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The Functional Impact of Neurocognitive Deficits in Pediatric Cancer Survivors and Associated Risk Factors

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**THE FUNCTIONAL IMPACT OF NEUROCOGNITIVE DEFICITS IN PEDIATRIC
CANCER SURVIVORS AND ASSOCIATED RISK FACTORS**

By

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DISSERTATION

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ABSTRACT

Childhood cancer survivors are at risk for long-term neurocognitive morbidities. Current research has only recently begun to examine how these neurocognitive late effects translate into impairments across important aspects of daily living. Additionally, research remains in its early stages of identifying risk factors associated with neurocognitive and broad functional impairments. The current study explores a proposed model of neurocognitive late effects by examining the relationship between neurocognitive deficits and broad functional impairment in cancer survivors relative to healthy controls. The current study also explores the contribution of associated risk factors including treatment severity and time since treatment among cancer survivors and long-term stress reactivity among both cancer survivors and healthy controls. Cancer survivors and healthy controls were between the ages of five and eighteen years. Hair samples were collected from the children to assess cortisol, a measure of long-term stress reactivity. Parents completed a functional impairment questionnaire while a brief neurocognitive exam was administered to the children. Results found no differences in neurocognitive performance or levels of functional impairment in

cancer survivors relative to healthy controls; however, verbal reasoning was found to be a more robust predictor of functional impairment (FI) in cancer survivors in comparison to healthy controls. Importantly, and calling into question the validity of FI measurement in children, approximately half of both cancer survivors and health controls reported clinically significant levels of FI. This was in excess of that reported by parents. Additionally, cortisol levels were found to differentially predict neurocognitive performance in cancer survivors relative to healthy controls. Taken together, these findings suggest that verbal reasoning predicts functional impairment, but only in cancer survivors. Additional risk factors require more exploration in future research.

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Introduction

Cancer represents one of the leading causes of death in children, accounting for eight percent of childhood mortalities (Institute of Medicine, 2003). Although cancer mortality rates continue to be a major concern, significant improvements in survival rates have been demonstrated over time. In the past 23 years alone, mortality rates for pediatric cancer have decreased by 50 percent and current 5-year survival rates have been estimated to be between 70 and 80 percent (Institute of Medicine, 2003).

The remarkable progress in survival rates can be attributed to the considerable advancements in treatment strategies, which include chemotherapy, radiation, and surgery. These treatment advances have resulted in a growing population of pediatric cancer “survivors.” The concept of “survivor” first emerged in the 1970s and was used to describe any individual with cancer alive at any point from the diagnosis forward (Meadows, 2003; Institute of Medicine, 2003). Due to modern therapeutic approaches, more and more children are surviving into adulthood and are receiving the status of long-term survivor (e.g., 5 years post-treatment). While aggressive treatments have helped contribute to this growing population of survivors, these treatments also come with a cost, as survivors are at risk for additional long-term morbidities (Dickerman, 2007; Patenaude & Kupst, 2005). These morbidities are referred to as late effects and are more formally defined as any adverse outcome related to the disease process, treatment, or both, occurring more than six months after the completion of treatment (Meadows, 2003; Pentheroudakis & Pavlidis, 2007).

Late effects represent a significant concern for pediatric cancer survivors, as two-thirds of survivors are likely to experience at least one late effect, while one-fourth of survivors are likely to experience late effects that are severe and even life threatening

(Institute of Medicine, 2003). These late effects can manifest as physical impairments (Oeffinger et al., 2006) or psychological impairments. Psychological late effects have been separated into two distinct domains including psychosocial (Patenaude & Kupst, 2005) and neurocognitive (Moore, 2005) late effects. In regards to physical late effects, there is a large degree of variability, as they can range from minor to severe (Meadows 2003). These late effects can influence growth and development, fertility and reproduction, as well as vital organ functioning such as cardiac, pulmonary, renal, endocrine, and gastrointestinal function (Meadows, 2003).

Psychosocial late effects have been well documented in pediatric cancer survivors. While these late effects are highly variable, common manifestations include behavior problems, decreased social competence, and engagement in peer activities, depression, anxiety, and post-traumatic stress symptoms (Schultz et al., 2007; Stam, Grootenhuis, & Last, 2001). Neurocognitive late effects have also been found to be highly variable, with impairments across a broad range of areas. These include attention, executive functioning, memory, information processing speed, visual-spatial skills, and general intellectual functioning (Moore, 2005; Moore, Ater, & Copeland, 1992; Mulhern, Wasserman, Fairclough, & Ochs, 1988).

Neurocognitive Deficits Among Pediatric Cancer Survivors

Neurocognitive impairment is one of the foremost psychological late effects experienced by pediatric cancer survivors and it has been estimated to impact as many as sixty percent of survivors (Nathan et al., 2007). The manifestation of these deficits, similar to other late effects, is somewhat variable. Previous research has documented impairments across the domains of attention, executive functioning, processing speed, working memory,

visuospatial skills, and fine motor skills (Askins & Moore, 2008; Nathan et al., 2007).

Declines in general intellectual functioning, as well as academic achievement, have also been documented (Campbell et al., 2007; Montour-Proulx et al., 2005).

Despite this heterogeneous presentation of cognitive impairment, research has consistently identified executive functioning and global intellectual functioning, as two domains that are particularly vulnerable to impairment (Campbell et al., 2007; Ellenberg et al., 2009; Montour-Proulx et al., 2005; Mulhern, Fairclough, & Ochs, 1991; Nathan et al., 2007;)

Intellectual functioning. Previous research suggests that pediatric cancer survivors are vulnerable to impairments in general intellectual functioning. Reddick and colleagues (2003) found evidence of intellectual impairments in survivors of brain tumors. A recent meta-analysis (Robinson et al., 2010) reported similar findings. A study conducted by Brinkman and colleagues (2012) also found that brain tumor survivors demonstrated intellectual functioning (i.e., IQ) scores one standard deviation below the normative population. Deficits in general intellectual functioning have also been identified in other cancer diagnoses such as leukemia/lymphoma. For example, a study examining general intellectual functioning in both pediatric cancer survivors of acute lymphoblastic leukemia (ALL) compared to healthy controls found statistically significant lower IQ scores among pediatric cancer survivors (Anderson et al., 1994). Montour-Proulx and colleagues (2005) also found evidence for mild intellectual deficits in childhood cancer survivors, as their scores fell consistently below the normative population by one standard deviation. Other studies suggest that while survivors demonstrate intellectual functioning within the average range, their scores are still lower than healthy controls (Lofstad et al., 2009).

While many studies provide evidence in favor of intellectual impairments in pediatric cancer survivors, there are a few studies that have not replicated these findings. For example, Copeland and colleagues (1996) examined intellectual functioning and found no consistent evidence for intellectual decline following cancer treatment. In a study conducted by Espy and colleagues (2001), children diagnosed with leukemia were evaluated two, three, and four years post diagnosis. Growth curve analysis found no evidence of declines in intellectual functioning. However, despite some inconsistencies among studies, general IQ deficits are frequently documented in pediatric cancer survivors. The discrepant research findings may be attributed, in part, to the multiplicity of factors that influence how neurocognitive late effects manifest, including disease and treatment related variables, how such late effects are evaluated, as well as individual difference variables. These discrepant findings also suggest that risk factors associated with more pronounced IQ deficits are not well enough understood.

Executive functioning. Executive functioning (EF) represents a complex cognitive construct with some disagreement with regard to the primary executive abilities, how they are organized, underlying neuroanatomy, as well as proper measurement. Despite this lack of clarity, EF has previously been conceptualized as those abilities that reflect a capacity to engage in goal oriented behavior (Lezak et al., 2012). Specific subdomains that have been identified as relevant components of executive functioning include attention, fluency, working memory, set shifting/task switching, and inhibitory control (Kramer et al., 2014). The prefrontal cortex has been implicated in these component processes (Wolfe et al., 2012). Additionally, white matter volumes, particularly in the frontal regions, have also been associated with executive functioning abilities. Research suggests that an increase in

myelination within the frontal lobes co-occurs with the development and solidification of EF abilities (Wolfe et al. 2012).

A significant body of literature has examined executive functioning in pediatric cancer survivors. Findings consistently reveal that survivors demonstrate impairments in executive functioning abilities such as processing speed, working memory, attention, and task switching (Anderson, Smibert, Ekert, & Godber, 1994; Ness et al., 2008). Brinkman and colleagues (2012) found that 75 percent of medulloblastoma survivors were impaired on at least one measure of executive function, while Maddrey and colleagues (2005) found that 78 percent of medulloblastoma survivors demonstrated impairments in sustained attention, and 90 percent demonstrated impairments on motor-based attention tasks. Impairments in executive functioning have also been documented among survivors with other cancer diagnoses such as leukemia. In pediatric survivors of ALL, significant executive functioning deficits have been observed, such as deficits in working memory, attention/orientation, and processing speed. A meta-analysis conducted by Peterson and colleagues (2008) found that survivors of ALL demonstrated significant impairments in processing speed, working memory, and executive functioning in the form of task switch (e.g. Trails B). Another meta-analysis documented similar impairments in attention, processing speed, and other areas of executive functioning (Campbell et al., 2007).

Although a common profile of deficits has been identified (i.e. deficits in attention, executive functioning, and general intellectual functioning), observed impairments still remain highly variable, and a review of the literature has revealed notable inconsistencies. The variability in research findings is partly due to the variability in research methodology. For example, many studies do not use a comparison group (e.g., healthy controls), and

instead make comparisons based on normative population values. Other studies use healthy control populations for comparisons, while others use sibling controls. Additionally, there are very few studies that employ a longitudinal approach that also includes premorbid cognitive functioning prior to diagnosis and treatment.

Additionally, the variability in neurocognitive performance is also due to the multiplicity of factors that influence how neurocognitive late effects manifest. Previous research has identified disease and treatment related risk factors as well as patient related risk factors, which may be relevant to understanding outcome heterogeneity.

Risk Factors for Neurocognitive Impairment

Specific risk factors have been proposed in an attempt to explain neurocognitive deficits in pediatric cancer survivors. Factors that have been identified include disease and treatment related variables, which appear to have influence over and above psychosocial and environmental factors.

Treatment. Previous research has identified disease and treatment related factors as potential contributors to the development and severity of general intellectual and executive function deficits. These studies have demonstrated that such deficits more commonly manifest with a diagnosis of leukemia or central nervous system (CNS) tumor, relative to other diagnostic groups (Campbell et al., 2007). The specific vulnerability of leukemia and brain tumor survivors is likely due to the similarities across treatment approaches for both groups. For example, aggressive CNS directed treatments are applied to both leukemia and brain tumors and represent a significant assault on the CNS. CNS directed treatments that are commonly associated with neurocognitive impairment include chemotherapy in the form of intrathecal (IT) methotrexate and cranial radiation therapy (CRT).

Cranial radiation therapy. Cranial radiation therapy (CRT) represents a common treatment used to treat both leukemia and brain tumors. The use of cranial radiation therapy has been implicated in the development of executive function impairments (Moore, 2005). For example, Moore, Ater, and Copeland (1992) examined the effects of CRT on neurocognitive performance in a group of child survivors of brain tumors. Results indicated that children treated with CRT demonstrated significantly lower performances on measures of attention, memory, motor, and visuo-spatial skills relative to those children who did not receive CRT. Anderson and colleagues (1994) compared neurocognitive performances across three groups: children who received CRT, children who did not receive CRT, and healthy controls. Results found that irradiated children performed more poorly on tests of intellectual functioning than non-irradiated children and healthy controls. The most pronounced deficits were found in verbal and attentional abilities.

There is also evidence to suggest that CRT disrupts and damages the structural integrity of the developing brain. Cortical atrophy, vascular damage, and leukoencephalopathy have all been associated with the use of CRT (Mulhern 1994), and approximately 50 percent of patients treated with CRT show changes in white matter (Askins & Moore 2008). Additionally, this white matter damage is irreversible and does not diminish with time. Reddick and colleagues (2003) found that patients treated with CRT demonstrated a significant decrease in normal-appearing white matter volume when compared to untreated individuals of the same age. The finding that CRT is associated with structural abnormalities and reductions in normal-appearing white matter has been replicated across additional studies (Mulhern et al., 1999; Reddick et al 2000; Reddick 2006).

Additional research has found a direct link between CRT induced structural damage and subsequent neurocognitive deficits. In a group of pediatric cancer survivors treated with CRT, Reddick and colleagues (2003) examined the relationship between changes in normal-appearing white matter (NAWM) and neurocognitive deficits such as general intellectual deficits, memory deficits, and attention deficits. Results found that decreases in normal-appearing white matter (NAWM) volumes were significantly associated with more pronounced deficits in attention. In a similar study, there was evidence for a significant relationship between smaller volumes of white matter and impairments in attention, intelligence, and academic achievement (Reddick 2006). Iuvone and colleagues (2002) also found a similar relationship between white matter abnormalities and neurocognitive performance in child cancer survivors treated with CRT.

Chemotherapy. Due to the long-term toxicity of CRT and the problematic outcomes associated with its use, most treatment protocols reserve CRT for high-risk leukemia patients and patients with brain tumors. With the declining use of high dose CRT, CNS prophylaxis treatments have begun to use chemotherapy, more specifically, intrathecal methotrexate (IT MTX). The delivery of chemotherapy intrathecally allows it to permeate the blood-brain barrier, and thus allowing the treatment to target the CNS. The use of CNS directed chemotherapy has historically been preferred over CRT, as it was originally thought to be benign in terms of long-term neurocognitive impairments. Despite this, an impressive body of literature seems to suggest CNS-directed chemotherapy is not quite so benign. In a review of the literature, Moleski (2000) found that approximately two thirds of research on the effects of CNS-directed chemotherapy documents some type of decline in general intellectual functioning, while one fourth of the research documented deficits in at least one area of

neurocognitive functioning including executive functioning. Most research surrounding the deleterious effect of chemotherapy has examined one specific chemotherapy agent, intrathecal methotrexate (IT MTX). Children treated with this type of CNS directed chemotherapy have experienced deficits in general executive function, as well as attention and processing speed (Moleski, 2000; Peterson et al., 2008).

Similar to CRT, CNS-directed chemotherapy has also been associated with structural damage within the CNS. More specifically, IT MTX has been implicated in structural damages due to its neurotoxicity. Iuvone and colleagues (2002) found intracerebral calcifications in 24 percent of child survivors of ALL who were treated with IT MTX. Damages and disruptions in normal-appearing white matter have also been associated with the use of IT MTX, as two thirds of children who received IT MTX demonstrated white matter alterations via neuroimaging (Moleski, 2000). Additional structural damages have been associated with the use of IT MTX including leukoencephalopathy, intracerebral calcifications, and cortical atrophy (Moleski, 2000).

A relationship between chemotherapy induced structural changes and neurocognitive deficits has also been established. Reddick and colleagues (2006) examined the relationship between impairments in neurocognitive performance and normal-appearing white matter following chemotherapy. Results indicated that children treated with chemotherapy still demonstrated significant reductions in normal-appearing white matter relative to healthy controls. These smaller volumes were significantly associated with more pronounced deficits in attention, intellectual functioning, and academic achievement. Carey and colleagues (2008) used voxel based morphology (VBM) to measure regional differences in brain functioning as a result of CNS directed chemotherapy. Results found two specific regions of

reduced white matter within the right frontal lobes of survivors, which were not evident in controls. Survivors also demonstrated poorer performance on measures of attention, visual construction abilities, mental flexibility, and math achievement.

Neurosurgery. While commonly implemented cancer treatments include chemotherapy and radiation therapy, children diagnosed with brain tumors often undergo initial treatment with neurosurgical intervention. Neurosurgical resection represents a particularly aggressive assault on the brain. As such, neurosurgical intervention has been associated with immediate and often long-term consequences to children's CNS. Carpentieri and colleagues (2008) found that patients with localized brain tumors treated with surgery only demonstrated deficits on neurocognitive measures of motor output, verbal memory, and visuospatial organization. Askins and Moore (2008) suggest that such late effects may occur as a result of the neurosurgical resection of tumors that encroach upon critical areas of the brain involved with attention and executive functioning. As such, it is not just the removal process, but also the actual location of the tumor that plays a critical role in the degree to which neurocognitive deficits are expressed.

Treatment dosage. CRT, CNS directed chemotherapy, and neurosurgery are treatments that have been associated with structural changes within the brain, as well as impairments in executive functioning and global intellectual functioning. Treatment dose has also been found to play a significant role in the manifestation of these deficits. For example, higher doses of CRT have been associated with more pronounced neurocognitive deficits, including executive function and global intellectual deficits (Moore, 2005). There is also evidence that structural damage resulting from CRT is moderated by treatment dosage, as brain tumor survivors have evidenced slower rates of white matter loss when exposed to

lower doses of radiation (Reddick et al., 2000). Evidence of a dose response relationship has been replicated across additional studies (Armstrong et al., 2010; Mulhern, Fairclough, Smith, & Douglas, 1992). CNS directed chemotherapy has also demonstrated a dose response relationship (Iuvone et al., 2002; Montour-Proulx et al., 2005), such that higher doses have been associated with more severe deficits.

Additional research suggests that the combined use of both CRT and IT MTX heightens the iatrogenic effects of either of these treatments when used in isolation. The relationship between treatment intensity and severity of neurocognitive impairment can be explained in terms of the aggregate assault on the CNS. Lower doses of CNS directed treatment result in lower neurotoxicity, less structural damage, and consequently, fewer deficits. Higher doses of CNS directed treatments result in higher neurotoxicity and consequently more structural damage and neurocognitive deficits. Additionally, the combined use of CRT and IT MTX has been suggested to interact synergistically, enhancing the effect on the CNS. More specifically, CRT is thought to induce alterations in the blood brain barrier, allowing IT MTX to permeate the blood brain barrier with greater ease and frequency. The outcome of this process is an intensification of the neurotoxic effects of IT MTX (Moleski, 2000). In general, the use of higher doses, as well the combination of treatment modalities, results in more severe manifestations of general intellectual and executive function deficits.

Thus, a wide body of research clearly reveals a significant relationship between cancer treatment (e.g., CRT and CNS-directed chemotherapy), reductions in normal-appearing white matter, and deficits in global intellectual functioning, as well as executive functioning. Children may be particularly vulnerable to this process, as myelination

continues throughout adolescence and young adulthood, specifically within the frontal lobes (Wolfe et al. 2012), thus resulting in pronounced neurocognitive deficits.

Patient related factors. Biological variables such as sex and age have also been found to influence the severity of neurocognitive deficits (Askins and Moore; 2008; Moleski 2000; Nathan et al. 2007). For example, girls are at higher risk of neurocognitive impairment than boys (Christie et al 1995; Nathan et al 2007). Von der Weid and colleagues (2003) found that female survivors scored, on average, ten points lower on measures of intellectual functioning than males. Similar findings have been consistently replicated across additional studies (Ellenberg et al 2009; Peterson et al. 2008; Waber et al 1990). The heightened vulnerability of females remains consistent regardless of treatment modality (Brown et al. 1998; Mulhern, Fairclough, and Ochs, 1991).

The severity of neurocognitive impairment also appears to be negatively correlated with age such that younger children are at heightened risk for experiencing more severe neurocognitive deficits. (Moore 2005). Children treated with CRT at a younger age have been found to demonstrate more pronounced deficits in intellectual functioning, whereas children treated at an older age do not demonstrate such dramatic deficits (Mulhern et al 1998; Nathan et al. 2007). Mulhern and colleagues (1992) found that young children treated with CRT demonstrated a 14-point difference in IQ score relative to older children. Other studies have reported similar findings (Kadan-Lottick et al. 2010).

Models of Neurocognitive Late Effects

Based on these findings, three separate models of neurocognitive deficits in pediatric cancer survivors have been proposed. In the first model, proposed by Reddick and colleagues (2003), neurocognitive deficits are explained as a function of decreases in normal-appearing

white matter in frontal regions of the brain. Reductions in normal appearing white matter are used to explain impairments in specific attentional abilities, which then impact IQ and academic achievement. Reddick and colleagues also proposed a direct link between attention and academic achievement. While this model was the first to highlight the neurobiological substrates of neurocognitive late effects, it failed to include additional measures of executive functioning, as well as treatment and patient related variables.

Palmer and colleagues (2008) introduced another model and included patient and treatment related variables. This model proposed a relationship between disease and treatment related variables and specific components of EF (e.g., processing speed, attention, and working memory). A relationship was also proposed between impairments in EF and impairments in global intellectual functioning and academic achievement. Palmer and colleagues also included the contribution of patient related variables such as age and sex. Wolfe and colleagues (2012) criticized this model for overlooking the contribution of underlying white matter changes, as well as additional components of EF including planning and metacognition.

As a result of these limitations, Wolfe and colleagues (2012) proposed their own comprehensive model, which included patient and treatment related factors (e.g., sex, age, and treatment), neurocognitive factors (e.g., EF), as well as neuroanatomical factors (e.g., changes in normal-appearing white matter). While previous models of neurocognitive impairment in cancer survivors have provided a strong foundation for understanding these late effects, as well as underlying etiology, these models remain limited in scope: while previous models have emphasized the neurobiological substrates of neurocognitive impairment, they have overlooked the functional impact of these deficits.

Functional impairment. Extant research has provided important information regarding specific types of late effects experienced by pediatric cancer survivors. However, very little is known regarding the severity of these late effects and how they disrupt children's day-to-day functioning. Functional impairment represents an emerging construct within pediatric health, as it provides a benchmark beyond isolated deficits observed in neuropsychological or psychosocial domains. The importance of functional impairment in the context of children's physical and psychological health has only recently emerged as a focus of research (Palermo et al., 2008). In 1980 the World Health Organization published the International Classification of Impairments, Disabilities, and Handicaps (ICIDH) which, for the first time, highlighted the consequences of the disease in terms of overall functioning. In other words, this new classification system helped shift the focus from cause to impact of disease on day-to-day functioning (World Health Organization, 1980).

For children, functional impairment refers to the ways in which a constellation of symptoms interfere with and reduce performance within important aspects of the child's life (Rapee, Bögels, van der Sluis, Craske, & Ollendick, 2012). In this regard, the importance of functional impairment lies in its ability to capture activities that are particularly salient to the child's life. Three major domains in which daily functioning may be disrupted include: interpersonal relations, school/work functioning, and self-care/self-fulfillment (Bird et al., 2005). Previous research has indicated that while a significant relationship exists between isolated psychological symptoms and broad functional impairment, the relationship is not perfect (Rapee et al., 2012). These findings suggest that while there is a relationship between symptoms and impairment, functional impairment represents an independent construct and should be measured in addition to specific psychological symptoms.

There are two major advantages to examining functional impairment in pediatric cancer survivors. First, information regarding multiple domains of deficits, such as physical, social, and personal are included. This type of assessment moves beyond the simple examination of isolated domains (Palermo et al., 2008), such as anxiety, depression, cognitive impairments, or social skills, and instead provides information regarding how a broad array of deficits interact and impede day-to-day activities. In other words, functional impairment encompasses the wide range of psychosocial deficits that manifest in pediatric cancer survivors. Second, measuring functional impairment provides clinically relevant information by indicating the severity of impairment and whether it demands clinical attention.

Although functional impairment has previously been linked to children with traumatic brain injury, Attention Deficit Hyperactivity Disorder, and other mental health problems (Fay et al., 2009; Huppert, Simpson, Nissenson, Liebowitz, & Foa, 2009; Lollar, 2008; Wille, Bettge, Wittchen, Ravens-Sieberer, & group, 2008), it has only begun to be examined in relation to the pediatric cancer experience. There is some preliminary evidence suggesting that pediatric cancer survivors do indeed suffer functional deficits. Hudson and colleagues (2003) examined functional status in a group of pediatric cancer survivors and found that survivors were significantly more likely to demonstrate functional deficits, such as needing help with personal care and routine daily rituals, and difficulty keeping and holding a job. Pediatric cancer survivors have also demonstrated difficulties with scholastic achievement and have been found to be significantly less likely to complete high school when compared to healthy controls (Mitby et al., 2003). Additionally, a study from the Childhood Cancer

Survivor Study (CSSS) reported that survivors were at higher risk for later employment difficulties and were more likely to be unemployed (Pang et al., 2008).

Quality of life (QOL) represents a construct similar to functional impairment in that it attempts to move beyond isolated domains in order to capture a comprehensive and holistic picture of the child's life. The World Health Organization (1948) defines QOL as a multidimensional construct encompassing physical, mental, and social well-being. Zeltzer and colleagues (2008) examined health related quality of life (HRQOL) in a group of cancer survivors and found survivors demonstrated poorer HRQOL relative to population norms. Additional studies have found similar results (Meeske et al., 2007; Waters, Sherman, Galaburda, & Denenberg, 1997). In sum, preliminary evidence suggests the presence of clinically significant functional impairments in pediatric cancer survivors. However, to date no research has comprehensively assessed functional impairment and determined whether rates of functional impairment are significantly different in pediatric cancer survivors relative to a normative population.

Neurocognitive deficits and functional impairment. Executive functions are necessary for responding adaptively to novel situations and they also form the basis of many cognitive, emotional, and social skills (Lezak, Howieson, and Loring, 2004). Executive functioning has been implicated in broad functional outcomes such as school readiness (Blair, 2002), academic achievement (Espy et al., 2004), theory of mind, and social competence (Hughes, Dunn, & White, 1998). Children with Attention Deficit Hyperactivity Disorder (ADHD), which is characterized by deficits in executive functioning, has been shown to demonstrate poorer functional outcomes in the form of lower educational, social, and occupational outcomes (Shaw et al., 2012).

The relationship between executive functioning and more broad functional outcomes has also received some attention within pediatric cancer populations. Campbell and colleagues (2009) examined the impact of executive functioning domains (working memory, inhibition, cognitive flexibility, and self-monitoring) on coping strategies and broad behavioral outcomes. Results indicated that performance on executive functioning tasks was related to coping strategies, as well as emotional and behavioral problems in pediatric survivors of ALL. Additional research has suggested that measures of selective attention are related to health related quality of life (Penn et al., 2010). A study conducted by Ellenberg and colleagues (2009) found that, in a group of cancer survivors, impairments in task efficiency, emotion regulation, organization, and memory were associated with lower socioeconomic achievement. Lower socioeconomic achievement was defined as lower education attainment, less household income, less full time employment, and fewer marriages. Reeves and colleagues (2006) found that impairments in attention were related to poor academic achievement in math and reading. Taken together, preliminary research provides compelling evidence suggesting that impairments in executive functioning might impact broader functional domains including academic achievement, social and emotional competence, and socioeconomic achievement; however, additional research is needed to provide further clarity the relationship.

In sum, pediatric cancer survivors are at heightened risk for experiencing impairments in general intellectual and executive functioning. While previous research has exposed a relationship between executive functioning deficits and more global functional impairments, this relationship has not been adequately characterized within pediatric cancer populations, and the functional impact of neurocognitive deficits remains unclear. Despite its clinical

relevance, previous models have not yet included the functional impact of neurocognitive late effects. The current study sought to expand on previous models by examining the functional impact of deficits in executive functioning and global intellectual functioning.

Associated risk factors. In addition to characterizing the functional impact of neurocognitive deficits, the current study also sought to expand on current knowledge regarding the neurobiological substrates of both neurocognitive late effects and functional impairment. As noted above, previous models have highlighted the role of white matter changes in neurocognitive deficits. Additionally, previous models have explained these changes in terms treatment toxicity and its impact on CNS development. However, absent from these models is the impact of adjustment factors, including chronic stress, on the neurobiological substrates that contribute to late effects.

Chronic stress. The diagnosis and treatment of pediatric cancer is an undeniably stressful event, involving an ongoing series of stressors. This includes the diagnosis itself, threat of mortality, lengthy and painful treatments, as well as long-term morbidities or late effects that persist throughout survivorship. According to Varni and Wallander (1988) pediatric cancer represents a “chronic strain” for both children and parents. “Chronic strains” are persistent and objective conditions that require continuous readjustments, which interfere with role-related activities (J. W. Varni & Katz, 1997). The “chronic strain” resulting from the pediatric cancer experience seems to impact global symptoms of stress and distress. Previous research suggests that child survivors demonstrate greater symptoms of global distress relative to healthy controls (Lesko, 1990; Zeltzer et al., 2008). Rodriguez and colleagues (2012) assessed a variety of cancer-related stressors and found that changes in functional roles were most salient stressor reported by child survivors, suggesting that a

child's inability to perform activities was more stressful than uncertainty surrounding the disease.

The chronic stressors associated with the pediatric cancer experience have also been found to manifest as more severe psychopathology. In the seminal paper by Nir (1995), it was first observed that cancer survivors demonstrated symptoms consistent with posttraumatic stress disorder (PTSD). However, Nir's observations were only qualitative and comparisons to the general population were not be made. Pelcovitz (1998), however, explored the lifetime frequency of PTSD in cancer survivors relative to individuals with an abuse history, as well as healthy controls. Results found significantly higher rates of lifetime PTSD in cancer survivors compared to individuals with a history of abuse (i.e. 23 percent, 7 percent respectively). Results also indicated higher rates of current PTSD in cancer survivors relative to those with an abuse history (i.e. 17 percent, 7 percent respectively). These rates were also significantly higher than rates found in the normative population.

The significant environmental changes facilitated by the cancer experience as well as the prevalence of global distress and posttraumatic stress, is particularly concerning given the allostatic load model proposed by McEwen and Wingfield (2003). Allostatic load has been proposed as a means of explaining the relationship between chronic stress and adverse outcomes (Johnston-Brooks et al. 1998). According to McEwen & Wingfield (2003), the term allostasis refers to a process by which the body "maintains stability through change." It is through this process that individuals are able to adapt to environmental changes and stressors, such as a cancer diagnosis. Allostatic load then refers to the cumulative physiological cost to the body that occurs when an individual adapts to these changes and stressors. When an individual is exposed to a number of unpredictable events in the

environment, such as disease, human disturbance, and social interaction, an individual's allostatic load can increase dramatically. When the stress is chronic, there is more strain on the physiological system, resulting in physiological and psychological damage. (McEwen & Sellar, 1993). Increases in allostatic load have been associated with adverse outcomes including hypertension, hyperlipidemia, diabetes, weight gain, amenorrhea, impotence and alterations in the immune system and brain regions (e.g. hippocampus; McEwen, 1998).

The process of maintaining stability or "allostasis" in the face of environmental change and chronic stressors requires a significant amount of energy and effort. The primary mediators of allostasis involve hormones of the HPA axis, such as glucocorticoids or cortisol, which become changes as a result of this process. It has been suggested that the adverse outcomes associated with chronic stress can be attributed to cortisol levels (Howell and Sanchez 2011; Lupien 2001). When confronted by a stressor, the body reacts by releasing cortisol. Cortisol represents the body's main stress hormone and works to mobilize the body's resources and to provide energy in the presence of a stressor (Kudielka & Kirschbaum, 2005). When a stressor continues to persist, the stress response fails to terminate, which results in elevated cortisol levels circulating throughout the body.

Extant research suggests that exposure to chronic stress is associated with higher cortisol levels. In one study, individuals exposed to chronic stress demonstrated higher cortisol concentrations in their body relative to individuals not exposed to chronic stress (Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2012). Additionally, higher cortisol levels have been found in conditions associated with chronic stress such as chronic pain (Vachon-Preseau et al., 2013; Van Uum et al., 2008), chronic fatigue (Torres-Harding, 2008) unemployment (Dettenborn et al., 2012; Dettenborn, Tietze, Bruckner, & Kirschbaum,

2010), and depression (Dettenborn et al., 2011). A meta-analysis conducted by Hunter and colleagues (2011) demonstrated that early life adversity and psychosocial stressors were related to increases in cortisol reactivity. Higher cortisol levels have also been found in shift workers, relative to day workers (Manenschijn, van Kruysbergen, de Jong, Koper, & van Rossum, 2011), and in individuals who experienced major life stressors (Karlén, Ludvigsson, Frostell, Theodorsson, & Faresjö, 2011). Low socioeconomic status (SES) is one particular source of chronic stress that has received significant attention in terms of its relationship to cortisol concentrations. In general, individuals with low SES report greater stressful life events (Lupien 2001). Additionally, children with low SES have higher salivary cortisol levels relative to children with high SES (Lupien 2001; Lupien 2005).

Only one study to date has examined the relationship between the chronic stress associated with the pediatric cancer experience and cortisol output. Gordijn and colleagues (2012) found that child survivors of acute lymphoblastic leukemia experienced elevated levels of cortisol relative to healthy controls.

In sum, previous research clearly reveals a relationship between chronic stress exposure and elevated cortisol levels. Previous research has also identified the pediatric cancer experience as a particularly salient chronic stressor. Given these findings, it stands to reason that the pediatric cancer experience is associated with elevated cortisol production. This conclusion has been supported by the one study to date that has examined cortisol levels in a pediatric cancer population.

Chronic stress and neurocognitive deficits. Cortisol levels following chronic stress exposure have been shown to impact the structural integrity of the CNS, as well as neurocognitive functioning. Lupien and colleagues (2005) suggest that cognitive processing

abilities, maintained within the frontal lobes, are sensitive to acute increases in glucocorticoids. A study conducted by Sheridan and colleagues (2012) found a relationship between changes in salivary cortisol levels and activity in the prefrontal cortex (PFC). Additionally, decreases in hippocampal volume have been documented in relation to chronic stress exposure and cortisol output (Lupien et al., 2005). In a study conducted by Carrion and colleagues (2007), posttraumatic stress symptoms and cortisol levels at baseline were found to predict reductions in hippocampal volumes across 12 and 13 months intervals.

In addition to structural changes, cortisol levels have also been associated with neurocognitive functioning including learning and memory (Heffelfinger 2001). It has been suggested that young children (e.g., preschool years) may be particularly vulnerable to the impact of cortisol, as young children are only beginning to develop these cognitive abilities and therefore may be vulnerable to the iatrogenic effects of cortisol (Heffelfinger 2001). The relationship between cortisol and cognitive outcomes was first demonstrated in animal models, as Mizoguchi and colleagues (2004) found that, in rodents, glucocorticoids were necessary for neurocognitive abilities associated with PFC activity such as working memory. Suppression of glucocorticoids was found to impair working memory.

Additional research in child populations supports a relationship between cortisol concentrations and neurocognitive functioning. For example, Keller and colleagues (2012) found evidence in favor of a relationship between cortisol levels and intellectual and academic achievement in children. Extreme levels of cortisol (e.g., high and low levels) predicted poor neurocognitive performance while moderate levels predicted better performances.

Impairments in executive functioning represent a particularly salient outcome related to chronic stress exposure. Previous research has documented a relationship between posttraumatic stress disorder, posttraumatic stress symptoms, and impairments in executive functioning (LaGarde et al. 2010). A meta-analysis conducted by Polak and colleagues (2012) found that patients with PTSD demonstrated more severe impairments in executive functioning relative to patients without PTSD. This relationship may be mediated by elevated cortisol levels that result from persistent exposure to stressors and elevated cortisol levels have been directly associated with impairments in executive functioning (S. Lupien et al., 1994; S. J. Lupien et al., 1999). A study conducted by Blair and colleagues (2011) found that higher resting cortisol levels in infants were related to poorer executive functioning. Tu and colleagues (2007) found that higher basal cortisol concentrations in infants were associated with poor focused attention. Another study conducted by Blaire and colleagues (2005) found that individuals who demonstrated a healthy cortisol profile when confronted with a moderate stress (i.e. brief increase in cortisol followed by a decrease) also demonstrated better executive functioning. Additional studies have found a relationship between healthy cortisol profiles and better executive functioning (Stawski et al., 2011). Berry and colleagues (2012) found that cortisol profiles at 7, 15, and 24 months predicted executive functioning at 17 and 36 months as well as academic achievement in kindergarten.

There is also preliminary research suggesting a relationship between cortisol levels and broader functional outcomes. Gordjin and colleagues (2012) examined the relationship between cortisol levels and quality of life in a group of pediatric cancer survivors. Results indicated a significant relationship between cortisol and quality of life, such that higher

cortisol levels were associated with poorer quality of life. Higher cortisol levels have also been associated with poor mental health in children (Essex et al. 2000)

In sum, the pediatric cancer experience represents a source that contributes to significant chronic stress. Chronic stress, as demonstrated through cortisol levels, has been implicated in structural changes within the CNS, as well as neurocognitive deficits, including impairments in memory and executive functioning, as well as impairments intellectual functioning and academic achievement. Despite such findings, previous research has not yet examined the degree to which cortisol concentrations contribute to neurocognitive impairments, as well as more global functional impairments, within pediatric cancer populations. Additionally, previous research so far has not been able to determine the relative contribution of chronic stress and treatment related factors on the manifestation of these impairments. Figure 1 represents a theoretical model of neurocognitive deficits following the pediatric cancer experience including associated risk factors, as well as the functional impact of deficits. The current study sought to provide preliminary evidence for this model by first characterizing some of the relationships highlighted in this model.

The Current Study

Objectives

This study sought to explore and characterize relationships within the proposed conceptual model of neurocognitive late effects by first examining the functional impact of deficits, as well as by determining the relative contribution of associated risk factors including treatment related variables (e.g., treatment severity and length of survivorship), and chronic stress measured through cortisol concentrations. There were three main objectives to this proposal: 1) determine the frequency and severity of deficits in EF, intellectual functioning, and functional impairment in a group of pediatric cancer survivors compared to healthy controls; 2) examine the relative contribution of child neurocognitive functioning to functional impairment in survivors relative to controls; and 3) examine how treatment severity, length of survivorship, and chronic stress are associated with neurocognitive and functional endpoints.

Hypotheses

There were three main hypotheses that corresponded to the study objectives: 1) Pediatric cancer survivors would demonstrate deficits in EF and global intellectual functioning, as well as an increased incidence of functional impairment, relative to healthy controls; 2) Poorer performances on neurocognitive tasks would be associated with greater functional impairment; 3) Pediatric cancer survivors would demonstrate significantly different cortisol levels than healthy controls, and both treatment severity and chronic stress would be significantly related to neurocognitive and functional endpoints for cancer survivors.

Methods

Participants

Participants included pediatric cancer survivors, healthy controls, and parents of each group of children. Eligibility criteria for cancer survivors included :1) ages 5 through 18; 2) a previous cancer diagnosis; 3) at least 1 year post-treatment; and 4) ability to follow instructions in English. Individuals were excluded from the study at the discretion of the investigator (e.g., child had a visual impairment) and/or if they had a history of intellectual disability (IQ<70).

Eligibility criteria for healthy controls included: 1) ages 5 through 18: and 2) ability to follow instructions in English. Individuals were excluded from the study at the discretion of the investigator (e.g., child had a visual impairment) or if they had a diagnosis that interfered with cognitive or functional abilities (IQ<70). Individuals were also excluded if they had been diagnosed with a chronic illness including severe asthma, diabetes, JRA, cystic fibrosis etc.

Procedure

Study procedures were reviewed and approved by the University of New Mexico Institutional Review Board.

Cancer survivors. Parents of potential participants were recruited and enrolled by a trained research assistant during the participant's routine clinic appointment at the University of New Mexico Health Sciences Center, Young Enduring Survivors (YES) Clinic. A few days prior to their clinic visit, eligible participants were identified by clinic staff as eligible, and were contacted via a phone call by the clinic coordinator. This was a routine call that served to confirm and remind patients of their clinic appointment. During this routine call,

participants were introduced to the study and informed that they would have the opportunity to participate during or after their clinic visit. Over 400 new patients have been seen at the YES clinic since its inception in February 2005. The YES clinic sees pediatric patients approximately three Fridays every month, where an average of four to six patients (ages 4-18 years) are examined. The current study was open for recruitment from September 2013 through June 2014 (approximately 36 weeks) allowing for a potential recruitment pool of approximately 144 pediatric cancer survivors.

From that potential recruitment pool, 109 survivors were scheduled and presented for their clinic appointment. Of those, 26 participants were not approached, as they did not meet eligibility (i.e., IQ<70, Spanish speaking, not within age range). Of the 83 family dyads that met criteria and were approached to participate, only 20 dyads agreed to participate, resulting in a recruitment success rate of approximately 24 percent.

Healthy controls. Healthy controls were recruited via multiple sources (online ads placed on Craigslist, flyers placed in the community, as well as word of mouth). A brief description of the study was provided, as well as the amount of compensation for participation. Contact information was also listed. Approximately 45 individuals volunteered to participate in the study. Forty-one of the 45 completed all study procedures. All 45 participants who responded to study advertisements in the community met eligibility based on a telephone screening.

Enrollment. Cancer survivors and healthy controls were scheduled for the study visit by one of the study RAs. The procedure began with reviewing consent/assent materials with the parent and child. Following the completion of consent materials, a hair sample was collected from parent and child. Child and parent were then separated into different rooms to

ensure independent responses. Immediately following hair collection, a neurocognitive and executive function exam was administered to the child by a trained psychometrist in a private clinic room. After completion of the neurocognitive exam, the child completed a questionnaire assessing functional impairment. This process required approximately 60 minutes of the child's time. At the same time, parents completed demographic questionnaires, as well as a questionnaire regarding their child's functional impairment. Upon completion of the study, parents and child each received a \$20 gift card as appreciation for their participation.

Measures

Functional impairment. Functional impairment (FI) was assessed with the Brief Impairment Scale (BIS; Bird et al., 2005). The BIS is a 23-item, parent completed assessment that provides a global measure of impairment along three domains of functioning: interpersonal relations, school/work functioning, and self-care/self-fulfillment. The assessment is intended to measure the degree to which the child struggles with various activities. Responses are on a four-point Likert scale ranging from 0 ("no problem") to 3 ("serious problem"). The assessment is prefaced by the statement "In general, how much of a problem do you think your child has with". It then includes item statements such as: "Getting involved in activities together with the rest of the family?" "Making friends?" and "Getting schoolwork done on time?" Data were obtained from one clinical sample (outpatient mental health clinics) and two community samples. Convergent validity was demonstrated by significant correlations ($r = -0.53, 0.52, \text{ and } -0.52; p < .001$) between the BIS and an established measure of the same construct, the CGAS (Shaffer et al., 1983). The BIS has

internal consistency with alpha ranging from .81 to .88 as well as fair to substantial test-retest reliability.

The BIS was designed for parents to complete yet was adapted for this study to be completed by children as the Brief Impairment Scale-Child Version. Thus we wanted to determine the extent to which children were able to report on their own functional impairment. The child-adapted version was based on the same four-point Likert scale as the original version. Similar to the original, items were introduced with the statement, “In general, how much of a problem do you think you have with.” It then included the same item content with the language simplified, as well as examples for children to reference: Some examples of items included “Getting involved in activities together with the rest of the family,” “Making friends,” and “Getting schoolwork done on time.”

In the current sample, the original BIS, intended for parent completion, demonstrated acceptable internal consistency ($\alpha=0.71$). The observed factor structure was inconsistent with the structure proposed by Bird et al. (2005). Instead of a three-factor structure, item responses yielded a seven-factor structure, accounting for approximately 66 percent of the variance. A three-factor solution only accounted for 41 percent of the total variance.

The Brief Impairment Scale-Child Version (BIS-CV) demonstrated acceptable internal consistency ($\alpha=.64$), which was slightly lower than what was demonstrated for parents. The factor structure of the BIS-CV was assessed using a principal components analysis, with varimax rotation. Findings were inconsistent with the three-factor structure proposed by Bird et al., (2005) for the parent questionnaire, which identifies three specific factors or areas of impairment (e.g., interpersonal functioning, school functioning, and self

care/self-fulfillment). Results instead favored a nine-factor structure, which accounted for approximately 72 percent of the variance.

Despite discrepancies, the original three-factor structure was maintained due to the low sample size of the current study. Additionally the three factor structure was based on the theoretical structure of subdomains encompassed within the broader construct of functional impairment (e.g., interpersonal, school, self-care). These subdomains were relevant to the study hypotheses and were therefore maintained in the proceeding analyses.

Executive function. Executive function was assessed using the NIH Examiner (Kramer et al., 2014). The Examiner assesses multiple domains of executive functioning including working memory, inhibition, set shifting, fluency, planning, insight, and social cognition/behavior. The Examiner also provides an executive function composite score as well factor scores across three sub domains: working memory, fluency, and cognitive control. The Examiner has demonstrated good psychometric properties. All tasks had appropriate internal consistency with alpha ranging from .64 to .98. Test-retest reliability across the executive function composite and factor scores ranged from 0.76 to 0.94. Convergent validity was demonstrated by significant correlations ($r=-0.21, p<.001$) between the NIH examiner composite score and a measure of parent report of real world executive function (BRIEF).

General intellectual function. General intellectual ability was assessed using the Reynolds Intellectual Screening Test (RIST; Reynolds & Kamphaus, 2003). This is comprised of two subtests and was administered to all children. The RIST was standardized on 2,438 individuals in 41 states and is representative of the 2001 US Census. Reliability coefficients range from 0.84 to 0.96. Test-retest reliability ranged from 0.79 to 0.86.

Correlations with the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) Full Scale IQ were 0.76. The RIST can be completed by children in less than 20 minutes.

Cortisol. Cortisol levels were obtained through children's hair. The measurement of cortisol through hair represents a novel, noninvasive, and standardized sampling procedure that allows for the measurement of long-term, chronic stress, as measured in cortisol production (Russell, Koren, Rieder, & Van Uum, 2012; Staufenbiel et al., 2012). Other methods of cortisol measurement, such as saliva and serum samples, measure concentrations of cortisol at a single point in time, and they offer information regarding acute changes in cortisol production. As a result, these measures are subject to major physiological daily fluctuations, which in turn, make the assessment of long-term chronic cortisol exposure difficult to measure. In contrast, hair cortisol analysis captures systemic cortisol exposure over long periods of time of up to three months. In order to collect this sample, approximately 150 strands of hair were taken from the vertex posterior part of the head. This portion of hair was cut with sanitized scissors as close to the scalp as possible. For the hair sample to be accurate, three centimeters of hair was obtained. Hair dye has been shown to change the concentration of cortisol in the hair (Sauvé, Koren, Walsh, Tokmakejian, & Van Uum, 2007), therefore we asked each participant if his or her hair was chemically dyed. The hair samples were stored and sent off site for analysis.

Cancer variables. Child cancer variables were collected including diagnosis and time since treatment termination. Treatment severity was derived based on the procedure developed by Vannatta, Gerhardt, Wells, and Noll (2007) where categorical treatment component scores were summed to create an overall index of CNS treatment intensity. Scores of 0 or 1 were assigned for radiation exposure (0 for no CRT, 1 if CRT was

administered). The same coding procedure was implemented for the use of Methotrexate (0=No, 1=Yes), chemotherapy administered intrathecally (0=No, 1=Yes), and neurosurgery (0=No, 1=Yes). Scores then ranged from 0 through 4. Higher scores were indicative of more severe and multimodal CNS directed treatments. Cancer survivors demonstrated a mean treatment severity score of 1.2(1.03). This represents a relatively low treatment severity score and suggests that, in general, this particular sample had less severe CNS-directed treatments. On average, children in this sample received only one modality of CNS directed treatment, as opposed to combination treatments (e.g., methotrexate, intrathecal chemotherapy, and CRT). This is in comparison to another study that demonstrated medium to severe treatment severity scores in over half of the sample (Vannatta et al., 2007). Lower treatment severity scores were likely secondary to the specific cancer diagnoses that characterized this sample. Approximately 55 percent of the sample was made up of leukemia/lymphoma diagnoses and there were no CNS tumor survivors represented in the sample. Treatment severity did not differ between females (M=1.02, SD=1.04) and males (M=1.38, SD=1.06), $p=0.57$).

Length of survivorship was also recorded and ranged from 2.58 to 10.75 years (M=6.17, SD=2.38). Length of survivorship did not differ between males (M=6.93, SD=2.70), and females (M=5.61, SD=2.06), $p=0.24$.

Demographic measures. Standard demographic measures were collected for parent and child including age, sex, race, ethnicity, parent education, and employment status. Socio economic status was measured using the Barratt Simplified Measure of Social Status (BSMSS; Barratt, 2006). This measure was adapted from Hollingshead (1975), and was designed to be a proxy for socioeconomic status, and represents one of the more common SES measures. The measure uses both educational attainment and occupational prestige as a

way to approximate SES. The measure accounts for marital status, student status, as well as individuals currently retired. Scores range from 8 through 66 and higher values indicate higher SES. Scores between 8 and 30 are considered low, while scores above 30 are considered average (Cirino et al., 2010).

Statistical Analyses

Descriptive statistics were calculated for all child demographic variables and child cancer related variables. A series of independent samples t-tests were used to determine whether there were significant differences in demographic variables (e.g., age, SES) across cancer survivors and healthy controls. Additionally, a chi square test of independence was used to examine differences in sex and ethnicity across cancer survivors and healthy controls.

BIS concordance rates across parent and child reports were determined using simple Pearson bivariate correlations across BIS total score, as well as BIS sub domain scores (e.g., interpersonal, school, self-care). Child age was included as a covariate. A chi square test of independence determined if child age affected concordance rates. This was done by breaking age group into two categories (e.g., 5-11 and 12-18). Clinically significant impairment was defined as a score equal or greater than 14 (Bird et al., 2005). Child and parent total BIS scores were first recoded to reflect clinical caseness (>14) or nonclinical caseness (<14). Item content and scoring remained consistent across the original BIS and BIS-CV. Given this, it was considered appropriate to determine clinical caseness for the child version based on criteria specified by Bird and colleagues (2005) for the original version. Finally, in order to determine if parent-child concordance differed according to age group, a parent-child agreement (concordance) variable was coded based on agreement between parent and child on clinical caseness.

One-way ANOVA compared mean scores on the parent BIS to mean scores on the BIS Child Version (BIS-CV). A chi square analysis was also used to determine significant differences in clinical impairment. Finally, a chi square test of independence was run in order

to determine if there was a relationship between parent-child agreement/concordance and disease group.

Statistical Analysis for Objective One: Neurocognitive Deficits and FI

In order to determine the severity of functional impairment in cancer survivors relative to healthy controls, an independent samples t-test compared parent and child BIS total score in pediatric cancer survivors relative to healthy controls. Comparisons of BIS subdomain scores (e.g., interpersonal, school, and self-care) were also executed.

Additionally, a 2x2 ANOVA explored the sex by cancer interaction effect. The first variable was cancer status and was composed of two levels (e.g., healthy control versus cancer); the second variable also had two levels (e.g., female, male). The dependent variable included the BIS total score and subdomain scores for parent and child. An additional chi square test of independence examined whether there was a significant difference in casesness across cancer survivors relative to healthy controls. Finally, an omnibus 3x2 MANOVA determined whether the levels of impairment across the three domains (e.g., work/school, interpersonal, and self-care/self-fulfillment) were different in cancer survivors compared to healthy controls (i.e., were survivors more vulnerable to experiencing a specific domain of deficit). This analysis was conducted for BIS parent and child reports.

In order to determine the severity of neurocognitive deficits in cancer survivors relative to healthy controls, a series of independent samples t-tests were used to compare verbal and nonverbal intellectual functioning, as well as global intellectual functioning, in cancer survivors compared to healthy controls. Additionally, a 2x2 ANOVA was executed in order to determine the sex by cancer interaction effect. The first variable was cancer status, and was composed of two levels (e.g., healthy control versus cancer survivor). The second

variable also had two levels (e.g., female, male). This same approach was used to evaluate differences in pediatric cancer survivors and healthy controls across performances on the NIH Examiner tasks.

Statistical Analysis for Objective Two: Neurocognitive Functioning Predicts FI

Exploratory and preliminary simple bivariate Pearson correlations were run in order to characterize relationships among the primary variables of interest (e.g., BIS scores, RIST score, and NIH Examiner scores).

Multiple regression analyses, using stepwise selection was used to examine neurocognitive predictors of child and parent report of FI collapsed across cancer survivor and health control groups in order to first examine the main effects of neurocognitive functioning. The contribution of child demographic factors (e.g., child age and SES) were controlled for and included in the regression as the first block. Verbal and nonverbal reasoning t scores from the RIST were entered as the second block. Finally, NIH Examiner domain scores were entered as the third block. Executive functioning was entered after broad intellectual functioning because executive functioning is considered to be a cognitive process that supports intellectual functioning and is highly correlated; however, it remains an independent construct with unique variance that should be considered separately. Stepwise regression was selected as the analytic technique given the exploratory nature of the study and recognizing the limitation that this technique capitalizes upon chance relationships.

Finally, a one-way ANCOVA examined the relationship between general intellectual functioning and broad functional impairment across both groups. In this analysis, group was the primary independent variable, with two levels (cancer survivor, healthy control), while verbal and nonverbal reasoning was included as a covariates Child age and SES were also

included in the model as covariates. The interaction between the primary independent variable and verbal and nonverbal reasoning covariates was also included in the model. This analysis was conducted using both parent and child BIS scores as dependent variables. A similar second analysis was conducted using performance on the NIH Examiner tasks as covariates, while the primary independent and dependent variables stayed constant. The interaction term between NIH Examiner covariates and the primary independent variable was also included in the model.

Objective Three: Treatment, Length of Survivorship, and Chronic Stress Predictors

First, descriptive statistics were calculated for treatment and illness variables including treatment severity, length of survivorship, as well as cortisol level. Independent samples t tests compared cortisol levels in cancer survivors relative to healthy controls, controlling for child age and SES. A 2x2 ANOVA examined the group (cancer, healthy) by sex (male, female) interaction on cortisol. Next, exploratory preliminary bivariate correlations were used to characterize the relationships between cortisol, treatment severity, length of survivorship and the primary outcomes measures of interest including neurocognitive functioning (e.g., RIST and NIH Examiner scores) and functional impairment (e.g., BIS parent and BIS-CV scores).

Multiple stepwise regression analyses were employed, collapsed across both groups, with age and SES entered as covariates in the first block, and then treatment severity (treatment severity was coded as 0 for healthy controls) and cortisol level entered in the second block. This analysis was conducted several times using different dependent variables including performance on executive functioning (e.g., NIH Examiner) and general intellectual functioning measures (e.g., RIST), as well as parent and child report of functional

impairment (e.g., BIS parent and BIS-CV). The purpose of this analysis was to determine the main effect of cortisol on neurocognitive and functional endpoints.

Additional regression analyses were executed in order to examine the degree to which chronic stress, as measured through cortisol, contributed to neurocognitive and functional endpoints in addition to variance already accounted for by cancer related variables including treatment severity and length of survivorship, specifically in cancer survivors. Again, demographic variables including child age and SES were entered into the first block. Illness and treatment related factors, including treatment severity and length of survivorship, were entered in the second block. Finally, cortisol was entered as the final block.

Finally, a one-way ANCOVA examined the group (cancer vs. healthy control) by predictor (cortisol) interaction, controlling for child age and SES. In this analysis, group was the primary independent variable with two levels (cancer survivor, healthy control), while cortisol was included as a covariate. The interaction term between cortisol and the primary independent variable was also included in the model. This analysis was conducted using both neurocognitive and functional endpoints.

Results

Demographics

Given the relatively low rate of study participation within the cancer survivors, additional analyses examined the possibility of a selection bias. Non-participant data was limited to child sex, child age, and diagnosis. A chi square test of independence assessed whether child sex was associated with study participation. Results were significant $\chi^2=5.3$, $p=.021$ such that boys were more likely to decline participation than girls. Additionally, an independent samples t-test compared child age across participants and non-participants. Results were non-significant $t=-1.11$, $p=0.27$. Finally, an additional chi square test of independence test determined whether there was a relationship between cancer diagnosis (e.g., CNS vs. Non-CNS cancers) and study participation. Results were non-significant, $\chi^2=2.89$, $p=0.09$. Follow up frequency analysis indicated that 55 percent of children who participated in study procedures had CNS related cancers, while 44 percent of participants had non-CNS cancers. In contrast 75 percent of non-participants had CNS related cancers and only 29 percent of non-participants had non-CNS cancers. While this difference was not statistically significant, more children with more severe CNS related cancers chose not to participate. This suggests that cancer severity may have been related to participation decisions.

A total of 20 cancer survivors and 41 healthy controls were enrolled in the study. Descriptive statistics were calculated for all demographic variables across cancer survivors and healthy controls. Results are presented in Table 1. There were no significant differences in age or sex across cancer survivors and healthy controls. Additionally, the ethnic make-up of participants was consistent across both groups. Differences in socioeconomic status (SES)

across cancer and healthy control groups approached significance ($p=0.054$) and suggested that healthy controls demonstrated slightly higher SES relative to cancer survivors.

Parent and Child Concordance on the BIS

Bivariate Pearson correlations were used to measure parent and child concordance rates across child and parent reports of FI. For analyses on BIS concordance rates, findings were collapsed across both groups (e.g., cancer survivors and healthy controls), as the focus was on the psychometric properties of the measure, rather than group differences. Table 2 reveals a significant positive relationship between parent and child report of global impairment (i.e., BIS total score), $r=0.27$, $p=0.04$. Higher levels of overall functional impairment as reported by the child were associated with higher levels of overall impairment per parent report. However, concordance rates across BIS subscales were somewhat inconsistent. While there was a positive relationship between parent and child reports of interpersonal functioning, this relationship was non-significant, $r = 0.18$ $p=0.17$. In contrast, there was a significant positive relationship between parent and child report of school functioning $r=0.41$, $p=0.00$. Parent and child report of self-care/self-fulfillment demonstrated a positive and non-significant relationship, $r = 0.23$ $p=0.09$. These results suggest that parent perceptions of child functioning are somewhat consistent with the child's own perceptions. Parents and children appear to agree more on broad functional limitations, as well as impairment in the domain of school functioning, but they demonstrate less agreement on interpersonal relationships and self-care.

Given the wide age range of participants (i.e., 5-18), the same bivariate correlations described above were computed across parent and child BIS scores while also controlling for child age. With regard to total BIS scores, the relationship remained positive and significant,

and the strength of the relationship increased slightly, $r=0.34$, $p=0.01$. The correlation between interpersonal functioning scores became significant, $r=0.31$, $p=0.02$, as did self-care/self-fulfillment, $r=0.30$, $p=0.03$, while school functioning remained significant, $r=0.30$, $p=0.003$. In sum, the relationship between parent and child report of impairment became stronger after accounting for the additional error variance in age given the wide age distribution. Given this, a one-way ANOVA determined whether there were mean differences in child reports of functional impairment based on age. This was done by breaking age into two categories (e.g., 5-11, and 12-18). Results were non-significant, $F(1, 57)=1.53$, $p=0.22$. Additionally, a chi square test of independence was used to determine if child age affected concordance rates, again, by breaking age group into two categories. Results were non-significant and there was no relationship between child age and parent-child agreement of impairment ratings ($X^2=1.11$, $p=0.29$).

Despite a significant and positive association between parent and child BIS scores, there were still significant differences across parent and child scores $F(1, 118)=33.34$, $p=0.00$, Partial eta squared was equal to 0.22, which can be interpreted as a medium to large effect. Further descriptive statistics revealed that children endorsed much higher levels of FI ($M=14.48$) relative to parent reports of child impairment ($M=7.53$). These values include both cancer survivors and healthy controls. Additionally, a chi square test of independence revealed significant differences in reports of clinical caseness across parent and child report ($X^2=19.73$, $p=0.00$), such that 51 percent ($n=29$) of children endorsed clinically significant levels of functional impairment while only 13 percent ($n=8$) of parents endorsed clinically significant levels functional impairment in their child. Again these percentage values were collapsed across groups (i.e., cancer survivors, healthy controls). There was agreement in

approximately 59 percent of parent child reports (n=35). Out of the eight cases identified as clinically significant by the parents, seven were also identified as clinically significant per child report. Taken together, these results indicate that while there is a significant and positive relationship in parent and child reports of child FI, children tend to endorse more clinically significant rates of impairment relative to their parents.

Finally, concordance rates were evaluated in cancer survivors relative to healthy controls, using a chi-square test of independence. A parent-child agreement variable was coded based on agreement between parent and child on clinical caseness, which was defined as a score >14 (Bird et al., 2005). Results were non-significant, and there were no differences in parent-child concordance rates in cancer survivors as compared to healthy controls $\chi^2=0.40, p=0.53$, and concordance rates were not affected by disease group. Further descriptive analyses revealed that 65 percent of cancer survivor dyads demonstrated agreement in reports of clinically significant impairment while 56 percent of healthy controls demonstrated agreement.

Objective One: Neurocognitive Deficits and FI

The purpose of objective one was to determine the frequency and the severity of neurocognitive deficits and functional impairments in pediatric cancer survivors relative to healthy controls. This was accomplished by comparing parent and child report of BIS scores across cancer survivors and healthy controls, as well as comparing performances on EF (e.g., NIH Examiner) and IQ (e.g., RIST) measures across cancer survivors and healthy controls.

Functional impairment. Inconsistent with the study hypothesis, cancer survivors did not show elevated levels of functional impairment relative to healthy controls. Means and standard deviations for the BIS and BIS-CV scores across cancer survivors and healthy

controls, as well as significance levels, are presented in Table 3. Child sex did not moderate the effect of cancer survivorship on functional impairment per parent report $F(1,57)=0.36$, $p=0.56$ and child report $F(1, 55)=2.07$, $p=0.16$.

An omnibus 3x2 repeated measures MANOVA determined whether there were differences in domains of impairment (e.g. work/school, interpersonal, and self-care/self-fulfillment) across groups (e.g., cancer survivor, healthy control). Results were non-significant per BIS-CV $F(2, 55)= 0.65$, $p=0.93$. Results were also non-significant, $F(2, 58)= 1.20$, $p=0.34$, for parent BIS. Both cancer survivors and healthy controls endorsed similar levels of impairment across all domains of functioning and cancer survivors were not more vulnerable to a specific domain of impairment (e.g., school, interpersonal, self-care/self-fulfillment).

An additional chi square analysis determined whether there were significant differences in rates of clinically significant impairment (e.g., scores>14) across cancer survivors and healthy controls. Results were not significant per BIS-CV, $\chi^2=0.009$, $p=0.93$, or per BIS, $\chi^2=0.09$, $p=0.76$. In sum, with regard to functional impairment, cancer survivors and their parents did not report greater impairment than healthy controls and contrary to our initial hypothesis, cancer survivors and their parents reported rates of clinically significant impairment comparable to healthy controls.

Intellectual functioning. Means, standard deviations, and significance levels are presented for verbal reasoning, non-verbal reasoning, and global intellectual functioning across cancer survivors and healthy controls in Table 4. Differences were non-significant, and our initial hypothesis was not supported, as cancer survivors demonstrated IQ scores comparable to healthy controls. Group means were also consistent with population norms

and fell within one standard deviation of population values. This relationship did not change after controlling for SES and child age. Child sex did not moderate the effect of cancer survivorship on Verbal IQ score, $F(1,57)=0.77, p=0.39$, Nonverbal IQ, $F(1, 57)=1.11, p=0.30$ or Full Scale IQ, $F(1, 57)=0.04, p=0.83$.

Executive functioning. Means, standard deviations, and significance levels are presented for all NIH Examiner scores across pediatric cancer survivors and healthy controls in Table 5. Contrary to study hypotheses, there were no significant differences in executive functioning across cancer survivors and healthy controls, as cancer survivors demonstrated EF scores comparable to healthy controls. Child sex did not moderate the effect of cancer survivorship on verbal fluency $F(1, 55)=0.42, p=0.52$. However, child sex significantly moderated the effect of cancer survivorship on planning, $F(1, 56)=4.58, p=0.04$. This was not in the expected direction. Male cancer survivors demonstrated lower planning scores ($M=0.38, SD=0.19$) than female cancer survivors ($M=0.45, SD=0.23$), which is inconsistent with previous research (Christie et al., 1995; Nathan et al., 2007). However, female healthy *controls* demonstrated the lowest planning scores ($M=0.34, SD=0.15$). Child sex did not significantly moderate the effect of child survivorship on sustained visual attention (e.g., CPT), $F(1, 55)=0.14, p=0.71$, working memory, $F(1, 55)=0.52, p=0.42$, or set shifting, $F(1, 55)=0.41, p=0.84$.

Objective Two: Neurocognitive Functioning Predicts FI

The purpose of objective two was to characterize the contribution of neurocognitive deficits on functional impairment more broadly (e.g., main effects collapsed across groups), as well as within groups (e.g., cancer survivors and healthy controls). An additional goal was to determine if the contribution of neurocognitive functioning on FI was different in cancer

survivors relative to healthy controls. This was accomplished by first employing exploratory and preliminary simple bivariate correlations across neurocognitive variables and FI, collapsed across groups, and then separately within cancer survivors. Additional multiple regression analyses were employed to determine the degree to which neurocognitive functioning predicted FI, more broadly (i.e., collapsed across groups). Finally, a one-way ANCOVA was then used to determine if the relationship between neurocognitive functioning and FI was different across groups (e.g., cancer survivors and healthy controls). These analyses were conducted using both parent and child reports of FI as dependent variables.

Child report of FI. With regard to child report of functional impairment more broadly (e.g., collapsed across groups), Verbal IQ was significantly related to interpersonal functioning ($r=-0.26, p=0.05$), self-care/fulfillment ($r=-0.39, p=0.00$), and global impairment ($r=-0.38, p=0.00$). This was in the expected direction and higher Verbal IQ was related to lower impairment scores with regard to interpersonal, self, and global impairment. Full Scale IQ was significantly related to interpersonal functioning ($r=0.28, p=0.03$), self-care ($r=-0.30, p=0.02$), and total impairment ($r=-0.36, p=0.01$). These relationships were in the negative direction and were consistent with expectation, such that greater IQ scores were associated with lower levels of impairment. Various measures of executive functioning were also associated with functional impairment. Verbal fluency was significantly related to self-care/self-fulfillment ($r=-0.32, p=0.03$). Child planning abilities (e.g., NIH unstructured task) was significantly associated with school functioning ($r=0.31, p=0.02$); however, this was not in the expected direction. As expected, working memory was negatively associated with self-care/self-fulfillment ($r=-0.33, p=0.01$); and set shifting was also negatively related to self-care/self-fulfillment ($r=-0.28, p=0.03$). Table 6 includes a full correlation matrix.

Multiple regression analyses were executed with all neurocognitive variables entered stepwise into the model, again collapsed across groups. Because SES has previously been shown to be associated with neurocognitive performance, preliminary bivariate correlations determined the relationship between SES, EF, IQ, and FI. SES was significantly related to verbal reasoning ($r = 0.46, p=0.00$) and full scale IQ ($r =0.41, p=0.00$). SES, as well as child age, was therefore controlled for in all subsequent analyses. Results indicated that verbal reasoning was the only significant predictor of global impairment, and accounted for 16 percent of the variance, $F(1,54)=10.50, p =0.002$. Verbal reasoning was also found to significantly predict interpersonal impairment, accounting for eight percent of the variance, $F(1,54)=4.45, p=0.04$. Verbal reasoning was also found to be a significant predictor of self-care, accounting for 14 percent of the unique variance, $F(1, 53)=10.18, p =0.002$. With regard to school impairment, planning, as measured through the NIH Unstructured Task accounted for eight percent of the variance, $F(1,53)=4.49, p =0.04$. In sum, verbal reasoning and planning abilities significantly predicted broad FI, as well as impairment across school, self-care, and interpersonal domains, per child report.

Within group analyses were also executed with the sample of cancer survivors to examine the relationship between neurocognitive functioning and FI for this group specifically. Verbal reasoning and full scale IQ were found to demonstrate the most robust relationship with global and school impairment. Bivariate correlations are presented in Table 7.

An additional one-way ANCOVA was used to determine if the relationship between all neurocognitive variables and FI differed in cancer survivors compared to healthy controls. With regard to child report of FI, there was a significant group by verbal reasoning

interaction $F(1,41)=6.58, p=0.01$, indicating that the relationship between verbal reasoning and child report of global impairment was different for cancer survivors relative to healthy controls. Additional within group follow up regression analyses revealed that for cancer survivors, verbal reasoning accounted for 36 percent of the unique variance in global impairment, after controlling for age and SES $F(1, 16) =9.49, p=0.01, b=-0.62$. In healthy controls, verbal reasoning accounted for only three percent of the unique variance in functional impairment, which was non-significant $F(1, 33)= 1.49, p=0.23, b=-0.27$. This interaction is depicted in Figure 2. There was also a significant two way interaction effect with respect to school impairment $F(1,40)=4.91, p=0.03$, such that, in cancer survivors, verbal reasoning accounted for 28 percent of the variance in school impairment. This was significant $F(1,16)=5.41, p=.02, b=-0.55$. However, in healthy controls, verbal reasoning accounted for less than one percent of the variance, which was non-significant $F(1,32)=0.12, p=0.72, b=-0.07$. The interaction is shown in Figure 3.

Parent report of FI. With regard to parent report of functional impairment more broadly (e.g., collapsed across cancer survivors and healthy controls), Full Scale IQ was significantly related to school functioning, ($r=-0.29, p=0.02$). This was in the expected direction. Additionally, a significant relationship was observed between verbal fluency and interpersonal functioning ($r=0.39, p=0.00$). Verbal fluency was also significantly related to global impairment ($r=0.26, p=0.05$). Child planning abilities (e.g., NIH Unstructured Task) were significantly associated with interpersonal impairment ($r=0.26, p=0.05$). However, these relationships were not in the expected direction. Table 6 includes a full correlation matrix. Within group analyses were also executed to examine the relationship between neurocognitive functioning and parent report of FI, specifically within the sample of cancer

survivors. Results indicated that Full Scale IQ was significantly related to parent report of school impairment $r=-0.29, p=0.02$. While verbal reasoning and planning were significantly related to total impairment and interpersonal impairment, these relationships were not in the expected direction. A full correlation matrix is presented in Table 7.

Following broad multiple regression analyses, including both groups (e.g., cancer survivors and healthy controls), no neurocognitive variables were retained in the model, as none significantly predicted parent report of global impairment, school impairment, interpersonal impairment, or self-care.

Additional analyses using ANCOVA revealed a similar two-way interaction that was previously demonstrated based on child reports of functional impairment. Verbal reasoning differentially predicted global impairment in cancer survivors relative to healthy controls, $F(1, 43)=4.13, p=0.048$. The same two way interaction was evident with regard to self-care/self-fulfillment $F(1, 43)=5.43, p=0.02$. Additional follow up analyses, comparing regression slopes in cancer survivors relative to healthy controls, indicated that for cancer survivors, verbal reasoning accounted for 19 percent of the unique variance in global impairment, after controlling for child age and SES. This was marginally significant, $F(1,16)= 4.35, p=0.05, b=-0.46$. For healthy controls, verbal reasoning accounted for less than one percent of the variance in global impairment, which was non-significant, $F(1, 35)=0.02, p=0.88, b=-0.03$. The interaction is plotted in Figure 4.

With regard to self-care/self-fulfillment, a similar pattern emerged. For cancer survivors, verbal reasoning accounted for 28 percent of the variance in self-care/self fulfillment, which was significant $F(1,16)=7.00, p=0.01, b=-0.56$. For healthy controls, verbal reasoning accounted for less than one percent of the variance in self-care/self-

fulfillment, which was non-significant, $F(1, 35)=0.03$, $p=0.85$, $b=-0.04$. The interaction is plotted Figure 5. Taken together, these findings suggest that the relationship between neurocognitive functioning and broad functional impairment was more robust in cancer survivors relative to healthy controls, such that verbal reasoning was more predictive of FI in cancer survivors.

Objective Three: Treatment, Survivorship Length, and Chronic Stress Predictors

The purpose of objective three was to determine the relative contribution of additional risk factors including treatment related variables, and chronic stress, on both neurocognitive functioning and functional impairment. To do this, first, descriptive statistics were calculated for the primary variables of interest (e.g., treatment severity, survivorship length, and cortisol level). Table 8 presents descriptive findings. Overall, the average treatment severity score for cancer survivors was relatively low ($M=1.21$). While cancer survivors demonstrated slightly higher cortisol levels relative to healthy controls, this difference was not significant. After controlling for child age and SES, this relationship still remained non-significant, $F(1,43)=0.97$, $p=0.33$. There was a main effect of child sex, $F(1,41)=5.63$, $p=0.02$, such that males demonstrated higher cortisol levels ($M=16.99$, $SD=8.51$), than females ($M=12.01$, $SD=5.29$); however, child sex did not moderate the relationship between survivorship status and cortisol, $F(1,41)=0.377$, $p=0.54$.

Next, exploratory and preliminary simple bivariate correlations characterized the relationships among cortisol levels, treatment severity, and length of survivorship, as well as neurocognitive functioning, and functional impairment, in cancer survivors only. With regard to cancer related variables, a significant relationship between FI and length of survivorship was demonstrated ($r=0.60$, $p=0.01$). This relationship was in the positive direction, indicating

longer survivorship was associated with more school impairment, per parent report. Treatment severity was also related to cortisol levels, $r=0.30$, $p=0.04$. This positive relationship suggested that the more severe the treatment, the higher the cortisol levels.

Multiple regression analyses were again used to examine the degree to which cancer treatment and cortisol levels predicted both neurocognitive functioning and functional impairment (per child and parent report), collapsed across groups (healthy controls received a score of 0 for treatment severity, indicating no treatment). Results indicated that treatment severity and cortisol level did not significantly predict verbal reasoning, nonverbal reasoning, verbal fluency, planning, sustained attention, working memory, or set shifting. With regard to FI, treatment severity and cortisol level did not significantly predict child or parent report of FI.

Additional within group regression analyses were executed in order to examine the degree to which chronic stress, as measured through cortisol, contributed to neurocognitive and functional endpoints, in addition to variance already accounted for by cancer related variables including treatment severity and length of survivorship. This analysis was conducted for cancer survivors only. Again demographic variables including child age and SES were entered into the first block. Illness and treatment related factors including treatment severity and length of survivorship were entered in the second block. Finally, cortisol was entered in the final block. With regard to neurocognitive endpoints, no variables were retained in the model. For child and parent report of FI, no variables were retained in the model.

A one-way ANCOVA was then used to determine if the relationship between cortisol levels, neurocognitive functioning, and functional impairment was different in cancer

survivors compared to healthy controls. Results indicated a significant group by cortisol interaction for verbal reasoning $F(2, 37)= 3.18, p=0.05$. Follow up analyses revealed that for cancer survivors, cortisol accounted for only six percent of the variance in verbal reasoning, after controlling for SES and child age, which was not significant, $F(1, 13)=0.95, p=0.34, b=0.342$. For healthy controls, cortisol accounted for only four percent of the variance in verbal reasoning, after controlling for SES and child age, which was also not significant $F(1, 26)=2.36, p=0.13, b=-0.22$. While variance accounted for was similar across groups, slope values were significantly different and are plotted in Figure 6. There was also a significant group by cortisol interaction for sustained attention $F(1, 36)=4.61, p=0.01$. Follow up analyses revealed for cancer survivors, cortisol level did not account for any unique variance above what was already accounted for by child age and SES $F(1,13)=0.00, p=0.97, b=0.01$. For healthy controls, cortisol accounted for three percent unique variance, which was non-significant, $F(1,25)=1.20, p=0.28, b-0.20$. The interaction is plotted in Figure 7. There was also a significant group by cortisol interaction for set shifting, $F(1, 36)=11.93, p=0.00$. Follow up analyses revealed that for cancer survivors, cortisol did not account for any unique variance in set shifting $F(1, 13)=0.00, p=0.98, b=-0.00$. For healthy controls, cortisol accounted for 10 percent unique variance $F(1,13)=6.14, p=0.02, b=-0.33$. The interaction is plotted in Figure 8.

There were no significant two-way interactions for either child or parent report of FI and cortisol did not differentially predict FI across cancer survivors relative to healthy controls.

Discussion

Summary of Findings

The purpose of this study was to provide preliminary evidence regarding the relationships between neurocognitive deficits, functional impairment, and associated risk factors (treatment severity, time since treatment, chronic stress) following the pediatric cancer experience. The goal was not only to characterize the frequency and severity of deficits, as has previously been done in the research, but to also examine the functional impact of deficits across salient daily activities in school, interpersonal, and self-care/self-satisfaction domains. An additional goal was to identify the relative contribution of associated risk factors including treatment severity and chronic stress.

Objective one: Neurocognitive deficits and FI. Broadly speaking, there has been limited research examining the overall functional impact of neurocognitive late effects in pediatric populations. One particular barrier involves a lack of validated measures assessing functional impairment. A previous study conducted by the primary author (Hile et al., 2014) attempted to examine the functional impact of neurocognitive late effects using the Brief Impairment Scale (Bird et al., 2005). However, study methods were limited by a potential confound, as parent reports of impairment were significantly related to parental stress levels. This suggested a potential negative bias in which parents experiencing high levels of stress were more likely to endorse higher levels of impairment in their children. It was unclear as to whether this reflected true levels of impairment or just a negative response bias. In order to control for this potential confound and obtain a more valid estimate of functional impairment, the current study also required that children report on their own functioning and the Brief Impairment Scale was adapted for children (e.g., BIS-CV).

Given the use of both measures, the concordance rate between the two was examined. In general, there was a significant positive correlation across parent and child reports of impairment. Higher reports of impairment as reported by the children were related to higher reports of impairment as reported by the parent. This is consistent with previous findings on concordance between parent and child reports (Rodenberry and Renk, 2007). Similar concordance rates were also found across the specific subdomains of impairment (e.g., school, interpersonal, self-care). Child age did not moderate the concordance rates, as concordance rates remained consistent regardless of whether the child reporting was younger (e.g., <12 years) or older (e.g., >12 years). Additionally, concordance rates across parent and child reports remained consistent regardless of whether the child was a cancer survivor or healthy control.

Despite a significant and positive relationship between parent and child reports of impairment, children endorsed significantly higher levels of impairment relative to parent reports. A previous study examining concordance rates in parent and child reports of quality of life in cancer survivors also found similarly low concordance levels (Rodenberry and Renk, 2007); however, these results also found that parents tended to overestimate the psychosocial difficulties relative to child reports. The current study demonstrated opposite findings, with children reporting more impairments than their parents. This finding was evidenced across both cancer survivors and healthy controls. When survivorship status was specifically examined, it did not moderate concordance rates. In sum, there was a small but significant correlation between parent and child reports of functional impairment; however, children, regardless of age or group, tended to endorse higher rates of impairment relative to their parents.

Given the discrepancy between parent and child reports of functional impairment, both respondents (e.g., parent and child) were included when examining the degree of FI in cancer survivors relative to healthy controls.

Contrary to our hypotheses, cancer survivors did not demonstrate increased rates of functional impairment relative to healthy controls. This was true for both parent and child reports of impairment. There was also no difference in the rates of clinically significant impairment or “caseness” in cancer survivors relative to healthy controls. Additionally, cancer survivors were not more vulnerable to any specific domain of impairment (e.g., school, interpersonal, and self-care). Taken together, this suggests that both cancer survivors and healthy controls report similar levels of impairment. The cancer experience does not appear to confer additional risk for impairment, as measured in the current study, in salient daily activities across school, interpersonal, and self-care domains.

A previous study conducted by the primary author (Hile et. al., 2014) found that approximately 26 percent of cancer survivors demonstrated clinically significant levels of Functional Impairment, as endorsed by primary caregivers. The current study found similar rates of parent endorsed impairment (e.g., 20 percent); however the current study further contextualizes this finding, as this rate was not different than rates of impairment in healthy controls.

Cancer survivors demonstrated performances on neurocognitive measures, including both verbal and nonverbal reasoning, and executive functioning domains (i.e., attention, verbal fluency, working memory, set-shifting, and planning) comparable to healthy controls. This finding was contrary to our original hypothesis and is highly inconsistent with previous findings, as extant research has found that cancer survivors demonstrate notable impairments

in neurocognitive functioning (Campbell et al., 2008; Robinson et al., 2010). Cancer survivors have been found to be particularly vulnerable to EF deficits, as performance has generally been impaired by one standard deviation based on normative comparisons (Hile et al., 2014; Peterson et al., 2008). One explanation for these null findings is that pediatric cancer survivors demonstrate strong resiliency that is not completely understood and therefore not considered in the context of the current study. Some of these factors related to resiliency may include family and peer dynamics characterized by an increase in support systems at home and academically.

Objective two: Neurocognitive functioning predicts FI. The purpose of this objective was to characterize the relationship between neurocognitive functioning and functional impairment more broadly, as well as explore this relationship within cancer survivors relative to healthy controls. While previous research regarding this broad relationship is limited, a theoretical basis has been well established. Additional research is also favorable and has established a relationship between general intellectual functioning, executive functioning, and more broad functional activities such as academic achievement, social competence, and employment (Blair, 2002; Espy et al., 2004; Hughes, Dunn, & White, 1998). Additionally, previous research has identified cancer survivors as particularly vulnerable for experiencing neurocognitive late effects (Moleski, 2001; Moore, 2008). These two independent findings are the driving force for examining the impact of neurocognitive deficits on more broad impairments in salient daily activities.

With regard to child self-reports of FI, preliminary and exploratory bivariate correlations found a significant relationship between verbal reasoning and impairments in interpersonal, self-care/self-fulfillment, and more global impairment. There was also

evidence of a relationship between additional EF measures (e.g., verbal fluency, set shifting, and working memory) and self-care/self-fulfillment. The directionality of these relationships suggested that higher neurocognitive performances were related to lower impairment scores.

When all neurocognitive variables were included in a model predicting FI, only verbal reasoning accounted for a significant amount of variance in the domains of functional impairment, while planning abilities accounted for a significant amount of variance specifically in school functioning.

However, the degree to which neurocognitive functioning predicted functional impairment was different in cancer survivors relative to healthy controls. In cancer survivors, verbal reasoning was a more robust predictor and accounted for a significant amount of variance in global impairment (i.e., 36 percent); however, in healthy controls verbal reasoning accounted for only three percent of the variance. A similar pattern emerged with respect to verbal reasoning and school impairment. Generally speaking, the slope values demarcating the relationship between neurocognitive functioning and FI were much steeper and more robust in cancer survivors. This suggests that for cancer survivors, neurocognitive functioning is related to broad functional impairment to a greater degree than the degree demonstrated for healthy controls.

Findings were somewhat discrepant when parent reports of functional impairment were examined in relation to neurocognitive functioning. When considering the relationship more broadly (e.g., collapsed across groups), general intellectual functioning was significantly related to school functioning, and higher IQ scores were related to lower school impairment. However, this was the only notable finding. While verbal fluency and child planning abilities were related to impairment, this was not in the expected direction. While a

relationship was established between neurocognitive functioning and FI per parent report, these variables did not account for a significant amount of variance in parent report of functional impairment.

While there were no main effect findings, a significant two-way interaction emerged similar to what was found with respect to child self-reports. In cancer survivors, verbal reasoning was more predictive of impairments in global impairment and self-care/self-fulfillment when compared with healthy controls.

Taken together, these findings suggest neurocognitive functioning is significantly related to broad daily functioning, but only in cancer survivors. This was consistent regardless of reporting source (e.g. child vs. parent). This finding is particularly notable given that, in this sample, cancer survivors did not demonstrate significant deficits in neurocognitive functioning, and performances were comparable to healthy controls. So, while cancer survivors did not demonstrate explicit deficits in neurocognitive functioning relative to healthy controls, their neurocognitive status significantly predicted their broad daily functioning.

While current findings are not consistent with previous research, it has been well established that cancer survivors are more vulnerable to cognitive deficits following pediatric cancer treatment (Campbell et al., 2008; Robinson et al., 2010), which has been linked to structural changes in the brain (Zeller et al., 2013). Given the notable structural changes within the central nervous system, cancer survivors may be more vulnerable to the functional impact of those neurocognitive deficits, as they have fewer resources and less cognitive reserve to buffer or compensate for the impact of neurocognitive abilities on their daily activities. Conversely, this relationship may reflect one of resiliency, wherein cancer

survivors who demonstrate intact neurocognitive functioning are then able to draw more from this resource to influence and bolster their daily functioning, while healthy controls do not need to rely so heavily on their neurocognitive status.

Objective three: Treatment, survivorship length, and cortisol predictors. The purpose of objective three was to examine the impact of chronic stress, as measured through hair cortisol levels, on neurocognitive and functional endpoints. The purpose was also to examine this in conjunction with other established risk factors, primarily treatment severity. While cortisol levels were slightly higher in cancer survivors relative to healthy controls, the difference was not significant; however, children who experienced more intensive and severe treatments also tended to demonstrate higher levels of cortisol. There was also a significant relationship between length of survivorship and school functioning, such that longer survivorships were associated with more impairment per parent report. This could potentially be explained by an increase in academic expectations as the child moves farther away from their initial treatment and diagnosis. As expectations increase, parents may observe a growing gap between the academic expectations and the child's abilities. Additionally, previous research also suggests that neurocognitive late effects are slow to emerge, as they manifest progressively over time (Annett et al., 2014; Spiegler et al., 2004).

While there were no main effect findings regarding the relationship between cortisol and neurocognitive functioning, there was a significant group by cortisol interaction in relation to verbal reasoning. In cancer survivors, higher cortisol levels were related to higher verbal reasoning scores; however, this relationship was non-significant. In healthy controls, the findings were in the opposite direction, such that lower cortisol concentrations were associated with higher verbal reasoning scores. Again, this relationship was non-significant.

A similar interaction was demonstrated in additional neurocognitive outcome measures including sustained attention, as well as set shifting. Taken together, these findings suggest that higher cortisol levels were related to better neurocognitive performances in the specific domains of verbal reasoning, sustained attention, and set-shifting; whereas in healthy controls, lower cortisol levels were related stronger neurocognitive performances.

The differential relationship between cortisol and neurocognitive performance has been previously documented in the literature. For example, a complex relationship between cortisol levels and neurocognitive functioning has been established, specifically in animal models. This relationship has been found to follow a dose dependent relationship, such that moderate levels of cortisol produce the most optimal cognitive functioning, while extreme levels of cortisol (e.g., too high or too low) result in more impaired functioning (de Kloet et al., 1999; Joels, 2006). Additional research even suggests that the timing of cortisol exposure can determine whether it promotes or hinders cognitive functioning (Het, Ramlow, & Wolf, 2005). Results from the current study suggest that the relationship between cortisol and neurocognitive performance may be even more complex, as different groups, primarily cancer survivors, may respond differently to cortisol levels. However, there was no evidence to suggest that survivorship impacted cortisol levels, as survivors demonstrated cortisol levels comparable to healthy controls.

One proposed model of stress and cognition suggests that optimal cognitive functioning occurs in the context of mildly elevated glucocorticoids (Diamond et al., 1992). Given structural and functional changes in the CNS following pediatric cancer, it may be that even higher levels of cortisol are necessary for optimal cognitive functioning in cancer survivors relative to healthy controls.

In sum, there were no differences in neurocognitive performances or functional impairment in pediatric cancer survivors relative to healthy controls. Broadly speaking, verbal reasoning was the most strongly associated with impairments across both groups; however, for cancer survivors, the relationship between verbal reasoning and functional impairment was much stronger. Treatment severity was unrelated to neurocognitive functioning and broad functional impairment, which was inconsistent with study hypotheses. However, treatment severity was related to cortisol. Finally, the effect of cortisol on neurocognitive performance was different for cancer survivors relative to healthy controls, as cancer survivors appeared to have a different association between neurocognitive performance and cortisol levels relative to healthy controls.

Implications

First, findings from the current study suggest that there are significant differences in how children and parents perceive and report on child functional impairments. This has significant implications for how we assess and measure impairment both clinically and in future research. Rates of clinically significant functional impairment, as self-reported by children were more than two times higher than rates of impairment as reported by parents. This represents a significant discrepancy and suggests error in current assessment techniques. In particular, the continued use of self-report or parent-report measures as the sole means of assessing impairment is not adequate. Instead, these findings speak to a need to access additional sources of information, such as teacher reports and behavioral observations, as well as develop more objective and standardized formal performance based measures.

Second and most notably, cancer survivors did not demonstrate deficits in neurocognitive functioning. They also did not demonstrate more pronounced functional

impairments relative to healthy controls. While the current study found rates of clinically significant functional impairment similar to those found in our previous study with a different sample (Hile et al., 2014), these rates did not differ significantly from healthy controls. Overall, this suggests that despite toxic and aggressive treatment protocols, prolonged hospital stays, and absences from school and peer activities, pediatric cancer survivors are not necessarily at higher risk for reporting functional impairments than the general population. This then may speak to underlying resilience factors in pediatric cancer survivors that should be further explored in future research. Current study findings suggest that verbal reasoning may represent a specific resilience factor, as well as optimal levels of stress.

However, previous and current research paradigms invoke a deficit model, as research has been primarily concerned with identifying, characterizing, and predicting deficits within pediatric cancer survivors. In contrast to this model, current findings suggest that examining resilience, as well as variables that predict and promote resilience may also be particularly relevant in understanding the nature of pediatric cancer survivorship, as well as understanding how to promote improvements in survivors' quality of life.

Although cancer survivors reported rates of functional impairment comparable to healthy controls, these findings occurred within the context of lower treatment severity scores. Therefore, these findings can only be generalized to the sample of pediatric cancer survivors that have been exposed to lower levels of or no CNS directed treatments. It should also be noted that performances on intellectual and executive functioning tasks were also comparable to healthy controls. This is largely inconsistent with a substantial body of research that finds notable deficits in neurocognitive functioning approximately one standard

deviation lower than the normative sample (Hile et al., 2014; Campbell et al., 2008; Robinson et al., 2010). Given this, it may be that the normal range performances on neurocognitive measures may have been driving the low rates of functional impairment. This is further supported by additional findings indicating that verbal reasoning abilities significantly predicted functional impairment, a finding that was particularly robust in cancer survivors. Therefore, given their normal range performances on neurocognitive measures, it is less surprising that cancer survivors did not demonstrate higher rates of FI. Taken together, this suggests that resilience may be related to neurocognitive functioning, and verbal reasoning in particular may serve as a buffer or a protective factor against more global impairments.

Cancer survivors may also be more vulnerable to the impact of neurocognitive deficits on global functioning. This finding has significant implications regarding survivorship care and management of late effects, as well as highlights the need for neuropsychological assessments and even brief neuropsychological screenings. This can help inform and discern risk and resilience with regard to broader daily functioning, as well as identify the need for additional accommodations and services to help address cognitive and functional impairment findings.

Finally, while previous research in childhood chronic illness populations has suggested a relationship between increases in parental stress and poor overall child outcomes (Chaney et al., 1997; Davis et al., 2001; Thompson, Gil, Burbach, Keith, & Kinney, 1993), this finding appears to be specific to self-reported parental stress. With regard to child stress, pediatric cancer survivors who demonstrated higher chronic stress, as indexed by hair cortisol, were not more likely to demonstrate impairments in neurocognitive functioning or

broad functional impairment. In fact, the opposite relationship was demonstrated, as higher cortisol levels were associated with better performance on intellectual and executive measures. However, this was only true for cancer survivors and not healthy controls. Given this, it may be that slightly elevated stress levels may be optimal for cognitive functioning and may represent another protective factor for cancer survivors. Future research should further examine chronic stress and stress reactivity in relation to neurocognitive and functional outcomes, as well as investigate the directionality of the relationship. This has important implications for how we perceive stress both clinically and in future research, as stress has generally been examined in relation to iatrogenic effects.

Limitations and Directions for Future Research

This study represents a rather novel approach to the study of late effects in pediatric cancer survivors. As such, there were many limitations to the study and many directions in which future research may proceed.

First, a selection bias is possible and recruitment strategies may not have yielded an accurate representation of pediatric cancer survivors as a whole. The low recruitment rate of cancer survivors (24 percent) speaks to the possibility that cancer survivors who agreed to participate differed systematically from those who were approached but declined participation. This is further supported by the current study finding that cancer survivors did not demonstrate more deficits in executive and intellectual functioning relative to healthy controls, which is highly inconsistent with extant research. This discrepant finding suggests that the current sample may not have been representative of the broader population of pediatric cancer survivors.

The possibility of a selection bias was evaluated to the extent that relevant variables were made available for non-participants. Non-participant data were limited to child sex, age, and diagnosis. Based on these variables, males were more likely to decline participation than females, indicating that female cancer survivors were overrepresented in the study sample, while males were underrepresented. There were no significant differences in age and diagnosis across participants and non-participants. However, there were additional variables that may have affected study participation that were not evaluated including SES and location of residence (e.g., rural vs. urban).

The current study procedures placed high demands on potential participants and their families, as participants were required to return to a different location on a different scheduled day, which often required significant travel time. Additionally, study procedures ranged from 1-2 hours. The ability to participate in study procedures may have been difficult for families with limited resources (e.g., lower SES) and for families who lived in more rural areas in which travel time was extended. Additionally, the ability to participate in study procedures may also have been more difficult for families with children with cognitive and functional impairments. Given this, it may be that cancer survivors who were willing and able to participate in study procedures were systematically different, perhaps reflecting higher SES and lower overall impairments. Future research should include modified study procedures so as to lessen the potential demands on families in order to increase recruitment rates and reduce the possibility of a selection bias.

Another limitation involves the low concordance rates between parent and child reports of child functional impairment and the tendency for children to report significantly higher levels of impairment relative to parents. The lack of consistency across informant

reports begs the question of whether the construct of functional impairment was accurately assessed, suggesting underlying issue with construct validity. In particular, the reliability and validity of the child version of the BIS was questionable given the lower internal consistency score relative to the adult version. This was the first attempt to extend a parent self-report measure to children, which may account for lower internal consistency scores. Additionally, there were a surprisingly large percentage of children who endorsed clinically significant impairment. Approximately half of children, including both cancer survivors and healthy controls, endorsed clinically significant levels of functional impairment. These rates are much higher than rates found in both clinical and community samples. One hypothesis was that younger children demonstrated poorer insight and understanding of questions, which may have driven the elevated rates. However, further analyses examining mean scores on the BIS across younger and older children did not support this hypothesis. At this point it is unclear as to why children endorsed higher rates of impairment relative to their parents; however, it is clear that further research is needed to develop a psychometrically sound measure of functional impairment completed by children. As noted above, future research should also work to develop more objective and reliable measures of functional impairment using both observational methods and informant reports.

Additionally, while the combined sample size was sufficient to achieve adequate power (.80), given the relatively small sample size, the specific data analytic techniques were limited and additional variables of interest were excluded from the tested models, particularly within models of pediatric cancer survivors. These variables included gender, age at diagnosis, occurrence of relapse and transplant.

The current study helped to determine the feasibility of implementing this particular research design within a clinical sample. As noted above, future research could modify the design so as to lessen the participant burden and increase sample size so additional variables of interest can be included in the model. This will help determine the relative contribution of chronic stress and treatment and illness related variables on the presentation of neurocognitive and functional deficits. Additionally, a larger sample size would also allow for the examination of additional resiliency factors and their impact of neurocognitive and functional outcomes. This would also allow for a more detailed characterization of the relevant relationships including mediating and moderating relationships. Although research is rather limited in this area, one study found that illness related variables, including diagnosis and length of treatment, were unrelated to resiliency. However, environmental factors, such as family cohesion, teacher support and positive peer relationships, were highly predictive of resilience (Kim and Yoo, 2010). Given this, future research should include environmental and family factors in developing a comprehensive model of outcomes associated with the pediatric cancer experience.

Additionally, while future research should continue to identify risk and resilience factors, additional research should also determine their impact on intervening brain structures and how that relates to neurocognitive and functional outcomes.

Conclusion

In sum, this study represents a novel approach to the study of neurocognitive late effects in pediatric cancer survivors by providing evidence in favor of a relationship between neurocognitive performance and broad functional impairment, as well as characterizing the relationship between other risk factors and neurocognitive and functional outcomes. This offers a new perspective to the study of late effects by helping to quantify the functional impact of neurocognitive deficits, as well as identify associated risk factors. Associated risk factors included treatment and illness related factors, as well as chronic stress measured through hair cortisol.

Overall, there were no differences in neurocognitive performances or reports of functional impairment in pediatric cancer survivors relative to healthy controls. Verbal reasoning was the neurocognitive measure most highly associated with broad Functional Impairment; however, this was only true in cancer survivors. With regard to illness and treatment related variables, there was a significant relationship between length of survivorship and school impairment. Additionally, treatment severity was related to cortisol levels. Cortisol was not significantly associated with neurocognitive functioning or FI; however, there was a significant interaction such that cancer survivors appeared to benefit from higher cortisol levels. Conversely, healthy controls appeared to benefit from lower cortisol levels. However, this study is only a pilot study and more research needs to be done to provide further information regarding the proposed model, as well as explore additional risk and resiliency factors.

Figures

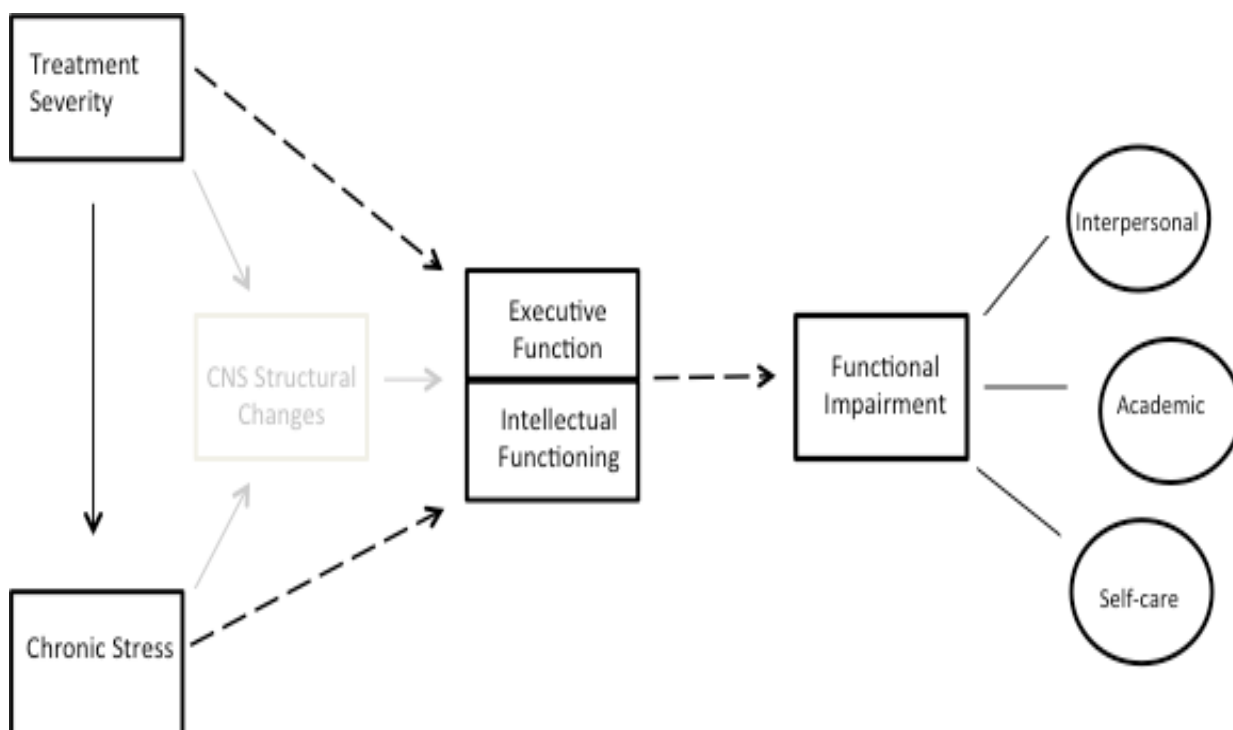


Figure 1: Conceptual Model of Neurocognitive Late Effects. A theoretical model of the neurocognitive late effects of pediatric cancer. Solid lines represent established relationships, while dotted lines represent relationships that have not yet been characterized within pediatric cancer populations and will be examined within the current study.

Note: CNS structural changes is included within the theoretical model given the significant empirical evidence; however further exploration of the relationship between CNS structural changes and other variables characterized within the model remains outside the scope of the current study and should be included in future research

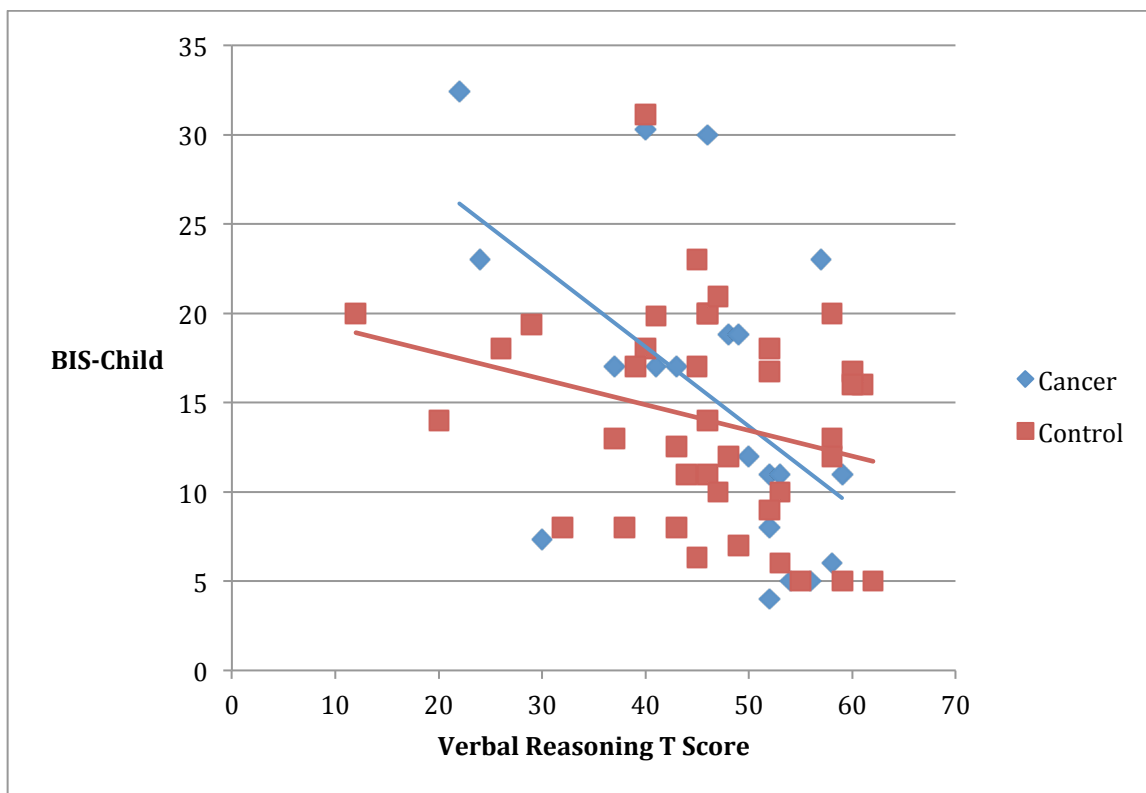


Figure 2: Group by Verbal Reasoning Interaction on BIS-CV Scores

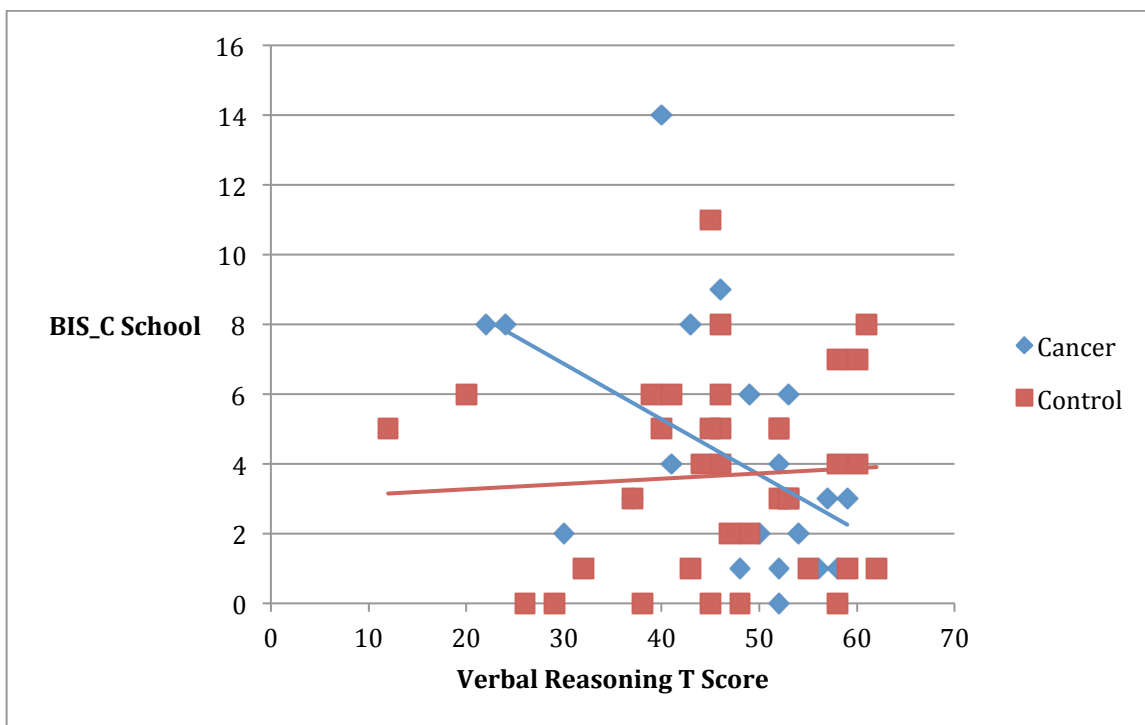


Figure 3: Group by Verbal Reasoning Interaction on BIS-CV School Scores

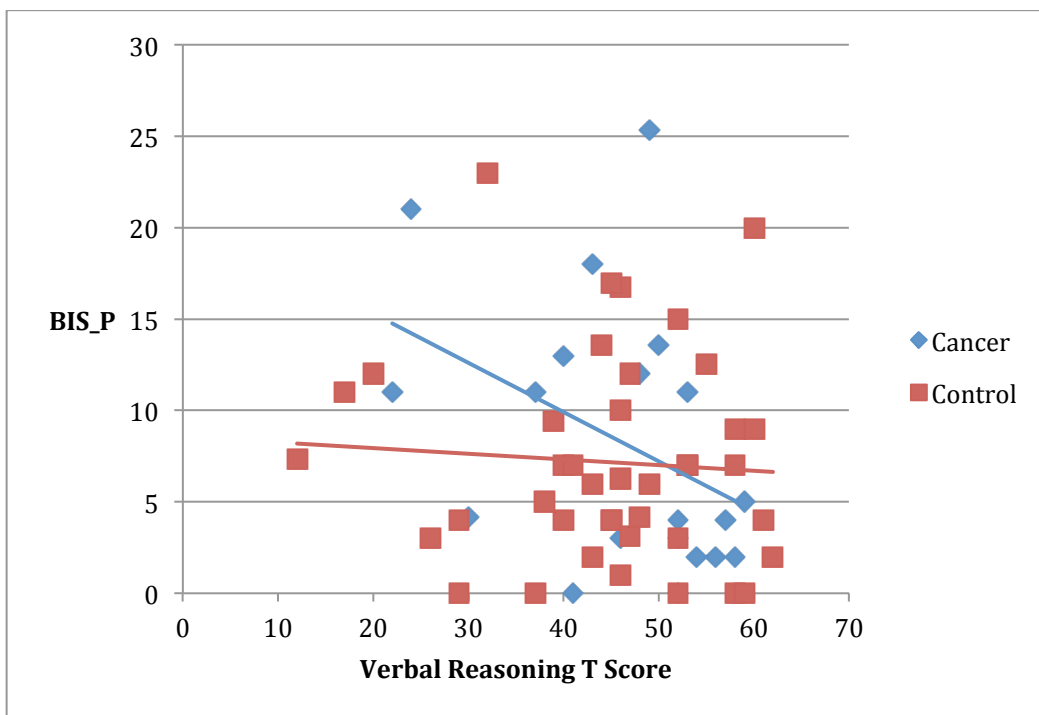


Figure 4: Group by Verbal Reasoning Interaction on BIS-P Total Scores

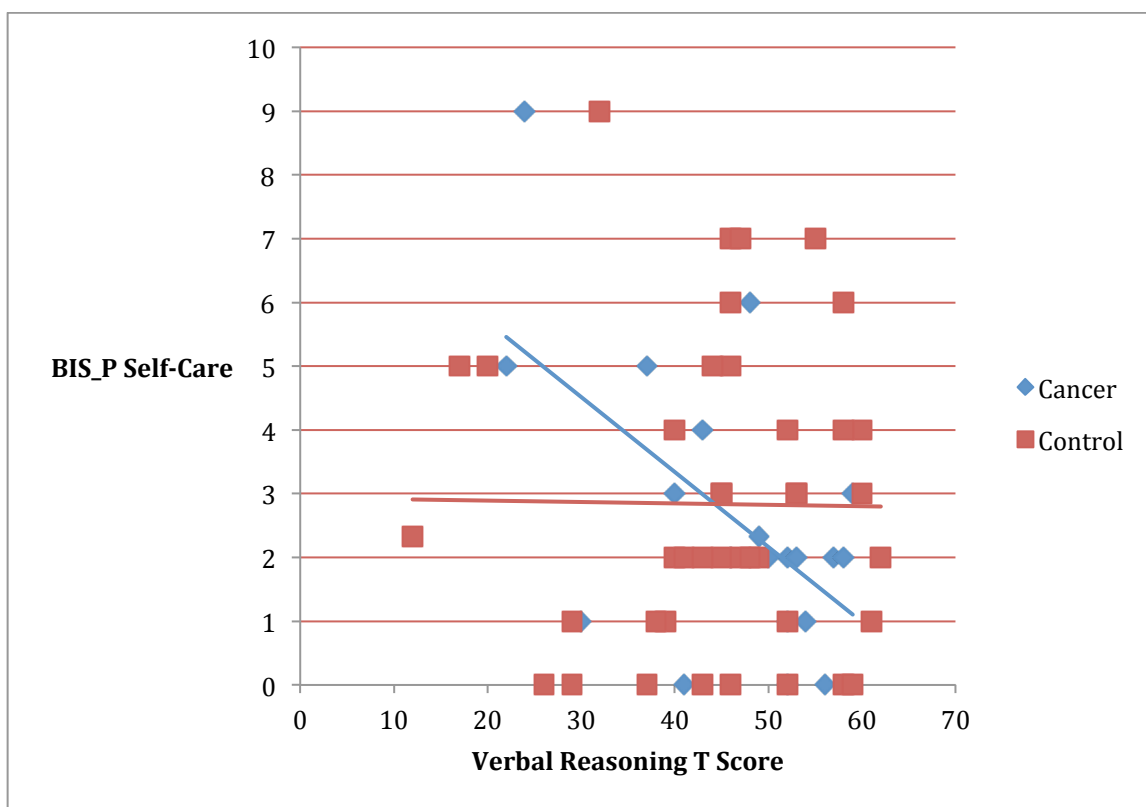


Figure 5: Group by Verbal Reasoning Interaction on BIS-P Self-Care Scores

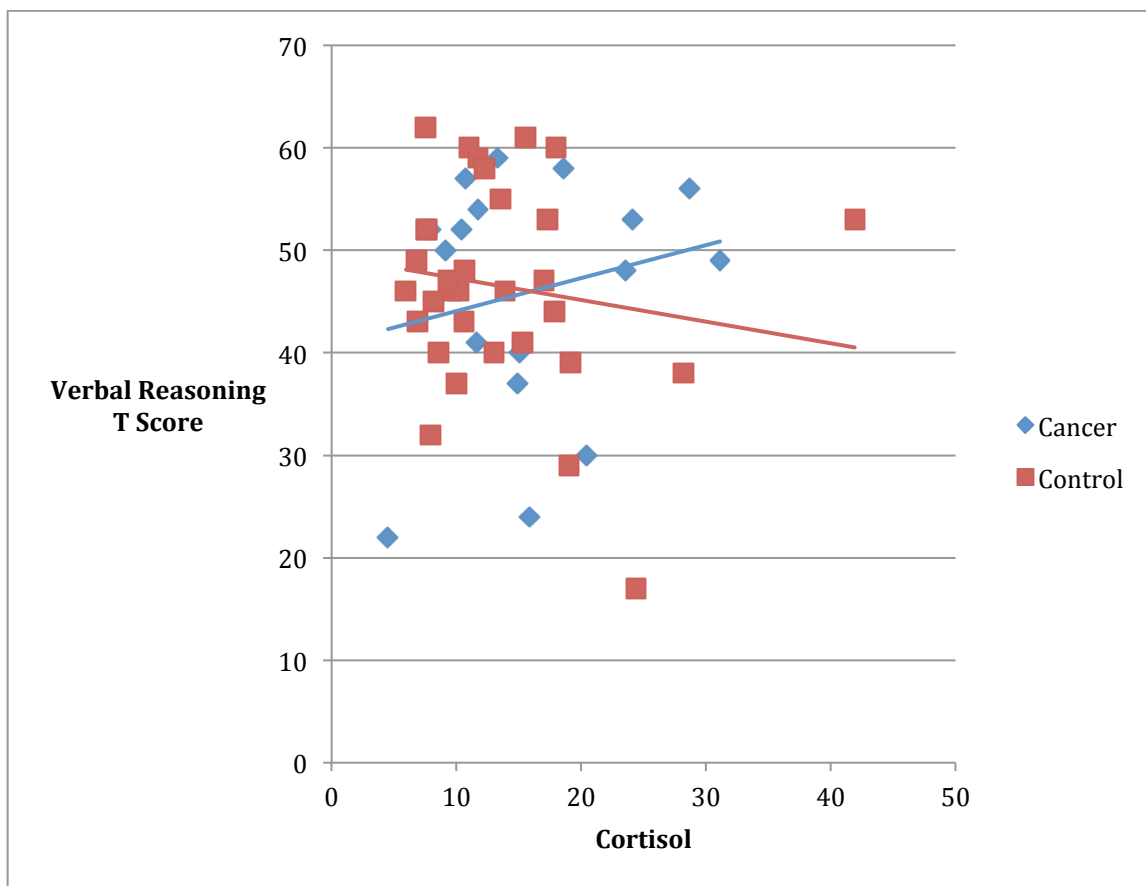


Figure 6: Group by Cortisol Interaction on Verbal Reasoning T Scores

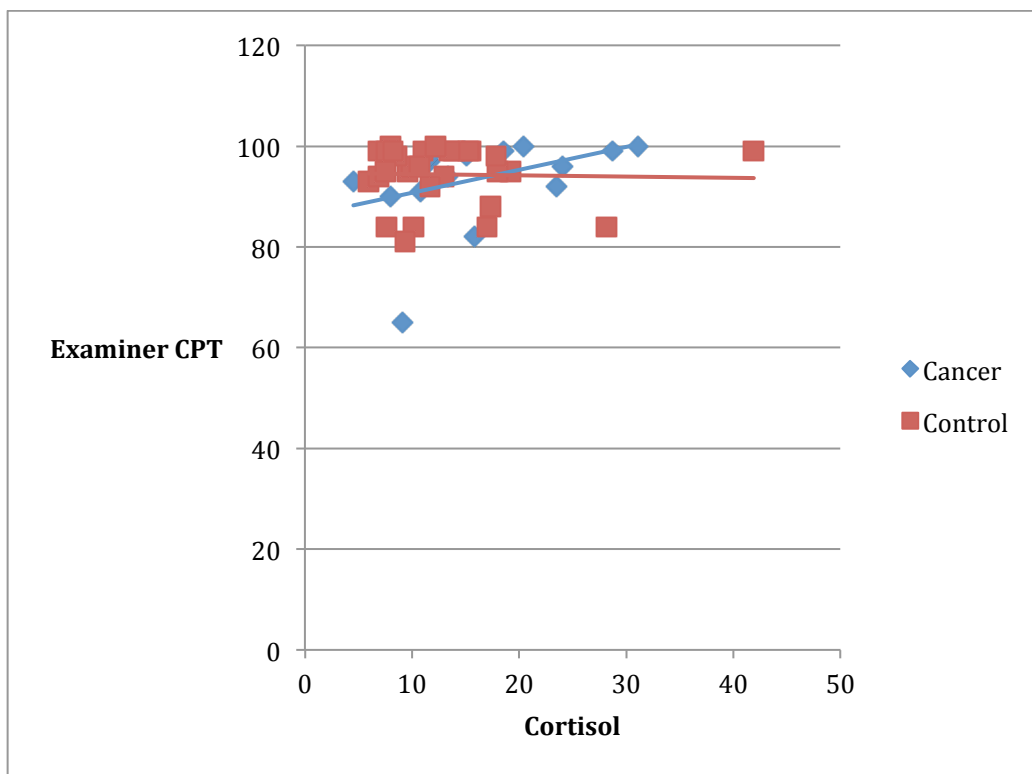


Figure 7: Group by Cortisol Interaction on NIH Examiner CPT Scores

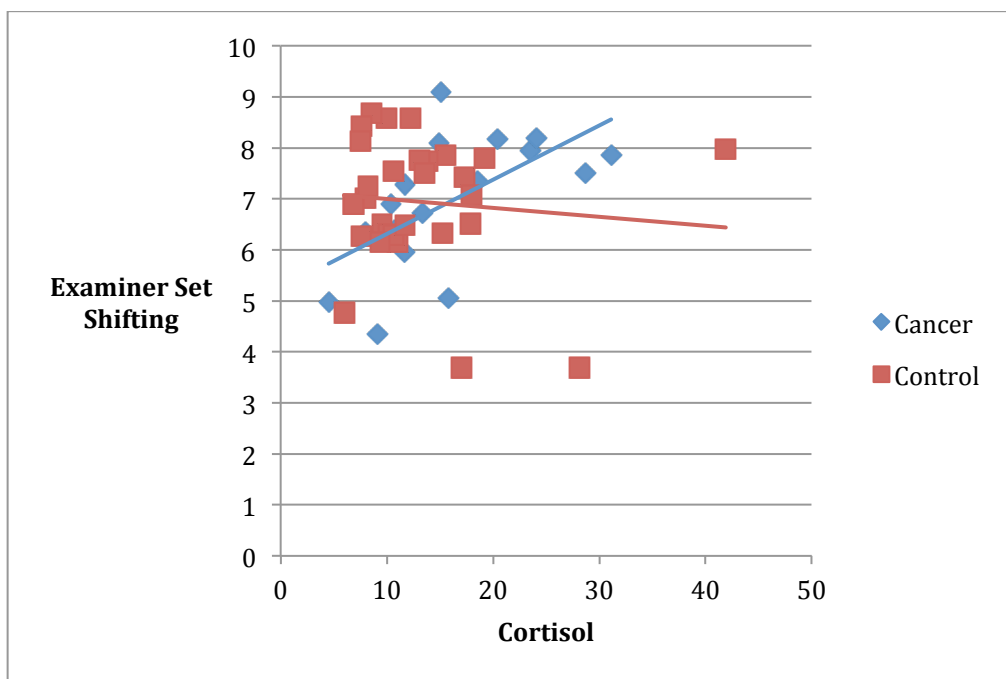


Figure 8: Group by Cortisol Interaction on NIH Examiner Set Shifting Scores

Tables

Table 1: Demographic Characteristics

Variable	Cancer (n=20)	Control (n=41)	Significance (p)
Child age (years)	11.55 (4.08) ^a	10.32(3.67)	0.24
SES ^b	31.36 (11.35) ^a	37.59(11.56)	0.054
	N(%)	N(%)	
Child ethnicity			0.25
White	6(30%)	9(22%)	
Hispanic	9(45%)	18(44%)	
Native American	2(10%)	1(2%)	
Asian	1(5%)	0(0%)	
Hawaiian/Pacific Islander	0(0%)	1(2%)	
Other	2(10%)	12(29%)	
Gender			0.49
Female	14(70%)	25(61%)	
Special Education			0.44
Yes	2(20%)	12(29%)	
Cancer Diagnosis			
Leukemia/Lymphoma	11(55%)	NA	
LCH	2(10%)	NA	
Aplastic Anemia	1(5%)	NA	
Malignant Germ Cell Tumor	1(5%)	NA	
Wilm's Tumor	2(10%)	NA	
Ewings Sarcoma	1(5%)	NA	
Rhabdomyosarcoma	1(5%)	NA	
Neuroblastoma	1(5%)	NA	

^aM(SD)^b Barratt Simplified Measure of Social Status (BSMSS), higher values indicate higher SES

Table 2: Parent-Child Concordance on the Brief Impairment Scale

Parent Report ^b	Child Report ^a			
	Total Impairment	Interpersonal	School	Self-Care/Self-Fulfillment
Total	0.27*	0.12	0.38**	0.06
Interpersonal	0.24	0.18	0.34**	-0.01
School	0.24	0.09	0.41**	-0.05
Self-Care/Self-Fulfillment	0.16	0.01	0.16	0.23

* $p < 0.05$, ** $p < 0.01$

^aBrief Impairment Scale-Child Version adapted from Bird et. al., (2005)

^bBrief Impairment Scale (Bird et al., 2005)

Table 3: Brief Impairment Scores Across Cancer Survivors and Healthy Controls

BIS score	Cancer M (SD)	Control M (SD)	T	Significance
Parent report^a				
Total score	8.25 (7.28)	7.18 (5.66)	0.635	0.53
% Above clinical cutoff	20%	13%		
Interpersonal	2.26(3.21)	2.03(2.03)	0.34	0.73
School	3.25(3.45)	2.30(2.45)	1.25	0.23
Self	2.62(2.25)	2.84(2.85)	-0.35	0.73
Child report^b				
Total score	15.38(8.87)	14.04(5.91)	0.69	0.49
% Above clinical cutoff	45%	46%		
Interpersonal	5.51(4.09)	5.40(3.80)	0.10	0.92
School	4.3(3.60)	3.62(2.71)	0.80	0.43
Self	5.33(2.96)	5.05(2.62)	0.37	0.71

^aBrief Impairment Scale (Bird et al., 2005)

^bBrief Impairment Scale-Child Version adapted from (Bird et. al., 2005)

Table 4: *IQ Scores Across Cancer Survivors and Healthy Controls*

IQ Score ^a	Cancer M (SD)	Control M (SD)	T	Significance
Full Scale IQ	99(12.65)	98(12.97)	0.41	0.69
Verbal IQ	46(10.89)	45(12.11)	0.45	0.65
Non-Verbal IQ	52(9.38)	52(10.13)	0.09	0.93

^a The Reynolds Intellectual Screening Test (RIST; Reynolds & Kamphaus, 2003).

Table 5: *EF Scores Across Healthy Controls and Cancer Survivors*

NIH Examiner ^a	Cancer M(SD)	Control M(SD)	F	Significance
Verbal Fluency	24.80(9.12)	22.02(9.40)	0.19	0.67
Planning	0.49(0.21)	0.37(0.18)	0.10	0.76
Continuous Performance	94(8.17)	89(21.5)	0.36	0.55
N Back Task	0.54(2.93)	0.28(2.81)	0.25	0.62
Set Shifting	6.97(1.27)	5.92(3.35)	0.81	0.37

^aNIH Examiner (Kramer et al., 2014)

Table 6: Pearson Bivariate Correlations Collapsed Across Groups

		BIS scales (Child)^d			
Neurocognitive Measures	Total	Interpersonal	School	Self Care	
IQ^b					
Full Scale IQ	-0.36**	-0.28*	-0.18	-0.30*	
Verbal IQ	-0.38**	-0.26*	-0.15	-0.39**	
Nonverbal IQ	-0.09	-0.08	-0.11	-0.03	
EF^c					
Verbal Fluency	-0.18	-0.21	0.15	-0.32*	
Planning	0.23	0.20	0.31*	-0.04	
Set-shifting	-0.09	-0.13	0.23	-0.28*	
N-Back	-0.11	-0.11	0.16	-0.33*	
Continuous Performance	0.02	-0.01	0.11	-0.08	
		BIS scales (Parent)^a			
Neurocognitive Measures	Total	Interpersonal	School	Self Care	
IQ^b					
Full Scale IQ	-0.24	-0.08	-0.29*	-0.21	
Verbal IQ	0.74	0.15	-0.01	0.04	
Nonverbal IQ	-0.21	-0.09	-0.22	-0.21	
EF^c					
Verbal Fluency	0.26*	0.39**	0.14	0.07	
Planning	0.16	0.26*	-0.02	0.17	
Set-shifting	0.07	0.15	-0.01	0.04	
N-Back	0.18	0.28	0.02	0.13	
Continuous Performance	-0.02	0.04	-0.02	-0.08	

* $p < 0.05$, ** $p < 0.01$ ^aBrief Impairment Scale (Bird et al., 2005)^bThe Reynolds Intellectual Screening Test (RIST; Reynolds & Kamphaus, 2003).^cNIH Examiner (Kramer et al., 2014)^dBrief Impairment Scale Child version adapted from (Bird et al., 2005)

Table 7: Pearson Bivariate Correlations within cancer survivors

BIS scales (Child)^d				
Neurocognitive Measures	BIS-Total	BIS- Interpersonal	BIS- School	BIS-Self Care
IQ^b				
Full Scale IQ	-0.49*	-0.42	-0.37	-0.41
Verbal IQ	-0.55*	-0.37	-0.48*	-0.50
Nonverbal IQ	-0.21	-0.23	-0.14	-0.16
EF^c				
Verbal Fluency	-0.04	0.17	0.16	-0.33
Planning	0.25	0.27	0.27	0.12
Set-shifting	-0.14	-0.25	0.13	-0.39
N-Back	-0.19	-0.10	0.01	-0.42
Continuous Performance	-0.08	-0.12	0.07	-0.17
BIS scales^a (Parent)				
Neurocognitive Measures	BIS-Total	BIS- Interpersonal	BIS- School	BIS-Self Care
IQ^b				
Full Scale IQ	-0.24	-0.08	-0.29*	-0.22
Verbal IQ	-0.18	-0.05	-0.21	-0.18
Nonverbal IQ	-0.21	-0.09	-0.22	-0.21
EF^c				
Verbal Fluency	0.26*	0.39**	-0.14	-0.07
Planning	0.16	0.26*	-0.02	0.18
Set-shifting	0.07	0.15	-0.01	0.04
N-Back	0.03	0.12	-0.03	-0.04
Continuous Performance	-0.02	0.04	-0.02	-0.08

* $p < 0.05$, ** $p < 0.01$

^aBrief Impairment Scale (Bird et al., 2005)

^bThe Reynolds Intellectual Screening Test (RIST; Reynolds & Kamphaus, 2003).

^cNIH Examiner (Kramer et al., 2014)

^dBrief Impairment Scale Child version adapted from (Bird et al., 2005)

Table 8: *Descriptive Statistics across Cancer Treatment Severity, Survivorship, and Cortisol*

Cancer variables	Cancer M(SD)	Control M(SD)	F	Significance
Treatment severity	1.21(1.03)	n/a	n/a	
Length of Survivorship	6.17(2.38)	n/a	n/a	
Cortisol (ug/dl)	15.97(7.44)	13.64(7.40)	1.102	0.299

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