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PSYCHOSOCIAL FUNCTIONING IN CHILDHOOD CANCER SURVIVORS, MEASURED BY PARENT, TEACHER & CHILD SURVEYS

A Thesis Submitted to the
Yale University School of Medicine
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Degree of Doctor of Medicine

by
Tamara Porter Miller
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PSYCHOSOCIAL FUNCTIONING IN CHILDHOOD CANCER SURVIVORS, MEASURED BY PARENT, TEACHER & CHILD SURVEYS

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The purpose of the current study is to understand emotional and neurocognitive functioning in childhood cancer survivors.

In this single-evaluation cross sectional study, 41 childhood cancer survivors (53.2% of those eligible) in the Health Education Research Outcomes in Survivors (HEROS) Clinic at Yale-New Haven Hospital between the ages of six and eighteen and their parents and teachers completed the Behavior Assessment System for Children, Second Edition (BASC-II), Behavior Rating Inventory of Executive Functioning (BRIEF) and Pediatric Quality of Life Inventory (PedsQL). Patient's, parents' and teachers' scores were compared to those of normative populations for emotional, neurocognitive and quality of life measures. Frequencies of impairment and within population differences in the study sample were calculated. Responses by patients were compared to those of parents and teachers to determine inter-rater reliability. The patterns of co-existing neurocognitive and emotional difficulties in the sample were described. Lastly, elements of emotional functioning, neurocognitive impairment, and patient characteristics predictive of impaired quality of life were identified with unadjusted and multivariate analyses.

Overall, 56.1% patients were female, the mean age at diagnosis was 3.6 years, and the mean age at study completion was 12.8 years. In examining inter-rater reliability, for most areas of emotional functioning there was poor agreement (kappa < 0.40). Parents and teachers showed moderate agreement in reporting problems with attention (kappa $= 0.57$), memory (kappa $= .61$), and metacognition (kappa $= 0.52$). Parents and children showed greater inter-rater reliability when reporting quality of life than symptoms, with agreement in every realm of the PedsQL (kappa > 0.40). Co-morbidities between emotional and neurocognitive impairments for the most part did not occur together. However, impairments in somatization and withdrawal tended to co-exist with impairments in memory, shift and metacognition ($p < 0.05$). In the multivariate analyses looking at social, emotional and school functioning, only neurocognitive functioning was a consistent predictor of poor quality of life (OR $= 12.94$, $p = 0.008$; OR $= 11.48$, $p = 0.044$; OR $= 33.5$, $p = 0.003$, respectively). Poor emotional functioning was also predicted by female gender (OR $= 15.58$, $p = 0.025$).

Similar to previous studies, a significant proportion of childhood cancer survivors in our sample endorse difficulties with internalizing symptoms and executive functions, as well as lower physical, emotional and social functioning, than normative populations. The current study shows inter-observer variability, especially among indexes of emotional symptoms, indicating a need for multiple reporters to determine areas of deficit and true levels of functioning. Problems with memory, shift, initiation and coordination of problem-solving behaviors co-exist with symptoms of somatization and social withdrawal in our study. However, it is the neurocognitive rather than emotional symptoms that are shown to be key predictors of how child-age survivors perceive their quality of life after therapy. These results highlight neurocognitive impairments as a target for intervention during and after treatment for pediatric cancers.

Acknowledgements

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Introduction

Great strides in treatment of childhood cancer have resulted in dramatic improvements in overall survival rates. With the advent of effective therapies, childhood cancer has been transformed from an almost fatal disease to one associated with survival rates of almost 80% in patients who are at least five years post-treatment (1, 2). While the rates of survivorship are encouraging, there is now a growing need to determine late outcomes in survivors, most of whom received toxic therapies in order to cure their malignancies. Depending on the specific treatments they received, survivors are at increased risk for multiple complications later in life, including subsequent malignancies, early mortality, growth delay, obesity, pulmonary and cardiovascular disease, and infertility (3, 4).

Studies have shown that, while the majority of survivors do not experience difficulties later in life, a small but significant subset are at increased risk for problems related to neurocognitive and psychosocial impairment, including emotional and social adjustment (5, 6). Lower socioeconomic status, less educational attainment, and female gender have been identified as potential risk factors (7, 8). Patients diagnosed during adolescence may also be particularly vulnerable to psychosocial distress and difficulties with adjustment (9). Neurocognitive and psychosocial difficulties experienced by survivors can have a significant impact on their quality of life, which includes and is defined by social and emotional global functioning (2).

Emotional and Social Functioning in Childhood Cancer Survivors

Based on the improvements in treatment for childhood cancer, survivorship no longer refers only to cure rates, but also encompasses the ability of patients to maintain a good quality of life after treatment. Emotional functioning is a crucial component of quality of life in survivors, and is defined by an individual's ability to regulate his or her feelings and thoughts, including his or her fears, sadness, anger or worries (5, 6, 10). Social functioning is also a key part of quality of life, and encompasses development of good and satisfying relationships with peers and feelings of competence in these interactions. Difficulty controlling one's emotional and social functioning may lead to an increase in internalizing symptoms and maladaptive behaviors.

Internalizing Symptoms

Internalizing symptoms include depression, anxiety, withdrawal and somatization. Depression is described as a disorder characterized by feelings of sadness, inactivity, crying, physical complaints and changes in behaviors that persist over time, affecting an individual's life (11, 12). Anxiety includes feelings of apprehension or fear that can include physical sequelae (13, 14). Withdrawal refers to detachment from social situations, while somatization is described as experiencing over-sensitization to relatively minor physical injuries or complaints (7, 13). Several chemotherapeutic agents have been associated with altered behavior, anxiety, and depression in different disease populations, and greater treatment intensity has been shown to play a role in development of these symptoms in previous studies (8, 15).

Overall adult and pediatric survivors experience clinically significant levels of depression and anxiety estimated at two- to three-times that of the general population during and after treatment combined (16). While studies of quality of life and psychosocial functioning report that the majority do well, a small but significant group of survivors have been shown to experience anxiety, depression and low self-esteem many years after treatment (1). In the Childhood Cancer Survivor Cohort, Zebrack et al. evaluated 11,000 patients and showed that 5.4% of patients report symptoms of depression compared to 3.4% in the sibling comparison group (8). In another study, parents of 2,979 survivors reported a 1.5-fold increase in depression and anxiety for survivors compared to a sibling control group (13). Children who have survived childhood cancer also have been shown to report higher scores on tests that measure tension and apprehension than age-matched healthy peers (17). Recklitis et al. described that when screened for psychological distress using the Symptom Checklist-90, 31.7% of survivors showed impairments (18). These studies indicate the existence of internalizing symptoms in the population of pediatric cancer survivors, but further understanding of the reasons for and impact of this distress is necessary.

Social Adjustment

Childhood cancer survivors have also been shown to exhibit impairments in social functioning and adjustment. Social functioning is the individual’s ability to communicate, make friends, and match the pace of peers, as well as the character of his or her peer interactions. Analysis of social functioning includes examining adaptability, leadership skills, and tendencies toward withdrawal and atypicality (9). Previous studies have shown that childhood cancer survivors participate in activities less often and spend more time by themselves than their siblings and age-matched peers (19). Furthermore, adolescent survivors have been reported to have a less well-developed sense of identity (10).

A number of disease and treatment factors have been shown to correlate with increased difficulty with social functioning. Survivors of brain tumors endorse impairments in social skills and social adjustment (20). Children who received cranial radiation or intrathecal chemotherapy, such as methotrexate, have been shown to exhibit more social and psychological difficulties (14, 21). In a study of long-term adolescent and young adult survivors, with the majority having had leukemia or lymphoma, older age at treatment and greater frequency of relapse were also associated with more impairments in psychosocial functioning (22).

Relationships with peers and family members have also been shown to be affected in the survivor population. Spirito et al reported that survivors have fewer friends (19), while Barrera et al. found that survivors were less likely to use friends as confidants than healthy children (23). Survivors may also be less satisfied with their relationships with their friends than are their peers, as shown by Gray et al. (24). Family interactions are influenced by a child having cancer. In one study adolescent survivors reported lower levels of family cohesion than healthy controls, with nearly 40% labeling their families as disengaged (25). Perceived family cohesion and social support is strongly related to overall psychological well-being in all populations (25, 26).

Rates at which survivors achieve independence in adulthood are also altered. Outcome studies suggest that, compared to normative populations, survivors are more likely to live with their parents and are less likely to marry (27-31). A large report of 8,900 patients through the Childhood Cancer Survivor Study showed that survivors are

1.6 times less likely to marry than the general population, and 1.8 times less likely than a sibling comparison group (32). This lower marriage rate may indicate deficits in social functioning and interactions with peers.

Neurocognitive and School Functioning in Childhood Cancer Survivors

Fifty to sixty percent of childhood cancer survivors are also at risk for neurocognitive impairments due to the therapies they received (33). These neurocognitive late effects include difficulties with attention, concentration, memory, processing speed, and executive function. Attention and concentration are defined by the ability to focus on tasks without distraction (15, 34). Memory describes an individual's ability to hold on to and recall information (33, 35), and processing speed refers to the speed and efficacy with which individuals understand and mentally compute information (33). Executive functions are the processes necessary for organizing and guiding behaviors during problem-solving, which include planning, insight, organization and initiation of behaviors (33, 36). Executive functioning is highly correlated with neurocognitive functioning, as executive functioning is thought to be located in the prefrontal cortex (36).

Difficulties with neurocognitive functioning are especially pronounced in survivors of cancers of the brain and central nervous system; outcomes are most impaired in survivors of brain tumors and acute lymphoblastic leukemia, who generally received therapies directed at the central nervous system (33, 37, 38). Cranial radiation and neurotoxic chemotherapeutic agents, including methotrexate, corticosteroids, and possibly cytarabine hydrochloride, have been associated with neurocognitive late effects

(15, 33, 37, 39). Younger age at diagnosis and therefore treatment has been associated with greater impairment in neurocognitive functioning because of the degree of brain maturation at the time of therapy (33).

These difficulties can play a role in many aspects of daily functioning, ranging from school performance to social interactions, and therefore it is important to understand their impact on an individual's quality of life. Studies have shown a correlation between neurocognitive exposures and poor decision-making leading to risky behaviors (40). Neurocognitive and behavioral outcomes are highly interrelated, so neurocognitive deficits must be considered when examining psychological and social functioning.

Further studies also document reduced school functioning in the population of childhood cancer survivors (41). This includes the ability to pay attention and remember information, as well as to regularly attend and keep up with work for school. Evans et al. revealed that 67% of survivors felt that their education had suffered because of their cancer (42). Studies have shown that childhood cancer survivors are more likely to repeat grades (7, 24), and that survivors of central nervous system tumors have lower school functioning (43). Even when obtaining similar levels of educational attainment as their healthy peers, survivors have reported feeling at a disadvantage because of their illness experience and underestimating their abilities, which can negatively affect school performance (44, 45). School functioning plays a role in the individual's quality of life, even outside of the isolated school setting, as children are in part defined by themselves and by their peers by their performance in the academic environment. In some previous studies, school functioning has been shown to be the prime determinant of social skills and psychological adjustment in pediatric survivors (41).

Social Cognitive Theory

Social and neurocognitive functioning are important to examine in populations of individuals who have undergone treatments for serious illnesses. However, it is crucial to not only understand the treatment-related impairments found in this population, but also to examine how these impairments affect the patients' self-perceptions of their performance and quality of life, and this is the goal of the current study. Psychological ability plays a direct role in determination of an individual's own efficacy expectation. In 1977, Albert Bandura described efficacy expectation as "the conviction that one can successfully execute the behavior required to produce the outcomes" (46). He theorized that development of self-efficacy is affected by the individual's experiences and the context of his or her life. Bandura wrote that this expectation ultimately determines how an individual is able to develop and exhibit coping behavior, and subsequently also drives selection of behaviors (46).

Wheeler and Ladd, in developing a scale to analyze the interaction between self-efficacy and peer relationships, reinforced this concept. They found that children endorse higher levels of self-efficacy in non-conflict situation, strengthening the notion that an individual's experience shapes his or her self-perceptions (47). This self-assessment of competence also determines how individuals interact with their peers. Wheeler and Ladd theorized that a key aspect of social competence is the individual's skill at appropriately interacting with their peers, and that a high level of social competence is crucial to the development of relationships. They found that anxiety and other emotions are associated with self-perception of competence in social behaviors (47). Harter later added that children tend to judge their social popularity based on how they judge their physical abilities and athletic skills (48). Children analyze their own thoughts, behaviors and perceptions of their capabilities, thus determining their self-efficacy and ultimately affecting their social interactions. Negative symptoms endorsed by an individual will therefore play a large role in the individual's experiences and quality of life.

Given that self-efficacy is dependent on the individual's situation and environment, children's self-perceptions are influenced not only by the experience of their illness and treatment, but also by those they interact with the most -- their parents and guardians. A child's self-perceptions may be affected by his or her parents' attitudes and subsequent treatment. Ladd and Price found in 1986 that parent's perception of the difficulty of a situation had a correlation with the child's ability to perform a measure, but not necessarily the child's own self-perception of competence (49). The current study aims to further investigate this concept by examining the importance of the reporter -- looking at how parents and teachers report children are performing and comparing those results to children's self-reports of their own quality of life. Understanding these differences in perception will serve to describe the forces that help drive how survivors of childhood cancer develop their self-efficacy expectation. Integrating reported levels of competence and self-perceptions, and therefore the relationships between impairments and self-perception of quality of life, can help target therapies with a goal of improved functioning.

A range of studies have revealed the existence of impairments in childhood cancer survivors and other research has detailed the importance of self-efficacy in the development of behaviors. With the identification of the spectrum of late outcomes, it is crucial to move forward and work to understand the effects of these deficits on self-efficacy and the daily quality of life of survivors. Survivorship no longer only describes cure, it also entails maximizing life experience after treatment. While it is known that the late outcomes of childhood cancer treatments are significant enough to influence quality of life, the ways in which this happens have not yet been characterized. It remains unclear which groups are most at risk for psychosocial deficits and what is the relative contribution of these impairments in emotional functioning to global quality of life in survivors.

Building on the work of other studies that have identified areas of deficit, the current study simultaneously measures emotional functioning, neurocognitive functioning, and quality of life in a small sample size to understand how these deficits in functioning predict qualify of life. Using descriptive data of emotional and neurocognitive impairments to characterize the study population, the study compares differences in perception depending on the reporter and analyzes emotional and neurocognitive deficits to determine co-morbidities. This information is then used to understand predictors of poor quality of life as perceived by childhood cancer survivors.

Statement of Purpose and Hypothesis

The overall purpose of the current study is to describe and analyze the emotional and social functioning of childhood cancer survivors using a sample of patients from the Yale University Health Education Research Outcomes for Survivors (HEROS) Clinic. Building on the work of previous studies, patients in the present study undergo simultaneous measurement of emotional functioning, neurocognitive functioning, and quality of life to accomplish three primary aims.

First, the study aims to determine if there is inter-rater reliability between respondents. This goal is accomplished by looking at agreement between results of parent-, teacher-, and self-reports. The current study hypothesizes that parents and teachers will report impairments in different areas than those self-reported by survivors.

Second, the study aims to characterize the co-existence of neurocognitive and emotional domains of impairment. In accomplishing this aim, the study tests the primary hypothesis that, as shown by these instruments, impairments in internalizing symptoms, emotional symptoms and executive functioning tend to occur together. It is hypothesized that the current study will support the results of previous literature in describing emotional and neurocognitive impairments to characterize the study population. These results would indicate that childhood cancer survivors endorse higher levels of internalizing symptoms, show impairments in the social domains of adaptability, leadership and social skills, and exhibit problems with executive functioning, including attention and memory.

Third, the study aims to identify factors of impairment in neurocognitive functioning, emotional functioning, and patient characteristics that predict worse quality of life as reported by the survivors themselves. The study hypothesizes that neurocognitive and emotional impairments will correlate with and predict lower levels of quality of life functioning as shown by the self-report version of the Pediatric Quality of Life Inventory. Lastly, it is hypothesized that, because of the unique developmental challenges of transitioning to independence during adolescence, adolescent age at the time of testing will predict worse self-perception of quality of life. Determining the predictors of impaired quality of life in the study population, this research hopes to set the stage for learning more about possible areas and methods of therapeutic intervention both during and after treatment.

Methods

Study Population

Eligibility for participation in this cross-sectional study was limited to patients enrolled in the Yale University Health Education Research Outcomes for Survivors (HEROS) Clinic. Attendees of the HEROS clinic must be in remission and at least three years post-diagnosis of their primary malignancy. Eligibility was restricted to patients aged six to eighteen years of age who either spoke English of Spanish. These criteria match the age ranges and languages for which the survey instruments were available. In addition, the parent or guardian was required to have a written knowledge of English or Spanish. Children who could not yet read could have the surveys read to them by a parent, guardian or member of the research team.

Prior to initiation of this study, the co-investigator for this study, Tamara Porter Miller, completed and submitted an application to the Human Investigations Committee with the assistance of the principal investigator, Dr. Nina Kadan-Lottick.[1] This protocol was approved on first review.

Participation and Recruitment Procedures

Patient recruitment began on July 19, 2005 and completed when the study closed on November 30, 2008. Patients and their families were approached about participation in the present study during their routine annual appointments by the co-investigator or a member of the HEROS Clinic staff. The co-investigator trained clinic staff to describe

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[1] The Principal Investigator for the current study was Dr. Nina Kadan-Lottick, M.D., M.S.P.H. The co-investigator was Tamara Porter Miller. Clinic staff also assisted in the execution of the present study. These staff members included Beverly Crowther M.Ed., Sheila Santacroce, Ph.D., Jodi Emir, R.N., and Kim Trotta, R.N. Additional guidance and assistance with data analysis was provided by other members of the HEROS Clinic Team, including Sui Tsang and Dr. Natasha Buchanan, Ph.D.

and consent patients for the study prior to study recruitment. If interested, the risks and benefits of the study were discussed. The parent and child then signed consent and assent forms respectively, as well as a research authorization form, while in the clinic waiting room. These consent and research authorization forms were written by the co-investigator and principal investigator and were approved each year by the Human Investigations Committee prior to use.

The parent and children were given the survey instruments to complete while waiting for their appointments. The parents were also given a survey that they were instructed to give to the most recent teacher who knew their child best. This survey was attached to a stamped, addressed envelope in which the teacher could return the survey. Parents and children could decline to include a recent teacher in the study and still participate in the study. The co-investigator or a trained HEROS clinic staff member was available at all times during the visit to answer questions about the consent process, risks and benefits, and survey instruments. The parents and children were given a phone number to call with questions.

When recruited in clinic the majority of patients did not have enough time to complete the surveys, and took the packets of questionnaires home to complete and return in self-addressed, stamped envelopes. Per protocol, as approved by the Human Investigations Committee, patients were contacted by phone if they had not returned the questionnaires. Families were asked if they had any questions about the surveys and were encouraged to send the packets back as soon as possible. If necessary, a second packet of surveys was sent. In rare cases, the patiens and their parents did not complete the packets for the entire year between recruitment and their regularly scheduled clinic appointment the following year. In these situations, the patients were called prior to the visit and asked to bring the completed surveys with them, or were re-recruited at the second clinic visit.

Patients were also recruited by mail, as approved by an amendment to the original protocol accepted by the Human Investigations Committee. At the end of the first summer of recruitment, in September, 2005, the co-investigator sent packets to every current patient in the HEROS Clinic who had not already been recruited in clinic. These packets included a letter explaining the study, age-appropriate assent and consent forms for the patients and their parents, the research authorization form, age-appropriate study instruments, and two addressed, stamped envelopes. Prior to distribution of the packets, each member of the HEROS Clinic was assigned a Clinic identification number. This number was written on the survey instruments in place of the patient name in order to provide anonymity. The envelopes in the package were addressed directly to the Principal Investigator.

The patients and parents were asked to put the signed consent and assent forms, the signed research authorization form, and the completed surveys into the large envelope and to return it as soon as possible. The smaller envelope in the packet was for the family to give to the most recent teacher who knew the child best. When received at Yale, the consent and authorization forms were separated in order to ensure future confidentiality. All further analyses of the data in the surveys were performed based on HEROS Clinic identification number instead of patient name.

A number was provided in the recruitment letter for patients to call with questions or to decline participation. If patients had not called to refuse participation, they were contacted with two further mailings and, if they came to clinic for their regularly scheduled appointments, were approached in person. Per protocol approved by the Human Investigations Committee, patients and their families could also be contacted by phone after the second mailing if they had not returned the packets or called to decline participation to determine if they had any questions. It was made clear both in the mailing letter and during recruitment in clinic that refusal to participate would not affect the child or family's relationship with their doctors in the HEROS Clinic.

Despite efforts to follow-up with patients and encourage return of packets, three families who had consented to participate did not return the surveys before the study period ended and were categorized as passive refusals. In addition, two families reported mailing packets that were never received. These families were approached about repeating the surveys, but declined to do so.

Study Procedures

The self-report surveys took child respondents approximately fifteen to twenty minutes to complete, and parent and teacher respondents thirty to forty minutes to complete. Participants were informed that each child would be assigned an identification number so that their names would not be directly listed on the surveys with their responses. Once completed, surveys were stored in a locked area separately from the consent forms to maintain confidentiality.

The patient, parent and identified teacher all completed age-appropriate and audience-specific versions of the Behavior Assessment System for Children, Second Edition (BASC-II). The parent and teacher completed parent- and teacher-versions of the

Behavior Rating Inventory of Executive Function (BRIEF). The parent and child also completed age-appropriate parent- and child-versions, respectively, of the Pediatric Quality of Life Inventory, Version 4.0 (PedsQL). The parent answered an intake questionnaire, the Family and Social History Questionnaire, collecting information about family, social, school, pre-treatment, birth and cancer treatment history.

Patients enrolled in the HEROS clinic were asked a variety of demographic, family and social history, and treatment-history related questions during their initial visit. This information, combined with information in the patient's medical record related to their diagnosis and treatment history, was compiled in the HEROS Clinic database. Information in this database was collected for the patients enrolled in the present study and used to stratify and characterize patients during the analysis. This data included information about the primary diagnosis, subsequent malignancies, chemotherapy and radiation history, and complications and outcome history.

Study Measures

Behavior Assessment Scale for Children, Second Edition (BASC-II)

The BASC-II (Reynolds, CR and Kamphaus, RW, 2004) is a set of surveys that examines adaptive and maladaptive behaviors, thoughts and emotions of children and adolescents (50). The BASC-II is often used to examine affective and mood disorders in children as perceived from the parent's and teacher's point of view or as self-reported from the child.

Self-, teacher- and parent-report versions of the BASC-II were used in the age categories between ages six and eighteen years. The SRP-C, a self report for ages eight through eleven, has 139 items. The SRP-A, a self report for age twelve through twenty-one, has 176 items. The PRS-C, or parent rating scale for ages six through eleven, has 160 items. The PRS-A, completed by parents for their children aged twelve to twenty-one has 150 questions. The teacher versions, the TRS-C for ages six to eleven and the TRS-A for ages twelve to twenty-one, each have 139 items. The parent, teacher or child completing the survey is asked to read each statement and mark the response that best describes how the child has acted over the previous six months (never, sometimes, often, or always). The self-report version also requires the child to respond to a series of true or false questions.

On the parent and teacher versions, the scales are divided as described below. The first scale, Externalizing Problems, includes Aggression, Hyperactivity and Conduct Problems. The second scale, Internalizing Problems, includes Anxiety, Depression, and Somatization. The next scale, School Problems, includes Attention Problems and Learning Problems. The Adaptive Scale includes Adaptability, Leadership, Social Skills and Study Skills. There is also an Atypicality scale that is used with Withdrawal and Social Skills to gauge unusual behaviors and impaired relations. Lastly, there is a broad scale called the Behavioral Symptoms Index; this includes Hyperactivity, Aggression, Depression, Attention Problems, Atypicality, and Withdrawal. There is also a subscale called Activities of Daily Living, which analyzes the individual's skills at completing routine daily tasks, and a subscale called Functional Communication, which evaluates the ability to effectively communicate thoughts and ideas (50) (for definitions of each scale, see *Table 1*).

Table 1 - Definitions of Scales on the Behavior Assessment Scale for Children, Second Edition (50)

Scale	Definition
Externalizing Problems	
Aggression	Behaviors of physical or emotional harm towards others
Hyperactivity	Impulsive and excessively active tendencies
Conduct Problems	Disruptive behaviors in school or at home
Internalizing Problems	
Anxiety	Feelings of apprehension or fear that can include physical sequelae (13, 14)
Depression	Feelings of sadness, inactivity, crying, or changes in behavior (11, 12)
Somatization	Over-sensitization to relatively minor physical injuries or complaints (7, 13)
Atypicality	Behaviors that are unusual for the child’s age
Locus of Control	Control over external situations, only on self-report
Social Stress	Tension and anxiety felt by children in social situations, only on self-report
Sense of Inadequacy	Self-perceptions of ability, only on the self-report
School Problems	
Attention Problems	Difficulties with maintaining focus and ease of distractibility
Learning Problems	Deficits in understanding academic problems and obtaining high levels of academic achievement
Adaptive Skills Composite	
Adaptability	The ability to change and to positively react to change
Social Skills	Interactions with others
Leadership	Tendencies to take charge when working with others
Study Skills	Abilities in an academic setting
Personal Adjustment	
Relations with Parents	Interactions with parents, only on self-report
Interpersonal Relations	Interactions with peers, only on self-report
Self esteem	The child’s happiness with his or her self, only on self-report
Self-Reliance	Self-perception of decision making capability, only on self-report
Withdrawal	Behaviors of social avoidance and being reclusive
Activities of Daily Living	The individual’s skills at completing routine daily tasks
Functional Communication	The ability to effectively communicate thoughts and ideas
Behavioral Symptoms Index	

On the self-report the first scale is School Problems, and includes Attitude to School, Attitude to Teachers and Sensation Seeking. The Internalizing Symptoms scale includes Atypicality, Locus of Control, Social Stress, Anxiety, Depression, Sense of Inadequacy and Somatization. The Inatttention/Hyperactivity scale includes Attention

Problems and Hyperactivity. The Emotional Symptoms Index is a broad scale that includes Social Stress, Anxiety, Depression, Sense of Inadequacy, Self-Esteem and Self-Reliance. Lastly, the Personal Adjustment scale includes Relations with Parents, Interpersonal Relations, Self-Esteem and Self-Reliance (50) (for definitions of each scale, see *Table 1*).

Answers to the survey questions are inputted into a computer program that calculates the scaled scores for each index. Scores were compared to the general, combined sex normative population. The Adaptive Scales include Functional Communication, Adaptability, Activities of Daily Living, Leadership, Social Skills and Study Skills; the other scales are considered Clinical Scales. In scoring the surveys, T-scores on the Adaptive Scales are considered at-risk below forty and clinically significant at thirty and below. For the Clinical Scales T-scores are considered at-risk when greater than sixty and clinically significant when greater than seventy (50).

The BASC-II has been used in a variety of populations to analyze emotional and behavioral problems in children. These groups have included healthy children, children with a range of illnesses, and children from a variety of socioeconomic and ethnic backgrounds. The instrument has been compared to other assessment surveys and been shown to be a valid and useful tool for maladaptive behaviors. Reliability was studied by the authors. Reliability scores for the teacher version ranged from 0.85 to 0.95, with composite scores having the highest reliability. Reliability scores are reported by the authors to range from 0.83 to 0.87 for the parent version and the mid-0.70s to the mid-0.80s for the self-report version (51).

Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF (Gioia, GA, Isquith, PK, Guy, SC, Kenworthy, L, 2000) is a parent- and teacher-completed instrument that assesses the child's emotional control, ability to inhibit and short attention, initiation, working memory, planning, and organization of materials (36). There is one parent version and one teacher version; the scaled score adjusts for the age of the individual. It is an 86-item questionnaire divided into eight clinical scales and two validity scales. These are grouped into two broader indexes of Behavioral Regulation and Metacognition. The parent or teacher is asked to read each statement and answer how much of a problem the child has had with each statement in the previous six months (never, sometimes, often).

The results are tallied and the raw scores are converted to scaled, or T-scores. The results are divided into the following scales: the Behavioral Regulation Index (BRI) and the Metacognition Index (MI). The BRI includes the subscales of Inhibit, Shift, and Emotional Control, and describes the individual's ability to appropriately control and modulate emotions and behaviors. The MI includes the subscales of Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor. The MI reveals the child's ability to start, arrange and coordinate problem solving in working memory. All of the subscales are combined into one summary scale, the Global Executive Composite (GEC) (36) (for definitions of each scale, see *Table 2*).

The T-scores are compared to a standardization sample to determine if the results are clinically significant. Higher T-scores indicate more problems with executive function. In evaluation of results from both the teacher and parent versions of the

Table 2 - Definitions of Scales on the Behavior Rating Inventory of Executive Functioning (36)

Scale	Definition
Behavioral Regulation Index	The ability to appropriately control and modulate emotions and behaviors
Inhibit	The ability to control impulses and stop behavior
Shift	Aptitude in moving freely between activities and problem-solving flexibility
Emotional Control	Emotional regulation and expression of executive functioning
Metacognition Index	The ability to start, arrange and coordinate problem solving in working memory
Initiate	The ability to begin activities and generate ideas
Working Memory	The ability to retain and recall information during problem solving
Plan/Organize	The ability to coordinate tasks
Organization of Materials	The tidiness of a child's work and play areas
Monitor	The tendency to check work and assess one's own performance
Global Executive Composite	Summary analysis of executive functioning

BRIEF, T-scores equal to or greater than 65 are considered at risk for clinical significance on all scales (36).

The BRIEF was normalized with a set of 1419 parent forms and 720 teacher forms. The sample represented both genders and a broad socioeconomic and ethnically-diverse group (52). The reliability and validity for the BRIEF were studied and are reported in the manual for the study instrument. Content and construct validity were studied by the authors and a group of neuro-psychologists. The reliability scores, which measure internal consistency, ranged from 0.80 to 0.98 for both the parent and teacher versions of the BRIEF (36, 52).

Pediatric Quality of Life Inventory, Version 4.0 (PedsQL)

The PedsQL (Varni, JW, 1998) is a global quality of life survey that assesses children's emotional and social status. It is intended to be given to both healthy populations and children with acute and chronic diseases. It is intended to distinguish between these populations and determine disease severity within the group of children with chronic illnesses. The instrument includes parent and child versions for each age group. The current study used the surveys targeted for the ages 5-7, 8-12, and 13-18. The PedsQL is a twenty-three-item survey divided into four sections: physical functioning, emotional functioning, social functioning, and school functioning. There are eight questions about physical functioning, and five questions in each of the other three categories.

The parent or child is asked to read each statement on the questionnaire and mark the response that best describes how much of a problem the statement has been in the previous month (never, almost never, sometimes, often, almost always). The answers are converted to numerical z-scores. They are tabulated to give a Total Scale Score, a Physical Health Summary Score (eight items), and a Psychosocial Health Summary Score (fifteen items). Higher z-scores correlate with better quality of life. Lower z-scores indicate reports of worse quality of life. In the current study physical functioning data was obtained but not used for further analysis, as this was out of the scope of this research.

The author of the PedsQL studied the reliability and validity of the instrument in a population of 963 children and 1629 parents. Varni et al. found that there was internal consistency reliability for the Total Scale Score of 0.88 for the child surveys and 0.90 for the parent surveys. Validity was proven through positive correlations with indicators of mortality and illness burden and through ability to distinguish between healthy and sick children (53). The PedsQL was analyzed in an ethnically diverse and socio-economically heterogeneous populations of healthy and sick children (53).

Family and Social History Questionnaire

The Family and Social History Questionnaire is an intake survey written by the co-investigator and principal investigator and completed by the parent. The survey aims to collect demographic data and information about the child's school and treatment history. It was used to stratify results from the other surveys by patient characteristics. This data was used with the information from the HEROS database to understand the type of cancer and therapy each child received, as well as the child's daily living situation. Data collected included: Race, Living Situation (Parents divorced/married, Siblings, Who Lives at home, Who is the primary caregiver), Present age, Current grade, If the child attended school during therapy, What type of school the child attends, If and what type of special education services the child receives, Medication history and current medications (Anti-depressants, Ritalin, etc.), and History of mental health services (Psychotherapy, Behavioral Therapy, Psychotropic drugs).

Data Analysis

The pattern of impairment in the study population was described in order to characterize the population and to be used for further analyses. This was accomplished by comparing the data from the BASC-II, BRIEF and PedsQL to the scores of published age- and gender-specific normative populations. Two-sided one sample student T tests were then conducted to compare observed frequency of impairment in the research population with the expected proportions in the general population. Outcomes were examined as mean scores as well as percentages of the population in the impaired range. Percentages of impairment were compared using Fisher's test to evaluate for significant differences between groups. P-values less than 0.05 were considered statistically significant.

In order to further describe the emotional, neurocognitive and quality of life functioning in the study population, children were divided by gender and by age at diagnosis of less than 3.5 years of age or greater than or equal to 3.5 years of age. Age at diagnosis was analyzed because previous literature has shown that younger age at diagnosis impacts symptoms of late effects, especially in neurocognitive functioning. The age cutoff was chosen because, in the current study population, the mean was 3.6 years and the median was 3.4 years.

Patients were also analyzed by age at study completion because prior studies indicate different presentation of late effects in adolescents and younger populations. Adolescent age was considered from twelve to eighteen years of age and pre-adolescent age was six through eleven years of age. This was determined using the age breakdowns of "Child" and "Adolescent" on the BASC-II. Patients were also divided based on their receipt of central nervous system-directed therapies, which included intrathecal chemotherapy and cranial irradiation.

To accomplish the first aim of the study -- to describe inter-rater reliability -- kappa statistics analyzed agreement of perceptions reported on the parent, teacher and self-report versions of the survey instruments. Inter-rater reliability for a given scale was evaluated to produce kappa coefficients, which are measures of agreement. Kappa coefficients of 0.41 to 0.60 were considered moderate strength of agreement, and values of 0.61 to 0.80 were considered substantial strength of agreement. A kappa value between 0.81 and 1.00 was considered almost perfect strength of agreement (54). P-values were used to determine if the agreement was due to chance.

Specifically, the attention scales on the parent and teacher versions of the BASC-II were analyzed. Parent and self-report versions of the BASC-II were evaluated for agreement on the scales of depression, anxiety, withdrawal, somatization, attention and internalizing problems. Inter-observer reliability between parent and teacher perceptions of executive functioning were analyzed with reports on the BRIEF of memory, inhibition, shift, planning and organization, initiation, monitor, the Metacognition Index (MI) and Global Executive Cognition (GEC). Parent and child perceptions of quality of life were analyzed for agreement using the parent and self-report versions of the PedsQL on the school, emotional and social functioning scales. The physical functioning scale was not examined because it was out of the scope of this study. There is no teacher-report version of the PedsQL. To understand different perceptions of school functioning between teachers and children, self-report of school functioning on the PedsQL was evaluated for agreement with teacher-report on the BRIEF of problems with memory, planning, initiation, and organization of materials.

The second aim of the current study is to characterize co-morbidities between neurocognitive and emotional problems. To accomplish this goal, two-by-two comparison analyses were created evaluating specific scales on different survey instruments. Among the group of parents reporting impairment in an emotional outcome, the percentage of parents reporting co-existing impairment in a given neurocognitive outcome was assessed. Fisher's tests were run to determine the presence of a significant association with p-values less than 0.5 showing statistically significant association. Chi-square analysis could not be performed due to the small sample size of the study.

Using the descriptive data of emotional and neurocognitive functioning in the study population from the study instruments, anxiety and depression, somatization, withdrawal and internalizing symptoms on the parent-report BASC-II were each compared in two-by-two tables to the memory, organization of materials, initiation, shift, monitor, inhibition and metacognition index scales on the parent version of the BRIEF. To determine these co-morbidities, the parent versions of the BASC-II and BRIEF were used. The parent versions were utilized due to the parent's ability to examine the child in several environments. This was chosen based on previous literature using parent-report to analyze behaviors in childhood cancer survivors (2, 19). While parent-report cannot provide a sole substitute for child-report, it has been shown to be a useful and valid measure (55). For consistency, the parent versions were used in all further analyses examining endorsement of symptoms. Self-report could not used because the BRIEF, the most reliable and valid measure of problems with neurocognition used in this study, does not include a self-report version.

The study's third aim is to identify factors that predict poor quality of life functioning. To accomplish this aim an unadjusted and adjusted multivariate analysis was performed. The parent- report versions of the BASC-II and BRIEF were used for these analyses. However, the self-report version of the PedsQL, the quality of life inventory, was selected to obtain the best understanding of the effects of impairments on childhood cancer survivors.

The demographic predictors of female gender and adolescent age were selected to be analyzed as predictors of poor quality of life. These were selected based on reports in the literature and the results of the current study showing greater impairments in these populations. Age at diagnosis and age at study completion were shown by this and previous studies to be correlated, and age at testing is considered a better determinant of functioning, so it was chosen for the multivariate analysis. Additionally, in order to test the hypothesis that endorsement of internalizing symptoms and problems with executive functioning predict lower quality of life, parent rating of impairment on the internalizing symptoms scale on the BASC-II and parent rating of impairment on the metacognition index of the BRIEF were used in the linear regression. The internalizing symptoms scale on the BASC-II was selected as a strong measure of emotional functioning, and the metacognition index on the BRIEF was chosen as a good overall measure of neurocognitive function. These demographic and symptom predictors were used to analyze the scales of school functioning, emotional functioning and social functioning on the self-report PedsQL via an unadjusted and adjusted linear regression.

Results

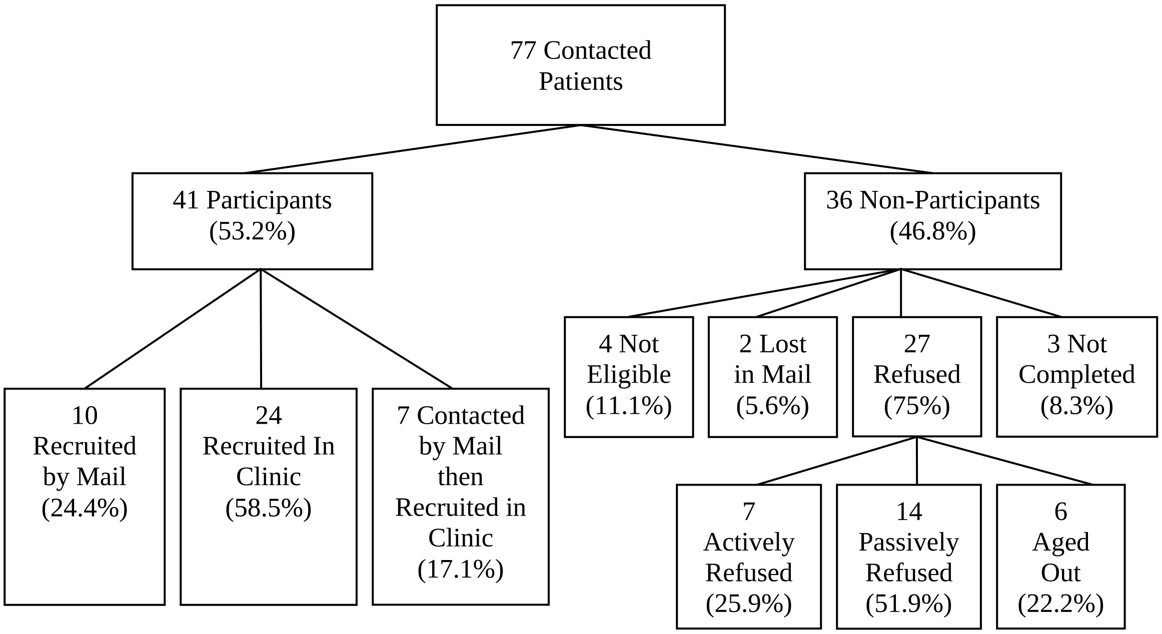
Characteristics of the Study Sample

Forty-one of the seventy-seven (53.2%) patients contacted consented to participate in the current study. A combined twenty-seven (35.1%) patients actively or passively refused participation. Three patients out of the seventy-seven contacted (3.9%) were recruited and consented to participate, but never returned the study instruments. Two (2.6%) of the contacted patients consented to participate and reported putting the completed surveys in the mail, but these surveys were never received. These patients were approached about re-completing the surveys but declined to do so; these packets are considered lost in the mail. Four (5.2%) recruited patients were deemed to be ineligible (see *Figure 1*). Of these recruited, ten (24.4%) were recruited by mail and twenty-four (58.5%) were recruited in clinic. Seven (17.1%) of those recruited were contacted by mail and did not respond, but were later recruited in clinic (see *Figure 1*).

Of the twenty-seven who refused participation, seven (25.9%) actively refused participation in the study in clinic. Fourteen (51.9% of refusals) patients who were sent packets never responded nor came to clinic, and are considered passive refusals. Six patients (22.2% of refusals) who were mailed surveys did not respond or have clinic appointments before they turned nineteen, which was too old for the study; these patients aged-out and are also considered passive refusals (see *Figure 1*).

The mean age at diagnosis in the study population was 3.63 years, with a standard deviation of 2.55 and a range of zero to 12.66 years (see *Table 3*). The median was 3.37 years. The age at diagnosis was skewed to the left, with 23 patients (56.1%) diagnosed before age 3.5, and 18 (43.9%) diagnosed at age 3.5 or older.

Figure 1 - Diagram Showing Success of Study Recruitment and Reasons for Refusal of Participation



The mean age at testing, defined as the time of study completion by the parent, child and teacher, was 12.85, with a standard deviation of 3.54 and a range of 6.67 to 18.98 years. Patients were considered too old for the current study once they turned nineteen. Sixteen (39%) of patients were pre-adolescent, defined as ages six through eleven, and 25 (61%) were adolescents, aged twelve through eighteen (see *Table 3*). The variation in age at testing was great, with the most numbers of patients aged nine, twelve and fourteen, with five patients each. The mean age since completion of cancer treatment was 9.21 years, with a standard deviation of 3.53 and a range of 4.16 to 16.37 years.

The largest group of patients was white; thirty-two (78.1%) of the patients studied were Caucasian and non-Hispanic. Five (12.2%) were Hispanic and two (4.9%) were

Table 3 – Comparison of Participants and Non-Participants in Terms of Demographics and Treatment Factors [A]

	Participants N (%)	**Non-Participants N (%)**	**p-value**
Gender			
Female	23 (56.1%)	12 (44.4%)	0.458
Male	18 (43.9%)	15 (55.6%)	
Ethnicity			
White	36 (87.8%)	16 (88.9%)	0.831
Non-White[B]	4 (9.8%)	2 (11.1%)	
Unknown	1 (2.4%)		
Household Income			
< $40,000	3 (7.3%)		
$40,000 - $80,000	13 (31.7%)		
> $80,000	18 (43.9%)		
Unknown	7 (17.1%)		
Cancer Diagnosis			
ALL	21 (51.2%)	7 (26%)	**0.014**
Central Nervous System Tumor	4 (9.8%)	0	
Sarcoma	4 (9.8%)	3 (11.1%)	
Neuroblastoma	3 (7.3%)	4 (14.8%)	
Wilm’s Tumor	3 (7.3%)	6 (22.2%)	
Non-Hodgkin’s Lymphoma	1 (2.4%)	6 (22.2%)	
Hodgkin’s Lymphoma	1 (2.4%)	0	
Other	4 (9.8%)	1 (3.7%)	
CNS-Directed Treatment			
CNS-Directed Treatment[C]	25 (62.5%)	7 (25.9%)	
No CNS-Directed Treatment	15 (37.5%)	20 (74.1%)	
Treatment History			
Chemotherapy Only	25 (61%)	6 (22.2%)	0.000
Chemotherapy and Radiation	14 (34.1%)	6 (22.2%)	
No Chemotherapy or Radiation	2 (4.9%)	15 (55.6%)	
Mean Age at Diagnosis ± SD (Range) in Years	3.6 ± 2.6 (0-12.7)	3.2 ± 2.7	0.554
Mean Age at Time of Study Opening ± (Range) in Years	12.0 ± 3.7 (6.7-18.99)	14.5 ± 2.9	**0.004**
Mean Age at Study Completion ± SD (Range) in Years	12.8 ± 3.5 (6.7 – 18.99)		
Time Since Therapy Completion in Years[D]			
0-4	15 (38.5%)	0 (0%)	
5-9	15 (38.5%)	6 (54.6%)	**0.041**
10-14	8 (20.5%)	4 (36.4%)	
>15	1 (2.5%)	1 (9%)	

A - Bold numbers indicate statistical significance.

B - Non-white includes African-American, Hispanic, Central American Indian and other.

C - CNS-Directed Therapy includes intrathecal chemotherapy or cranial radiation. In the group of participants, twenty-one patients received intrathecal chemotherapy and six patients received cranial radiation.

D – Years since therapy completion was determined using the date of study completion for participants and using the date on which the study was opened for non-participants. Data about the date of therapy completion was only available for 11 non-participants.

African-American. One (2.4%) patient refused to answer and one (2.4%) was listed as other (see *Table 3*).

Parents reported their total family income on the Family and Social History Questionnaire. The majority of parents, eighteen (43.9%), listed their annual family income as greater than 80,000 per year. Eight (19.5%) reported income of 60,000 to 80,000. Five (12.2%) listed their incomes as 40,000 to 60,000, and three (7.3%) as less than 40,000 annually. Three (7.3%) patients refused to answer and four (9.8%) reported that they did not know their average annual income (see *Table 3*).

The study population included a wide range of cancer diagnoses. Twenty-one patients (51.2%) were diagnosed with acute lymphoblastic leukemia. Four patients (9.8%) had been diagnosed with sarcomas and four patients (9.8%) with tumors of the central nervous system. Three patients (7.3%) were diagnosed with each of the following cancers: Neuroblastoma and Wilm’s tumor. Two patients (4.8%) were diagnosed with lymphomas, one patient with Hodgkin’s Lymphoma and one patient with Non-Hodgkin’s Lymphoma. Four patients (9.8%) had other cancers (see *Table 3*).

Of these patients participating in the study, twenty-five (61%) received only chemotherapy. Fourteen (34.1%) of the patients received both chemotherapy and radiation. Two (4.9%) patients received neither chemotherapy nor radiation as part of their cancer treatment (see *Table 3*).

The group of participants was compared to those who declined participation in the present study. There were no significant differences in the two populations in terms of gender, ethnicity, or age at diagnosis. In the participant group twenty-three (56.1%) were female, while in the non-participant group twelve (44.4%) were female. There was a significant difference in the age at testing. The mean age in the study population was 12.0 years, while the mean age at time of study opening in the non-participant group was 14.5 (p-value = 0.004) (see *Table 3*).

The set of diagnoses was significantly different (p-value = 0.014) when comparing overall range of diagnoses for each group. The study population had a greater percentage of patients with acute lymphoblastic leukemia (51.2%) than the non-participant group (25.9%). Diagnoses of Neuroblastoma (7.3% in the study population), Wilm's tumor (7.3%), and Non-Hodgkin Lymphoma (2.4%) were underrepresented in the group of participants (14.8%, 22.2% and 22.2% respectively in the non-participant group). Of the forty patients for which data was available, twenty-five (62.5%) participants received central nervous system-directed therapy, which included either cranial radiation or intrathecal chemotherapy, and fifteen (37.5%) did not. This was different from the non-participant group, in which seven (25.9%) received central nervous system-directed therapies and twenty (74.1%) did not. Analyses of treatment and years since therapy completion in the non-participant group was confounded by missing information, as complete data was available for only a minority of non-participants (see *Table 3*).

When analyzing the data in order to describe the study population, the mean values in the sample were in the standard range reported for each survey instrument. However, when examining percentage of impairment compared to the expected in a normative population, there were significant differences. Therefore percentages of impairment and their respective significance, as indicated by p-values less than 0.05, are reported throughout the text and tables.

Table 4 - Emotional Functioning as Measured by the Parent Version of the Behavior Assessment Scale for Children, Second Edition (BASC-II), Stratified by Gender[A]

	Norm	All patients			Female			Male		
	%	#/N	%	p-value	#/N	%	p-value	#/N	%	p-value
Externalizing Problems	16	5/40	12.5	0.670	3/22	13.6	1	2/18	11.1	0.756
Hyperactivity	16	5/40	12.5	0.670	2/22	9.1	0.562	3/18	16.7	1
Aggression	16	4/40	10	0.391	3/22	13.6	1	1/18	5.6	0.34
Conduct Problems	16	7/40	17.5	0.828	4/22	18.2	0.77	3/18	16.7	1
Internalizing Problems	16	11/40	**27.5**	**0.053**	9/22	**40.9**	**0.005**	2/18	11.1	0.756
Anxiety	16	7/40	17.5	0.828	5/22	22.7	0.382	2/18	11.1	0.756
Depression	16	13/40	**32.5**	**0.008**	9/22	**40.9**	**0.005**	4/18	22.2	0.515
Somatization	16	13/40	**32.5**	**0.008**	9/22	**40.9**	**0.005**	4/18	22.2	0.515
Behavioral Symptoms Index	16	11/40	**27.5**	**0.053**	5/22	22.7	0.382	6/18	**33.3**	**0.055**
Atypicality	16	9/40	22.5	0.278	3/22	13.6	1	6/18	**33.3**	**0.055**
Withdrawal	16	12/40	**30.0**	**0.027**	8/22	**36.4**	**0.017**	4/18	22.2	0.515
Attention Problems	16	11/40	**27.5**	**0.053**	5/22	22.7	0.382	6/18	**33.3**	**0.055**
Adaptive Skills Composite	16	10/40	22.5	0.278	5/22	22.7	0.382	5/18	27.8	0.192
Adaptability	16	9/40	22.5	0.278	6/22	27.3	0.149	3/18	16.7	1
Social Skills	16	7/40	17.5	0.828	3/22	13.6	1	4/18	22.2	0.515
Leadership	16	8/40	20.0	0.515	4/22	18.2	0.77	4/18	22.2	0.515
Activities of Daily Living	16	9/40	22.5	0.278	3/22	13.6	1	6/18	**33.3**	**0.055**
Functional Communication	16	9/40	22.5	0.278	5/22	22.7	0.382	4/18	22.2	0.515

Significance is determined if the percentage of study patients with T scores $\geq$ 84 percentile ($\leq$ 16 percentile for adaptive scales) is greater than the expected 16%.
A - Bold numbers indicate statistical significance.

The data from the BASC-II was analyzed to characterize impairments in emotional functioning in the study population. Using the parent reports of their children's behavior on the BASC-II, 27.5% reported impairments in internalizing symptoms, with clinically significant endorsement of symptoms of depression (32.5%), somatization (32.5%) and withdrawal (30.0%). In addition, 27.5% showed impairments in attention and 27.5% endorsed symptoms of impairment on the behavioral symptoms index compared to normative populations (see *Table 4*).

Table 5 - Neurocognitive and Executive Functioning as Measured by the Parent Version of the Behavior Rating Index of Executive Functioning (BRIEF), Stratified by Gender[A]

	Norm	**All Patients**			**Female**			**Male**		
	%	**#/N**	**%**	**p (vs. norm)**	**#/N**	**%**	**p (vs. norm)**	**#/N**	**%**	**p (vs. norm)**
Inhibit	10	8/38	**21.1**	**0.05**	5/21	**23.8**	**0.052**	3/17	17.6	0.238
Shift	10	13/38	**34.2**	**0.000**	7/21	**33.3**	**0.003**	6/17	**35.3**	**0.005**
Emotional Control	10	7/38	18.4	0.098	4/21	19.0	0.152	3/17	17.6	0.238
BRI	10	12/38	**31.5**	**0.000**	7/21	**33.3**	**0.003**	5/17	**29.4**	**0.022**
Initiation	10	6/38	15.8	0.270	2/21	9.5	1	4/17	23.5	0.083
Working Memory	10	13/37	**35.1**	**0.000**	6/21	**28.6**	**0.014**	7/16	**43.7**	**0.0005**
Planning	10	6/38	15.8	0.270	4/21	19.0	0.152	2/17	11.8	0.684
Organization of Materials	10	7/38	18.4	0.098	4/21	19.0	0.152	3/17	17.6	0.238
Monitor	10	7/38	18.4	0.098	4/21	19.0	0.152	3/17	17.6	0.238
MCI	10	11/38	**28.9**	**0.001**	6/21	**28.6**	**0.014**	5/17	**29.4**	**0.022**
GEC	10	9/38	**23.6**	**0.011**	6/21	**28.6**	**0.014**	3/17	17.6	0.238

Significance is determined if the percentage of study patients with T scores $\geq$ 65 percentile is greater than the expected 10%.
A - Bold numbers indicate statistical significance.

The parent BRIEF was also analyzed to describe neurocognitive functioning in the study population. Parents reported impaired scores for 23.6% of the study population on the Global Executive Composite (GEC) scale, which includes all of the subscales. For the cohort of forty-one patients, 31.5% showed impaired scores on the Behavior Regulation Index (BRI), with clinically significant endorsement of problems on the inhibit (21.1%) and shift (34.2%) scales. On the Metacognition Index (MI), 28.9% of the population showed impairment, with clinically significant scores on the memory sub-scale (35.1%) (see *Table 5*).

The results of the parent-version survey instruments were also divided into subgroups of gender, age at diagnosis and age at study completion and analyzed for comparison to further characterize the study population. When the results of the parent-report BASC-II were divided by gender, female patients (40.9%) endorsed more internalizing symptoms than male patients (11.1%), as confirmed by Fisher's test (p = 0.073). Specifically, female patients endorsed more symptoms of depression (40.9%), somatization (40.9%) and withdrawal (36.4%) than their male counterparts (22.22%, 22.22% and 22.22% respectively). Male patients endorsed more problems with attention (33.3%), activities of daily living (33.3%) and overall impairment on the behavioral symptoms index (33.3%) than female patients (22.7%, 13.6% and 22.7% respectively). Fisher's tests performed for this data were not clinically significant (see *Table 4*).

The results of the parent report of the BRIEF, when divided by gender, revealed greater proportion of impairment in female patients on the GEC (28.6%) and BRI (33.3%) than male patients (17.6% and 29.4% respectively). Male patients had slightly higher percentage of problems with shift (35.3%) and memory (43.7%) than female patients (33.3% and 28.6% respectively). However female patients endorsed more problems with inhibition (23.8%) than male patients (17.6%). Fisher's tests were run comparing percentage of impairment in male and female patients, and revealed no clinically significant differences (see *Table 5*).

When the results of the parent-report BASC-II were divided by age at diagnosis, children diagnosed at greater than or equal to 3.5 years were reported to have more symptoms of withdrawal (52.9%) than those diagnosed at younger ages (13%). This was confirmed by Fisher's test (p-value = 0.013). Children diagnosed in the older age group also were reported on the parent BASC-II to have more symptoms of anxiety (35.3%), depression (35.3%), atypicality (35.3%), internalizing problems (41.2%) and problems with attention (41.2%), adaptability (35.3%), and on the overall behavioral symptoms

Table 6 - Emotional Functioning as Measured by the Parent Version of the Behavior Assessment Scale for Children, Second Edition (BASC-II), Stratified by Age at Diagnosis[A]

	Norm	Age at Diagnosis					
		< 3.5 yrs			≥ 3.5 yrs		
	%	#/N	%	p (vs. norm)	#/N	%	p (vs. norm)
Externalizing Problems	16	3/23	13	1.000	2/17	11.8	1.000
Hyperactivity	16	2/23	8.7	0.567	3/17	17.6	0.745
Aggression	16	2/23	8.7	0.567	2/17	11.8	1.000
Conduct Problems	16	3/23	13	1.000	4/17	23.5	0.336
Internalizing Problems	16	4/23	17.4	0.778	7/17	**41.2**	**0.012**
Anxiety	16	1/23	4.3	0.160	6/17	**35.3**	**0.042**
Depression	16	7/23	30.4	0.080	6/17	**35.3**	**0.042**
Somatization	16	8/23	**34.8**	**0.022**	5/17	29.4	0.174
Behavioral Symptoms Index	16	5/23	21.7	0.400	6/17	**35.3**	**0.043**
Atypicality	16	3/23	13	1.000	6/17	**35.3**	**0.042**
Withdrawal	16	3/23	13	1.000	9/17	**52.9**	**0.000**
Attention Problems	16	4/23	17.4	0.778	7/17	**41.2**	**0.012**
Adaptive Skills Composite	16	6/23	26.1	0.247	4/17	23.5	0.336
Adaptability	16	3/23	13	1.000	6/17	**35.3**	**0.042**
Social Skills	16	3/23	13	1.000	4/17	23.5	0.336
Leadership	16	5/23	21.7	0.400	3/17	17.6	0.745
Activities of Daily Living	16	6/23	26.1	0.247	3/17	17.6	0.745
Functional Communication	16	4/23	17.4	0.778	5/17	29.4	0.174

Significance is determined if the percentage of study patients with T scores ≥ 84 percentile (≤ 16 percentile for adaptive scales) is greater than the expected 16%.
A - Bold numbers indicate statistical significance.

index (35.3%) than patients diagnosed at ages younger than 3.5 (4.3%, 30.4%, 13%, 17.4%, 17.4%, 13%, and 21.7% respectively). Conversely, on the BASC-II, parents reported that children diagnosed before age 3.5 showed more symptoms of somatization (34.8%) than those diagnosed at older ages (29.4%). These results were not significantly different by Fisher's test (see *Table 6*).

When divided by age at study completion, parents reported that pre-adolescent patients endorsed more symptoms of somatization (37.5%) than adolescent patients (29.2%). However, adolescents were reported by their parents on the BASC-II to exhibit more symptoms of depression (33.3%) and withdrawal (33.3%) than pre-adolescents. These differences were not significant when compared by Fisher's tests.

Table 7 - Neurocognitive and Executive Functioning as Measured by the Parent Version of the Behavior Rating Index of Executive Functioning (BRIEF), Stratified by Age at Diagnosis and Age at Study Completion[A]

	Age at Diagnosis						**Age at Study Completion**					
	< 3.5 yrs			**≥ 3.5 yrs**			**≤ 11 yrs**			**≥ 12 yrs**		
	#/N	**%**	**p**	**#/N**	**%**	**p**	**#/N**	**%**	**p**	**#/N**	**%**	**p**
Inhibit	2/20	10.0	1.000	6/18	**33.3**	**0.006**	1/16	6.3	1	7/22	**31.8**	**0.004**
Shift	5/20	**25.0**	**0.043**	8/18	**44.4**	**0.000**	4/16	25.0	0.07	9/22	**40.1**	**0.0001**
Emotional Control	3/20	15.0	0.445	4/18	22.2	0.098	2/16	12.5	0.67	5/22	22.7	0.062
BRI	5/20	**25.0**	**0.043**	7/18	**38.9**	**0.001**	3/16	18.6	0.21	9/22	**40.1**	**0.0001**
Initiation	2/20	10.0	1.000	4/18	22.2	0.098	2/16	12.5	0.67	4/22	18.2	0.27
Working Memory	4/20	20.0	0.133	9/17	**52.9**	**0.000**	3/16	18.6	0.21	10/22	**45.5**	**0**
Planning	3/20	15.0	0.445	3/18	16.7	0.146	1/16	6.3	1	5/22	22.7	0.062
Org, of Materials	3/20	15.0	0.445	4/18	22.2	0.098	3/16	18.6	0.21	4/22	18.2	0.27
Monitor	2/20	10.0	1.000	5/18	**27.8**	**0.028**	2/16	12.5	0.67	5/22	22.7	0.062
MCI	4/20	20.0	0.133	7/18	**38.9**	**0.001**	4/16	25.0	0.07	7/22	**31.8**	**0.004**
GEC	3/20	15.0	0.445	6/18	**33.3**	**0.006**	2/16	12.5	0.67	7/22	**31.8**	**0.004**

Significance is determined if the percentage of study patients with T scores ≥ 65 percentile is greater than the expected 10%. P-value is as compared to the norm, which was 10% for each analysis. Org. of Materials refers to Organization of Materials.

A - Bold numbers indicate statistical significance.

When results of the BRIEF were analyzed by age at diagnosis, parents reported a higher percentage of impairment of working memory in children diagnosed at age 3.5 or older (52.9%) than those in the younger age at diagnosis group (20.0 %). This clinically significant difference was confirmed by Fisher's test (p-value = 0.047). Children diagnosed at age 3.5 or older also had more problems with inhibition (33.3%), shift (44.4%), and monitor (27.8%) compared to the younger population (10%, 25% and 10% respectively). Parents reported higher rates of impairment in children diagnosed at 3.5 years or older on the summary scales of the behavioral regulation index (38.9%), metacognition index (38.9%), and global executive composite (33.3%) than in children diagnosed before 3.5 years of age (25%, 20%, and 15% respectively) (see *Table 7*).

Table 8 - Self-Report of Quality of Life as Measured by the Pediatric Quality of Life Inventory (PedsQL), Stratified by Gender^{A}

	Norm	All Patients			Female			Male		
	%	#/N	%	p (vs. norm)	#/N	%	p (vs. norm)	#/N	%	p (vs. norm)
Physical Functioning	15	13/40	**32.5**	**0.006**	9/22	**40.9**	**0.002**	4/18	22.2	0.333
Emotional Functioning	14	12/40	**30.0**	**0.009**	10/22	**45.5**	**0.0003**	2/18	11.1	1
Social Functioning	16	11/40	**27.5**	**0.053**	6/22	27.3	0.149	5/18	27.8	0.192
School Functioning	17	12/40	**30.0**	**0.035**	6/22	27.3	0.249	6/18	33.3	0.106
Psychosocial Summary Score	16	10/40	25.0	0.129	7/22	31.8	0.071	3/18	16.7	1
Total Score	17	13/40	**32.5**	**0.018**	8/22	**36.4**	**0.023**	5/18	27.8	0.214

Higher Z-scores indicate better quality of life. Significance is determined if the percentage of study patients is greater than the expected percentile listed in the Norm column. The expected percentiles change with each subscale.
A - Bold numbers indicate statistical significance.

The results of the self-report PedsQL were also compared to normative populations in order to characterize quality of life functioning in the study population and to prepare for analyses of the three aims. On the self-report PedsQL, 32.5% showed impairments on the total score scale, with clinically significant impairments in emotional (30.0%), social (27.5%), and school (30.0%) functioning. This indicated that the impairments reported could affect any of the realms of quality of life (see *Table 8*).

The results of the self-report PedsQL were also divided into subgroups and compared to healthy controls. When divided by gender, female patients showed more impairment on the total score (36.4%) than male patients (27.8%). Female patients also endorsed more clinically significant impairment on the emotional (45.5%) functioning scales than male patients (11.1%), as confirmed by Fisher's test (p = 0.035) (see *Table 8*).

When separated by age at diagnosis, children who were diagnosed at 3.5 years or older reported greater impairment in every realm -- emotional functioning (33.3%), social

Table 9 - Self-Report of Quality of Life as Measured by the Pediatric Quality of Life Inventory (PedsQL), Stratified by Age at Diagnosis[A]

	Norm	**Age at Diagnosis**					
		< 3.5 yrs			**≥ 3.5 yrs**		
	%	**#/N**	**%**	**p (vs. Norm)**	**#/N**	**%**	**p (vs. Norm)**
Physical Functioning	17	6/22	27.3	0.128	7/18	**38.9**	**0.012**
Emotional Functioning	16	6/22	27.3	0.113	6/18	**33.3**	**0.031**
Social Functioning	19	4/22	18.2	0.77	7/18	**38.9**	**0.017**
School Functioning	19	5/22	22.7	0.406	7/18	**38.9**	**0.023**
Psycho-social Summary Score	18	5/22	22.7	0.381	5/18	27.8	0.192
Total Score	18	6/22	27.3	0.249	7/18	**38.9**	**0.023**

Higher Z-scores indicate better quality of life. Significance is determined if the percentage of study patients is greater than the expected percentile listed in the Norm column. The expected percentiles change with each subscale.
A - Bold numbers indicate statistical significance.

functioning (38.9%) and school functioning (38.9%) than those diagnosed before age 3.5 (27.3%, 27.3%, 18.2%, 22.7% respectively). This was also reflected in greater impairment in total score in older age at diagnosis (38.9%) than younger age at diagnosis (27.3%) (see *Table 9*). When divided by age at evaluation, pre-adolescent patients reported clinically significant percentages of impairment in emotional functioning (33.3%) while adolescent patients did not (24% and 28% respectively).

The remaining sets of surveys -- the teacher-report and self-report versions of the BASC-II, the teacher version of the BRIEF, and the parent version of the PedsQL -- were also scored and compared to normative populations. The results of these instruments were divided into subgroups and compared for differences. The data from these surveys was mostly used to characterize the study population, and can be found in *Appendix I* for further reference.

Perceptions of Impairment and Inter-Rater Reliability

Key data from the different versions of each survey instrument were analyzed to determine if there was inter-observer reliability and agreement. Differences in perception of impairment based on the respondent were evaluated with kappa statistics, which analyze agreement. First, agreement was analyzed on the attention subscale on the parent and teacher versions of the BASC-II (see *Appendix I* for results of teacher-report BASC-II). This analysis showed that of the seven patients rated as impaired by parents, teachers rated 4 as impaired (kappa = 0.57, p = 0.0015), indicating moderate strength of agreement with a significant p-value labeling this result as not due to chance alone (see *Table 10*).

The parent and child versions of the BASC-II were also evaluated to determine if the raters agreed on the attention and emotional functioning scales (see *Appendix I* for results of the self-report BASC-II). When parents rated attention as impaired (N = 11), children rated themselves as impaired 7 times (kappa = 0.59, p = 0.0001), indicating moderate strength of agreement not due to chance. However, there was no strength of agreement shown for the depression, anxiety, somatization, or internalizing symptoms scales (see *Table 10*).

The parent and teacher versions of the BRIEF were analyzed to understand perceptions of executive functioning (see *Appendix I* for results of the teacher-report BRIEF). Of the 9 survivors rated as having problems with memory by parents, five were rated as impaired by teachers (kappa = 0.61, p = 0.0006), showing substantial strength of agreement not due only to chance. The level of agreement was moderate for shifting behaviors, as parents rated children as having problems seven times and teachers also

Table 10 - Inter-rater Reliability Between Different Respondents[A]

Perceptions of Impairment	Kappa[E]	P-value
Parent BASC vs. Teacher BASC		
Attention	**0.57**	**0.002**
Parent BASC vs. Self-Report BASC		
Depression	0.08	0.295
Anxiety	0.21	0.098
Attention	**0.59**	**0.000**
Somatization	0.10	0.265
Internalizing Symptoms	0.00	0.487
Parent BRIEF vs. Teacher BRIEF		
Memory	**0.61**	**0.001**
Inhibition	0.05	0.3925
Shift	**0.43**	**0.011**
Planning	**0.52**	**0.002**
Organization of Materials	-0.07	0.672
Initiation	0.35	0.037
Monitor	0.17	0.191
Metacognition Index	**0.52**	**0.002**
Global Executive Composite	**0.59**	**0.001**
Parent PedsQL vs. Self-Report PedsQL		
School Functioning	**0.70**	**0.000**
Emotional Functioning	**0.48**	**0.001**
Social Functioning	**0.44**	**0.002**
Self-Report PedsQL School Functioning vs. Teacher BRIEF		
Memory	**0.57**	**0.002**
Planning	**0.57**	**0.002**
Organization of Materials	0.12	0.738
Initiation	0.40	0.022

A - Bold numbers indicate statistical significance.

E - Kappa Statistics were used to analyze the agreement against what might be expected by chance alone. For these results, Kappa values from 0.41-0.60 were considered moderate agreement and from 0.61-0.80 were considered substantial agreement. Kappa values from 0.81-1.00 indicated almost perfect agreement.

rated impairment 3 times (kappa = 0.43, p = 0.011). In terms of problems with planning, for the 2 patients parents rated as impaired, teachers rated both as impaired (kappa = 0.52, p = 0.0016) indicating moderate strength of agreement despite small numbers. Of the 7 patients parents rated as having impairments on metacognition, 3 were also rated as impaired by teachers (kappa = 0.52, p = 0.0015). Similarly, of the 5 patients parents rated as having impairments on the global executive composite, 3 were rated as impaired by teachers (kappa = 0.59, p = 0.0013). These results indicate moderate strength of agreement not due only to chance. There was no agreement shown in terms of inhibition, organization of materials, initiation or monitor (see *Table 10*).

The parent and self-report versions of the PedsQL were analyzed to assess variability in perceptions of quality of life and showed agreement in all realms (see *Appendix I* for results of the parent-report PedsQL). The level of agreement was substantial for impairment of school functioning, as of the 11 reports of impairment by parents, children also rated impairment 9 times (kappa = 0.70, p = 0.000). Among the 15 patients reported as having impaired emotional functioning by parents, 8 children self-reported impairment (kappa = 0.48, p = 0.0013). Parents reported impairment in social functioning in 15 patients, and of these 8 self-reported impairment (kappa = 0.44, p = 0.0023). These results show moderate agreement for emotional and social functioning between parents and survivors not due to chance alone (see *Table 10*).

Due to the limitations of the surveys, in order to understand different perceptions of school functioning between the child and the teacher, the self-report of school functioning on the PedsQL was compared to the teacher version of the BRIEF (see *Appendix I* for results of the teacher-report BRIEF). Among those patients reporting impaired school functioning (N = 7), teachers reported impairments in memory in 4 patients (kappa = 0.56, p = 0.0019) and impairments in planning and organization in 4 patients (kappa = 0.56, p = 0.0019). These results indicate moderate strength of agreement not due to chance. There was no agreement between self-report of impaired school functioning and teacher perception of problems with organization of materials or initiation (see *Table 10*).

Co-morbidities between Neurocognitive and Emotional Impairments

Data was compared between survey instruments in order to determine which emotional problems tended to co-exist alongside neurocognitive difficulties. The anxiety and depression scales on the parent BASC-II were compared to executive functioning scales on the parent version of the BRIEF. Among the 14 patients reported by their parents to have impairments in either anxiety or depression on the BASC-II, 57.1% (N = 8, p-value = 0.039) had co-existing impairment in shift, defined as ability to freely shift between activities, on the BRIEF. Parent reports did not show that anxiety and depression co-existed with memory, organization of materials, initiation, monitor, inhibition or the metacognition index (see *Table 11*).

Among the 13 patients reported to have impairments in somatization on the BASC-II, 61.5% (N = 8, p = 0.03) had co-existing impairments in memory, 69.2% (N = 9, p = 0.003) had co-existing impairments in shift, and 53.9% (N = 7, p = 0.028) had co-existing impairments on the metacognition index on the BRIEF. Within the group of parent reports of impaired somatization on the BASC-II, parents did not rate impairments in organization of materials, initiation, monitor, or inhibition as significantly impaired on the BRIEF (see *Table 11*).

Of the 12 patients rated by their parents as impaired on the withdrawal scale on the BASC-II, 66.7% (N = 8, p = 0.011) had co-existing impairments in memory, 66.7% (N = 8, p = 0.011) had co-existing impairments in shift and 58.3% (N = 7, p = 0.018) had co-existing impairments on the metacognition index shift. Within this group there was no co-existence shown with organization of materials, initiation, monitor and inhibition as significantly higher rates of impairment than no impairment (see *Table 11*).

Table 11 - Co-existence of Impairments in Emotional and Neurocognitive Outcomes[A]

Co-Morbidities: Parent BASC-II vs. Parent BRIEF	Proportion[F] (%)	P-value
Anxiety and Depression vs.		
Memory	42.9	0.723
Organization of Materials	35.7	0.080
Initiation	21.4	0.653
Shift	**57.1**	**0.039**
Monitor	35.7	0.080
Inhibition	21.6	0.215
Metacognition Index	50.0	0.063
Somatization vs.		
Memory	**61.5**	**0.030**
Organization of Materials	38.5	0.072
Initiation	46.2	0.001
Shift	**69.2**	**0.003**
Monitor	38.5	0.072
Inhibition	30.8	0.413
Metacognition Index	**53.9**	**0.028**
Withdrawal vs.		
Memory	**66.7**	**0.011**
Organization of Materials	33.3	0.183
Initiation	41.7	0.009
Shift	**66.7**	**0.010**
Monitor	50.0	0.002
Inhibition	33.3	0.394
Metacognition Index	**58.3**	**0.018**
Internalizing Symptoms vs.		
Memory	45.5	0.475
Organization of Materials	36.4	0.163
Initiation	27.3	0.335
Shift	**72.7**	**0.006**
Monitor	45.5	0.016
Inhibition	36.4	0.203
Metacognition Index	54.6	0.051

A - Bold numbers indicate statistical significance.
F - Proportion is described as the following: of those who are reported by parents to be impaired on the BASC-II, the proportion also reported by parents as impaired on the BRIEF. For example, among the 14 patients reported to have impairments in either anxiety or depression on the BASC-II, 57.1% (N = 8, p-value = 0.039) had co-existing impairment in shift on the BRIEF. Fisher's exact test was used for this analysis.

Among the 11 patients whose parents reported impairment in internalizing symptoms on the BASC-II, 72.7% (N = 8, p = 0.006) had co-existing impairments in shift on the BRIEF. Within this group of parent reports there was no co-existing impairment shown in memory, organization of materials, initiation, monitor, inhibition or on the metacognition index (see *Table 11*).

Predictors of Poor Quality of Life

An unadjusted and an adjusted logistic regression was performed in order to determine the extent to which factors of female gender, adolescent age at study completion, parent-rating of impaired metacognition and parent-rating of endorsement of internalizing symptoms were associated with self-perception of poor quality of life. Specifically, the realms of school functioning, emotional functioning and social functioning were examined from the results of the self-report PedsQL. Age at study completion was chosen instead of age at diagnosis due to high correlation between the two realms and better data in the literature about the significance of age at testing in revealing late effects of childhood cancer treatments.

Worse school functioning was predicted by impaired metacognition on the parent BRIEF in the unadjusted model (OR = 23, CI = 3.52-150.48, p = 0.001). When adjusted for the other predictors, the odds ratio (OR) increased (OR = 33.5, CI = 3.2-351.39, p = 0.003), indicating that metacognition was a very strong predictor of poor school functioning. Female gender, age at testing and parent rated impairment of internalizing symptoms on the BASC-II were not good predictors of school functioning (see *Table 12*). Poor emotional functioning was also predicted by parent-rating of impaired metacognition on the BRIEF on the unadjusted model (OR = 5.25, CI 1.11-24.91, p = 0.037). When adjusted for the other predictors, the odds ratio increased (OR = 11.48, CI = 1.07-123.17, p = 0.044), indicating that impaired metacognition was a strong

Table 12 - Predictors of Self-Report of Impaired Quality of Life Functioning Among Survivors, Unadjusted and Adjusted Regression Analysis[A]

	Unadjusted		Adjusted	
	OR (95% CI)	P-value	OR (95% CI)	P-value
School Functioning				
Female Gender	0.79 (.02-3.12)	0.73	1.18 (0.18-7.61)	0.86
Age at Testing >= 12	1.57 (0.37-6.61)	0.54	1.39 (0.22-8.94)	0.73
Parent-rated Impairment of Metacognition[G]	23.00 (3.52-150-48)	**0.001**	33.51 (3.2-351.39)	**0.003**
Parent-rated Impairment in Internalizing Symptoms[H]	1.50 (0.33-6.82)	0.6	0.34 (0.03-4.39)	0.41
Emotional Functioning				
Female Gender	7.50 (1.35-41.72)	**0.021**	15.58 (1.41-172.85)	**0.025**
Age at Testing >= 12	0.93 (0.23-3.78)	0.92	0.56 (0.09-3.53)	0.54
Parent-rated Impairment of Metacognition[G]	5.25 (1.11-24.91)	**0.037**	11.48 (1.07-123.17)	**0.044**
Parent-rated Impairment in Internalizing Symptoms[H]	5.00 (1.05-23.79)	**0.043**	2.11 (0.33-13.58)	0.43
Social Functioning				
Female Gender	1.03 (0.25-4.24)	0.97	1.07 (0.17-6.77)	0.94
Age at Testing >= 12	0.75 (0.18-3.12)	0.69	0.38 (0.06-2.48)	0.31
Parent-rated Impairment of Metacognition[G]	13.42 (2.40-74.89)	**0.003**	13.94 (2.00-97.22)	**0.008**
Parent-rated Impairment in Internalizing Symptoms[H]	3.33 (0.72-15.54)	0.125	2.17 (0.3-15.64)	0.44

A - Bold numbers indicate statistical significance.
G - As measured on the parent-report version of the Behavior Rating Inventory of Executive Function.
H - As measured on the parent-report version of the Behavior Assessment Scale for Children, Second Edition.

predictor of poor emotional functioning. Worse emotional functioning was predicted by female gender on the unadjusted model (OR = 7.5, CI = 1.35-41.72, p = 0.021) and when adjusted for the other predictors (OR = 15.58, CI = 1.41-172.85, p = 0.025), indicating that female gender was also a strong predictor for poor emotional functioning. Poor emotional functioning was predicted by parent-rating of endorsement of internalizing symptoms on the BASC-II in the unadjusted model (OR = 5, CI 1.05-23.79, p = 0.043). However, when adjusted for other factors, impairment in internalizing symptoms was not as good of a predictor (OR = 2.11, CI = 0.33-13.58, p = 0.43). Age at testing was not a good predictor of emotional functioning (see *Table 12*).

Poor social functioning was only predicted by impaired metacognition as reported by parents on the BRIEF. On the unadjusted model, impaired metacognition predicted poor social functioning (OR = 13.42, CI = 2.40-74.89, p = 0.003), and this remained true when adjusted for the other predictors (OR = 13.94, CI = 2.00-97.22, p = 0.008). Poor self-report of social functioning was not predicted by age at testing, female gender, or parent rated impairment of internalizing symptoms on the BASC-II (see *Table 12*).

Discussion

In this single institution cross-sectional study of forty-one childhood cancer survivors who were simultaneously assessed for neurocognitive processing, emotional functioning, and quality of life, a better understanding of psychosocial functioning in childhood cancer survivors was obtained. This was accomplished through reaching the three proposed aims of the study.

In accomplishing the first aim of the study, modest inter-observer variability was found, especially among indexes of emotional symptoms. Moderate levels of agreement were found between parent and teacher reporting on the BASC-II and BRIEF in terms of attention, memory, ability to freely shift between behaviors, planning, metacognition and global executive functioning. However, when reporting inhibition, monitoring and initiation of behaviors, and organization of materials, agreement was not shown. Similarly there was moderate strength of agreement in memory and planning between teacher perceptions of executive functioning on the BRIEF and self-report of school functioning on the PedsQL, but reports of other realms of executive functioning did not show agreement.

These results reveal differences in perception between reports from teachers and reports from parents and patients. Overall, teachers did not report as many deficits as parents or children. This could indicate that the problems children report are sub-clinical or potentially partially compensated for by diligent effort, and therefore are unable to be perceived by teachers in the school setting. Internalizing symptoms and psychosocial deficits may be more difficult for teachers to assess, as they only see children in the limited school environment. Similarly, given the activities at school, problems with memory and attention may be easier to perceive than impairments in other realms of executive functioning, such as problems with initiation, inhibition, shift, planning and organization. Supporting the findings of other studies, the results of the current study indicate that survivors' deficits are less pronounced in some settings than others (19, 41). Additionally, these results could also reveal that teachers are not getting to know their students well enough. Teachers may need to delve deeper with cancer survivors to ensure that they do not miss symptoms or problems with which the students could benefit from help. Due to varying expression of symptoms in different settings and the variability in perceptions of impairment between teachers and parents and children, feedback about children's well-being from a variety of complementary sources is necessary to fully assess functioning.

Parent and self-reporting also lacked agreement in some realms of functioning. In analyses of emotional symptoms on the BASC-II, there was moderate agreement only on the attention scale. Inter-rater variability existed for the remaining emotional symptom scales, such as depression, anxiety, somatization, and internalizing symptoms. On the PedsQL, however, there was agreement between parents' perceptions and children's self-perceptions of their quality of life in every area of functioning. Despite the small sample size, reports of school functioning showed substantial agreement and reports of emotional and social functioning showed moderate agreement by kappa statistics.

Inter-rater agreement was found for quality of life functioning, but not for specific emotional symptoms. Children perceive that they are not doing well, and parents tend to agree with them. However, when parents recognize specific internalizing symptoms exhibited by their children, the survivors do not report the same impairment. This could represent a lack of ability to definitively identify symptoms, even when children sense poor quality of life. As Wheeler and Ladd described, parents' perceptions of ability in performing specific tasks correlates better with children's actual abilities than do children's own perceptions (47). Children may not always have the capacity to pinpoint specific deficits, but are able to sense overall deficit. Previous studies have also shown that childhood cancer survivors feel more apprehension and tension than age-matched peers (17) and often underestimate their abilities (44, 45). The results of the current study may therefore indicate a tendency to overestimate poor quality of life, even when children do not endorse specific symptoms, due to increased levels of apprehension. However independent of cause, it is important to understand children's self-perceptions of their feelings because this determines their self-efficacy and subsequent behaviors.

These results could also indicate over-reporting of specific symptoms by parents due to their own biases. Parents are affected by a child having had cancer, as evidenced by more reported symptoms of post-traumatic stress disorder in mothers of survivors than parents of healthy children (56, 57). Parents may, when completing surveys about their children's behaviors, overestimate the presence of symptoms. This could stem from knowledge that their child has had an illness experience or the subsequent hyper-vigilance instilled by parents experiencing post-traumatic stress. Significant associations between survivors' psychological and behavioral adjustment and parental psychological distress and coping strategies have previously been reported (58). A parent may perceive symptoms in a child as a projection of his or her own psychosocial functioning and feelings about a situation. Given the combination of children's potential deficits in identifying or overestimating functioning and parent's own biases based on their experiences, the results of this study highlight the need to include perceptions of functioning from a variety of sources in order to fully understand a survivor's emotional and social state.

Beyond exhibiting the need for multiple perceptions to determine functioning, the current study provides a better understanding of impairments by detailing co-morbidities of deficits. In reaching the second aim of the study, the present research showed that, as a whole, neurocognitive and emotional difficulties did not co-exist. Impairments of internalizing symptoms and of anxiety and depression co-existed only with impairments in shift and not with any other realm of executive functioning. More targeted emotional symptoms, such as symptoms of somatization and social withdrawal, co-existed with problems with memory, shift, initiation and coordination of problem-solving behaviors. In the overall population, anxiety and depression often coincide with social withdrawal and symptoms of somatization (11, 12). However, the current study indicates that childhood cancer survivors who exhibit problems with executive functioning might be more socially withdrawn and over-sensitive to physical complaints, but do not exhibit signs of anxiety or depression. These results help elucidate reasons behind specific emotional impairments. Symptoms of somatization or social withdrawal may stem from underlying difficulties with neurocognition, as children are self-conscious about their impaired executive functioning. However these neurocognitive deficits do not result in clinically significant anxiety or depression. Knowledge of these co-morbidities can be used to determine targeted treatments for different sets of impairments.

The ultimate downstream outcome of these deficits, survivor perception of quality of life, was measured by the self-report PedsQL and used to accomplish the study's third aim. Interestingly, neurocognitive impairment was again the causative factor. Neurocognitive deficits, as measured by the metacognition index on the BRIEF, were consistently associated with worse school, emotional, and social quality of life. In the present study, problems with metacognition, an analysis of a child's ability to plan and initiate problem-solving, were shown to profoundly impact the child's self-perception of his or her overall competence. As Bandura reported in 1977, self-efficacy is impacted by the child's experiences, which ultimately shapes his or her behaviors and coping mechanisms (46). Neurocognitive problems clearly play a role in a child's experiences. Problems with neurocognition and executive functioning can have a direct impact on academic performance, and therefore self-perception of school functioning. Emotional functioning may be depressed due to a child's awareness of and feelings about his or her deficits in neurocognition, and from the social withdrawal and symptoms of somatization that co-exist with neurocognitive problems.

Similarly, children may feel less capable or socially awkward because of their difficulties with executive functioning, and this can impact self-esteem, interactions with peers and, eventually, overall social functioning. Previous studies have describe that, as a whole, childhood cancer survivors have fewer friends, are less satisfied with their relationships, and spend more time by themselves than their peers (19, 24). The current study showed that impairments in withdrawal co-exist with neurocognitive difficulties and problems with executive functioning predict poor social functioning. Self-efficacy, here measured by the self-report PedsQL, drives social competence. Survivors who suffer from neurocognitive deficits may feel less comfortable with themselves, creating a tendency toward social withdrawal. This ultimately results in poor emotional and social functioning that may impact survivors' quality of life as a whole.

Impaired metacognition was a stronger predictor of emotional quality of life than endorsement of emotional symptoms as measured by the BASC-II. While impaired internalizing symptoms on the BASC-II predicted poor emotional functioning in the unadjusted analysis, this did not remain true when adjusted for other factors. Endorsement of emotional symptoms also did not predict worse school or social functioning. Feelings of anxiety, depression, withdrawal and somatization can clearly impact a child's emotional quality of life. However these symptoms are neither the only nor the greatest cause of dissatisfaction with emotional functioning. Interventions targeting internalizing symptoms may help improve emotional quality of life, but co-existing deficits need to be screened for to ensure proper treatment for these patients. Additional research is necessary to further characterize and understand the impact of these symptoms on childhood cancer survivors.

Unlike endorsement of internalizing symptoms, female gender was found to be a predictor of poor emotional functioning in both the unadjusted and adjusted analyses. Parents reported that female patients endorsed more internalizing symptoms and problems with behavioral regulation and inhibition than male patients, and female patients and their parents both reported worse quality of life functioning. This is consistent with previous studies reporting that female patients endorse more internalizing symptoms, including depression, anxiety and somatic distress (7, 8, 14, 59). However these results also reveal that not only do female patients report more late effects than male patients, but these deficits are also correlated with impaired self-perception of emotional quality of life. Due to societal norms, female patients may be more willing to admit to problems with emotional functioning than male patients, which could bias these results. Alternatively, female patients may internalize their illness experience in different ways than male patients, ultimately impacting their ability to cope and their emotional quality of life. However, independent of the reason behind these results, emotional functioning is highlighted as an area of deficit that needs to be targeted in female survivors.

Age at study completion was also analyzed, and neither adolescent nor pre-adolescent age at study completion was shown to be a predictor of self-perception of poor quality of life. These results were surprising, as parents reported more impairment in quality of life functioning, as well as more symptoms of withdrawal, anxiety, depression, atypical behaviors and internalizing symptoms, in adolescent patients than in pre-adolescent patients. However, it should be noted that adolescent patients did not self-report these same results, and self-report of quality of life was used to determine predictors of functioning. Adolescents may underreport difficulties or may not be as influenced by deficits as parents perceive them to be. In 1982 Harter theorized that upon entering junior high school, due to the social and academic changes of this time period, children lose a percentage of their ability to accurately self-perceive their competence (48). This theory could explain the discrepancy in parent and child reporting, as well as the conclusion that age was not a predictor of poor quality of life. Further work is necessary to understand how patients of different ages view their quality of life and if interventions should be altered depending on patient age.

Due to a participation rate of only 53.2% and the small sample size, the authors of the current study were cautious about reporting frequencies of specific outcomes as being able to be generalized to both HEROS Clinic patients and all childhood cancer survivors. Therefore, a focus was placed on case-case comparisons rather than reports of overall risk. Because of the heterogeneous cancer treatments received by patients in the sample, it was not possible to examine the role of various treatment characteristics in greater detail. Instead, patients were grouped by broad categories based on if they had received cranial radiation or intrathecal chemotherapy.

Patients who had received central nervous system-directed treatment were reported to have fewer problems with both school maladjustment and attitude towards teachers. These results are not consistent with previous literature, which indicates increased risk for psychological and social difficulties in patients who received cranial radiation or intrathecal methotrexate (8, 33). However, studies have also indicated that more intense or prolonged treatment is associated with poorer adjustment and greater endorsement of symptoms of psychological distress (60, 61). Treatment intensity and duration were not analyzed in the current study, and could be confounding factors. Additionally, these therapies may render children more quiet and passive, making it more difficult for teachers, or even parents, to observe deficits. Further analyses with the data reported here should take advantage of the simultaneous analysis of neurocognitive, emotional and quality of life functioning, one of the great strengths of the current study. Central nervous system-directed therapies should be evaluated as a predictor of worse self-report of quality of life in this population.

It is important to note the limitations of the current study. Participation suffered from a high rate of passive refusal. The majority of non-participants passively declined participation by neither returning the surveys mailed to them nor scheduling clinic appointments. Recruitment by mail was inefficient, as only 13% of those contacted participated by mail, and the number of surveys returned by teachers was small, with only twenty-seven packets returned. It is unknown if patients did not respond by mail due to lack of interest in the study or for other reasons. When families completed surveys at home, they often reported forgetting about the study and needing reminders to return their answers. This may indicate that patients to whom packets were mailed simply overlooked the study rather than actively deciding not to participate. Of those patients who did actively decline, the reasons cited were that the parent did not desire for the child to have to think about the psychosocial side effects of his or her cancer or that the child was not interested in participating in a study.

These reasons for declining of participation may highlight possible biases of the study population and of patients who choose to enroll in the HEROS Clinic. As evidenced by the range of household incomes, the patients who attend the HEROS clinic tend to be middle-class, which is not representative of the entire population of survivors of childhood cancer. Those who choose to participate may be more comfortable with their current quality of life and therefore willing to think about the issues raised by the surveys. Alternatively, families of patients who attend clinic and agreed to complete the surveys may exhibit and observe more impairment, and therefore desired to participate in order to assist in discovering helpful interventions. The current study may represent two ends of a spectrum and may under-represent patients with milder deficits that could play a different role in quality of life than is reported in this study. The current study also over-represents patients diagnosed with acute lymphoblastic leukemia compared to the non-participant group, which may have affected the results of the study.

Despite these limitations, the current study provides an important addition to the literature about emotional and psychosocial functioning in childhood cancer survivors. In accomplishing three aims, this study provides a better understanding of which symptoms endorsed by survivors have the greatest impact on how patients perceive their quality of life. The current study shows inter-observer variability, especially among indexes of emotional symptoms, indicating a need to obtain and understand perspectives from multiple reporters to determine areas of deficit and true levels of functioning. When taking care of survivors of childhood cancer, clinicians need to assess functioning from a variety of angles in order to fully address the needs of their patients. Additionally, the current study reveals that certain neurocognitive and emotional deficits co-exist, while others do not. Problems with memory, shift, initiation, and coordination of problem-solving behaviors co-exist with symptoms of somatization and social withdrawal, but not with anxiety and depression. Further, it is the neurocognitive rather than emotional symptoms that are shown to be key predictors of how child-age survivors perceive their quality of life after therapy. These results indicate that problems in specific areas of executive functioning may help to explain somatization and social withdrawal behaviors, as well as poor quality of life in survivors. Clinicians need to screen for co-morbidities in survivors who present with specific emotional or neurocognitive deficits in order to fully address both these impairments and issues of quality of life.

Despite the recognition of late effects of treatment for childhood cancer, the impact of these outcomes on children's overall well-being has remained unclear. The primary goal of therapy for childhood cancer is to cure the malignancy. However, as cure rates improve, the concept of survivorship has expanded to include not only cure, but also global functioning after treatment. Closely examining neurocognitive outcomes and showing that these deficits tend to predict self-reported worse global functioning, the current study helps develop a better understanding of quality of life in childhood cancer survivors. Further research analyzing parent, teacher and self-report in a larger sample size would continue to clarify the discordance between perceptions of functioning and the benefits of these differences to patient care. Furthermore, studies analyzing the effects of neurocognitive deficits on specific areas of global functioning could continue to elucidate co-morbidities of symptoms and ultimately determine treatments that can help survivors optimize their quality of life.

Appendix I

Self-Report and Teacher-Report of Emotional Functioning on the BASC-II

Using the self-report versions of the BASC-II, there were no realms in which the percentage of impairment was statistically significant compared to the normative populations. When divided by gender, patients did not report any symptoms of impairment at significantly higher rates than the published norms. On the self report BASC-II children diagnosed at age 3.5 or older reported higher rates of problems with attention (33.3%) and hyperactivity (33.3%) compared to those diagnosed at younger ages (15% and 15% respectively). This was not significant by Fisher's test ($p = 0.26$).

By teacher report, patients did not show statistically significant impairment on any scale. When comparing female and male patients, a Fisher's test revealed a statistically significant difference on the withdrawal scores ($p = 0.047$). On the self and teacher versions of the BASC-II there were no statistically significant symptoms reported when divided by age at study completion.

When divided by history of central nervous system-directed therapy and comparing the means for each population, children who had received either cranial radiation or intrathecal chemotherapy reported fewer symptoms of school maladjustment (p value = 0.037) and problems with their attitudes towards teachers (p-value = 0.019) than those who did not.

Teacher-Report of Executive Functioning on the BRIEF

As reported on the teacher version of the BRIEF, 28% of patients showed impairments on the initiation subscale. Data analysis did not reveal any other realms in which there was statistically significant impairment compared to the normative populations. When divided by gender, male patients endorsed more problems with initiation (35.7%) and planning (28.6%) than female patients (18.2% and 9.1% respectively). Fisher's tests comparing male and female patients on these scales did not reveal statistically significant differences.

When divided by age at diagnosis, teachers reported higher rates of impairment in children diagnosed at age 3.5 years or older on the inhibit (30.8%), shift (30.8%) and initiation (30.8%) subscales, and on the BRI (30.8%) summary scale (compared to 0%, 0%, 25% and 0% respectively in the younger population at diagnosis). When separated by age at evaluation, teachers reported more endorsement of problems with shift (28.6%), initiation (35.7%), and planning (28.6%) in the adolescent population compared to pre-adolescents (0%, 18.2% and 9.1% respectively). Teachers also revealed significant percentages of impairment in adolescent patients on the BRI (28.6%) and GEC (28.6%). When analyzed by Fisher's tests, no statistically significant differences were found.

Parent-Report of Quality of Life Functioning on the PedsQL

On the parent report of survivors' quality of life on the PedsQL, 36.6% of patients had impaired total scores and 34.1% had impaired psychosocial health summary scale scores. Analysis of the study population revealed statistically significant proportion of impairment on the physical (29.3%), emotional (34.1%), and social (39.0%) functioning scales. When divided by gender, female patients endorsed more impairment in overall quality of life (39.1%), emotional functioning (39.1%) and psychosocial health summary scale (34.7%) compared to their male counterparts (33.3%, 27.8% and 33.3%

respectively). Male patients, however, showed greater endorsement of impairment in social functioning (44.4%) than female patients (34.7%). Fisher’s tests did not show any statistically significant differences between male and female patients.

When divided by age at diagnosis, parents reported greater impairment of social functioning (44.4%) and on the psychosocial summary score (44.4%) and total score (44.4%) scales for children diagnosed at 3.5 years or older compared to those diagnosed at younger ages (34.8%, 26.1% and 30.4% respectively). Children diagnosed before age 3.5, however, endorsed greater difficulty with emotional functioning (34.8%) than those diagnosed at older ages (33.3%). When separated by age at study completion, adolescent patients showed more impairment in emotional functioning (36%) and social functioning (40%) and on the psychosocial (36%) and total (36%) score scales than pre-adolescent patients (31.3%, 37.5%, 31.3% and 37.5% respectively). There were no statistically significant differences in impairment when analyzed by Fisher’s tests.

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