The Report Committee for Leah Alyssa Wang

Certifies that this is the approved version of the following report:

Executive Functioning, Social Skills and Social Anxiety in Adolescent Survivors of Acute Lymphocytic Leukemia

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Kevin Stark

Stephanie Cawthon

Executive Functioning, Social Skills and Social Anxiety in Adolescent Survivors of Acute Lymphocytic Leukemia

by

Leah Alyssa Wang, B.S.

Report

Presented to the Faculty of the Graduate School of
The University of Texas at Austin
in Partial Fulfillment
of the Requirements
for the Degree of

Master of Arts

The University of Texas at Austin
May 2014

Abstract

Executive Functioning, Social Skills and Social Anxiety in Adolescent Survivors of Acute Lymphocytic Leukemia

Leah Alyssa Wang, M.A.
The University of Texas at Austin, 2014

Supervisor: Kevin D. Stark

This document proposes a study designed to investigate the association between executive function abilities and social anxiety in a group of adolescent survivors of Acute Lymphocytic Leukemia (ALL) who were treated with chemotherapy for central nervous system prophylaxis. The proposed study is also designed to evaluate a possible interaction effect between executive function abilities and social skills in their impact on social anxiety in this population. The report provides detailed background information describing ALL and available treatments for the disease. It also reviews the literature on both acute and late effects of chemotherapy, with particular attention placed on understanding both neurocognitive and psychosocial effects in the context of adolescent development. The proposed project involves collecting parent and teacher reports to measure the constructs of Executive Function and Social Skills. Parent measures may be completed in English or Spanish. Self-reports of Social Anxiety symptoms in the adolescent survivor sample will also be collected. Simultaneous regression analyses will

be used to analyze the influence of executive function abilities on social anxiety. Sequential multiple regression analyses will then be conducted to check for differences in the magnitude of the relationship between executive function abilities and social anxiety with varying levels of social skills. Significant results would inform the development of targeted interventions. For example, if it is determined that executive function abilities are indeed associated with social anxiety symptoms, existing programs focused on neurocognitive remediation could begin to monitor participants for anxiety and provide preventative therapeutic intervention. Additionally, if social skills is confirmed as a moderator, evidence-based interventions targeting the development of social skills in the survivor population would be warranted as well.

Table of Contents

Chapter 1: Introduction

Acute Lymphocytic Leukemia (ALL) is the most common type of childhood cancer, being diagnosed in approximately 3,000 youth under age 19 in the U.S. each year (Hunger, Conter, Raetz, Valsecchi & Henze, 2011). Treatment for ALL is standardized and highly effective. Five-year survival rates are estimated to be almost 90% today in contrast to just 60% in the 1970s (Smith et al., 2010). Survival does not come without cost, however. Although radiation and its subsequent side effects are much less often utilized today (Temming & Jenney, 2010), ALL treatment is intense, often involving intrathecal chemotherapy for CNS prophylaxis and lasting two to three years (Hunger et al., 2011). Children treated for ALL experience acute effects that can be physically painful and socially isolating. Researchers are increasingly realizing that these children also experience "late effects" of treatment, which are chronic and progressive, and often do not emerge for two to five years following treatment (Oeffinger et al., 2006).

It is generally accepted that the majority of childhood cancer survivors experience some late effects, most often neurocognitive deficits in areas of executive function (EF) such as attention and working memory (Gragert & Kahalley, 2012). Research has also shown generally positive psychosocial adjustment with the exception that many survivors have impaired social relationships following treatment (Lund et al., 2011), and a subset of 25-30% of survivors seem to experience more pronounced difficulties in some aspects of psychological or social functioning (Patenaude & Kupst, 2005). In terms of social skills, there is no consensus in the literature, suggesting that some survivors have adaptive social skills while others experience impairment in this area. Almost no studies to date have examined associations between neurocognitive and psychosocial variables in this population. Researchers that have examined these associations have not restricted their samples to focus on one specific type of cancer, one type of treatment, limited time since treatment or limited developmental range.

The purpose of the present study is to use simultaneous and sequential regression to first examine the association between EF and social anxiety, and then test social skills as a moderator. Participants will be adolescent ALL survivors (minimum three years off treatment) who have been treated with chemotherapy (but not radiation) for CNS prophylaxis. The developmental stage of adolescence was chosen because it is characterized by increasing social and academic demands, and evaluation of self in relation to peers. Social phobia was selected as an outcome variable because it peaks in adolescence, is correlated with EF dysfunction in other populations, and it has been under-researched in the pediatric cancer literature. Understanding the associations between these variables can have important implications for the development of targeted psychosocial interventions.

Chapter 2: Integrative Analysis

Acute Lymphocyctic Leukemia

Incidence. Although there has been a steady increase in the incidence rate for all childhood cancers between 1975 and 2006, combined mortality rates declined 50% (Smith et al., 2010). Childhood cancer remains the leading cause of death by disease in children under age 15, but there have been remarkable advances in treatment (Brown, 2006). One of the biggest success stories is that of children with acute lymphocytic leukemia (ALL). Five-year survival rates for children under 15 diagnosed with ALL improved from less than 10% in the 1960s to 61% in 1975-1978, and 88.5% in 1999-2002 (Smith et al., 2010). As of 2005, there were an estimated 49,271 survivors of childhood ALL living in the United States (Mariotto et al., 2009). This number is expected to increase as it is estimated that 85-90% of children and adolescents diagnosed with ALL in the 21st century will be long-term survivors.

Improving cure rates of ALL was a particular priority for researchers, as ALL is the most common type of childhood cancer, accounting for 75% of pediatric leukemias and 25% of childhood cancers overall (Mulhern & Butler, 2006; Riccio, Sullivan, & Cohen, 2010)

Data taken from the Surveillence, Epidimiology and End Results (SEER) Program of the National Cancer Institute (NCI) between 1992 and 2006, as reported by Ross, Johnson, Spector & Kersey (2011) explains recent incidence rates and trends in childhood ALL: Incidence rates peak between the ages of two and five in the U.S., but vary greatly by ethnicity. Some of the highest rates for childhood ALL occur in U.S. Whites (45.4/million) and U.S. Hispanics (44.9/million), while low rates occur in U.S. Blacks (18.7/million). Approximately 3,000 cases of ALL are diagnosed in youth under age 19 the U.S. each year (Hunger et al., 2011). Males are slightly more affected than females, with an incidence ratio of 1.2:1 for those diagnosed before age 15 and 2:1 for those diagnosed between 15 and 19 (Ross et al., 2011).

Characteristics. The word leukemia comes from the Greek *leukos* "clear, white" + *haima* "blood". Leukemia is a blood disorder characterized by the uncontrolled proliferation of immature white blood cells called lymphoblasts (Daly, Kral, & Brown, 2008). ALL is a type of rapidly progressing leukemia that affects a type of white blood cells known as lymphocytes (T-cells and B-cells). Lymphocytes are important because they fight infection; B-cells make antibodies while T-cells protect against viruses. In children with ALL, B-cells (or 15% of the time, T-cells) are affected and no longer function (Keene, 2012). Instead of developing into healthy and mature B-cells or T-cells within the bone marrow, lymphoblasts multiple rapidly and crowd out other healthy blood cells, including other white blood cells, red blood cells and platelets both in bone marrow and other organs. A diagnosis of leukemia is confirmed if a bone marrow sample shows more than 25% of blood cells to be the immature lymphoblasts (Keene, 2012).

Diagnosis. The signs and symptoms of ALL often mimic those of other conditions, so arriving at a diagnosis is not always straightforward. Some common symptoms include tiring easily and resting often, pale looking skin, bruising without cause, a fever that comes and goes, and swelling of the abdomen or lymph nodes (Keene, 2012; Mulhern & Butler, 2006; Riccio et al., 2010). Because of the relatively low incidence of childhood cancers, it may not be until after repeated visits to a child's primary care physician that cancer is suspected and blood counts are ordered. Once diagnosis is confirmed by a pediatric oncologist through bone marrow aspiration or lumbar puncture, the child's family is presented with the diagnosis and treatment plan (Brown, 2006)

Treatment for ALL

Overview. The treatment plan typically depends on whether the oncologist has characterized the child's leukemia as low-risk, standard-risk, high-risk, or very high-risk (Riccio et al., 2010). Risk is determined by a variety of factors including the child's age at diagnosis, his or her initial white blood cell count, and the location & type of leukemia cells (Keene, 2012). Treatment always consists of one or more of three primary modalities: chemotherapy, radiation therapy, and stem cell transplant (from either donated bone marrow or cord blood), (Brown, 2006; Armstrong, 2006). Treatment is standardized as more that 70% of children diagnosed with cancer in the US and Canada are treated on research protocols within cooperative, multicenter clinical trials as part of the Children’s Oncology Group (Liu, Krailo, Reaman, & Bernstein, 2003). There are nearly 250 institutions across three continents that enroll children in COG clinical trials (Armstrong & Reaman, 2005)

Treatment phases. Treatment for ALL is divided into induction, consolidation (or intensification) and maintenance phases (Keene, 2012). During induction, doctors try to induce complete first remission in the shortest amount of time possible. This is most often achieved in 4-6 weeks with intensive multi-agent chemotherapy (3-5 systemic agents) (Hunger et al., 2011). Over 95% of children diagnosed with ALL enter remission in the first four weeks of Induction (Hunger et al., 2011). Those who don't are among those considered for stem cell transplant. The second phase, consolidation, begins once 95% of the leukemia cells are destroyed and lasts about six months. Without this intensification of treatment, most children with ALL would quickly relapse. The consolidation phase consists of new combinations of chemotherapy drugs aimed at continuing to kill any remaining leukemic cells while stopping new ones from forming. Maintenance is the final phase and consists of long-term, lower-dose chemotherapy. Girls on standard ALL treatment receive maintenance chemotherapy for two years while boys receive it for three years (Hunger et al., 2011). The goal is to eliminate all remaining leukemic cells during that time. Children classified as high-risk typically receive larger doses of chemotherapy and sometimes are also treated with cranial radiation (Keene, 2012).

CRT & CNS prophylaxis. Beginning in the 1960s and 1970s, craniospinal irradiation therapy (CRT) became part of the standard of care for childhood cancer in an attempt to reduce relapse after first remission (Hunger et al., 2011). This vastly improved survival rates, but resulted in the development of secondary brain tumors and significant neurocognitive decline for survivors (Pui & Howard, 2008; Armstrong & Reaman, 2005). A series of clinical trials were then conducted to attempt to reduce exposure to potentially adverse iatrogenic effects while sustaining or improving survival (Rowland, 2005). As a result, physicians realized CRT was not necessary in all cases, and that chemotherapy could be used to delay radiation for very young brain tumor patients in other cases (Duffner et al., 1993). As protocols were modified to reduce the use of CRT, chemotherapy regimens began to involve more drugs in higher doses and for longer periods of time than previously (Noll et al., 1999). Currently, CRT is avoided unless there is evidence of leukemia cells in the cerebral spinal fluid or if there is a high risk of CNS relapse. Given an understanding of the increased magnitude of negative iatrogenic effects of radiation in the youngest patients, those under age two even with CNS disease usually do not get any CRT (Temming & Jenney, 2010). Now only 15-25% of patients with ALL are treated with cranial irradiation (Hunger et al., 2011).

An important part of ALL treatment during all phases is CNS prophylaxis (Buizer, De Sonneville, & Veerman 2009). This is because although less than 5% of children diagnosed with ALL have leukemic cells in the CNS at diagnosis (Keene, 2012), without prophylaxis, up to 80% of children and adolescents would experience CNS relapse (Buizer et al., 2009). In standard protocol ALL where radiation can be avoided, CNS prophylaxis consists of injecting chemotherapy agents into the spinal fluid (intrathecally; IT) (Armstrong & Reaman, 2005). IT chemotherapy typically consists of methotrexate (MTX) either alone or as part of "triple IT therapy" (MTX + cytosine arbinoside, hydrocortisone and systemic steroids) (Bleyer & Poplack, 1985). The effectiveness of IT chemotherapy paved the way for the reduction in the use of CRT. Even after substituting IT chemotherapy for CRT, CNS relapse occurs in less than 10% of cases of ALL (Moleski, 2000).

Acute Effects of Treatment

Children on cancer treatment experience both physical and psychosocial acute effects. First, the delivery of cancer treatment is often painful and aversive. In addition, there are many physical side effects of chemotherapy. Chemotherapy medications prevent the proliferation of leukemia cells, but also sometimes damage healthy cells. Because chemotherapy can affect cells in the brain, bone marrow, mouth, stomach, intestines, hair follicles, and skin (Keene, 2012), side effects include hair loss, nausea/vomiting and other gastrointestinal problems, alteration of taste and smell, mouth and throat sores, and severe fatigue (Armstrong, 2006). Although children have benefitted from new conscious sedation procedures to reduce pain and antiemetic medications to reduce acute nausea/vomiting since the 1990s (Armstrong, 2006), cancer treatment and its side effects remains an unpleasant and sometimes traumatic experience for children.

Other challenges for children on treatment depend on their age and developmental level. Toddlers and pre-schoolers find that their struggle for mastery and developing sense of initiative are hampered (Marsland, Ewing, & Thompson, 2006). School-age children fight to keep up with academics and maintain friendships while grieving the loss of "normal" life (Kupst & Bingen, 2006). Adolescents must juggle their desire for autonomy and identity consolidation with the need to be dependent in the role of patient. Patients in this age group may also experience an increase in normative worry with regard to self-esteem in the face of treatment-related physical changes.

High-risk patients experience additional challenges related to medically necessary isolation (Armstrong, 2006), while almost all children and adolescents on treatment experience a disruption in the ability to attend school and participate in other peer activities. These patients may experience sadness and anger, frustration, or feelings of abandonment by peers who are unable to visit them (Kupst & Bingen, 2006). Older children and adolescents may also be affected by knowledge of the seriousness of their diagnosis, and a feeling of being different from their peers or no longer fitting in. These feelings of social-isolation can contribute to depression and altered self-esteem (Madan-Swain & Brown, 1991).

Survivorship & Late Effects

Survivorship. At some point after children diagnosed with ALL finish their last round of maintenance chemotherapy, when they are in remission and have recovered from the acute effects of therapy, they enter into survivorship. The timing of entry into this long-term follow-up care varies depending on the clinic; some enroll survivors at a set time following diagnosis (usually five years) while others begin long-term follow-up at a set interval following completion of active treatment (usually one-two years) (Landier, 2007). Survivorship clinics vary around the United States, but at minimum, typically follow-up with the survivor and family through yearly comprehensive visits focused on risk-based screening and health promotion (Landier, 2007).

At the annual visit, physicians and nurses review the patient's interval health history and health habits, discuss developmental milestones and school performance, ask about health related quality of life and emotional concerns, and importantly, monitor for the development of "late effects", which can affect a survivor's physical, cognitive, and psychosocial health over time after the completion of treatment (Landier, 2007). When concerns arise, the survivorship clinics provide education and counseling about late effects and refer the family to specialists and community resources as needed.

Late effects overview. "Late effects" refer to the medical, physical, cognitive or psychosocial outcomes of cancer treatment that are different than acute effects because they generally emerge two to five years after the diagnosis of ALL. These late effects are often chronic and progressive. Oeffinger and colleagues (2006) studied over 10,000 childhood cancer survivors treated in the 1970s and 1980s, and found two-thirds reported at least one chronic late effect, with the incidence increasing over time.

Physical late effects. Reported physical late effects include: damage to the heart, pulmonary difficulties, endocrine abnormalities (including growth problems), impairment in thyroid function, infertility, and risk of second malignancies (Mody et al., 2008; Neglia, O'Leary & Bhatia, 2011). Fatigue is also prevalent among ALL survivors, with incidence rates approaching 30% (Neglia et al., 2011).

Mody et al. (2008) surveyed 4,151 survivors of childhood ALL and their siblings, and found that significantly more survivors reported poor general health, activity limitations and functional impairment than siblings. The authors found that all survivors reported late effects, with 50% of survivors reporting one or more chronic medical conditions 25-years after diagnosis as compared with 37.8% of siblings ($p < .001$) (Mody et al., 2008). It is important to note that physical late effects can impact health-related quality of life, the ability to perform daily activities, and the ability to plan for the future (Hudson et al., 2003).

Neurocognitive late effects. In addition to medical and physical late effects, research has shown pediatric cancer survivors also experience neurocognitive late effects as a result of treatment. Like the other kinds of late effects, deficits in neurocognitive functioning often do not present until several years after treatment (Neglia et al., 2011). The effects of treatment are progressive, but seem to be delayed in onset (Moore, 2005).

***Global cognitive ability*.** The first studies investigating neurocognitive outcomes in pediatric cancer survivors focused on the effects of cranial irradiation on overall cognitive ability. An early meta-analysis conducted by Cousens, Waters, Said, & Stevens (1988) reviewed 30 studies of childhood leukemia survivors who had received irradiation. They concluded that IQ was 2/3 of a standard deviation lower in the survivor groups as compared to control groups of healthy peers, siblings, and children with other types of cancers. Madan-Swain & Brown (1991) reviewed 20 studies of ALL survivors that mostly used IQ and academic achievement as outcome measures and included patients treated with CRT. Many of these early studies were confounded, however, because patients in the CRT groups often also received IT MTX (Moleski, 2000). Therefore, it could not be concluded that CRT alone was the cause of neurocognitive late effects.

Madan-Swain & Brown (1991) reported that chemotherapy "may have similar effects" to that of CRT. One study that separated survivors who had received CRT + IT MTX from those who had received only CRT as part of their treatment found that the combined treatment group scored approximately 11 IQ points lower (Bleyer et al., 1990). Three studies out of St. Jude's, however, randomly assigned patients to either IT chemotherapy or CRT and found that longitudinally, the groups showed equivalent declines in intellectual ability (Ochs, Parvey & Mulhern, 1986). Buizer et al. (2009) reported eight out of 10 studies in their meta-analysis that specifically compared ALL survivors treated with chemotherapy only and controls did not find a decline in total IQ.

Moleski (2000) conducted a review of studies that included a group of ALL survivors treated with IT MTX and no CRT. She reviewed 33 studies completed between 1981 and 1997. Although some did not find differences between groups treated with and without CRT, two-thirds reported declines in cognitive, neuropsychological or academic domains (Moleski, 2000). Interestingly, all four studies using sibling controls and seven of eight using a non-CNS treated cancer control group found declines in cognitive ability for the group of survivors treated with IT MTX (Moleski, 2000). This may be because repeated findings have shown siblings and pre-treatment ALL patients have a mean IQ of

112 (Buizer et al., 2009). Similarly, Oeffinger et al. (2006) compared the health of over 10,000 adult survivors of childhood cancer and over 3,000 of their siblings and found that survivors are 10 times more at risk for cognitive difficulties than their siblings. Cancer treatment may result in declines in IQ for survivors that do not result in scores outside the normative range.

The few studies of the effects of chemotherapy in isolation on global cognitive ability have had varying outcomes (Moore, 2005). Reviews suggest that at least 30% of survivors exhibit some degree of impairment (Mulhern & Butler, 2006). Temming & Jenney (2010) suggested that with chemotherapy treatment alone, global IQ is relatively preserved but specific deficits in areas including attention, information processing and memory emerge.

Executive functioning. According to Gragert & Kahalley (2012), common presenting concerns of parents of cancer survivors include: "inattention, distractibility, forgetfulness, poor “short-term memory,” inconsistent learning, slowed processing and task completion, organizational difficulties, and specific areas of academic deficit". Many of these complaints fall under the umbrella of executive functioning (EF). EF is a multidimensional construct defined broadly by Vriezen & Pigott (2002) as "higher order cognitive processes that control and regulate a variety of cognitive, emotional and behavioral functions".

Working memory. One of the core EF deficits affected in cancer survivors is working memory. Without the ability to effectively store and manipulate information, cancer survivors have trouble completing tasks. Poor working memory has been documented in ALL survivors treated with IT chemotherapy alone (Campbell et al., 2009; Peterson et al., 2008). Campbell et al. (2009) compared the working memory abilities of 30 ALL survivors and 30 healthy controls. They compared the two groups on the basis of a z-score composite created from the working memory index (WMI) of the Woodcock-Johnson Test of Cognitive Abilities-3rd Edition (WJ III-Cog) and the working memory subscale of the Behavior Rating Inventory of Executive Functioning (BRIEF) parent questionnaire. The ALL survivors achieved significantly lower scores ($t = -2.61$, $p < .01$), with a medium effect size (-.75) (Campbell et al., 2009).

In Peterson et al. (2008)'s meta-analysis of 13 studies of the impact of chemotherapy alone on ALL survivors, reported EF weaknesses in addition to working memory included processing speed and attentional shifting. In addition to working memory, research appears to show that attention problems are a second core deficit among pediatric ALL survivors.

Attentional difficulties. Reviews of the literature demonstrate that problems with attention have been consistently reported among survivors as compared to a variety of controls (Buizer et al., 2009; Campbell et al., 2007; Moleski, 2000). In fact, as early as 1983 researchers were comparing the profile of pediatric cancer survivors to that of children with attention deficit/hyperactivity disorder (ADHD), noting commonalities in "distractibility, impulsivity, and difficulty processing information" (Pavlovsky, 1983). Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, (2005) used neuropsychological measures to compare the attentional abilities of 36 children who had completed chemotherapy-only ALL treatment with 39 Wilm's tumor patients (non-CNS cancer control) and 110 healthy children. They detected difficulties in sustained attention and attention flexibility for the ALL patients but not Wilm's tumor patients (Buizer et al., 2005).

Non-dominant hemisphere & other deficits. Along with EF difficulties, ALL survivors who have been treated with CRT and/or IT chemotherapy have been shown to experience most difficulty with functions of the non-dominant hemisphere (Mulhern & Butler, 2006). These include nonverbal reasoning, math achievement, visual-motor integration, and processing speed (Buizer et al., 2009; Moleski, 2000; Mulhern & Butler, 2006; Temming & Jenney, 2010).

CNS sequelae; frontal lobe dysfunction & white matter alterations. Researchers became interested in investigating if there was a neurological impact of treatment that correlated with cognitive late effects early on. Carey et al. (2008) reported eight articles from 1981-2006 finding white matter changes, four more (plus two in the first group) also citing widening of the ventricles and/or sulci, and two that discussed cerebral calcifications. In their study, Carey et al. (2008) used voxel-based morphometry to examine grey and white matter differences in ALL survivors treated with IT-MTX (and no CRT) and controls. They found two specific regions of reduced white matter in the right frontal lobes (Carey et al., 2008). Demyelination, which impedes neuronal transmission, has been a frequently reported phenomenon in long-term survivors, especially in the prefrontal cortex (Moore, Copeland, Reid & Levy, 1992). Cerebral calcifications in leukemia survivors have also been found in the basal ganglia and its connections to the frontal lobes (Brouwers, Riccardi, Fedio & Poplac, 1985).

These are not surprising findings given the above explanation that behavioral and neuropsychological assessment of ALL survivors has shown difficulties related to frontal lobe dysfunction (Madan-Swain & Brown, 1991).

Risk factors for neurocognitive late effects. Several researchers, but not all (Campbell et al., 2007), have reported differential neurocognitive outcomes based on certain risk factors. Those most commonly identified include female gender, younger age at diagnosis, and treatment intensity (Gragert & Kahalley, 2012; Temming & Jenney, 2010).

Gender. The first study to call attention to potential gender differences in the development of neuropsychological late effects was Waber & colleagues (1990). They investigated the cognitive abilities of ALL survivors who were between five and 12 years post-diagnosis, and concluded that male survivors had higher IQ and achievement scores (Waber et al., 1990). The females in Waber et al. (1990)'s sample had particular difficulties with visuospatial tasks when compared to males. Brown et al. (1998) and Butler, Rizzi, & Bandilla (1999) replicated these findings, with Brown & colleagues (1998) showing female but not male ALL survivors achieved nonverbal scores that were below average, and Butler et al. (1999) reporting that female survivors had significantly lower Performance IQ and parent reported cognitive development scores than male survivors. A 13 study meta-analytic review recently completed by Peterson et al. (2008) concluded that girls may be at a higher risk for developing these kinds of neurocognitive late effects than boys.

Age at diagnosis. The review completed by Cousens et al. (1988) concluded that the effects of radiation were larger for children diagnosed and treated at a younger age. A meta-analytic review by Campbell & colleagues (2007) suggested that age five is the most frequent categorical age split in the literature, and it is widely accepted that children diagnosed before age five are more vulnerable to late effects. Fletcher & Copeland (1988) explained this pattern by differential rates of myelination in the brain. Myelin develops more rapidly in younger brains, and without insult, will continue to increase throughout early childhood and into adolescence (Moore, 2005). When white matter proliferation does get disrupted and white matter is destroyed, however, executive function difficulties may emerge.

Treatment intensity. A relationship between treatment intensity and neurocognitive outcome has also emerged in the literature. Children who receive radiation, higher doses of systemic or IT MTX, or TIT chemotherapy have been shown to have worse cognitive outcomes than non-CNS treated cancer controls or ALL patients who do not require as severe doses (Buizer et al., 2005; Mulhern & Butler, 2006). However, few studies report treatment protocol details, so some meta-analyses have not been able to definitively calculate the effect of this variable as a moderator (Peterson et al., 2008).

Methods & measures. Neurocognitive late effects have been measured in two main ways, standardized clinical cognitive/ neuropsychological assessment, and behavioral rating scales. Although standard neuropsychological batteries are some of the best tools available to measure neurocognitive constructs objectively, some have criticized their ecological validity (Vriezen & Pigott, 2002). Because the testing environment is highly structured, it may not mimic the child's day-to-day environment.

Parents are most often asked to complete rating scales, but even the earliest researchers recognized the value in obtaining teacher reports. Deasy-Spinetta & Spinetta (1980) asked teachers to report on cancer survivors' inattention, abstract thinking and learning problems as compared to healthy children. It is recommended that researchers cross-validate parent reports with teacher reports, in order to obtain the best picture of the child's abilities in multiple environmental settings.

Psychosocial late effects. Research into the possible psychosocial consequences of cancer treatment has not benefitted from the same international collaboration characterizing the study of medical treatment and physical late effects (Eiser, Hill & Vance, 2000). However, awareness of the importance of the topic is growing, and as a result, more focused research is being conducted.

Null results in most studies of overall adjustment. In terms of overall adjustment, most reviews show few differences in studies making comparisons between survivors and control groups of healthy peers or normative data on standardized measures of depression, anxiety or self-esteem (Eiser et al., 2000; Stam, Grootenhuis & Last, 2001). It seems as though most children with cancer are able to adapt well during survivorship. Noll & Kupst (2007) suggest a theory of remarkable "hardiness" in the face of multiple challenges. Parry & Chesler (2005) suggest that survivors are "thriving". Studies of health-related quality of life among adult survivors of childhood cancer have shown that survivors "engage in all aspects of life", and achieve education, employment and marriage at levels similar to peers (Lund, Schmiegelow, Rechnitzer & Johansen 2011).

A sub-group of survivors have psychosocial difficulties. Although research shows that most survivors appear to be functioning well, an estimated 25-30% of children and family members experience significant personal and social difficulties after the transition to survivorship (Patenaude & Kupst, 2005). This sub-group of survivors can have serious adjustment and emotional issues (Eiser et al., 2000) including clinically significant symptoms of PTSD (Marsland et al., 2006) and relationship problems that may be long-lasting (Koocher & O'Malley, 1981). This number has been consistent in studies conducted outside the U.S. and Europe as well. A recent study in Thailand showed 28% of 258 survivors of ALL reported psychosocial problems (Pakakasama et al., 2010).

Methods and Measures. Methodological problems may explain some contradictory and null findings (Marsland et al., 2006; Stam et al., 2001). First, very few studies have used cancer-specific measures. The majority use broad-based behavioral reports or rating scales and only utilize one reporter (Eiser et al., 2000). The importance of using multiple raters is underscored by the few studies who have used both parent and teacher questionnaires and reported low interrater reliability (Wakefield et al., 2010), or those where self-reports showed no significant differences between survivors and controls while parent reports described more internalizing and externalizing problems (Reinfjell, Lofstad, Nordahl, Vikan, & Diseth, 2009). In addition, most studies have very small sample sizes but include a wide age-range of survivors of a variety of childhood cancers who have undergone different treatment protocols without controlling for all of these variables. Another potential problem is under-reporting of symptoms out of a desire to appear "supernormal" and present oneself favorably (Madan-Swain et al., 1994). It has been suggested that survivors may even unconsciously report fewer negative outcomes due to adaptive repression or denial (Lund et al., 2011).

Global anxiety, social anxiety & social skills. There have been no reviews to date focusing only on the presence of social anxiety or social skills deficits in survivors. However, 46 studies including one or more variations on these variables were identified through a search of seven global reviews of psychosocial effects (Eiser et al., 2000; Lund et al., 2011; Madan-Swain & Brown, 1991; Marsland et al., 2006; Noll & Kupst, 2007; Stam et al., 2001; Wakefield et al., 2010) and a Google Scholar search of specific terms. Those articles reviewed represented research from nine different countries.

Global anxiety. The majority of studies did not show differences between survivors and controls on global measures of anxiety (Marsland et al., 2006 reported seven) and one even showed that survivors scored below the published norms for anxiety (Elkin, Phipps, Mulhern, & Fairclough, 1997). However, a few showed elevated scores on the State-Trait Anxiety Inventory (Servitzoglou, Papadatou, Tsiantis, & Vasilatou-Kosmidis, 2008; Hobbie et al., 2000; Bauld, Anderson, & Arnold, 1998). In addition, Shelby, Nagle, Barnett-Queen, Quattlebaum, & Wuori (1998) broadly reported more internalizing problems, and Schultz et al. (2007) reported that ALL survivors were 1.5x more likely to show signs of anxiety or depression than their siblings.

Social anxiety. Only three studies examined social anxiety directly. Bessel (2001) found that 42% of their sample of survivors reported clinically significant social anxiety scores. The other two studies showed age differences, although in opposite directions. Pendley, Dahlquist, & Dreyer (1997) reported no group differences on social anxiety overall, but more social anxiety and negative body image among the older group of survivors. In contrast, Kazak et al. (1997) reported that younger survivors had more social anxiety than age matched controls. Servitzoglou et al. (2008) reported an interesting finding that 67% of surveyed survivors "rarely" or "never" disclosed their cancer past to new friends or current partners, potentially indicating socially anxious avoidance.

Social skills. There was no clear consistency across studies for social competence. Several studies reported more antisocial behaviors or problems with social skills as compared to siblings (Schultz et al., 2007) or clinical cutoffs/ published norms (Shelby et al., 1998). Others found no differences between survivors and controls (Anderson, Smibert, Ekert, & Godber, 1994; Levin Newby, Brown, Pawletko, Gold, & Whitt, 2000; Madan-Swain et al., 1994). With respect to peer relationships, however, there is agreement. Several studies showed that survivors had fewer close friends than healthy peers (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Sloper, Larcombe, & Charlton, 1994; Lund et al., 2011) and participated in fewer activities than peers (Pendley et al., 1997). Mackie, Hill, Kondryn, & McNally (2000) reported that young adult survivors have overall impaired close relationships including both friendships and love/sex relationships.

Risk factors for psychosocial late effects. Differential psychosocial outcomes have been found based on certain risk factors. Those most commonly identified include gender, current age, age at diagnosis, and treatment intensity.

Gender. Unlike the neurocognitive literature, which shows females tend to have worse outcomes, the psychosocial literature has not been consistent (Marsland et al., 2006), with the exception that Lund et al. (2011) reports that female young adult survivors have worse outcomes in terms of health-related quality of life. Younger female survivors have been found to be more at risk for poor social functioning and intimate relations (Wu et al., 2007), anxiety (Servitzoglou et al., 2008) and symptoms of post-traumatic stress (Stam et al., 2001), but male gender has also been identified as a risk factor. Males were found to be more at risk for psychosocial problems (Van Dongen-Melman, 1995) anxiety (Chang, Nesbit, Youngren & Robison, 1988), poor social adjustment (Vannatta, Gerhardt, Wells, & Noll, 2007) peer difficulties (Barrera et al., 2005), depression & behavioral problems (Stam et al., 2001).

Current age. Older survivors consistently showed worse adjustment, more distress, and more socio-behavioral problems than younger survivors (Marsland et al., 2006; Stam et al., 2001). With increasing time since diagnosis, psychosocial adjustment seems to stay the same or get worse. Older age at time of study has been associated with more psychological distress or social problems than age-matched controls or standardized norms (Lesko, 1990; Mulhern, Wasserman, Friedman, & Fairclough, 1989; Van Dongen-Melman 1995; Wu et al., 2007). Pendley et al. (1997) showed that survivors who had been off treatment longer had more social anxiety, more negative body image, and a lower sense of self-worth. Similarly, Bauld et al. (1998) found that 15-17 year old survivors worried more than 12-14 year old survivors. Elkin et al. (1997) reported that although survivors overall scored lower than norms on a symptom checklist, older age was a risk factor for scoring in the clinical range for somatization, anxiety, and the global index.

Age at diagnosis. Younger or older age at diagnosis has not been proven as a consistent risk factor for worse outcomes (Stam et al., 2001). In fact, von Essen, Enskär, Kreuger, Larsson, & Sjödén (2000), showed that the middle age group (10-14) had more depression and anxiety than those diagnosed at younger or older ages. Lund et al. (2011) suggested that being diagnosed before age 10 resulted in worse long-term psychosocial outcomes. Barrera et al., (2005) found stronger social relationships among those diagnosed after age five. Lesko (1990) and Van Dongen-Melman (1995), on the other hand, suggested that older age at diagnosis resulted in more psychological distress.

Treatment intensity. Those studies that included CRT or CRT+MTX seemed to find that survivors previously treated with radiation were more withdrawn and more prone to anxiety, depression and social problems (Anderson et al., 1994; Reiter-Purtill, Vannatta, Gerhardt, Correll, & Noll, 2003; Schultz et al., 2007).

Associations Between Neurocognitive and Psychosocial Late Effects

Madan-Swain & Brown (1991) assert that a "reciprocal relationship" likely exists between cognitive and affective symptoms among young survivors, but that relatively few studies have examined associations between the two.

Limitations in Executive Functioning have been associated with worse overall health-related quality of life (HRQOL) in adult survivors of childhood cancer (Gragert & Kahalley, 2012). The Childhood Cancer Survivor Study (CCSS) has followed over 20,000 survivors of a variety of childhood cancers who were diagnosed at one of 26 institutions between 1970 and 1986 into adulthood in order to gain a better understanding of the late effects of treatment (Ness et al., 2008). Studies from the CCSS have shown that limitations in EF and/or emotional health among survivors are associated with poor HRQOL including being less likely to be employed, married, or have an income greater than $20,000 (Ness et al., 2008). Ellenberg et al. (2009) showed an association specifically between lower neurocognitive scores and poorer educational and employment outcomes.

Cognitive and academic problems have been linked to internalizing problems in the general population. Rourke & Fuerst (1991) report that "learning failure" leads to an increase in anxious symptoms, which leads to feelings of inferiority. Kazak, Chistakis &

Alederfer (1994) hypothesized that this relationship may hold for survivors who experience learning problems. They suggested survivors with lower EF may be at higher risk for poor psychological functioning after identifying survivors receiving special education services as having higher levels of anxiety (Kazak et al., 1994). The reverse is also true, as higher levels of cognitive functioning have been associated with better overall adjustment (Mackie et al., 2000; Levin Newby et al., 2000). Campbell and colleagues (2009) introduced the idea of coping ability as a mediator, demonstrating a relationship between EF deficits, disengagement (avoidant) coping, poor regulation of emotions and social stress, and increased emotional problems.

Relationships between cognitive impairment and social skills among pediatric cancer survivors are also emerging. Gragert & Kahalley (2012) suggest that treatment-related EF may make it more difficult for survivors to attend to, process and respond in social situations, but point to a lack of published research to test the hypothesis. In one study of brain tumor survivors, Vannatta, Gartstein, Short & Noll (1998) suggested that treatment negatively impacted social skills, and that survivors with more cognitive impairments felt and were perceived as more socially isolated. Similarly, Levin Newby et al. (2000) found a positive association between academic functioning and social skills/adjustment. Barrera et al. (2005) reported that their sample of survivors experienced more academic and social difficulties than a comparison group, but did not indicate if the same children experienced both.

Finally, two studies included variations on all constructs of interest without directly assessing associations between them. First, Koocher, O'Malley, Gogan & Foster (1980) found that within their sample, patients with the most difficulties with "psychosocial adjustment" also had less effective social skills and lower EF. Bessell (2001) found that repeating a grade or being in special education following cancer treatment resulted in more social problems while also noting that 42% of their sample reported symptoms of social anxiety.

Neurocognitive & Psychosocial Demands of Adolescent Development

Adolescent development is a time marked by transition (Erath, Flanagan & Bierman, 2007). Children in the U.S. experience changes in school structure as they move to a larger system of multiple classrooms and teachers. High school classes have much less structure and scaffolding and youth have to learn time management strategies. This is more difficult with increasing distractions. Peer networks shift, and friendships become of supreme importance. There are more opportunities to participate in extracurricular activities, but there is more competition. Adolescents engage in increased social comparisons, and bullying and peer victimization is more prevalent too. In this atmosphere of change, adolescents need to use more sophisticated metacognitive and social skills.

Metacognitive (EF) skills are required for strategizing, planning goal-directed behavior, monitoring, evaluating and reflecting. New social skill demands include the need to initiate and sustain spontaneous conversation in dyads and groups, o reciprocate self-disclosure and to regulate negative affect (Erath et al., 2007). Some skills, such as understanding how choices impact friendships, and how to take another's perspective, could be characterized as involving both EF and social competence.

EF is considered to be "a general overarching construct that includes all supervisory or self-regulatory functions, which organize and direct cognitive activity, emotional response, and overt behavior" (Gioia, Isquith, Kenworthy & Barton, 2002). EF involves initiation, inhibition, goal selection, problem solving, and self-evaluation (Gioia et al., 2002). Problems with EF have a broad impact on functioning, affecting social, emotional, behavior and academic domains (Sparrow & Hunter, 2012a). Children with EF deficits show an enhanced vulnerability to internalizing disorders (Sparrow & Hunter, 2012b). EF deficits can be particularly problematic for adolescents, as it puts them at risk for involvement in reckless behavior, especially as they become more self-conscious and sensitive to the opinions and evaluations of peers (Hunter, Edidin, & Hinkle, 2012).

Social skills can be defined as "specific adaptive behaviors needed to perform a social task" (Hupp, LeBlanc, Jewell & Warnes, 2009). According to Gresham (1981), social skills deficits typically fall into three categories: acquisition (the child "can't"), performance (the child "won't"), and fluency. Impairments in social skills have been linked to a broad range of problems including social isolation and withdrawal, aggressive and antisocial behavior, dropping out of school, and juvenile delinquency (Matson & Wilkins, 2009). Social skills deficits may also be a diagnostic criterion, direct consequence or both, of a variety of psychological disorders (Jewell, Jordan, Hupp &

Everett, 2009). In depression, for example, social skills deficits may affect perception (in attending to the negative), cognition (due to a decreased ability to judge another's emotions), and performance (withdrawal). On the contrary, positive social skills are associated with academic achievement, psychological adjustment, effective coping and employment (Hupp et al., 2009)

Social Anxiety in Adolescence

Anxiety disorders are among the most commonly diagnosed psychological disorders in children, with reported prevalence rates ranging from eight to 27% (Costello, Egger, & Angold, 2004). The presence of an anxiety disorder can impair general functioning (Ezpeleta, Keeler, Erkanli, Costello, & Angold, 2001) and can be chronic, leading to increased risk for a psychiatric disorder later in life (Kessler et al., 2005). Social Phobia (SoP, also known as Social Anxiety Disorder) is one of the most common anxiety disorders in youth. It affects 5-16% of adolescents (Mesa, Nieves & Beidel, 2011) and has a median onset of 13 years (Kessler et al., 2005). SoP peaks at around age 15 (Erath et al., 2007). The symptoms of anxiety disorders including SoP can be divided into three categories that serve as intervention targets: physiology, cognition, and behaviors.

Self-reported physical symptoms associated with SoP include tachycardia, blushing, trembling and sweating when in (or anticipating) social or performance situations (Mesa et al., 2011). Interestingly, adolescents with SoP were shown to have higher perceived physiological reactivity during a speech and conversation task even though measured heart rate and blood pressure did not differ significantly between the SoP and control group (Anderson & Hope, 2009).

Youth with SoP are plagued by unreasonable anxious thoughts that they will do or say something that will be seen by others as embarrassing (Mesa et al., 2011). Negative thoughts of SoP individuals have been elicited on self-statement questionnaires, during role-play scenarios, and in read aloud tasks. These individuals are constantly expecting bad things to happen; they anticipate rejection and isolation.

Behavioral avoidance is the third important feature of SoP. According to Rao et al. (2007), adolescents with SoP report avoiding a broad range of social interactions including: speaking to unfamiliar people, initiating/joining conversations, asking teachers for help at school, speaking aloud or writing on the board in class, attending parties or other social events, and inviting a friend to do something. One of the developmental tasks of adolescence is to initiate and maintain friendships without the assistance of parents. For this reason, adolescents with SoP may have more opportunities to engage in behavioral avoidance (Mesa et al., 2011). This unfortunately limits opportunities for positive social interactions and the development of social support. Expectations of rejection are reinforced with avoidance. Although avoidance may temporarily reduce anxiety, it also reduces the chance for mastery of both anxiety and social skills, thus perpetuating the cycle of SoP.

SoP has been linked to several negative outcomes including loneliness, decreased peer acceptance and increased peer victimization, school avoidance and diminished work productivity substance abuse, and suicidal ideation (Erath et al., 2007; Mesa et al., 2011)

Summary

International collaboration has led to phenomenal progress in the treatment of childhood cancer. Five-year survival rates for children diagnosed with ALL before the age of 15 are now almost 90% (Smith et al., 2010). With increasing numbers of survivors, researchers have begun to focus on morbidity. It is now generally accepted that most survivors who were treated with chemotherapy for CNS prophylaxis experience late effects in at least one area of functioning (Moleski, 2000).

Neurocognitive late effects are common in areas of executive functioning including attention and working memory (Campbell et al. 2007; 2009). Those at highest risk include females, children diagnosed at younger ages, and those who have to undergo more intense treatment (Gragert & Kahalley, 2012).

Psychosocial outcomes have also been studied in this population, although there have been methodological challenges, and almost no studies have focused exclusively on ALL survivors. Findings generally show that the majority of childhood cancer survivors adjust well as reported on global measures of functioning. However, a subset of 25-30% of survivors experience marked difficulty in psychological and/or social functioning (Patenaude & Kupst, 2005). Factors consistently associated with higher risk are older age at time of study (adolescents) and treatment intensity (Marsland et al., 2006).

Only three studies examined social anxiety, but they all reported significant symptoms in at least a subset of the samples. Survivors' peer relationships appear to be limited or impaired, but no conclusion could be made about social competence (Stam et al., 2001). It is likely that some survivors struggle with social skills while the majority do not.

Few studies have examined associations between neurocognitive and psychosocial late effects, and those that have included a wide age range and multiple cancer diagnoses. Lower EF was correlated with lower HRQOL in a sample of young adult survivors of pediatric cancer (Ness et al., 2008). In addition, school-aged survivors with academic difficulties have been shown to experience more internalizing problems (Kazak et al., 1994). Campbell and colleagues (2009) showed a connection between EF, disengagement coping (avoidance) and emotional problems. Finally, Bessel (2011) found evidence of academic difficulties, social anxiety and social skills problems in the same sample of survivors.

Adolescence is a time of increasing social and academic demands, and evaluation of self in relation to peers. Social phobia peaks in adolescence. Middle and high school is likely very overwhelming both academically and socially for survivors who are beginning to experience neurocognitive late effects for the first time. Among adolescents who have not had cancer, deficits in EF are associated with both internalizing and risk behaviors (Sparrow & Hunter, 2012b; Hunter, Edidin, & Hinkle, 2012). Similarly, social anxiety has been linked to various negative outcomes including loneliness, school/work problems and risk behaviors (Erath et al., 2007). Adaptive social skills on the other hand, are associated with good adjustment and effective coping abilities (Hupp et al., 2009).

Chapter 3: Proposed Research Study

Problem Statement

Research has shown that at least 30% of survivors of pediatric ALL experience neurocognitive late effects as a result of their treatment experience (Campbell et al., 2007). Less is known about the psychosocial sequelae of treatment, although many studies of global functioning find the majority of pediatric cancer survivors to be well-adjusted. It has been documented, however, that a subset of 25-30% of survivors also experience some psychosocial problems following treatment. It is unclear if this subset experiencing psychosocial difficulty is more likely to also have severe neurocognitive late effects. A relationship between neurocognitive late effects and psychosocial late effects has been hypothesized, but not proven definitively in the literature.

Social phobia is one specific psychosocial difficulty that may be particularly relevant for adolescent cancer survivors. SoP is characterized by persistent, irrational fears of being judged negatively or embarrassing oneself. Adolescence is marked by changes in the social fabric including increased peer comparisons and a feeling of needing to fit in. This may be more difficult for survivors given all they have been through and the likelihood that they are experiencing EF deficits relative to healthy peers. Youth who are overcoming ALL have been found to be involved in much fewer activities, which may be a result of anxiety-related avoidance. Only three studies were found that examined social anxiety symptoms in this population, but each of them had significant results.

The main purpose of the present study is to investigate the association between executive functioning and social anxiety in a group of adolescent ALL survivors who have been treated with chemotherapy for CNS prophylaxis.

The second aim of the study is to examine a possible interaction between executive functioning and social skills in their impact on social anxiety. It is hypothesized that adaptive social skills, which have been shown to be associated with good adjustment and effective coping, may protect against the development of social anxiety symptoms even in the presence of EF deficits. Understanding these associations can have important implications for the development of targeted psychosocial interventions for survivors of pediatric ALL. Since social skills is a somewhat modifiable construct that could be incorporated into a variety of therapeutic interventions, it would be useful to determine its association with these variables.

Research Questions & Hypotheses

Research question 1. What is the association between EF and social anxiety in a sample of adolescent survivors of ALL (when controlling for gender, current age and age at diagnosis)?

Hypothesis 1. It is hypothesized that both parent and teacher reported EF will significantly predict self reported social anxiety symptoms among cancer survivors when gender, current age and age at diagnosis are controlled for.

Rationale 1. Youth whose parents and/or teachers report more difficulties in EF domains are hypothesized to be more likely to have higher levels of self-reported social anxiety for a variety of reasons. Although there is not yet much empirical research to support this hypothesis, assumptions based in theory and clinical experience support the hypothesis.

Anxious thoughts surrounding academic fears (answering a question in class, writing on the board, taking a quiz) and appearing unintelligent in front of peers are common in SoP (Rao et al, 2007). For pediatric cancer survivors beginning to experience neurocognitive late effects and EF difficulties, irrational anxious thoughts may be perpetuated by actual experiences of failure in the classroom (Rourke & Fuerst, 1991). Students with EF problems may find themselves needing more time to complete tasks, or needing to hear the directions repeated more often than peers. Their school may even put a Section 504 Plan into place, providing the student with needed accommodations, but potentially increasing anxious fears of being perceived in a negative light.

In addition, ALL survivors who are aware of slower processing, word finding difficulties, or increased difficulty with EF tasks may feel embarrassed about needing friends to slow down or have extra patience in order for them to keep up with adolescent conversations. Their bodies may begin to react physiologically to the stress of anticipating social interactions, which could make anxious thoughts worse (and focusing on the task at hand even more difficult). All of this will likely lead to avoidant behavior. EF deficits have been shown to predict avoidant coping strategies among pediatric cancer survivors (Campbell et al., 2009).

Poor planning and forgetfulness due to EF difficulties could also lead to missing out on peer activities. Since much adolescent conversation is focused on shared activities, the ALL survivor who did not share in an experience may feel embarrassed and more anxious about being in the presence of peers who did.

Research question 2. Does EF interact with social skills in their effect on social anxiety? Is the magnitude of the relationship between EF and social anxiety consistent among children with varying levels of social skills?

Hypothesis 2. EF will have a weaker effect on social anxiety among children with higher levels of reported social skills; the association between EF and social anxiety will be stronger for those with lower levels of reported social skills. Specifically, it is hypothesized that:

a) parent-reported social skills will moderate the relationship between parent-reported EF and self-reported social anxiety

b) parent-reported social skills will moderate the relationship between teacher-reported EF and self-reported social anxiety

c) teacher-reported social skills will moderate the relationship between parent-reported EF and self-reported social anxiety

d) teacher-reported social skills will moderate the relationship between teacher-reported EF and self-reported social anxiety

Rationale 2. The idea that high social skills abilities may protect against social anxiety in the presence of reported deficits in EF is derived in part from Yeates et al.

(2007)'s model *Social Outcomes in Childhood Brain Disorder.* It emphasizes the impact of social-cognitive processes on social adjustment, but could also be adapted to explain affective experience (Willard, 2011). The model suggests that social skills (social cognitive processes) affect one's ability to accurately perceive and process social cues, stimuli and environments. Individuals with adaptive social skills are more likely to perceive affect (facial expressions) in others accurately and thus to have thoughts that are more coping than anxious in nature. It is hypothesized that this would be the case even if the individual had other difficulties with attention or working memory. In addition, adaptive social skills such as cooperation evoke reciprocity in others, which provides evidence against anxious thoughts common for individuals developing SoP.

Finally, individuals with higher social skills in this population may have experienced cancer treatment differently from those with lower social skills, in a way that left them less vulnerable to the development of an anxiety disorder. For example, children with higher social skills may have been able to stay better connected with peers while on treatment (through the use of social media, for example) and thus be less likely to develop anxious avoidance of social situations after a period of social isolation.

Methods

Participants. This study will include at least 85 pre-adolescent and adolescent survivors of acute lymphoblastic leukemia (ages 12 – 16) who have been treated with chemotherapy-only and have achieved full remission. One goal of this study is to facilitate a more precise understanding of the neuropsychological and psychosocial sequelae of one specific type of treatment for ALL. For this reason, only survivors who were treated with chemotherapy, including CNS-directed chemotherapy such as intrathecal methotrexate (IT-MTX) will be included. Survivors who were also treated with cranial irradiation or who received a stem cell transplant as part of their treatment will be excluded. Youth who experienced CNS relapse during or following ALL treatment will also be excluded. It is expected that survivors in this group will have been diagnosed between the ages of two and 10, as it is within that range that children have the best overall prognosis (Mulhern & Butler, 2006). The mean age at diagnosis will be approximately five-years-old.

Because the goal of the study is to examine associations between potential late effects of cancer treatment, which often do not emerge until a few years after treatment, participants in the survivor group must have completed treatment a minimum of three years ago. It is expected that the mean amount of time elapsed since treatment completion will be about seven years.

All participating survivors will be recruited through the Survivorship Clinic at the Children's Blood and Cancer Center of Dell Children's Medical Center in Austin, T.X. Survivors are expected to be predominantly of Caucasian and Hispanic ethnic background in accordance with national rates of ALL and the demographics of Central Texas (Deviney & Phillips, 2011).

Youth will be excluded from the study if they have impaired global cognitive ability (i.e. mental retardation), or documented pre-cancer attention difficulties including attention-deficit/hyperactivity disorder (ADHD). Inclusionary criteria will be the ability of the youth participant to read, write and speak English, willingness of at least one parent to complete written measures in English or Spanish, and willingness of one teacher to complete measures about the child in English. The decision to allow parents to choose to complete measures in Spanish was made given the availability of standardized measures in both languages, and a desire not to exclude a large and growing segment of the survivor population served at Dell Children's Medical Center.

Instruments. Multiple informants will be utilized in the measurement of the three constructs of interest: Executive Function (EF), Social Skills and Social Anxiety. Youth participants will be asked to complete a self-report measure of anxiety symptoms as adolescents are considered to be the most accurate reporters of internalizing behaviors. Parent and teacher participants will be asked to complete questionnaires assessing the youth participant's EF abilities and social skills. Teachers can be particularly valuable raters because they have a good sense of appropriate functional levels and how the child compares to same-age peers. Teachers also have more opportunities to view the child with peers than their parent might (Schneider & Byrne, 1989). However, given the age of the participants (middle and high school), the participating teacher may only interact with the participant one period out of the school day, or even every other day in the case of block scheduling. For this reason parents are also included as raters in the present study.

Demographic Form. Participating parents will be asked to complete an intake information form that includes demographic (gender, current age, ethnicity), school history (current grade and school, two teacher's names, IEP/504 information) and cancer treatment questions (diagnosis, age at diagnosis, treatment protocol, length of treatment, time in survivorship).

Executive Functioning (EF).

Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000). The BRIEF consists of two 86-item questionnaires (parent and teacher) designed to collect standardized observational reports of youth's everyday functioning. Items are scored on a 3-point scale (never, sometimes, often), and comprise eight subdomains of executive functioning. The first five, initiation, working memory, planning/organizing, organization of materials, and monitoring, make up the Metacognition Index (MI). The other three domains (inhibition, shifting and emotional control) make up the Behavioral Regulation Index (BRI). The MI and BRI are combined into a Global Executive Composite (GEC).

The BRIEF was normed with reports from 1419 parents and 720 teachers from urban, suburban and rural areas of Maryland. Reported Chronbach's alpha's range from .80 to .98, supporting the measure's internal consistency. Adequate test-retest reliability has also been demonstrated (parent = 0.82, teacher = 0.88). Finally, moderate correlations exist between parent and teacher reports (0.32-0.34). The BRIEF is available in English and Spanish. It has been used extensively with ADHD and pediatric TBI populations, and more recently with pediatric cancer survivors as well (i.e. Campbell et al., 2007). The

GEC from both the parent and teacher forms of the BRIEF will be used as measures of Executive Functioning for this study.

Social Anxiety Symptoms.

Social Anxiety Scale for Children-Revised (SASC-R; La Greca & Stone, 1993) & Social Anxiety Scale for Adolescents (SAS-A; La Greca & Lopez, 1998). The SASC-R and SAS-A are self-report measures used to assess anxiety in social interactions with peers. In the SASC-R, for each of 22-items, youth are asked to report how much they feel the item is true for them on a five-point scale (not at all, hardly ever, sometimes, most of the time, all the time). The SASC-R is written at between a second and third grade reading level; psychometric properties were determined with a sample of fourth through sixth graders, and published studies using the measure have tended to focus on elementary and middle school children (La Greca & Lopez, 1998). Confirmatory Factor Analysis with the SASC-R confirmed the validity of the proposed three-factor structure (Fear of Negative Evaluation from Peers (FNE), Social Avoidance and Distress Specific to New Situations (SAD-N), and Generalized Social Avoidance and Distress (SAD-G)) and showed good internal consistency (*r*'s ranged from .69 to .86) (La Greca & Stone, 1993). Associations between SASC-R scores and children's self-appraisals and peer-rated sociometric status provided support for construct validity (La Greca & Stone, 1993).

The SAS-A was developed for use with high-school-aged youth. It contains the same 18 descriptive and four filler items as the SASC-R with modified wording (i.e. "peers" in place of "other kids"). Exploratory and Confirmatory Factor Analysis supported a satisfactory fit of the three-factor model, and internal consistencies were found to be even higher than for the SASC-R (alpha ranged from .76 to .91) (La Greca & Lopez, 1998). The SASC-R and SAS-A have previously been used with pediatric cancer patients and survivors (Bessell, 2001; Pendley et al., 1997; Varni, Katz, Colegrove, & Dolgin, 1995).

All youth participants will complete either the SASC-R or the SAS-A. Scores are calculated by summing the ratings on the items comprising each subscale, and then by combining the scores on each subscale to obtain a total score ranging from 18-90. The overall score on the SASC-R or SAS-A will be used as the measure of self-reported social anxiety symptoms for this study.

Social Skills.

Social Skills Rating System (SSRS; Gresham & Elliot, 1990). The SSRS asks raters to report on the frequency of specific, concrete, observable social behaviors on a 3-point Likert scale ("never occurs", "sometimes occurs" or "very often occurs"). The parent and teacher forms of the SSRS will be used in this study in order to obtain information about the child's behavior in multiple settings. Most participants will use the secondary forms for grades 7-12, but an elementary version is also available for any participants still in the sixth grade. The SSRS consists of a social skills scale and problem behaviors scale. The teacher version also includes an academic competence scale. All social skills items are rated on two dimensions: frequency and importance, allowing each rater to specify how important the social behavior is for success. This study will use the social skills composite score; higher scores indicate more positive social behaviors. The social skills scale consists of four factors: cooperation, assertion, responsibility, and self-control.

The SSRS is one of the most widely used and extensively researched measures of social skills available (Boisjoli & Matson, 2009). It was standardized on a national sample of more than 4,000 children in grades 3-10; 1,027 parents and 259 teachers participated (Gresham & Elliot, 1990). The SSRS provides separate norms for boys and girls at different age levels. It demonstrates sound psychometric properties, with internal consistency estimates ranging from 0.83 to 0.90 for the social skills composite. Test-retest reliabilities have been calculated for both the parent version (0.87) and the teacher version (0.75-0.93). Construct, criterion-related and content validity have also been demonstrated (Gresham & Elliot, 1990). The SSRS has been studied internationally; the factor structure of the adolescent version was replicated in a Norwegian sample and it has been translated into four languages (Boisjoli & Matson, 2009) including Spanish (Jurado, 2006). The SSRS has also been used with special populations including Attention Deficit/ Hyperactivity Disorder (Van der Oord, et al., 2005) and survivors of pediatric cancer including brain tumors and ALL (Carey, Barakat, Foley, Gyato, & Phillips, 2001; Levin Newby et al., 2000).

Procedure.

IRB Approval. This research study will be conducted in compliance with all ethical standards. All study materials including recruitment paperwork, consent/assent forms and questionnaires will be approved by the UT-Austin Institutional Review Board.

Recruitment of Participants. Participants for this study will be recruited in two ways. First, research assistants will approach survivors who meet criteria for the study during regularly scheduled appointments at the Survivorship Clinic at Dell Children's Medical Center. Because survivors who are not experiencing difficulty typically only come to the clinic once per year, information about the study will also be mailed to survivors of ALL who have been in recently and are identified by an oncologist, psychologist or neuropsychologist as meeting criteria for participation. Instructions for how to indicate a desire to participate will be provided on the flyer.

Consent Procedures. Participants and one parent will be consented (and assented) to participate in person, according to IRB approved procedures. They will be informed that participation is optional, and they are free to withdraw at any time, for any reason. Bilingual families will be consented by a bilingual research assistant or with the assistance of a Seton-approved hospital translator. Consent forms will be printed front/back in English and Spanish so participants have the opportunity to complete it and ask questions about the study in either language.

One teacher identified by each survivor will be contacted by phone and invited to participate in the study. Consent forms will then be mailed and the teacher will have another opportunity to speak with a research assistant before deciding to participate. If the first teacher declines, the second teacher identified by the student will be contacted.

Data Collection. Families interested in participating in the study will schedule an appointment to complete the consent process and rating scales/ questionnaires in the same visit. The parent will be asked their language of preference before the appointment is made to ensure that a bilingual research assistant is available to meet with them if necessary. Families will meet research assistants at either the Survivorship Clinic or the Texas Child Study Center, depending on their preference. After being consented together, parents and youth will be asked to complete the questionnaires in separate rooms. There will be a research assistant present in both rooms to answer any questions that arise. The youth participant will be given the option to have the research assistant read each item aloud from a separate identical questionnaire. As incentive for participating, parents will be entered into a raffle for one of three $25 HEB gift cards. All youth participants will be entered into a raffle for one of 15 gift cards for $5 to iTunes.

After being identified by participants on the demographic/intake form, potential teacher participants will be contacted by researchers and asked if they would like to participate. Teacher participants will not be mailed the questionnaires until after the researchers receive their signed consent form. Once teachers receive the questionnaires, they will be asked to complete them and return them in a sealed envelope with their signature across the flap.

Analyses & Expected Results

Analytic Plan. The first hypothesis for this study will be tested with two simultaneous regression analyses. One will use parent-reported EF as a predictor and the other will use teacher-reported EF as a predictor. The second hypothesis will be tested using four sequential multiple regression with each combination of parent/teacher measures for the cross-product of social skills and executive functioning (interaction term) entered in a second step.

Preliminary Analyses.

Power analyses. The minimum number of participants (85) was obtained from a power analysis for a fixed simultaneous regression with four predictor variables with alpha = .05, power = .80, and an anticipated medium effect size: f-squared =.15. The power analysis for the sequential regression to test social skills as a moderator was also conducted. For one tested predictor (the interaction) and five total predictors (three control variables, and one measure each of EF and social skills) and the same alpha, power and anticipated effect size levels, 55 participants are required. Because both hypotheses will be tested in this study, a minimum of 85 participants will be recruited.

Preparing variables. When entering the original data, gender will be dummy coded with males=0 to assist interpretation. All other data will be entered in its original form. For the present analyses, the age variable will be left as a continuous variable (not dichotomized into middle/ high school). Additionally, it was decided that parent and teacher measures of EF and social skills be left separate rather than combined into a z-score composite.

In order to facilitate the moderation analysis, new centered variables for parent and teacher reported EF and social skills will also be added to the data set. The following cross product terms will also be computed and added to the data set: BRIEFp_cen*SSRSp_cen; BRIEFp_cen*SSRSt_cen; BRIEFt_cen*SSRSt_cen; BRIEFt_cen*SSRSp_cen.

Checking the data. Once the data set is complete, descriptive statistics (means, standard deviations, ranges, maximums & minimums) will be computed and examined for age at diagnosis, current age, BRIEF_parent, BRIEF_teacher, SSRS_parent, SSRS_teacher, and SAS_self. Frequencies will be examined for gender. Next scatterplots will be checked for violations and sensitivity analyses will be conducted if necessary to assess outliers. The data will also be checked to make sure no statistical assumptions are violated. Finally, correlation matrices will be computed to assess if the variables of gender, age at diagnosis and current age are significantly correlated with independent or dependent variables, and should therefore be controlled for in the regression analyses. It is assumed that all three will be included in the analyses.

Tests of Research Questions.

Hypothesis 1a; Association between parent reported EF and self reported social anxiety symptoms. This hypothesis will be examined by a simultaneous regression of age at diagnosis, gender, current age, & BRIEF_parent (parent reported executive function) on SAS_self (self reported social anxiety symptoms). The SAS_self variable consists of the participant's score on either the SAS-A or SASC-R (depending on age). The hypothesis will be confirmed if the overall regression is significant (as determined by the F-statistic and associated p-value) and if the BRIEF_parent score contributes significantly to the variance in the SAS_self score (as indicated by the t-statistic and associated p-value). The obtained R-squared value reports how much variance in social anxiety scores the four explanatory variables account for in combination. Effect sizes for each variable can be determined from the b and beta coefficients; the b-value for BRIEF_parent provides an estimate of the expected increase (or decrease) in SAS_self score for each one point increase in BRIEF_parent score.

Hypothesis 1b; Association between teacher reported EF and self reported social anxiety symptoms. This hypothesis will be examined and confirmed using identical procedures to hypothesis 1a, except the BRIEF_teacher variable will be included as the fourth independent variable in place of the BRIEF_parent variable.

Hypothesis 2a; Moderating effect of parent-reported social skills on the association between parent-reported EF and self-reported social anxiety symptoms. This hypothesis will be examined with a sequential regression and confirmed if the addition of the interaction term leads to a statistically significant increase in R-squared. The three control variables will be entered into the first step of the equation along with the centered versions of the BRIEF_parent and SSRS_parent variables. The interaction term, represented by the cross-product between these two variables (BRIEFp_cen*SSRSp_cen) will be entered into the second step. SAS_self remains the dependent variable. If examination of change in R-squared indicates a statistically significant increase, it can be concluded that the interaction term helps explain social anxiety above and beyond the explanation provided by the control variables, parent reported EF and parent reported social skills.

In order to examine the significant interaction, the continuous SSRS_parent variable will be divided into three groups (low, medium and high scores) and entered into the data set as a new variable (SSRSp_tri). Next, separate regressions will be computed for the low and high groups separately (by selecting certain cases and still controlling for age at diagnosis, gender and current age) and graphed on a plot of SAS_self x BRIEFp_cen. The regression lines will not be parallel indicating that parent reported EF does not have the same influence on self reported social anxiety for those reported by parents as having differentially higher or lower social skills. The hypothesis that parent reported EF will matter less for the development of social anxiety symptoms for the group reported by parents as having high social skills will be confirmed if the low social skills group has a steeper regression line.

Hypothesis 2b; Moderating effect of parent-reported social skills on the association between teacher-reported EF and self-reported social anxiety symptoms. This hypothesis will be examined and confirmed using identical procedures to hypothesis 2a, except the centered version of the BRIEF_teacher variable will be included in step one of the regression (along with the centered SSRS_parent variable and three control variables as in hypothesis 2a), and the interaction term entered into the second step will be changed to BRIEFt_cen*SSRSp_cen. If there is a statistically significant increase in

R-squared, the interaction could again be examined using separate regressions with selected cases from the SSRSp_tri variable.

Hypothesis 2c; Moderating effect of teacher reported social skills on the association between parent-reported EF and self reported social anxiety symptoms. This hypothesis will be examined and confirmed using identical procedures to hypothesis 2a, except the centered version of the SSRS_teacher variable will be included in step one of the regression (along with the centered BRIEF_parent variable and three control variables as in hypothesis 2a), and the interaction term entered into the second step will be changed to BRIEFp_cen*SSRSt_cen. If there is a statistically significant increase in R-squared, in order for the interaction to be examined as previously, a new SSRSt_tri variable would need to be computed as before.

Hypothesis 2d; Moderating effect of teacher reported social skills on the association between teacher reported EF and self reported social anxiety symptoms. This hypothesis will be examined and confirmed using identical procedures to hypothesis 2a, except the centered version of the SSRS_teacher variable and BRIEF_teacher variables will be included in step one of the regression (along with the three control variables as in hypothesis 2a), and the interaction term entered into the second step will be changed to BRIEFt_cen*SSRSt_cen. If there is a statistically significant increase in R-squared, the SSRSt_tri variable from hypothesis 2c will be utilized in examining the interaction.

Chapter 4: Conclusions

Summary

The proposed study seeks to fill a gap in the literature by examining associations between variables that represent potential neurocognitive and psychosocial late effects. It is unique in that very few studies have been as highly focused. Only adolescents with one type of pediatric cancer (ALL) who are off treatment a minimum of three years, and who were treated with intra-thecal chemotherapy but not radiation will be included. Additionally, rather than assess global functioning, this study seeks to examine social anxiety specifically, a construct which has been under-researched in the literature. This study will examine the association between executive functioning as reported by parents and teachers and self-reported social anxiety in adolescent survivors of pediatric ALL while controlling for variables identified in the literature as differentially affecting outcomes (gender, current age and age at diagnosis).

It is anticipated that EF will explain a significant amount of the variance in social anxiety scores as deficits in EF and related effects (such as academic difficulties) have been associated with internalizing problems in the literature. Social anxiety is likely to be specifically implicated given that participants are in the developmental stage of adolescence. This study will also examine social skills as a potential moderator of the relationship between EF and social anxiety symptoms. It is hypothesized that adaptive social skills may serve as a protective factor against the development of psychosocial problems including social anxiety even in the presence of EF deficits. Well-developed social-cognitive skills help with accurate perception and processing that are incongruent with symptoms of social anxiety. In addition, social skills encourage reciprocity, which may reduce a tendency toward social avoidance.

Implications

This study could have potentially important implications for the development of targeted interventions. It is important to determine factors associated with increased risk for adjustment difficulties so that they can be monitored and subsequently addressed through the embedded psychosocial survivorship clinic at Dell Children's and elsewhere. If it is determined that EF is indeed associated with social anxiety symptoms, programs that currently exist to target neurocognitive remediation could begin to monitor participants for symptoms of social anxiety and provide preventative therapeutic interventions where possible. Additionally, if it is determined that social skills moderates the relationship between EF and social anxiety, evidence-based interventions targeting social skills could be developed for survivors as well.

Limitations

This study has several limitations, but also some important strengths. A limitation is that only one measure of each construct has been included, and those measures were not designed specifically for survivors. All of them have been previously used with cancer survivors, however, and multiple reporters were utilized for two of the constructs. A rating scale was selected over neuropsychological measures for EF given its presumed ecological validity. The SAS-A and SASC-R were chosen to measure a specific concern, social anxiety, rather than a measure of broad symptomatology.

Another potential limitation is sample bias. Although every effort will be made to include participants that vary on the constructs of interest, those who choose to participate in an optional research study may be more socially outgoing/competent or less socially anxious than those who do not. Another potential bias in the sample is that all participants will be recruited from the same context and be required to travel to Dell Children's or the Texas Child Study Center to participate. Bus routes to both locations and free parking are available, however lower SES participants may still be less likely to participate. Attempts to counter this bias include offering raffles for participation and not excluding families on the basis of parental inability to speak English.

Finally, this study is limited in scope. It is a cross sectional design so causality cannot be inferred. Causality between the factors could only be established with a large-scale prospective study that tracked changes within individuals over time. Additionally, this study may be criticized for the lack of a control group. However, given the goal of the study to examine relationships between neurocognitive and psychosocial late effects within a specific population, it was not considered necessary to explore differences between survivors and controls on the different constructs.

Future Research

Future research could re-examine the model using additional measures of each construct. For example, neuropsychological measures of attention and working memory may be able to be combined with teacher and parent ratings of EF with exploratory factor analysis. The measurement of social skills could be expanded to include specific skills such as facial emotion recognition or nonverbal communication, which may differentially moderate the relationship between EF and social anxiety.

Another avenue of research could be to see if the relationships between these variables hold for younger ALL survivors or for other groups including brain tumor survivors who have received CRT as part of therapy, non-CNS cancer survivors, siblings or children with ADHD. A desire of the primary investigator is to expand the Latino sample of adolescent ALL survivors and examine associations between variables within that group alone. Research has shown that Latino youth in general are at a higher risk for developing anxiety symptoms and disorders than European American Youth (Anderson & Mayes, 2010). Psychosocial late effects in Latino cancer survivors and cultural factors that may affect cognitions, behaviors or experiences of physiology associated with late effects have yet to be explored.

Research could also focus on the impact of both EF deficits and social anxiety following cancer treatment on meeting developmental tasks in comparison to healthy peers. Additionally, the model could be expanded to include additional variables such as coping skills or problem solving abilities, or the impact of physical late effects such as fatigue. Additional internalizing outcome variables affecting HRQOL such as depression could be researched. Investigations into adolescent survivors' perceptions of body image are also warranted.

Intervention research should be a primary focus with this group. As investigators learn that it is possible to reverse some of the attentional and working memory problems survivors face through cognitive remediation, they may extend their research to target additional factors of adjustment including social anxiety and social skills.

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