and preparation regarding specific health conditions as the most important concern related to the education of children with chronic health conditions (Johnson, Lubker & Fowler, 1988).

Psychologists who work with children, especially in the school setting, play an important role in addressing the needs of these students and they can serve as valuable resources for teachers, as well (Phelps, 1998; Power, DuPaul, Shapiro & Kazak, 2003). The importance of providing psychosocial and educational support services for children with chronic health conditions has just begun to be addressed (Phelps). In addition, only recently have psychologists been recognized in the literature as an important resource for assisting during the child's return to school following cancer diagnosis and treatment (Cruce & Stinnett, 2006). Psychologists are able to provide comprehensive evaluations of neurocognitive and academic functioning, but they can also recommend intervention ideas and assist in determining whether a student might benefit from special education. Categories under IDEA (2004) that may be used to provide special education services to children with chronic health conditions include Other Health Impaired, Orthopedic Impairment, and Traumatic Brain Injury (Lee & Janik, 2006).

*Strengths of the study*

The current study was successful in avoiding some of the limitations found in previous studies and attempting to address some of the common methodological issues in childhood cancer research. The only other study known to have examined neurocognitive late effects in survivors of childhood cancer who were diagnosed and treated prior to age 5 without CNS-directed therapies (Mulhern et al., 1992a), was published 15 years ago. The current study improved upon Mulhern et al. by including a non-cancer comparison group composed of survivors' healthy siblings.

The research design was cross-sectional, meaning that data was collected for each participant on a single occasion. Matching was used to control for confounds such as home environment, genetic potential, SES, and school quality, by inviting the sibling closest in age to the survivor, with no history of malignancy, to participate. Attrition and withdrawal were not concerns because participants were only required to attend one appointment. The test battery was broad in scope, and assessed several domains of functioning in addition to IQ and achievement. Furthermore, all of the neurocognitive testing was conducted by a single data collector who was experienced with the instruments which maximized standardization and consistency in scoring and interpretation. Because the study was confined to a single institution, it was possible for one person to conduct all record reviews to identify eligible participants, record the treatment and demographic information, and administer and score all of the measures. Since recruitment and data collection procedures were virtually identical for all participants, the results are likely to be reliable than when multiple people and institutions are involved in these activities. However, because the same person managed recruitment and data collection, the experimenter was not blind to whether a participant was a cancer survivor or a sibling, meaning the potential effects of experimenter bias could not be fully controlled.

To minimize this source of bias in the current study, significant efforts were made to recruit all eligible survivors and their siblings by inviting those who moved away from the treatment facility and by using all available tracing methods to locate those survivors whose contact information was no longer current. Eligible participants with outdated contact information were traced through the use of telephone directories and internet search engines.

Attempts were made to control for potential confounds through study design and statistical analyses. First detailed inclusion and exclusion criteria were used to identify eligible participants. Survivors who experienced a CNS tumor (e.g., brain or nervous system) or who received any CNS-directed treatments were excluded from the sample. Participants with previously diagnosed attention or neurological problems were also excluded. As discussed earlier, the effects of missed school and cancer- or treatment-related side effects on school functioning were minimized by including only those survivors who were diagnosed and treated prior to school age. Furthermore, to ensure that performance was not influenced by the acute side-effects often associated with cancer and its treatment, all survivors were in remission and off treatment for a minimum of 2 years.

*Limitations of the study*

The most obvious limitation of the current study is its small sample size. Since this is a common limitation in childhood cancer research, seeking to understand the factors that may have contributed to the small sample is an essential task. Other limitations of the study include potential sources of bias, confounds, issues of statistical power and methods and design.

*Sample size.* Obtaining adequate participation can be a major challenge in childhood cancer research. Although the participation rate of 31% of eligible survivors in the current study is comparable to some other childhood cancer studies, enrollment was lower than expected. Several factors may have contributed to the enrollment of a less than desirable

number of participants in the current study. First, although childhood cancer is rare in the population, childhood cancer occurring outside of the CNS is even less common. There are still fewer survivors of non-CNS cancer who did not receive any CNS-directed treatment. As a result, the population from which to draw eligible participants is very small.

Second, due to their prior illness and medical history, even those who are eligible might not be willing to enroll in a cancer-related study. Cruce and Stinnett (2006) discuss the issues of anxiety, fear, and the avoidance of the topic of cancer in some survivors. They state that post-traumatic stress symptoms "may lead to reluctance of parents or survivors to participate in long-term studies due to avoidance" (p. 47). As a result, it is possible that survivors who had particularly long or difficult hospitalizations and treatment protocols might have been less interested in returning to the hospital where they were treated and more likely to decline. Findings from the current study seem to lend support to Cruce and Stinnett's assertions. For instance, some of the specific reasons that survivors or their parents gave for declining participation were that they did not want to be told they were "dumb," they did not want to be compared to a sibling, and parents felt the survivor "needed a break."

Third, the majority of survivors and siblings who declined the study indicated a lack of interest or time, or they simply reported no reason. Unfortunately, some of the siblings who were willing to participate were determined to be ineligible based upon their age or other exclusion criteria. In addition to those who declined, there were many survivors who could not be reached and were considered lost to follow-up.

Finally, participation may have been affected by factors related to the method of data collection. One limitation of using a comprehensive battery of neurocognitive tests involves the time and resources needed to administer the battery to every participant. In the current study, the entire appointment required approximately 3 hours per participant or 5 hours for siblings who were scheduled together. In the national Childhood Cancer Survivor Study

(Robison et al., 2002), the participation rate was 70%, but participants were only asked to complete a questionnaire and then return it by mail. The greater time commitment and less convenient method of data collection in the current study, combined with the fact that only one participant could be tested at a time, may have prevented the enrollment of a larger number of participants.

*Biases and confounds.* Clearly, the presence of bias in the obtained sample is a significant concern given the sensitive nature of the research question and the low rate of participation in the study. The primary issue is that those who participated may not truly represent the population in terms of demographic or disease characteristics (e.g., severity), or other risk factors for learning problems. There are several ways that bias might have influenced the results.

First, because participation was voluntary, the sample was susceptible to bias in terms of gender, age, SES, and other characteristics. For example, most participants made a separate trip to the hospital for their study appointment which was not part of a routine follow-up clinic visit. Therefore, some survivors might have been more motivated to participate, as opposed to studies where data collection is offered as part of a regularly scheduled follow-up appointment. Moreover, because appointments were scheduled during typical work hours, participants who had one parent at home during the day were more likely to enroll. If a parent was home because a second source of income was not needed to support the family, then the sample might have been biased in terms of including higher SES households. Unfortunately, SES information was not available for non-participants, so it was not possible to determine whether significant socio-economic differences existed between participants and non-participants.

In a survey of educational attainment conducted by the Department of Education, 49% of American adults reported holding a high school degree or less (U.S. Department of

Education, 2003). In the current study, only 25% (4/16) of the parents of survivor-sibling pairs report having earned a high school degree or less. In the larger group of survivor participants, 28% (5/18) of fathers and 39% (7/18) of mothers report having earned a high school degree or less. As a group, it appears that the parents of study participants tend to be more highly educated than the average adult. This increases the likelihood that the survivors and siblings come from higher SES households, and if that is true, their mean IQ and achievement scores would be expected to fall above the mean of the normative population. Indeed, in the matched pairs, the survivors' mean global IQ, reading, and working memory index scores fell slightly above the normative mean. Yet, the siblings' mean scores fell above the mean on all of the tests, with the exception of math fluency. The larger group of survivors performed slightly below the mean on all of the tests, except for global IQ where they, too, performed slightly above the normative population.

A second source of bias might have resulted from the fact that randomization of the treatment and control groups was not possible because the treatment group was pre-existing. Third, survivors who were followed by the clinic were more likely to have up-to-date contact information which facilitated recruitment. This may have biased the sample in favor of survivors with more significant or on-going medical complications (Mertens et al., 2004). In this study, it appeared that some survivors who reported more negative outcomes used that as a reason to decline participation, while survivors with more positive outcomes seemed more likely to participate because they were functioning quite well and did not feel uncomfortable or anxious about being tested or returning to the hospital. Conversely, some high-functioning survivors might have declined because they, or their parents, did not perceive learning problems as an area of concern, while parents who perceived their child as struggling in school might have been more apt to enroll, with the hopes of obtaining additional assistance. It seems reasonable to believe that similar factors also influenced decisions about

participation in the healthy siblings. These issues are extremely important, since non-participation can cause bias if response rates differ between survivors and controls, especially when participation is somehow related to treatment exposure. The factors that might have influenced participation in the study are complex and not yet well-understood.

The issues with sample size, bias, and confounds described above are not surprising, nor are they unique to the current study. Tercyak et al. (2006) have discussed the challenges of recruiting participants for these kinds of studies. First, given that childhood cancer is rare, more than one recruitment site is needed to obtain large numbers of participants. Second, intense recruitment and enrollment efforts are required to obtain valid, representative results. These efforts require a significant amount of time, personnel, and resources to accomplish. All of those things are difficult to obtain in single-institution research and in studies that are not externally funded.

In the current study, efforts were made to recruit all eligible survivors who met the inclusion criteria, including those who had moved away or had outdated contact information. Participants and non-participants were compared with respect to their demographic, illness, and treatment characteristics. The only difference found between participants and non-participants pertained to race, with non-White survivors being under-represented among the participants. Such differences are not unheard of, since other childhood cancer studies have also reported the disproportionate representation of non-White participants (Robison et al. 2002).

*Power.* Another limitation of the current study, low statistical power, was primarily a consequence of the small sample. Power is highly dependent upon sample size, but is also influenced by effect size and the chosen alpha level. The problem with low power is that it makes it difficult to determine whether the lack of statistically significant results is because the two groups truly do not differ or if there is insufficient power to detect the differences

that do exist. Power was also affected by the use of non-parametric tests, which were selected to avoid violations of the assumptions of more powerful, parametric tests.

*Method and design.* Other limits of the study pertain to the issues of comparison groups, research design, and measurement. First, the study lacked an illness comparison group to control for the effects of having a chronic illness other than cancer. In addition, the sample did not include any cancer survivors who were treated without chemotherapy or radiation, making it impossible to attribute any effects specifically to the treatment, as opposed to any other aspect of the cancer experience.

Second, the cross-sectional design only measured performance on a single occasion, at least 2 years post-treatment. Without a pre-treatment assessment, it cannot be determined whether the survivors' scores are consistent with pre-treatment levels of functioning, or if they represent a decrease over time. Third, because the sample of cancer survivors was small, it was not possible to assess differences within the treatment group based upon factors such as type of cancer, treatment intensity, gender, or age at diagnosis. Thus, all survivors were treated as a single group, even though it is possible that certain characteristics might put some survivors at greater levels of risk. Fourth, in an attempt to keep the comprehensive test battery as short as possible, a brief measure of IQ was used and some subtests were administered on their own, not as part of a complete scale. It should be noted that abbreviated IQ tests tend to have lower reliability and validity (Sattler, 2001), and may not be as sensitive to subtle neurocognitive deficits as more comprehensive measures (Butler & Copeland, 1993). In addition, administering selected subtests from a comprehensive measure deviates from standardization, and the scores obtained in that manner may not be as reliable and valid when compared to the normative data collected during the administration of the entire scale. However, the scores obtained in the study were not used to make individual decisions about participants' education, and all tests were administered in a standardized order and according

to the procedures outlined in their manuals. Consequently, the scores were considered adequate for research purposes.

Finally, as with any research that is based upon a small sample, the results should not be extended beyond the current population. Furthermore, since the data were collected in a clinical setting, it is not clear whether similar results would also be obtained within the school setting. Participants were tested in a quiet room, with individual attention from the examiner, and with the knowledge that they would receive a small incentive at the end of the session. Thus, their performance may have been closer to optimal than would be observed on a day-to-day basis during typical academic tasks. Finally, since all participants were of a White racial background, the results may not apply to those of other races.

In summary, significant attempts were made to overcome the limitations of previous studies and minimize the influence of biases and confounding factors on the results of the current study. Unfortunately, no definitive conclusions can be drawn about the influence, if any, of specific risk factors, such as treatment or demographic characteristics, on the measured outcomes. Furthermore, questions remain about the areas of functioning that are most vulnerable following non-CNS cancer treatment and about the nature and extent of differences between cancer survivors and children not treated for cancer. Given knowledge of the study's limitations, this research is best considered an exploratory or pilot endeavor, upon which future research may be based.

*Conclusions*

In conclusion, much remains unknown about whether, and to what extent, non-CNS cancer or its treatment may result in damage to the developing brain and nervous system. If such damage does occur, it may or may not result in observable deficits in cognitive, academic, and behavioral functioning. Preliminary findings taken from the current study indicate that the possibility exists for neurotoxicity and subsequent neurocognitive deficits in

some survivors following non-CNS-directed cancer treatment. Further research with larger samples is needed to test this hypothesis.

By increasing our understanding of the effects that cancer and its treatment may have on learning and behavior, we may be able to make more informed recommendations for individual survivors and improve their quality of life. The first step in this process is to determine which survivors are at risk (Eiser & Vance, 2002). This is best accomplished by increasing our knowledge and understanding of the potential risk factors and then evaluating and monitoring survivors who possess, or have been exposed to those factors. Finally, parents, teachers, and psychologists should be prepared to address the difficulties faced by cancer survivors who return to school following treatment, but they must also be made aware of the potential for late effects in survivors who have been off treatment for months or even years. By preparing for a student's anticipated needs, monitoring for changes, and intervening to decrease learning difficulties we have the potential to greatly enhance survivors' quality of life following successful cancer treatment.

References

Achenbach, T. M., & Edelbrock, C. S. (1981). Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. *Monographs of the Society for Research in Child Development, 46*, 1-82.

Ahles, T. A., & Saykin, A. J. (2002). Breast cancer chemotherapy-related cognitive dysfunction. *Clinical Breast Cancer Supplement, 3*, S84-S90.

American Cancer Society. (2006). *Cancer Facts and Figures 2006*. Atlanta, GA: Author.

Anderson, V., Smibert, E., Ekert, H., & Godber, T. (1994). Intellectual, educational, and behavioural sequelae after cranial irradiation and chemotherapy. *Archives of Disease in Childhood, 70*, 476-483.

Armstrong, F. D. (2003). Childhood cancer and education. In N. Keene (Ed.) *Educating the child with cancer: A guide for parents and teachers* (pp. 15-24). Candlelighters Childhood Cancer Foundation.

Armstrong F. D., & Reaman, G. H. (2005). Psychological research in childhood cancer: The Children's Oncology Group perspective. *Journal of Pediatric Psychology, 30,* 89-97.

Balis, F. M., & Poplack, D. G. (1989). Central nervous system pharmacology of antileukemic drugs. *Journal of Pediatric Hematology & Oncology, 11,* 74-86.

Baron, I. S. (2000). Test Review [Review of the Behavior Rating Inventory of Executive Function]. *Child Neuropsychology, 6*, 235-238.

Barton, D., & Loprinzi, C. (2002). Novel approaches to preventing chemotherapy-induced cognitive dysfunction in breast cancer: The art of the possible. *Clinical Breast Cancer Supplement, 3*, S121-S127.

Bender, B. G., Lerner, J. A., & Poland, J. E. (1991). Association between corticosteroids and psychologic change in hospitalized asthmatic children. *Annals of Allergy, 66,* 414-419.

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

Brown, R. T., Sawyer, M. B., Antoniou, G., Toogood, I., Rice, M., Thomson, N., et al. (1996). A 3-year follow-up of the intellectual and academic functioning of children receiving central nervous system prophylactic chemotherapy for leukemia. *Journal of Developmental & Behavioral Pediatrics, 17,* 392-398.

Buizer, A. I., de Sonneville, L. M. J., van den Heuvel-Eibrink, M. M., Njiokiktjien, C., & Veerman, A. J. P. (2005). Visuomotor control in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. *Journal of the International Neuropsychological Society, 11,* 554-565.

Buizer, A. I., de Sonneville, L. M. J., van den Heuvel-Eibrink, M. M., & Veerman, A. J. P. (2006). Behavioral and educational limitations after chemotherapy for childhood acute lymphoblastic leukemia or Wilms tumor. *Cancer, 106,* 2067-2075.

Butler, R. W., & Copeland, D. R. (1993). Neuropsychological effects of central nervous system prophylactic treatment in childhood leukemia: Methodological considerations. *Journal of Pediatric Psychology, 18,* 319-338.

Butler, R. W., Hill, J. M., Steinherz, P. G., Meyers, P. A., & Finlay, J. L. (1994). Neuropsychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. *Journal of Clinical Oncology, 12,* 2621-2629.

Butler, R. W., & Mulhern, R. K. (2005). Neurocognitive interventions for children and adolescents surviving cancer. *Journal of Pediatric Psychology, 30,* 65-78.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Erlbaum.

Cohen, S. E., & Parmelee, A. H. (1983). Prediction of five-year Stanford-Binet scores in preterm infants. *Child Development, 54*, 1242-1253.

Conners, C. K. (1997). *Conners' Rating Scales–Revised*. North Tonawanda, NY: Multi-Health Systems.

Copeland, D. R., Moore, B. D., III, Francis, D. J., Jaffe, N., & Culbert, S. J. (1996). Neuropsychologic effects of chemotherapy on children with cancer: A longitudinal study. *Journal of Clinical Oncology, 14*, 2826-2835.

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

Cozby, P. C. (1997). *Methods in behavioral research* (6th ed.). Mountain View, CA: Mayfield.

Cruce, M. K., & Stinnett, T. A. (2006). Children with cancer. In L. Phelps (Ed.), *Chronic health-related disorders in children: Collaborative medical and psychoeducational interventions* (pp. 41-55). Washington, DC: American Psychological Association.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1994). *California Verbal Learning Test–Children's Version*. San Antonio, TX: Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test–Second Edition.* San Antonio, TX: Psychological Corporation.

Dennis, M., Hetherington, C. R., & Spiegler, B. J. (1998). Memory and attention after childhood brain tumors. *Medical and Pediatric Oncology, 30 (S1),* 25-33.

Dodge, K. A., Pettit, G. S., & Bates, J. E. (1994). Socialization mediators of the relation between socioeconomic status and child conduct problems. *Child Development, 65,* 649-665.

Dowell, R. E., Copeland, D. R., Francis, D. J., Fletcher, J. M., & Stovall, M. (1991). Absence of synergistic effects of CNS treatments on neuropsychologic test performance among children. *Journal of Clinical Oncology, 9,* 1029-1036.

Drigan, R., Spirito, A., & Gelber, R. D. (1992). Behavioral effects of corticosteroids in children with acute lymphoblastic leukemia. *Medical and Pediatric Oncology, 20,* 13-21.

Duffner, P. K. (2004). Long-term neurologic consequences of CNS therapy. In W. H. B. Wallace & D. M. Green (Eds.), *Late effects of childhood cancer* (pp. 5-17). London: Arnold.

Eiser, C., & Vance, Y. H. (2002). Implications of cancer for school attendance and behavior. *Medical & Pediatric Oncology, 38,* 317-319.

Espy, K. A., Moore, I. M., Kaufmann, P. M., Kramer, J. H., Matthay, K., & Hutter, J. J. (2001). Chemotherapeutic CNS prophylaxis and neuropsychologic change in children with acute lymphoblastic leukemia: A prospective study. *Journal of Pediatric Psychology, 26,* 1-9.

Fowler, M. G., Johnson, M. P., & Atkinson, S. S. (1985). School achievement and absence in children with chronic health conditions. *Journal of Pediatrics, 106,* 683-687.

Friedman, D. L. (2003). Physical effects of treatment. In N. Keene (Ed.), *Educating the child with cancer: A guide for parents and teachers* (pp. 119-136). Candlelighters Childhood Cancer Foundation.

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

Gortmaker, S. L., Walker, D. K., Weitzman, M., & Sobol, A. M. (1990). Chronic conditions, socioeconomic risks, and behavioral problems in children and adolescents. *Pediatrics, 85*, 267-276.

Grill, J., Renaux, V. K., Bulteau, C., Viguier, D., Levy-Piebois, M., Sainte-Rose, C. et al. (1999). Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. *International Journal of Radiation Oncology, Biology, Physics, 45*, 137-145.

Grill, J., Kieffer, V., & Kalifa, C. (2004). Measuring the neuro-cognitive side-effects of irradiation in children with brain tumors. *Pediatric Blood & Cancer, 42*, 452-456.

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

Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191, 110 Stat. 1936 (1996).

Hedges, L., & Olkin, I. (1985). *Statistical methods for meta-analysis*. New York: Academic Press.

Howe, G. W., Feinstein, C., Reiss, D., Molock, S., & Berger, K. (1993). Adolescent adjustment to chronic physical disorders: I. Comparing neurological and non-neurological conditions. *Journal of Child Psychology and Psychiatry, 34*, 1153-1171.

Individuals with Disabilities Education Improvement Act of 2004, 20 U.S.C. 1400 et seq. (2004).

Iuvone, L., Mariotti, P., Colosimo, C., Guzzetta, F., Ruggiero, A., & Riccardi, R. (2002). Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. *Cancer, 95*, 2562-2570.

Jannoun, L., & Bloom, H. J. (1990). Long-term psychological effects in children treated for intracranial tumors. *International Journal of Radiation Oncology, Biology, and Physics, 18*, 747-753.

Johnson, M. P., Lubker, B. B., & Fowler, M. G. (1988). Teacher needs assessment for educational management of children with chronic illness. *Journal of School Health, 58*, 232-235.

Kadan-Lottick, N. S., & Neglia, J. P. (2005). Central nervous system effects. In C. L. Schwartz, W. L. Hobbie, L. S. Constine, & K. S. Ruccione (Eds.), *Survivors of childhood and adolescent cancer: A multidisciplinary approach* (2nd ed., pp. 35-50). Berlin, Germany: Springer.

Katz, E. R., Dolgin, M. J., & Varni, J. W. (1990). Cancer in children and adolescents. In A. M. Gross & R. S. Drabman (Eds.), *Handbook of clinical behavioral pediatrics* (pp. 129-146). New York: Plenum Press.

Kazak, A., & Rourke, M. T. (2003). Psychological late effects. In N. Keene (Ed.), *Educating the child with cancer: A guide for parents and teachers* (pp. 137-154). Candlelighters Childhood Cancer Foundation.

Keenan, P. A., Jacobson, M. W., Soleymani, R. M., Mayes, M. D., Stress, M. E., & Yaldoo, D. T. (1996). The effect on memory of chronic prednisone treatment in patients with systemic disease. *Neurology, 47*, 1396-1402.

Keene, N. (Ed.). (2003). *Educating the child with cancer: A guide for parents and teachers.* Candlelighters Childhood Cancer Foundation.

Khong, P., Leung, L. H. T., Fung, A. S. M., Fong, D. Y. T., Qui, D., Kwong, D. L. W., et al. (2006). White matter anisotrophy in post-treatment childhood cancer survivors: Preliminary evidence of association with neurocognitive function. *Journal of Clinical Oncology, 24*, 884-890.

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

Kingma, A., Van Dommelen, R. I., Mooyaart, E. L., Wilmink, J. T., Deelman, B. G., & Kamps, W. A. (2002). No major cognitive impairment in young children with Acute Lymphoblastic Leukemia using chemotherapy only: A prospective longitudinal study. *Journal of Pediatric Hematology/Oncology, 24*, 106-114.

Komaki, R., Meyers, C. A., Shin, D. M., Garden, A. S., Byrne, K., Nickens, J. A. et al. (1995). Evaluation of cognitive function in patients with limited small cell lung cancer prior to and shortly following prophylactic cranial irradiation. *International Journal of Radiation Oncology, Biology, and Physics, 33*, 179-182.

Kraemer, H. C., Morgan, G. A., Leech, N. L., Gliner, J. A., Vaske, J. J., & Harmon, R. J. (2003). Measures of clinical significance. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*, 1524-1529.

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

Lee, S. W., & Janik, M. (2006). Provision of psychoeducational services in the schools: IDEA, Section 504, and NCLB. In L. Phelps (Ed.), *Chronic health-related disorders in children: Collaborative medical and psychoeducational interventions* (pp. 25-39). Washington, DC: American Psychological Association.

Lenth, R. V. (2006). Java Applets for Power and Sample Size [Computer software]. Retrieved February 4, 2007, from http://www.stat.uiowa.edu/~rlenth/Power

Lewis, B. L., & Khaw, K. T. (1982). Family functioning as a mediating variable affecting psychosocial adjustment of children with cystic fibrosis. *Journal of Pediatrics, 101*, 636-640.

McLoyd, V. C. (1998). Socioeconomic disadvantage and child development. *American Psychologist, 53*, 185-204.

Mertens, A. C., Walls, R. S., Taylor, L., Mitby, P. A., Whitton, J., Inskip, P. D. et al. (2004). Characteristics of childhood cancer survivors predicted their successful tracing. *Journal of Clinical Epidemiology, 57*, 933-944.

Mertens, A. C., & Yasui, Y. (2005). Methodological issues in the study of survivors of childhood cancer. In C. L. Schwartz, W. L. Hobbie, L. S. Constine, & K. S. Ruccione (Eds.), *Survivors of childhood and adolescent cancer: A multidisciplinary approach* (2nd ed., pp. 321-331). Berlin, Germany: Springer.

Mirkes, P.E. (1985). Cyclophosphamide teratogenesis: A review. *Teratogenesis, Carcinogenesis, and Mutagenesis, 5*, 75-88.

Mitby, P. A., Robison, L. L., Whitton, J. A., Zevon, M. A., Gibbs, I. C., Tersak, J. M., et al. (2003). Utilization of special education services and educational attainment among long-term survivors of childhood cancer. *Cancer, 97*, 1115-1126.

Moore, B. D., III. (2005). Neurocognitive outcomes in survivors of childhood cancer. *Journal of Pediatric Psychology, 30*, 51-63.

Mulhern, R. K., Kovnar, E., Langston, J., Carter, M., Fairclough, D., Leigh, L., et al. (1992a). Long-term survivors of leukemia treated in infancy: Factors associated with neuropsychologic status. *Journal of Clinical Oncology, 10,* 1095-1102.

Mulhern, R. K., Ochs, J., & Fairclough, D. (1992b). Deterioration of intellect among children surviving leukemia: IQ test changes modify estimates of treatment toxicity. *Journal of Consulting and Clinical Psychology, 60,* 477-480.

Mulhern, R. K., & Palmer, S. L. (2003a). Cognitive late effects. In N. Keene (Ed.), *Educating the child with cancer: A guide for parents and teachers* (pp. 101-118). Candlelighters Childhood Cancer Foundation.

Mulhern, R. K., & Palmer, S. L. (2003b). Neurocognitive late effects in pediatric cancer. *Current Problems in Cancer, 27,* 177-197.

Mulhern, R. K., Phipps, S., & White, H. (2004). Neuropsychological outcomes. In W. H. B. Wallace & D. M. Green (Eds.), *Late effects of childhood cancer* (pp. 18-36). London: Arnold.

Mulhern, R. K., Reddick, W. E., Palmer, S. L., Glass, J. O., Elkin, T. D., Kin, L. E. et al. (1999). Neurocognitive deficits in medulloblastoma survivors and white matter loss. *Annals of Neurology, 46,* 834-841.

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

Nagel, B. J., Delis, D. C., Palmer, S. L., Reeves, C., Gajjar, A., & Mulhern, R. K. (2006). Early patterns of verbal memory impairment in children treated for medulloblastoma. *Neuropsychology, 20,* 105-112.

National Center for Education Statistics (2006). *Grade retention*. Retrieved June 2, 2007 from http://nces.ed.gov/programs/coe/2006/section3/table.asp?tableID=506

Neglia, J. P., Friedman, D. L., Yasui, Y., Mertens, A. C., Hammond, S., Stovall, M., et al. (2001). Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. *Journal of the National Cancer Institute, 93*, 618-629.

Newacheck, P. W., & Halfon, N. (1998). Prevalence and impact of disabling chronic conditions in childhood. *American Journal of Public Health, 88*, 610-617.

Noll, R. B., Gerhardt, C. A., & Vannatta, K. (2003). Neurocognitive functioning after cancer: Is that all there is to QOL? *Journal of Pediatric Hematology/Oncology, 25*, 5-7.

Ober, M., Beaverson, K., & Abramson, D. (2004). Ocular complications. In W. H. B. Wallace & D. M. Green (Eds.), *Late effects of childhood cancer* (pp. 38-48). London: Arnold.

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

Oeffinger, K. C., & Hudson, M. M. (2004). Long-term complications following childhood and adolescent cancer: Foundations for providing risk-based health care for survivors. *CA: A Cancer Journal for Clinicians, 54*, 208-236.

Okeda, R., Shibutani, M., Matsuo, T., Kuroiwa, T., Shimokawa, R. & Tajima, T. (1990). Experimental neurotoxicity of 5-fluorouracil and its derivatives is due to poisoning by the monoflourinated organic metabolites, monofluoroacetic acid and alpha-fluoro-beta-alanine. *Acta Neuropathologica, 81*, 66-73.

Olson, A. L., Seidler, A. B., Goodman, D., Gaelic, S., & Nordgren, R. (2004). School professionals' perceptions about the impact of chronic illness in the classroom. *Archives of Pediatrics & Adolescent Medicine*, 158, 53-58.

Palmer, S. L., Goloubeva, O., Reddick, W. E., Glass, J. O., Gajjar, A., Kun, L., et al. (2001). Patterns of intellectual development among survivors of pediatric medulloblastoma: A longitudinal analysis. *Journal of Clinical Oncology, 19*, 2302-2308.

Peckham, V. C. (1991). Educational deficits in survivors of childhood cancer. *Pediatrician, 18*, 25-31.

Perrin, E. C., Newacheck, P., Pless, I. B., Drotar, D., Gortmaker, S. L., Leventhal, J., et al. (1993). Issues involved in the definition and classification of chronic health conditions. *Pediatrics, 91*, 787-793.

Phelps, L. (1998). Health-related disorders in children and adolescents: A guidebook for understanding and educating. Washington, DC: American Psychological Association.

Phelps, L. (2006). Introduction. In L. Phelps (Ed.), *Chronic health-related disorders in children: Collaborative medical and psychoeducational interventions* (pp. 3-5). Washington, DC: American Psychological Association.

Phillips, K., & Bernhard, J. (2003). Adjuvant breast cancer treatment and cognitive function: Current knowledge and research directions. *Journal of the National Cancer Institute, 95*, 190-197.

Power, T. J., DuPaul, G. J., Shapiro, E. S., & Kazak, A. E. (2003). *Promoting children's health: Integrating school, family, and community*. New York: Guilford Press.

Power, T. J., DuPaul, G. J., Shapiro, E. S., & Parrish, J. M. (1995). Pediatric school psychology: The emergence of a subspecialty. *School Psychology Review, 24*, 244-257.

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

Raymond-Speden, E., Tripp, G., Lawrence, B., & Holdaway, D. (2000). Intellectual, neuropsychological, and academic functioning in long-term survivors of leukemia. *Journal of Pediatric Psychology, 25*, 59-68.

Reddick, W. E., White, H. A., Glass, J. O., Wheeler, G. C., Thompson, S. J., Gajjar, A., et al. (2003). Developmental model relating white matter volume to neurocognitive deficits in pediatric brain tumor survivors. *Cancer, 97*, 2512-2519.

Reimers, T. S., Ehrenfels, S., Mortensen, E. L., Schmiegelow, M., Sonderkaer, S., Carstensen, H. et al. (2003). Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Medical & Pediatric Oncology, 40*, 26-34.

Reschly, D. J. (1997). Diagnostic and treatment utility of intelligence tests. In D. P. Flanagan, J. L. Genshaft, & P. L. Harrison (Eds.), *Contemporary intellectual assessment: Theories, tests, and issues* (pp. 437-456). New York: Guilford Press.

Ries, L. A. G., Harkins, D., Krapcho, M., Mariotto, A., Miller, B. A., Feuer, E. J., et al. (Eds.). *SEER Cancer Statistics Review, 1975-2003*, National Cancer Institute. Bethesda, MD. Retrieved November 12, 2006, from http://seer.cancer.gov/csr/1975_2003/

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

Robinson, K. (1998). Implications of developmental plasticity for the language acquisition of deaf children with cochlear implants. *International Journal of Pediatric Otorhinolaryngology, 46,* 71-80.

Robison, L. L., Mertens, A. C., Boice, J. D., Breslow, N. E., Donaldson, S. S., Green, D. M. et al. (2002). Study design and cohort characteristics of the Childhood Cancer Survivor Study: A multi-institutional collaborative project. *Medical & Pediatric Oncology, 38,* 229-239.

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

Rodgers, J., Marckus, R., Kearns, P. & Windebank, K. (2003). Attentional ability among survivors of leukaemia treated without cranial irradiation. *Archives of Disease in Childhood, 88, 147-150.*

Roid, G., Prifitera, A., & Weiss, L. G. (1993). The WISC-III and the fairness of predicting achievement across ethnic and gender groups. *Journal of Psychoeducational Assessment* [Monograph Series: WISC-III Monograph], 6-21.

Rosenzweig, M. R., Leiman, A. L., & Breedlove, S. M. (1996). *Biological psychology*. Sunderland, MA: Sinauer Associates.

Said, J. A., Waters, B. G. H., Cousens, P., & Stevens, M. M. (1989). Neuropsychological sequelae of central nervous system prophylaxis in survivors of childhood Acute Lymphoblastic Leukemia. *Journal of Consulting and Clinical Psychology, 57,* 251-256.

Sapolsky, R. M. (1993). Potential behavioral modification of glucocorticoid damage to the hippocampus. *Behavioural Brain Research, 57*, 175-182.

Sattler, J. M. (2001). *Assessment of children: Cognitive applications* (2nd ed.). San Diego, CA: Jerome M. Sattler.

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

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

Schwartz, C. L., Hobbie, W. L., & Constine, L. S. (2005). Facilitating assessment of late effects by organ system. In C. L. Schwartz, W. L. Hobbie, L. S. Constine, & K. S. Ruccione (Eds.), *Survivors of childhood and adolescent cancer: A multidisciplinary approach* (2nd ed., pp. 17-34). Berlin, Germany: Springer.

Sexon, S. B., & Madan-Swain, A. (1993). School reentry for the child with chronic illness. *Journal of Learning Disabilities, 26*, 115-125.

Shearer, P. D. (2004). Hearing impairment. In W. H. B. Wallace & D. M. Green (Eds.), *Late effects of childhood cancer* (pp. 49-54). London: Arnold.

Silber, J. H., Radcliffe, J., Peckham, V. Perilongo, G., Kishnani, P., Fridman, M., et al. (1992). Whole-brain irradiation and decline in intelligence: The influence of dose and age on IQ score. *Journal of Clinical Oncology, 10*, 1390-1396.

Sood, C., & O'Brien, P. J. (1996). 2-Chloroacetaldehyde-induced cerebral glutathione depletion and neurotoxicity. *British Journal of Cancer Supplement, 27*, S287-S293.

Stevens, J. (1996). *Applied multivariate statistics for the social sciences* (3rd ed.). Mahwah, NJ: Lawrence Erlbaum Associates.

Stuart, F. A., Segal, T. Y., & Keady, S. (2005). Adverse psychological effects of corticosteroids in children and adolescents. *Archives of Disease in Childhood, 90,* 500-506.

Tabachnick, B. G., & Fidell, L. S. (2001). *Using multivariate statistics* (4th ed.). Boston: Allyn and Bacon.

Tarnowski, K. J., & Brown, R. T. (2000). Psychological aspects of pediatric disorders. In M. Hersen & R. T. Ammerman (Eds.), *Advanced abnormal child psychology* (pp. 131-152). Mahwah, NJ: Lawrence Erlbaum Associates.

Taylor, H. G., & Alden, J. (1997). Age-related differences in outcomes following childhood brain insults: An introduction and overview. *Journal of the International Neuropsychological Society, 3,* 555-567.

Tercyak, K. P., Donze, J. R., Prahlad, S., Mosher, R. B., & Shad, A. T. (2006). Identifying, recruiting, and enrolling adolescent survivors of childhood cancer into a randomized controlled trial of health promotion: Preliminary experiences in the Survivor Health and Resilience Education (SHARE) program. *Journal of Pediatric Psychology, 31,* 252-261.

Thies, K. M., & McAllister, J. W. (2001). The health and education leadership project: A school initiative for children and adolescents with chronic health conditions. *Journal of School Health, 71,* 167-172.

Thompson, R. J., Jr., & Gustafson, K. E. (1996). *Adaptation to chronic childhood illness*. Washington, DC: American Psychological Association.

Thompson, S. J., Leigh, L., Christensen, R., Xiong, X., Kun, L. E., Heideman, R. L. et al. (2001). Immediate neurocognitive effects of methylphenidate on learning-impaired survivors of childhood cancer. *Journal of Clinical Oncology, 19,* 1802-1808.

Thorne, B. M., & Slane, S. (1997). *Statistics for the behavioral sciences* (2nd ed.). Mountain View, CA: Mayfield.

Twaddle, V., Britton, P. G., Craft, A. C., Noble, T. C., & Kernahan, J. (1983). Intellectual function after treatment for leukemia or solid tumors. *Archives of Disease in Childhood, 58,* 949-952.

United States Department of Education (2003). *Digest of Education Statistics, (2002)*, NCES 2003-060. Washington, DC: National Center for Education Statistics, United States Department of Education.

von der Weid, N., Mosimann, I., Hirt, A., Wacker, P., Nenadov Beck, M., Imbach, P. et al. (2003). Intellectual outcome in children and adolescents with acute lymphoblastic leukemia treated with chemotherapy alone: age- and sex-related differences. *European Journal of Cancer, 39,* 359-365.

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

Waber, D. P., Shapiro, B. L., Carpentieri, S. C., Gelber, R. D., Zou, G., Dufresne, A., et al. (2001). Excellent therapeutic efficacy and minimal late neurotoxicity in children treated with 18 grays of cranial radiation therapy for high-risk acute lymphoblastic leukemia. *Cancer, 92,* 15-21.

Waber, D. P., Tarbell, N. J., Kahn, C. M., Gelber, R. D., & Sallan, S. E. (1992). The relationship of sex and treatment modality to neuropsychologic outcome in

childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology, 10*, 810-817.

Waber, D. P., Urion, D. K., Tarbell, N. J., Niemeyer, C., Gelber, R., & Sallan, S. E. (1990). Late effects of central nervous system treatment of acute lymphoblastic leukemia in childhood are sex-dependent. *Developmental Medicine and Child Neurology, 32,* 238-248.

Wamboldt, M. Z., Fritz, G., Mansell, A., McQuaid, E. L., & Klein, R. B. (1998). Relationship of asthma severity and psychological problems in children. *Journal of the American Academy of Child & Adolescent Psychiatry, 37*, 943-950.

Watkins, M. W. (2003). Effect size calculator [Computer software]. Pennsylvania State University: Author.

Webb, S. J., Monk, C. S., & Nelson, C. A. (2001). Mechanisms of postnatal neurobiological development: Implications for human development. *Developmental Neuropsychology, 19*, 147-171.

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

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children-Fourth Edition.* San Antonio, TX: Psychological Corporation.

Wissler, K. H., & Proukou, C. (1999). Navigating the educational system: A practical guide for nurse practitioners. *Journal of Pediatric Oncology Nursing, 16*, 145-155.

Wolkowitz, O. M. (1994). Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. *Psychoneuroendocrinology, 19*, 233-255.

Woodcock, R. W., McGrew, K. S., & Mather, N. (2001). *Woodcock-Johnson III Tests of Achievement*. Itasca, IL: Riverside.

Appendix A

*Intercorrelations between Neurocognitive and Behavioral Outcome Measures and Demographic Variables in Paired Survivors and Siblings*

| | Age at Testing | Father Educ. | Mother Educ. | IQ | Letter-Word ID | Math Fluency | GEC | CPRS Cog/ Inatten. | Coding | WMI | CVLT List A T1-T5 | CVLT LDFR | CVLT LDCR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age at Testing | **0.73*** | 0.13 | 0.11 | 0.41 | -0.07 | 0.39 | 0.47 | 0.03 | -0.08 | 0.20 | 0.03 | 0.41 | 0.04 |
| Father Education | 0.35 | **1.00**** | 0.93** | 0.58 | 0.00 | -0.35 | -0.10 | 0.44 | -0.47 | 0.61 | 0.32 | -0.04 | -0.09 |
| Mother Education | 0.21 | 0.91** | **1.00**** | 0.43 | -0.04 | -0.45 | 0.12 | 0.56 | -0.69 | 0.33 | 0.29 | -0.17 | -0.35 |
| WASI | | | | | | | | | | | | | |
| Full Scale IQ | -0.37 | 0.46 | 0.63 | **-0.11** | -0.35 | 0.13 | 0.16 | 0.17 | 0.08 | 0.46 | -0.18 | 0.56 | 0.14 |
| WJ-III:Ach | | | | | | | | | | | | | |
| Letter-Word ID | -0.11 | 0.22 | 0.25 | 0.78* | **0.76*** | 0.55 | -0.38 | -0.46 | 0.22 | 0.26 | 0.48 | 0.05 | 0.40 |
| Math Fluency | 0.28 | 0.12 | 0.08 | 0.41 | 0.71 | **0.83*** | -0.17 | -0.66 | 0.58 | 0.14 | -0.13 | 0.56 | 0.46 |
| BRIEF GEC | -0.67 | -0.60 | -0.54 | -0.50 | -0.65 | -0.75 | **0.15** | 0.80* | -0.18 | -0.76* | 0.28 | 0.44 | -0.08 |
| CPRS | | | | | | | | | | | | | |
| Cognitive Problems/ Inattention | -0.70 | -0.32 | -0.16 | -0.29 | -0.79* | -0.82* | 0.86* | **0.41** | -0.41 | -0.47 | 0.47 | 0.10 | -0.16 |
| WAIS-III/WISC-IV | | | | | | | | | | | | | |
| Coding | -0.46 | -0.62 | -0.52 | 0.22 | 0.55 | 0.25 | 0.06 | -0.28 | **0.24** | 0.02 | 0.04 | 0.47 | 0.59 |
| WMI | -0.13 | -0.31 | -0.17 | 0.44 | 0.57 | 0.47 | -0.32 | -0.44 | 0.58 | **-0.72** | 0.08 | 0.11 | 0.43 |
| CVLT | | | | | | | | | | | | | |
| List A Trials 1-5 | -0.52 | -0.29 | -0.12 | 0.24 | 0.11 | 0.14 | -0.18 | 0.07 | 0.44 | 0.24 | **-0.63** | 0.08 | 0.32 |
| LDFR | -0.28 | -0.16 | -0.03 | 0.35 | 0.19 | 0.27 | -0.04 | 0.02 | 0.16 | 0.69 | 0.33 | **-0.76*** | 0.70 |
| LDCR | -0.24 | -0.08 | -0.12 | 0.26 | 0.24 | 0.44 | -0.15 | -0.17 | 0.13 | 0.38 | 0.41 | 0.86* | **-0.61** |

*Note*. Shaded cells contain survivors' intercorrelations ($n$ = 8). Unshaded cells contain siblings' intercorrelations ($n$ = 8). Cells on the diagonal (bold) contain the correlations between survivors and siblings. Table contains Spearman Rank Order correlations ($r_s$) of neurocognitive test scores and demographic variables in paired survivors and siblings. WASI = Wechsler Abbreviated Scale of Intelligence, WJ-III:Ach = Woodcock Johnson: Tests of Achievement–Third Edition, BRIEF = Behavior Rating Inventory of Executive Function, GEC = General Executive Composite, CPRS = Conners' Parent Rating Scale-Revised, WAIS-III = Wechsler Adult Intelligence Scale–Third Edition, WISC-IV = Wechsler Intelligence Scale for Children–Fourth Edition, WMI = Working Memory Index, CVLT-C = California Verbal Learning Test for Children, CVLT-II = California Verbal Learning Test-Second Edition, LDFR = long delay free recall, LDCR = long delay cued recall.
*$p$ < .05, **$p$ < .01

Appendix B

*Effect Sizes Associated with Differences between Survivors, Siblings, and the Normative Population*

| | Survivors and siblings | | | Survivors and normative population | | |
|---|---|---|---|---|---|---|
| Measure | *d* | Interpretation | *n* | *d* | Interpretation | *n* |
| WASI Full Scale IQ | -.14 | small | 8 | .27 | small | 17 |
| WJ-III | | | | | | |
| Letter-Word Identification | -.17 | small | 8 | -.07 | small | 18 |
| Math Fluency | -.19 | small | 8 | -.41 | small-medium | 18 |
| BRIEF General Executive | | | | | | |
| Composite | 1.21 | large | 6 | .59 | medium | 16 |
| CPRS Cognitive | | | | | | |
| Problems/Inattention | .98 | large | 6 | .56 | medium | 16 |
| WAIS-III/WISC-IV | | | | | | |
| Coding | -.15 | small | 8 | -.02 | small | 18 |
| Working Memory Index | -.03 | small | 7 | -.09 | small | 17 |
| CVLT-C/CVLT-II | | | | | | |
| List A Trials 1-5 | -1.14 | large | 8 | -.30 | small | 18 |
| Long Delay Free Recall | -.69 | medium | 8 | .03 | small | 18 |
| Long Delay Cued Recall | -.51 | medium | 8 | -.06 | small | 18 |

*Note*. Effect Size interpretation from Cohen (1988). A negative *d* value indicates that the survivors received lower scores on the outcome measure than the comparison group.

Appendix C

*Demographic, Illness, and Neurocognitive Test Data of All Survivor and Sibling Participants*

| ID | STATUS | STDMOS | TIMESTDX | GENDER | RACE | GRADE | REPEAT | SPED | LANG | EDUCFA | EDUCMO | AGEMOS | DIAGNOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 1 | 73 | 58 | 2 | 4 | 1 | 2 | 1 | 1 | 7 | 7 | 15 | 1 |
| 56 | 1 | 98 | 93 | 2 | 4 | 3 | 2 | 1 | 1 | 4 | 4 | 5 | 2 |
| 61 | 1 | 94 | 76 | 1 | 4 | 2 | 2 | 2 | 1 | 4 | 7 | 18 | 4 |
| 5 | 1 | 120 | 120 | 2 | 4 | 4 | 2 | 2 | 1 | 6 | 3 | 0 | 6 |
| 53 | 1 | 132 | 103 | 2 | 4 | 5 | 2 | 2 | 1 | 3 | 5 | 29 | 3 |
| 28 | 1 | 143 | 123 | 2 | 4 | 6 | 2 | 1 | 1 | 4 | 5 | 20 | 3 |
| 51 | 1 | 133 | 130 | 2 | 4 | 5 | 1 | 1 | 1 | 3 | 3 | 3 | 1 |
| 58 | 1 | 153 | 151 | 1 | 4 | 7 | 2 | 2 | 1 | 5 | 4 | 2 | 1 |
| 9 | 1 | 162 | 150 | 2 | 4 | 8 | 2 | 1 | 1 | 3 | 3 | 12 | 1 |
| 48 | 1 | 156 | 103 | 1 | 4 | 7 | 2 | 2 | 1 | 6 | 6 | 53 | 3 |
| 40 | 1 | 172 | 138 | 2 | 4 | 9 | 2 | 1 | 1 | 4 | 3 | 34 | 3 |
| 13 | 1 | 184 | 177 | 2 | 4 | 10 | 2 | 1 | 1 | 3 | 5 | 7 | 1 |
| 11 | 1 | 179 | 159 | 1 | 4 | 9 | 2 | 2 | 1 | 2 | 2 | 20 | 3 |
| 26 | 1 | 188 | 174 | 1 | 4 | 10 | 2 | 2 | 1 | 8 | 7 | 14 | 1 |
| 30 | 1 | 198 | 189 | 2 | 4 | 18 | 2 | 2 | 1 | 7 | 6 | 9 | 1 |
| 12 | 1 | 208 | 199 | 1 | 4 | 11 | 1 | 1 | 1 | 4 | 3 | 9 | 3 |
| 17 | 1 | 226 | 224 | 1 | 4 | 17 | 2 | 1 | 1 | 6 | 5 | 2 | 3 |
| 8 | 1 | 229 | 203 | 1 | 4 | 18 | 1 | 1 | 1 | 4 | 3 | 26 | 4 |
| 158 | 2 | 83 | 888 | 2 | 4 | 1 | 2 | 2 | 1 | 5 | 4 | 888 | 888 |
| 156 | 2 | 98 | 888 | 2 | 4 | 3 | 2 | 2 | 1 | 4 | 4 | 888 | 888 |
| 128 | 2 | 143 | 888 | 1 | 4 | 6 | 2 | 2 | 1 | 4 | 5 | 888 | 888 |
| 148 | 2 | 138 | 888 | 2 | 4 | 6 | 2 | 2 | 1 | 6 | 6 | 888 | 888 |
| 117 | 2 | 173 | 888 | 2 | 4 | 9 | 2 | 2 | 1 | 6 | 5 | 888 | 888 |
| 109 | 2 | 196 | 888 | 2 | 4 | 11 | 2 | 2 | 1 | 3 | 3 | 888 | 888 |
| 111 | 2 | 196 | 888 | 1 | 4 | 11 | 2 | 2 | 1 | 2 | 2 | 888 | 888 |
| 126 | 2 | 234 | 888 | 1 | 4 | 14 | 2 | 2 | 1 | 8 | 7 | 888 | 888 |

(Table continues)

(Table continued)

| ID | DIAGNOS | CHEMO | VCR | CTX | ADR | CDDP | VP16 | IFOS | 5-FU | CARBO | DACTIN | OTHER | NumbDrug | RADIAT | RADDOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 8 | 2 | 888 |
| 56 | 2 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 4 | 2 | 888 |
| 61 | 4 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 5220 |
| 5 | 6 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 3 | 2 | 888 |
| 53 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 2 | 888 |
| 28 | 3 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 1080 |
| 51 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 888 |
| 58 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 888 |
| 9 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 5 | 1 | 2400 |
| 48 | 3 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 1200 |
| 40 | 3 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 1080 |
| 13 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 888 |
| 11 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 2 | 888 |
| 26 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 4 | 1 | 2400 |
| 30 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 888 |
| 12 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 2 | 888 |
| 17 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 2 | 888 |
| 8 | 4 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 2 | 888 |
| 158 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 |
| 156 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 |
| 128 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 |
| 148 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 |
| 117 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 |
| 109 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 |
| 111 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 |
| 126 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 | 888 |

(Table continues)

(Table continued)

| ID | HEADINJ | CPRSCOG | GEC | FSIQ | DSTOT | LNS | COD | WMI | CVLT1-5 | LDFREE | LDCUED | LWID | MATHFL | SIBENR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 2 | 49 | 60 | 118 | 13 | 13 | 13 | 116 | 60 | 1.5 | 2.0 | 131 | 114 | 2 |
| 56 | 2 | 60 | 66 | 118 | 11 | 12 | 12 | 107 | 50 | -0.5 | -0.5 | 107 | 89 | 1 |
| 61 | 2 | 43 | 38 | 999 | 9 | 8 | 11 | 91 | 52 | 0.5 | 1.0 | 71 | 90 | 2 |
| 5 | 2 | 46 | 44 | 120 | 10 | 12 | 12 | 104 | 48 | -1.0 | -1.5 | 102 | 103 | 2 |
| 53 | 2 | 44 | 42 | 100 | 9 | 1 | 6 | 71 | 39 | -0.5 | -1.0 | 102 | 85 | 2 |
| 28 | 2 | 90 | 64 | 116 | 10 | 999 | 10 | 999 | 61 | 0.5 | 0.0 | 95 | 83 | 1 |
| 51 | 2 | 77 | 83 | 83 | 7 | 9 | 3 | 88 | 40 | -1.5 | -1.5 | 90 | 74 | 2 |
| 58 | 2 | 50 | 53 | 99 | 9 | 10 | 10 | 97 | 53 | 0.5 | 1.0 | 100 | 104 | 1 |
| 9 | 2 | 71 | 72 | 96 | 13 | 11 | 10 | 110 | 40 | 1.0 | 0.5 | 99 | 93 | 1 |
| 48 | 2 | 41 | 36 | 128 | 15 | 13 | 11 | 123 | 51 | 1.0 | 0.5 | 125 | 108 | 1 |
| 40 | 2 | 51 | 71 | 95 | 7 | 9 | 10 | 88 | 58 | 1.0 | 0.5 | 90 | 94 | 2 |
| 13 | 2 | 54 | 57 | 100 | 11 | 15 | 11 | 116 | 58 | 1.0 | 0.5 | 99 | 103 | 2 |
| 11 | 2 | 42 | 50 | 94 | 13 | 11 | 12 | 110 | 52 | 0.0 | 0.0 | 104 | 109 | 1 |
| 26 | 2 | 46 | 48 | 121 | 12 | 11 | 9 | 107 | 49 | 0.0 | 0.0 | 107 | 121 | 1 |
| 30 | 2 | 46 | 40 | 124 | 10 | 12 | 14 | 104 | 52 | 1.0 | 1.0 | 110 | 101 | 2 |
| 12 | 2 | 84 | 74 | 100 | 9 | 7 | 9 | 88 | 21 | -1.5 | -1.5 | 94 | 76 | 2 |
| 17 | 2 | 888 | 888 | 73 | 6 | 6 | 6 | 75 | 21 | -2.0 | -1.5 | 74 | 68 | 1 |
| 8 | 2 | 888 | 888 | 84 | 6 | 8 | 10 | 82 | 41 | -0.5 | -0.5 | 81 | 74 | 2 |
| 158 | 999 | 43 | 35 | 116 | 11 | 13 | 11 | 110 | 54 | 0.5 | 0.5 | 96 | 95 | 1 |
| 156 | 999 | 44 | 40 | 90 | 9 | 12 | 10 | 102 | 60 | 0.5 | 1.0 | 118 | 101 | 1 |
| 128 | 999 | 51 | 55 | 105 | 11 | 1 | 9 | 77 | 56 | 0.5 | -0.5 | 90 | 87 | 1 |
| 148 | 999 | 44 | 40 | 105 | 9 | 11 | 10 | 99 | 59 | 0.0 | -0.5 | 112 | 101 | 1 |
| 117 | 999 | 51 | 51 | 113 | 10 | 12 | 11 | 104 | 63 | 1.0 | 1.0 | 102 | 93 | 1 |
| 109 | 999 | 43 | 41 | 96 | 13 | 8 | 10 | 102 | 56 | 0.0 | 0.0 | 99 | 97 | 1 |
| 111 | 999 | 42 | 47 | 112 | 7 | 11 | 12 | 94 | 56 | 1.5 | 1.0 | 108 | 122 | 1 |
| 126 | 999 | 888 | 888 | 126 | 13 | 14 | 9 | 121 | 57 | 1.0 | 0.5 | 103 | 102 | 1 |

*Note*. 999=missing data. 888=not applicable.

Appendix D

*Codes for Demographic, Illness, and Neurocognitive Test Data of All Survivor and Sibling Participants*

| Variable | Name | Response or score | Code |
|---|---|---|---|
| Group | STATUS | Survivor | 1 |
| | | Sibling | 2 |
| Age at testing | STDMOS | Age in months at time of study | |
| Time since diagnosis | TIMESTDX | Months between cancer diagnosis and study | |
| Sex | GENDER | Male | 1 |
| | | Female | 2 |
| Race | RACE | American Indian/Alaska Native | 1 |
| | | Asian/Pacific Islander | 2 |
| | | Black, non Hispanic | 3 |
| | | White, non Hispanic | 4 |
| | | Hispanic | 5 |
| | | Other or unknown | 9 |
| Grade in 2005-2006 | GRADE | Kindergarten | 0 |
| | | 1st through 12th | 1-12 |
| | | 1st year college | 13 |
| | | 2nd year college | 14 |
| | | 3rd year college | 15 |
| | | 4th year college | 16 |
| | | Post-high school transition/BOCES | 17 |
| | | Not enrolled in school/college | 18 |
| Repeated a grade | REPEAT | Yes | 1 |
| | | No | 2 |
| Current special education services | SPED | Yes | 1 |
| | | No | 2 |
| Language | LANG | English | 1 |
| | | Spanish | 2 |
| | | Other | 3 |
| Educational attainment | | | |
| Father | EDUCFA | 8th grade or below | 1 |
| | | 9th-12th grade | 2 |
| | | H.S. Diploma/GED | 3 |
| | | Some college (<1-4 yrs) | 4 |
| | | Associate's degree | 5 |
| | | Bachelor's degree | 6 |
| | | Master's degree | 7 |
| | | Doctoral degree | 8 |
| | | Post-doctoral study | 9 |
| Mother | EDUCMO | 8th grade or below | 1 |
| | | 9th-12th grade | 2 |
| | | H.S. Diploma/GED | 3 |
| | | Some college (<1-4 yrs) | 4 |
| | | Associate's degree | 5 |
| | | Bachelor's degree | 6 |
| | | Master's degree | 7 |
| | | Doctoral degree | 8 |
| | | Post-doctoral study | 9 |

(Table continues)

(Table continued)

| Variable | Name | Response or score | Code |
|---|---|---|---|
| Age at diagnosis | AGEMOS | Age in months | |
| Type of cancer | DIAGNOS | Neuroblastoma (no bone marrow transplant) | 1 |
| | | Hepatoblastoma | 2 |
| | | Wilms tumor | 3 |
| | | Rhabdomyosarcoma (non-head/neck) | 4 |
| | | Germ cell tumor | 5 |
| | | Retinoblastoma | 6 |
| | | Other | 9 |
| Chemotherapy | CHEMO | Yes | 1 |
| | | No | 2 |
| Chemotherapy drug | VCR | VCR, Vincristine | 1 |
| | CTX | CTX | 3 |
| | ADR | ADR, Doxorubicin, Adriamycin | 4 |
| | CDDP | CDDP, Cisplatin | 5 |
| | VP16 | VP16, Etoposide | 6 |
| | IFOS | IFOS, Ifosfamide | 8 |
| | 5-FU | 5-FU, Fluorouracil | 9 |
| | CARBO | Carboplatin | 10 |
| | DACTIN | AMD, Dactinomycin | 11 |
| | OTHER | Other | 12 |
| Number of unique drugs | NumbDrug | | 2-8 |
| Radiation therapy | RADIAT | Yes | 1 |
| | | No | 2 |
| Cumulative radiation dose | RADDOS | cGy (centiGrays) | |
| History of head injury | HEADINJ | Yes | 1 |
| | | No | 2 |
| CPRS:L-PRS | | | |
| Cognitive Problems/Inattention | CPRSCOG | | 20-80 |
| BRIEF | | | |
| General Executive Control | GEC | | 20-80 |
| WASI | | | |
| Full Scale IQ | FSIQ | | 40-160 |
| WISC-IV/WAIS-III | | | |
| Digit Span Total | DSTOT | | 0-19 |
| Letter-Number Sequencing | LNS | | 0-19 |
| Coding | COD | | 0-19 |
| Working Memory Index | WMI | | 50-150 |
| CVLT-C/CVLT-II | | | |
| List A Trials 1-5 | CVLT1-5 | | 20-80 |
| Long-delay free recall | LDFREE | | -3.0-3.0 |
| Long-delay cued recall | LDCUED | | -3.0-3.0 |
| WJ-III:ACH | | | |
| Letter-Word Identification | LWID | | 40-160 |
| Math Fluency | MATHFL | | 40-160 |
| Sibling enrolled in study | SIBENR | | |
| | | Yes | 1 |
| | | No, declined | 2 |
| Other codes | | Missing data | 999 |
| | | Not applicable | 888 |

# Curriculum Vita

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|---|---|---|
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| B.A. (Psychology) | 1995-1999 | State University of New York at Geneseo |

**Professional Experience**

| | |
|---|---|
| August 2007 - Present | **School Psychologist**, *Bucks County Intermediate Unit #22*, Doylestown, PA. Full-time School Psychologist for the Multiple Disabilities and Autistic Support programs. |
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| February 2006 - June 2006 | **School Psychological Services Contractor**, *Bellefonte Area School District, PA*. |
| August 2005 - February 2006 | **Behavioral Specialist Consultant and Mobile Therapist**, *Northwestern Human Services of Centre County*, State College, PA. |

**Professional Memberships**

Pi Lambda Theta, International Honor Society and Professional Association in Education
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**Honors and Awards**

| | |
|---|---|
| 2005 | *The 2005 National Register New Millennium Fund Trainee Register Award* |
| 2004-2005 | *The Leopold Schepp Foundation Scholarship* |
| 2003-2004 | *Miriam E. Gray Scholarship for Outstanding Graduate Students,* Pennsylvania State University, Department of Education |

**Publications**

**FitzGerald, J. L.**, & Watkins, M. W. (2006). Parents' rights in special education: The readability of procedural safeguards. *Exceptional Children, 72*, 497-510.

Neisworth, J. T., & Wolfe, P. S. (Eds.). (2005). *The Autism Encyclopedia*. Baltimore: Paul H. Brookes

Watkins, M. W., Kuterbach, J. M., Morgan, R. J., **FitzGerald, J. L.**, Neuhard, R. M., Arthur, A. G., & Bucknavage, L. B. (2004). Structural validity of the WAIS-III among postsecondary students. *Journal of Postsecondary Education and Disability, 17*, 105-113.

Arthur, A.G., **FitzGerald, J. L.,** Kuterbach, J. M., Morgan, R. J., & Worrell, F. C. (2004). Examining the reliability and validity of school climate measures in a sample of Pennsylvania middle school students. *Pennsylvania Education Leadership*, *23 (2)*, 42-49.