Survivors Of Pediatric Brain Tumors: Psychosocial Outcomes And Executive Function

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SURVIVORS OF PEDIATRIC BRAIN TUMORS:
PSYCHOSOCIAL OUTCOMES AND EXECUTIVE FUNCTION

A dissertation presented in partial fulfillment of requirements for the degree of Doctor of Philosophy in the Department of Psychology
The University of Mississippi

by

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ABSTRACT

Children treated with CNS-directed therapy for brain tumor (BT) are at significant risk for developing late effects secondary to both disease and treatment. Executive functions (EF) encompass those skills necessary for appropriate problem solving and other goal-directed behaviors. Although no homogenous neuropsychological profile exists in patients with brain tumors, the most affected cognitive domains include EF and related processes, with the magnitude of effect increasing over time. Deficits in EF have been implicated in the etiology of internalizing, externalizing, and social disorders suggesting that EF is a foundational cognitive process.

With a growing population of pediatric BT survivors at risk for EF deficits, it is important to consider the relationship between EF and psychosocial outcomes. The aim of the current study was to determine the relationship between EF and psychosocial outcomes over time among pediatric BT survivors. This study examined divergent trajectories of psychosocial outcomes and the association of change in executive function with these trajectories.

Survivors of pediatric embryonal tumors ($n = 166$) treated on an international, multi-site protocol for newly diagnosed brain tumors were included in the current study. Participants were approximately 9 years at enrollment (SD = 3.10), mostly male (61.45%), Caucasian (75.90%), and treated for average risk disease (75.30%). Multiple tumor types were represented; however,
most were diagnosed with medulloblastoma (83.73%). Participants and their families completed measures of psychosocial and executive functioning at baseline and yearly thereafter for five years.

Growth mixture modeling revealed the presence of three latent class trajectories for Internalizing, Externalizing, and Total Problems. Two latent class trajectories were observed for Social Competence. Most did not report clinically significant concerns related to psychosocial functioning; however, a small subset did. Impairment persisted across 5-year follow-up. Working memory, attention, behavior regulation, and metacognition abilities declined over time. Binary and multinomial logistic regression demonstrated that change in EF over time is predictive of psychosocial trajectory. Findings suggest that a subset of pediatric BT survivors experience psychosocial difficulties secondary to disease and treatment that persist without intervention. EF appears to be foundationally related to psychosocial difficulties and may be an appropriate target of intervention.
DEDICATION

This work and the journey that it represents is dedicated to my family who have loved me, supported me, and guided me all of my life. Thank you for fostering the belief that I can do hard things and for walking with me as I do.
ACKNOWLEDGEMENTS

Thank you to Karen Christoff, PhD for the time and energy that you’ve invested in me and in my education over the past several years. I know you were always “just doing your job,” but thank you for doing it so very well. I would also like to thank Jane Schreiber, PhD for agreeing to supervise this project and for providing support from beginning to end. I am so grateful for your mentorship. Furthermore, thank you to the many researchers all over the globe who conceptualized and carried out the larger study, of which this project is a small part. Thank you also to the patients and families who provided a glimpse into their lives so we can work to make childhood cancer a much less formidable foe. Finally, I would like to acknowledge the guidance of my dissertation committee at the University of Mississippi, John P. Bentley, PhD, Carey Bernini Dowling, PhD, and Stephanie Miller, PhD, as well as Hui Zhang, PhD and Lu Huang, MA from the Department of Biostatistics at St. Jude Children’s Research Hospital for their support throughout this project.
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CHAPTER 1
BACKGROUND

Overview of Pediatric Brain Tumors

Cancer in children is relatively rare. Nevertheless, cancer is the leading cause of death by disease in children (Ward, DeSantis, Robbins, Kohler, & Jemal, 2014). An estimated 10,450 new cases among children (birth to 14 years of age) were expected to occur in 2014 (Ward et al., 2014). Of pediatric cancers, central nervous system (CNS) tumors comprise the second most common malignancy (Patel et al., 2014). While there are many different types of CNS tumors, medulloblastoma is the most common malignant childhood brain tumor, accounting for approximately 20% of all childhood CNS tumors (Fruhwald & Rutkowski, 2011).

Medulloblastoma is an embryonal tumor that arises below the tentorium in the cerebellum or fourth ventricle of the brain (Bartlett, Kortmann, & Saran, 2013). Embryonal tumors are comprised of undifferentiated cells, similar to those in a developing embryo (Packer, MacDonald, and Vezina, 2007). Median age at diagnosis is 5-7 years, with more than 70% of all pediatric medulloblastoma diagnosed in children under 10 years of age (American Brain Tumor Association, ABTA, 2012). Some genetic disorders are associated with increased risk for developing medulloblastoma, but generally, etiology is unknown (ABTA, 2012). Treatment for
embryonal tumors is multimodal and involves a combination of maximum surgical resection, radiotherapy, and chemotherapy that varies somewhat depending on degree of metastatic disease (Bartlett et al., 2013; Gajjar et al., 2006).

Scientific advancements in the treatment of medulloblastoma have significantly improved survival rates since the 1960s. Current five-year event-free survival ranges from 70% for individuals with metastatic disease to 85% for those with non-metastatic disease (Gajjar et al., 2006). Recent gains in understanding of the molecular makeup of medulloblastoma have revealed the presence of four molecular subtypes, each with different prognosis (Taylor et al., 2012). The most recent treatment protocol for medulloblastoma at St. Jude Children’s Research Hospital (SJCRH), achieved 100% event-free survival for the one of the four subtypes (A. Gajjar, personal communications, July 21, 2014). While only 10% of patients diagnosed with medulloblastoma are of that particular subtype, it is clear that significant improvements in treatment have been achieved.

Other embryonal tumors include atypical teratoid rhabdoid tumor (ATRT), primitive neuroectodermal tumor (PNET), and pineoblastoma. ATRT accounts for approximately 1-2% of childhood tumors with peak incidence in children under the age of three years (Buscariollo, Parks, Roberts, & Yu, 2012; Schrey et al., 2016; Tekautz et al., 2005). Approximately 50% of ATRTs occur in the posterior fossa, though they can arise anywhere within the CNS (Packer et al., 2002). Median survival, following diagnosis of ATRT, is 9-17 months (Athale, Duckworth, Odame, & Barr, 2009; Dufour et al., 2012). PNET accounts for approximately 2.5% of childhood brain tumors and can occur in both the central and peripheral nervous system (Packer et al., 2007). They occur mostly in children with peak incidence before three years. Five-year disease free survival rates for PNET is 78% (Lester et al., 2014). Pineoblastoma occurs mostly in the
pineal region of the brain and constitutes approximately 1% of childhood tumors. Due to tumor location, most pineoblastomas are inoperable; most are treated with a chemotherapy regimen similar to that used for medulloblastoma (Packer et al., 2007). Of note, medulloblastoma, ATRT, and PNET were historically thought to be the same; subsequent advances in tumor classification revealed the presence of distinct tumor types. Despite this, they continue to be treated similarly (Packer et al., 2007).

While survival for pediatric brain tumors remains variable depending on numerous clinical and demographic characteristics, significant improvement has occurred over the past few decades. Depending on tumor type, survival has now become the expectation rather than the exception, particularly for children diagnosed with medulloblastoma. Improved outcomes have resulted in a new and growing survivor population; as a result, issues of survivorship have become paramount (Armstrong, 2010).

**Late Effects**

While refinements in treatment have led to reduced mortality, survival comes at significant cost. Long-lasting effects secondary to disease and treatment persist well after the conclusion of therapy for the majority of childhood brain tumor survivors. Tumor location (i.e., cerebellum and fourth ventricle for those with medulloblastoma) and treatment (i.e., surgical resection, radiotherapy, chemotherapy) are the largest contributors to poor long-term health outcomes (Armstrong, 2010). Late effects impact the entire body and can include secondary malignancies, cardiovascular and pulmonary effects, altered growth and development, cognitive impairment, and psychosocial difficulties. As a result, survivors of childhood cancer are less likely to live independently (Madderey et al., 2005), obtain steady employment (deBoer, Verbeek, & van Dijk, 2006; Mostow, Byrne, Connelly, & Mulvihill, 1991), drive cars (Madderey
and marry (Janson et al., 2009) than their peers. With this in mind, much attention has been focused on neurocognitive and psychosocial sequelae among childhood cancer survivors.

**Neurocognitive Late Effects**

Neurocognitive late effects, which commonly involve diminished executive functions (EF) including working memory and related processes such as processing speed, attention, and concentration (Mulhern, Merchant, Gajjar, Reddick, & Kuhn, 2004; Moore, 2005) are relatively common among survivors of pediatric brain tumors. Several risk factors contribute to increased risk for neurocognitive late effects (Massimino et al., 2011). Younger age at diagnosis and treatment is associated with more pronounced cognitive effects (Mulhern et al., 2004; Mulhern et al., 2005). Tumor location in or near the cerebellum may also compromise cognitive abilities. The cerebellum is involved in higher cognitive functions via interaction with the frontal lobes. Damage to this structure, as a result of the mass effect of the tumor itself or treatment via neurosurgery, radiotherapy and/or chemotherapy, can contribute to long-term deficits in speech, language/communication, EF, visuospatial ability, and behavioral regulation (Massimino et al., 2011). Clinical complications such as hydrocephalus can also contribute to diminished cognitive outcomes. Hydrocephalus occurs when excess cerebrospinal fluid builds up in the brain because the ventricles are unable to move fluid properly due to blockage from the tumor. Cranial radiation, a mainstay of treatment for medulloblastoma, appears to be the most egregious contributor to neurocognitive late effects. Higher radiation dose and younger age at radiation treatment have been strongly associated with poorer intellectual outcome (Mulhern et al., 2004).

Historically, research on the neuropsychological outcomes of CNS tumors and treatment has focused on decreases in global intellectual functioning over time (Palmer et al., 2001; Palmer
et al., 2003; Mulhern et al., 2001; Mulhern et al., 1999). More recently, research has focused on domains that underlie global intellectual ability, such as EF. Although no homogenous neuropsychological profile exists in patients with brain tumors, the most affected cognitive domains include aspects of EF such as processing speed, working memory, and attention, as well as fine motor skills. The magnitude of the observed effect typically increases over time (Butler & Haser, 2006; Gerber et al., 2014).

Executive function is considered an umbrella term that subsumes several different cognitive processes regulated by the prefrontal cortex and other areas connected to that region. EF includes those skills necessary for appropriate problem solving and other goal-directed behaviors, including the ability to plan, organize, inhibit responses, and change behaviors based on feedback from the environment. Developmentally, EF deficits become more apparent as children age and are expected to function at increasing levels of independence (Askins & Moore, 2008).

While many different functions are considered to be executive processes, Miyake and colleagues (2000) distinguished three component processes: (1) inhibition, (2) set-shifting, and (3) working memory, as the most significant contributors to EF. Inhibition involves regulating automatic responses whereas set-shifting refers to the ability to shift between mental sets, rule sets, or tasks. Working memory involves holding and manipulating information in real time. Even slight impairment in EF may undermine self-care, independence, work, or maintenance of normal social relationships, despite preservation of overall intelligence (Lezak, Howieson, Bigler, & Tranel, 2012). Executive processes have been found to underlie self-regulatory abilities (Hoffman, Schmeichel, & Baddeley, 2012) such that EF appears to support broad control processes that facilitate behavioral regulation across multiple domains (Espy et al., 2011;
Schoemaker et al., 2014). Accordingly, it is crucial to examine the role that cognitive
dysfunction may play in emotional, behavioral, and social difficulties.

Edelstein and colleagues (2001) examined the neurocognitive status of adult survivors of
childhood medulloblastoma who were 6 to 42 years from diagnosis. Findings revealed global
deficits in IQ (Edelstein et al., 2001). Further, impairments in component processes that underlie
IQ were found as well. Working memory abilities were 1.2 standard deviations below normative
expectations. Deficits in processing speed and executive function were 2.4 and 3.4 standard
deviations below normative expectations, respectively. Findings highlight that survivors of
childhood medulloblastoma are at significant risk for impairment, not only in global intellectual
functioning (e.g., IQ), but also in decreased working memory and processing speed efficiency.

Additionally, survivors demonstrate poor performance on measures of attentional
capacity (Robinson et al., 2010; Mulhern et al., 2004). In a sample of 53 patients treated for
posterior fossa tumors, Mabbott and colleagues (2005) found a significant increase in attention
difficulties over time. Reeves and colleagues (2006) analyzed attention and memory among 38
survivors of medulloblastoma using multiple measures of neurocognitive function. On a
computerized test of sustained attention, participants demonstrated significant weaknesses in
attention on 8 of 11 indices. Neurocognitive late effects, including deficits in working memory,
attention, and processing speed, are common among survivors of childhood BT.

**Psychosocial Late Effects**

Pediatric BT survivors are also at risk for psychosocial late effects, including social skills
deficits as well as internalizing and externalizing difficulties. Meyer and Kieran (2002) examined
neurobehavioral functioning among a sample of 34 neuro-oncology patients treated with surgery
only. Over half of patients (56%) experienced significant psychological adjustment problems,
including depression, externalizing behavior problems, or academic difficulties. Survivors, as compared to siblings, experienced increased rates of depression, anxiety, and antisocial behaviors, in addition to reduced social competence (Schultz et al., 2007).

Mabbott and colleagues (2005) found clinically significant increases in social problems among patients with posterior fossa tumors treated with cranial radiation in childhood as time from diagnosis increased. A meta-analysis by Schulte and Barrera (2010) found significant social adjustment difficulties among childhood brain tumor survivors across several different studies using multiple formats (parent and teacher ratings) and across time (cross-sectional and longitudinal studies). Their findings suggest that social deficits constitute a significant portion of morbidity among brain tumor survivors. An earlier review by Fuemmeler, Elkin, and Mullins (2002) found similarly deficient social competence in the same population. Survivors often have fewer close friendships and appear to be more socially isolated as compared to peers (Barrera et al., 2005; Vanatta, Garstein, Short, & Noll, 1998). Importantly, underdeveloped social competence has been shown to be a significant risk factor for both internalizing and externalizing difficulties (Ladd, 2005).

Brinkman and colleagues (2012) conducted a prospective longitudinal analysis of parent-reported social outcomes following treatment for pediatric embryonal tumor survivors. Parents completed the Child Behavior Checklist (CBCL/6-18; Achenbach & Rescorla, 2001) at baseline and yearly thereafter for five years. Results indicated that parents of pediatric brain tumor survivors reported a decline in social competence during the first year after diagnosis, followed by a less distinct pattern beyond 1 year. Risk status, intellectual functioning, gender, and age contributed to trajectory of social competence for survivors.

Efforts to Remediate Late Effects
Survivors of childhood brain tumor evidence deficits in cognitive and psychosocial functioning following disease and treatment that often results in decreased quality of life. Efforts to improve neurocognitive function in survivors are of prime importance. As a result, clinical trials have evaluated medication-based (Conklin et al., 2007; Mulhern et al., 2004), therapist-directed (Butler et al., 2008; Patel, Katz, Richardson, Rimmer, & Kilian, 2009), and computerized interventions (Kesler, Lacayo, & Jo, 2011; Hardy, Willard & Bonner, 2011; Conklin et al., 2015) to remediate neurocognitive late effects among childhood cancer survivors. However, significantly less attention has been directed towards options for remediating psychosocial late effects once observed.

Barrera and Schulte (2009) conducted a group social skills intervention for 32 survivors of pediatric brain tumors. The intervention consisted of eight sessions focused on social skills training (i.e., friendship making and assertiveness). Results of this pilot study suggested feasibility, acceptability, and preliminary efficacy in this population. Findings demonstrate promise for improving psychosocial functioning among survivors of childhood brain tumors. Efficacy of this and similar interventions might logically be increased through targeting specific neurocognitive deficits in addition to psychosocial difficulties. Neurocognitive ability, specifically EF and associated processes, have been found to underlie aspects of psychosocial functioning. Working memory, processing speed, and attention are necessary for successful navigation of the social environment as well as behavioral and emotional regulation. All of these domains, therefore, constitute likely targets for intervention.

**Neurocognitive Function and Internalizing Problems**

Cognitive complaints are often reported among individuals with depression. Etkin, Gyurak, and O’Hara (2013) found impairments in inhibition, sustained attention, working
memory, and task shifting, suggesting a broad disruption in EF among individuals with major depressive disorder. Similar patterns were found among individuals treated for post-traumatic stress disorder including impairment in attention, set-shifting, and abstract reasoning (Etkin et al., 2013). Deficits in set-shifting have been associated with greater preservative tendencies among individuals with obsessive compulsive disorder (Etkin et al., 2013).

Impairment in EF is associated with anxiety (Toazza et al., 2014). In fact, executive dysfunction predicted onset of anxiety and affective problems among healthy twins with heritable risk for affective disorder (Vinberg, Miskowiak, & Kessing, 2013). Anxiety has also been negatively associated with working memory and shifting (Visu-Petra et al., 2014). Among youth with Spina Bifida, deficits in EF fully explained both internalizing and externalizing problems via parent-report (Kelly et al., 2012).

**Neurocognitive Function and Externalizing Problems**

Deficits in neurocognitive function have been implicated in the etiology of different externalizing disorders. Attention-deficit/hyperactivity disorder (ADHD) is characterized by inappropriate impulse control and hyperactivity as well as attentional deficits. Empirical investigation of the cognitive profiles of individuals with ADHD reveals poor performance on measures of EF that begins early in life (Barkley et al., 2001; Barkley, Murphy, & Bush, 2001). While different facets of EF have been related to the behavioral profile of ADHD, difficulties with inhibition seem to be most salient. In fact, difficulties with inhibition in preschool are predictive of ADHD later in childhood (Berlin, Bohlin & Rydell, 2003; Friedman et al., 2007). Response inhibition appears to be the driving cognitive factor underlying the behavioral profile associated with ADHD. Executive function impairment is also related to the behavioral profile of Conduct Disorder (CD), an externalizing disorder characterized by behavior that violates the
rights of others, major societal norms, or other rules (Morgan & Lilienfeld, 2000). Herba, Trahah, Rubia, and Yule (2006) found that adolescents with conduct problems (not necessarily meeting criteria for full CD) displayed impairment on tasks measuring response inhibition, one aspect of EF.

Aside from clinical disorders, impairment in EF is associated with greater behavioral problems and less regulatory control in middle school students (Jacobson, Williford, & Pianta, 2011). Furthermore, poor inhibition has been associated with aggression in preschool and school-age children (Raaijmakers et al., 2008; Ellis, Weiss, & Lochman, 2009). Deficits in EF have been shown to underlie behavioral regulation in several other medical populations, including children with new onset seizures (Baum et al., 2010), deaf and hard-of-hearing school-age children (Hintermair, 2013), and children with unilateral cerebral palsy (Whittingham et al., 2014).

**Neurocognitive Function and Social Problems**

Social skills are used to navigate interactions with others (peers, family members, and others in the community). EFs have been associated with the development of social skills, as the foundational cognitive processes necessary for social behavior (Moriguchi, 2014). Research among clinical and non-clinical populations has consistently demonstrated a relationship between cognitive function and social skills (Janusz, Kirkwood, Yeates, & Taylor, 2002; Nigg, 1999). Deficits in EF have been implicated in the etiology of different clinical populations known for disruptions in social abilities, including autism (Pelicano, 2012) and schizophrenia (Beauchamp & Anderson, 2010). Following traumatic brain injury, EF may also be an important determinant of social competence (Ganesalingam et al., 2011). Similar patterns of impairment have been demonstrated in non-clinical populations as well. For instance, preschool EF is
positively associated with social competence in both preschool and kindergarten (Razza, 2009). EF is also predictive of social skills in children with externalizing behavior problems (Clark, Prior, & Kinsella, 2002).

**Aims of Current Study**

Survivors of childhood brain tumor are at significant risk for neurocognitive late effects secondary to disease and treatment. They are also at risk for psychosocial impairment, including difficulties with socialization, emotional, and behavioral regulation. While neurocognitive abilities have been shown to underlie psychosocial functioning outside of hematology/oncology populations, this relationship has not been established for survivors of childhood brain tumor. The aim of the present study was to determine the relationship between EF and psychosocial outcomes over time, including internalizing behaviors, externalizing behaviors and social competence, among a sample of pediatric brain tumor survivors. It is hypothesized that the sample will be best characterized by three latent trajectories- a subset of survivors will improve over time, some will get worse, and others will exhibit little change over time, with respect to psychosocial functioning. Second, it is hypothesized that survivors will evidence declines in EF over time. Finally, it is hypothesized that change in EF over time will be predictive of psychosocial trajectory.

To accomplish these aims, data analysis was conducted in a series of phases, with each phase dependent upon the preceding phase. The first phase of data analysis involved characterization of the longitudinal trajectory of psychosocial outcomes. The second phase involved quantification of the change over time in executive function using both performance based and parent-report measures. The final step of analysis involved use of change over time in EF to predict psychosocial trajectory.
CHAPTER 2
METHODS

Participants

The current study drew participants from an international, multisite clinical trial for patients with newly diagnosed embryonal tumors (Treatment of Patients with Newly Diagnosed Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumor/Pineoblastoma, or Atypical Teratoid Rhabdoid Tumor; SJMB03). This trial included patients with different embryonal tumors, thus multiple tumor types are included in the present study. Data from patients between the ages of 6 and 18 with no prior history of radiotherapy or chemotherapy were included. Some patients were younger than 6 years of age when enrolled on the treatment protocol (i.e., age at diagnosis); however participant data was only included for those time points where the patient was 6 years of age or older. Per SJMB03 specifications, disease was considered average-risk ($\leq 1.5 \text{ cm}^2$ residual disease following surgical resection with no evidence of metastatic disease) or high-risk ($> 1.5 \text{ cm}^2$ residual tumor and/or evidence of metastatic disease). The Institutional Review Boards at St. Jude Children’s Research Hospital and the University of Mississippi approved the current study.

Treatment
Following surgical resection, SJMB03 patients were treated on average risk or high risk treatment arms, based on the presence of metastatic disease and/or residual tumor after resection. Patients received risk-adapted radiotherapy with average risk patients receiving less craniospinal irradiation than high risk patients. Average risk patients were treated with 23.4 Gray (Gy) craniospinal irradiation (CSI), with 3-D conformal boost to the primary site of disease to 55.8 Gy. High risk patients were treated with 36-39.6 Gy CSI, with 3-D conformal boost to the primary site of disease to 55.8-59.4 Gy. Six weeks following completion of CSI, all patients received four courses of high-dose chemotherapy, including cyclophosphamide, cisplatin, and vincristine with stem-cell support. Deviation from protocol-based chemotherapy occurred in a minority of patients based on clinical judgment.

Procedure

Neurocognitive evaluation. Routine evaluation of neuropsychological abilities was embedded within SJMB03 trial design. Baseline assessment was completed after surgical resection but before beginning CSI. Follow-up assessments at the primary site (SJCRH) were conducted yearly thereafter for 5 years following diagnosis. At each of the collaborating sites (Royal Children’s Hospital-Melbourne, Australia; Lady Ciento Children’s Hospital-Brisbane, Australia; Hospital for Sick Children-Toronto, Ontario; Texas Children’s Hospital- Houston, Texas; Children’s Hospital of Philadelphia-Philadelphia, Pennsylvania; and Duke University Medical Center- Durham, North Carolina) assessments were conducted 1, 3, and 5 years after diagnosis (See Table 1). A time window of ± 3 months was utilized for assessments to allow for scheduling. To be eligible for inclusion in the current study, participants and caregivers must have completed the neurocognitive measures of interest during routine protocol-based assessment for SJMB03 and have provided data from at least two time points on all of the
measures of interest.

**Measures.** Assessment of the neuropsychological profile of patients treated on SJMB03 involved measures of intelligence, EF, academic achievement, attention, family environment, coping, and patient behavior. The current study utilized three measures from the SJMB03 neuropsychological assessment battery.

**Child Behavior Checklist (CBCL).** The CBCL is a parent-report measure of child behavior and competencies (Achenbach & Rescorla, 2001). Two versions of the CBCL are available, depending on the age of the child. The current study included the version of the CBCL appropriate for children between the ages of 6 and 18 (CBCL/6-18). This measure contains 20 items that assess child competence in social relations, activities, and school performance. It also contains 118 items that assess specific behavioral and emotional problems as well as two open-ended items that allow raters to write in problems not specifically listed.

The current study included scores from the Internalizing, Externalizing, and Total Problems as well as the Social Competence scales of the CBCL/6-18 (Achenbach & Rescorla, 2001). The Internalizing Problems scale is a composite index reflecting problems related to anxiety, depression, and social withdrawal (Lands et al., 2009). The Externalizing Problems scale is a composite index reflecting conflict with others and violation of social norms. The Total Problems scale is comprised of the sum of scores for Internalizing, Externalizing, three syndrome scales, and other problems listed on the response sheet; it is a reflection of the number and severity of problems reported. The Social Competence scale assesses social participation, number and regularity of contact with close friends, how well the child gets along with others, and how well the child plays and works alone.

The scoring profile provides raw scores, *T* scores, and percentiles. For Internalizing
Problems, Externalizing Problems, and Total Problems, $T$ scores between 60-63 fall within the borderline significant range; scores of 64 and above are considered worthy of clinical attention. For the Social Competence scale, $T$ scores between 31-35 fall within the borderline significant range; scores of 30 or below are considered clinically significant.

The CBCL/6-18 was normed on a representative sample of the 48 contiguous states on the basis of socioeconomic status, ethnicity, region, and urban/suburban/rural residence. Test-retest reliability for Internalizing Problems ($r = 0.91$), Externalizing Problems ($r = 0.92$), Total Problems ($r = 0.94$), and Social Competence ($r = 0.93$) is high. Content and criterion-related validity for the CBCL is high as items are able to discriminate between referred and non-referred children ($p < 0.01$). Validity and reliability of the CBCL/6-18 are strong (Achenbach & Rescorla, 2001). Due to sound psychometric support, the CBCL/6-18 is commonly used in assessment of child behavior (Brinkman et al., 2012).

**Behavioral Rating Inventory of Executive Function (BRIEF).** The BRIEF is a measure of the behavioral indicators of executive function (Gioia, Isquith, Guy, & Kenworthy, 2000) that consists of 86 items rated on a three-point likert-type scale (anchors = never, sometimes, and always). The BRIEF is appropriate for individuals aged 5-18. Multiple forms exist; the current study included only the parent-report form. Items yield eight composite scales of EF (Inhibition, Shifting, Emotional Control, Initiation, Working Memory, Planning, Organization, and Monitoring). This measure also provides two global indices, the Behavioral Regulation Index (BRI) and the Metacognition Index (MCI). The MCI captures a child’s ability to self-manage tasks and monitor performance. It is directly applicable to active problem-solving skills across different contexts. The BRI captures a child’s ability to shift cognitive sets, modulate emotion, and regulate behavior through inhibitory control. The BRI is made up of the Inhibit, Shift,
Emotional Control scales (Gioia, et al., 2000). The MCI is comprised of the Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor scales. Age-standardized $T$-scores (Mean = 50, SD = 10), percentile ranks, and 90% confidence intervals are provided. Higher scores indicate greater levels of impairment.

The BRIEF was normed on a nationally representative sample of 1400 parents and demonstrates strong validity (internal consistency alphas of 0.80-0.98) and reliability (test-retest $r = 0.82$). The sample included ratings from parents of children with localized brain lesions, making this scale particularly well suited for this study (Gioia et al., 2000).

**Woodcock Johnson III Tests of Cognitive Abilities (WJ-III COG).** The WJ-III COG (Woodcock, McGrew, & Mather, 2001) is a comprehensive battery for assessing general intellectual function. It is comprised of multiple subtests that measure comprehension, memory, knowledge, thinking abilities, visual-spatial skills, auditory processing, reasoning, processing speed, attention, and concentration. The WJ-III COG measures both broad and narrow cognitive abilities based on the Cattell-Horn-Carroll theory of intelligence (Woodcock et al., 2001). Individual subtests of narrow cognitive abilities can be combined to quantify broad abilities via clinical cluster scores. Age-adjusted standard scores (Mean = 100, SD = 15) were used for analysis. Lower scores indicate greater impairment. The WJ-III COG is appropriate for individuals 2 years of age and older.

The current study included four clusters from the WJ-III COG in data analysis: Broad Attention, Executive Processes, Processing Speed, and Working Memory. The Broad Attention cluster includes the Auditory Attention, Pair Cancellation, Numbers Reversed, and Auditory Working Memory subtests. The Executive Processes cluster is comprised of the Concept Formation, Planning, and Pair Cancellation subtests. The Processing Speed cluster includes the
Visual Matching and Decision Speed subtests. Finally, the Working Memory cluster is made up of the Numbers Reversed and Auditory Working Memory subtests (Woodcock et al., 2001).

The WJ-III COG was normed on a nationally representative sample that contained both clinical and non-clinical populations across the lifespan. Internal consistency reliabilities for the Broad Attention (alpha = 0.92), Executive Processes (alpha = 0.92), Processing Speed cluster (alpha = 0.92), and Working Memory clusters (alpha = 0.91) are high. Confirmatory factor analysis provides evidence of the construct validity of the WJ-III COG (McGrew & Woodcock, 2001). The measure correlates strongly with similar measures including the Wechsler Preschool and Primary Scales of Intelligence- Revised (Wechsler, 1989), the Wechsler Intelligence Scale for Children- Third Edition (Wechsler, 1991), and the Stanford-Binet Intelligence Scale- Fourth Edition (Thorndike, Hagen, & Sattler, 1986), with correlation coefficients in the 0.70s (McGrew & Woodcock, 2001). As such, this measure has demonstrated sound psychometric properties, including reliability and validity (Woodcock et al., 2001).

**Statistical Considerations**

Data analysis consisted of three phases; passage through each phase utilized results of the previous phase. Descriptive statistics were estimated for all outcomes, predictors, and covariates used for analysis.

**Phase One.** Latent variable mixture modeling (LVMM) is designed to identify similarities and differences among individuals in the dataset, rather than distinct data points (Berlin, Williams, & Para, 2014). LVMM uses probabilities to assign individuals to unobserved (latent) classes based on similar patterns of cross-sectional or longitudinal data. (Berlin, Parra, & Williams, 2014). Each individual’s probability of being in each possible latent class is calculated. Fractional membership in all latent classes is allowed for each individual, reflecting variable
degrees of certainty and precision in classification. Different approaches to LVMM can be applied, based on the type of data (continuous or categorical, cross-sectional or longitudinal). The most appropriate LVMM for longitudinal data with continuous and categorical latent class variables and within-class variability is longitudinal growth mixture modeling (Berlin, Williams, & Parra, 2014).

Longitudinal growth mixture modeling (LGMM) is an application of LVMM that identifies multiple unobserved sub-populations, characterizes growth trajectories over time within each sub-population, and examines differences between sub-populations (Ram & Grimm, 2009). The goal of LGMM is to probabilistically assign individuals into subgroups by inferring membership in latent classes using growth model data (Berlin, Parra, & Williams, 2014). LGMM provides a more nuanced understanding of growth trajectories by determining if growth trajectory was consistent across participants or if variation in growth trajectory could be captured by the existence of latent subgroups (Schmiege, Meek, Bryan, & Petersen, 2012). In the current study, four LGMMs were created, one for each psychosocial outcome variable (Internalizing Problems, Externalizing Problems, Total Problems, and Social Competence from the CBCL/6-18). No deterministic rules for model selection exist; instead, selection of a final model was based on a combination of theory, past findings and experiences, as well as several statistical fit indices (Ram & Grimm, 2009). The statistical package M Plus 7.0 was used to determine latent class trajectories (Muthen & Muthen, 2015).

**Phase Two.** A linear mixed effects model (LMMM) was fitted to estimate change over time in EF in addition to age at diagnosis and risk status. A separate model was employed for each index on the BRIEF (Behavioral Regulation, Metacognition) and each cluster on the WJ-III COG (Broad Attention, Executive Processes, Processing Speed, and Working Memory) to
determine the slope of each trajectory. The statistical package SAS 9.3 was used to fit the LMEM (SAS Institute, 2012).

**Phase Three.** Based on the number of groups established for each individual outcome variable on the CBCL/6-18 (Internalizing Problems, Externalizing Problems, Total Problems, and Social Competence), either a binary (where two groups were found) or multinomial (where more than two groups were found) logistic regression was used to investigate if change in EF over time predicts latent class membership for each psychosocial outcome on the CBCL/6-18. The statistical package SAS 9.3 was used for logistic regression (SAS Institute, 2012).
CHAPTER 3
RESULTS

Demographic and Clinical Characteristics

One hundred sixty-six participants provided measurements from at least two time points across each of the 10 scales included (CBCL/6-18, BRIEF, WJ-III COG). Average age at diagnosis was 9 years (range = 3 - 18). The minority of the sample was female ($n = 64; 38.55\%$). The sample was predominantly Caucasian ($n = 126; 75.90\%$), followed by Black ($n = 18; 10.84\%$), and Asian ($n = 8; 4.82\%$). Participants were treated at several institutions across the world; however, most were treated at St. Jude Children’s Research Hospital ($n = 114; 87.68\%$), followed by Lady Cliento Children’s Hospital ($n = 20; 12.05\%$) and Hospital for Sick Children ($n = 17; 10.24\%$). Most participants were diagnosed with medulloblastoma ($n = 139; 83.73\%$) although other tumor types were represented as well. Most were treated as average risk; however, 41 were treated as high risk (24.7%). See Table 2 for a full description of demographic and clinical characteristics.

Phase One

The purpose of the first phase of analysis was to estimate the number of latent growth trajectories for each of the four psychosocial outcome variables from the CBCL/6-18. LGMM
was used to identify the number and form of latent classes based on growth trajectory that best fit the data. A series of unconditional (e.g., no covariates) LGMM’s with 2-, 3-, and 4-groups was tested for Internalizing Problems, Externalizing Problems, Total Problems, and Social Competence from the CBCL/6-18. Each of the CBCL/6-18 outcomes consisted of a T-score (mean = 100; SD = 10); they were treated as continuous variables for analytic purposes.

Models for each of the CBCL/6-18 variables were compared using relative fit information criteria, including Bayesian Information Criteria (BIC) and Aikake Information Criteria (AIC). Generally, lower AIC and BIC absolute values indicate greater fit (Ram & Grimm, 2009). Nylund, Asparouhov, and Muthen (2007) have shown that BIC often performs better, making it the information criteria of choice for some. Entropy functions as a summary indicator of the conditional probabilities of individuals’ group membership; higher values (> 0.80) suggest that individuals can be confidently classified to specific groups and there is considerable separation between groups (Ram & Grimm, 2009). Entropy is helpful when comparing models with similar AIC and BIC values. Vuong-Lo-Mendell-Rubell (VLMR) Likelihood Ratio Tests were used to evaluate whether the current model was a good fit in comparison to a reduced model where the number of latent classes is reduced by one class. The Bootstrap Likelihood Ratio Test (BLRT) is similar to the VLMR, except the p-value is found via the bootstrap method. For the current study, model selection was based on smaller information criterion and higher entropy as well as likelihood tests and interpretability.

**Latent Group Enumeration.** For Internalizing Problems, Externalizing Problems, and Total Problems, AIC, BIC, and entropy values were considerably close across 2, 3, and 4-group latent classes. Examination of fit estimates as well as conceptual considerations determined that the 3-group model was preferable for Internalizing, Externalizing, and Total Problems and was
retained as the final model for these outcomes. The 2-group model was preferable for Social Competence. See Table 3 for values of information criterion and likelihood ratio tests across 2-, 3-, and 4-, group models for each of the CBCL outcomes. Conceptual considerations that guided decisions regarding latent class enumeration included that some, but not all survivors have difficulties. With this in mind, models reflecting that were selected. Further, consideration of interpretability were employed, such that finding a balance between a number of latent groups that explains growth trajectories well, without providing too few versus too many classes was preferred. Finally, for the sake of interpretability, and as a result of the high similarity across indexes, a 3-class model was preferred for each of the Problems indexes (Internalizing, Externalizing, and Total).

For Internalizing Problems, AIC was the lowest for the 4-group model (AIC = 4644.24), BIC was lowest for the 3-group model (BIC = 4738.21), and entropy was highest for the 2-group model (Entropy = 0.82). The VLMR Likelihood ratio test was statistically significant for the 2-group model (VLMR = 230.94; \( p < 0.0001 \)). The BLRT was statistically significant across the 2-, 3-, and 4-group models (\( p = 0.0001 \)).

For Externalizing Problems, AIC was lowest for the 4-group model (AIC = 4398.35) and BIC was lowest for the 3-group model (BIC = 4499.66); entropy was highest for the 2-group model (Entropy = 0.85). The VLMR Likelihood Ratio Test was significant for the 2-group model (VLMR = 247.80, \( p = 0.0003 \)). The BLRT was statistically significant across the 2-, 3-, and 4-group models (\( p = 0.0001 \)).

For Total Problems, AIC and BIC were lowest for the 4-group model (AIC = 4751.21; BIC = 4673.90). However, the 2-group model had the highest entropy (Entropy = 0.82). The VLMR Likelihood Ratio Test was statistically significant for the 2-group model (VLMR =
254.55, \( p = 0.0010 \)). The BLRT was statistically significant across the 2-, 3-, and 4-group models \( (p = 0.0001) \).

For Social Competence, AIC was lowest for the 4-group model (AIC = 4484.60) and BIC was lowest for the 3-group model (BIC = 4570.57). Entropy was the same for both the 2- and 3-group model (Entropy 0.73). The VLMR Likelihood Ratio Test was statistically significant for the 2-group model (VLRM = 140.79, \( p = 0.0022 \)). The BLRT was statistically significant across the 2- and 3-group models \( (p = 0.0001) \).

**Latent Trajectory Interpretation.** The next step of analysis was to interpret each of the latent group trajectories for each of the CBCL/6-18 scales. Slight change over time is observed across each of the four CBCL/6-18 outcomes; trajectories are mostly stable. For Internalizing Problems, the Low Internalizing Problems class comprised 26.4% of the sample and represents no internalizing difficulties of clinical concern across the six time points. The Medium Internalizing Problems class is comprised of 38.8% of the sample and reflects higher mean scores than the Low Internalizing Problems class, but does not show mean scores in the clinical range. The High Internalizing Problems class is comprised of 34.8% of the sample. The mean score remains in the At Risk range across the six time points.
Figure 1. Internalizing Problems.

0 = baseline time point; 1 = 1 year post diagnosis; 2 = 2 years post diagnosis; 3 = 3 years post diagnosis; 4 = 4 years post diagnosis; 5 = 5 years post diagnosis. Scores above 60 are considered to be in the borderline significant range. Scores 64 and above are considered clinically significant.

Three classes were found for Externalizing Problems. The Low Externalizing Problems class is made up of 42.9% of participants and shows a mean score well below the clinical range. The Medium Externalizing Problems class is comprised of 39.8% of the sample. The Low and Medium Externalizing Problems classes do not evidence borderline or clinically significant levels of externalizing behavior across the six time points. The High Externalizing Problems class is made up of 17.3% of the sample. This class generally stays at or slightly below the clinical range across the six time points. The High Externalizing Problems class does exhibit scores in the borderline significant range at two and three years post diagnosis.
Figure 2. Externalizing Problems.

0 = baseline time point; 1 = 1 year post diagnosis; 2 = 2 years post diagnosis; 3 = 3 years post diagnosis; 4 = 4 years post diagnosis 5 = 5 years post diagnosis. Scores above 60 are considered to be in the borderline significant range. Scores 64 and above are considered clinically significant.

Three classes were found for Total Problems. The Low Total Problems class consists of 24.9% of the sample. The Medium Total Problems class consists of 42.3% of the sample. The High Total Problems class is comprised of 32.7% of the sample. The Low and Medium Total Problems classes stay well below the clinical range; however, the High Total Problems class exhibits scores in the borderline significant at 2 and 3 years post diagnosis.
Figure 3. Total Problems.
0 = baseline time point; 1 = 1 year post diagnosis; 2 = 2 years post diagnosis; 3 = 3 years post diagnosis; 4 = 4 years post diagnosis 5 = 5 years post diagnosis. Scores above 60 are considered to be in the borderline significant range. Scores 64 and above are considered clinically significant.

On Social Competence variable, two latent classes were found. The Moderate Social Competence class consists of 59.3% of the sample. The High Social Competence class is comprised of 40.7% of the sample. Mean scores on Social Competence are well within the normal range for both classes across all time points.

Figure 4. Social Competence.
0 = baseline time point; 1 = 1 year post diagnosis; 2 = 2 years post diagnosis; 3 = 3 years post diagnosis; 4 = 4 years post diagnosis 5 = 5 years post diagnosis. Scores below 30 are considered to be in the clinically significant range.
Phase Two

The second phase of data analysis involved modeling change in EF over time in addition to age at diagnosis and risk status. Both parent-report (BRIEF) and performance-based (WJ-III COG) measures of EF were included. The linear mixed effect model (LMEM) was applied with random intercept and time.

**Modeling Executive Function.** LMEMs were used for each of the EF variables to estimate change in each index over time, including estimation of rate of change (slope) over time. Each EF variable is modeled with linear mixed effect models, after controlling for risk status and age at diagnosis. Random effects included intercept and year, such that individual differences in year were obtained for each participant. The fitting results for change in EF over time are presented in Table 4. For the BRIEF indexes, each year that passes results in a 0.86 $T$-score point increase on the Behavior Regulation Index ($p < 0.0001$) and a 1.10 $T$-score point increase on the Metacognition Index ($p < 0.0001$). Results from the WJ-III COG measures suggest that for each year that passes, Working Memory decreases by 1.33 standard score points ($p < 0.0001$) and Broad Attention decreases by 1.53 points ($p < 0.001$). No statistically significant change over time was found for Executive Processes or Processing Speed.

Phase Three

To examine if change in EF over time was predictive of psychosocial trajectory, binary or multinomial logistic regression was performed. For Internalizing Problems, three classes were found via LGMM resulting in application of multinomial regression. Individual coefficients of year for each measure of EF were included separately in the model as the only predictor. For the BRIEF, the odds of being in the Medium Internalizing Problems class (versus Low Internalizing Problems class) increase by 1.74 times for every one-unit increase in slope on the BRI (95% Confidence Interval = 1.05-2.88). The odds of being in the High Internalizing Problems class
(versus Low Internalizing Problems class) increase by 3.17 times for every one-unit increase in slope on the BRI (95% Confidence Interval = 1.86-5.41). The odds of being in the Medium Internalizing Problems class (versus Low Internalizing Problems class) increase by 1.69 for every one-unit increase in slope on the MCI (95% Confidence Interval = 1.08-2.66). The odds of being in the High Internalizing Problems class (versus Low Internalizing Problems class) increase by 2.75 times for every one-unit increase in slope on the MCI (95% Confidence Interval = 1.68-4.51). The Broad Attention, Executive Processes, Processing Speed, and Working Memory clusters from the WJ-III COG were not predictive of Internalizing Problems class. See Table 5 for odds ratio estimates and significance.

For Externalizing Problems (See Table 6), 3 classes were found via LGMM resulting in application of a multinomial regression. For the BRIEF, the odds of being in the Medium Externalizing Problems class (versus the Low Externalizing Problems class) increase by 3.08 times for every one-unit increase in slope on the BRI (95% Confidence Interval = 1.82-5.22). The odds of being in the High Externalizing Problems class (versus Low Externalizing Problems class) increase by 6.66 times for every one-unit increase in slope on the BRI (95% Confidence Interval = 3.49-12.69). The odds of being in the Medium Externalizing Problems class (versus Low Externalizing Problems class) increase by 1.87 times for every one-unit increase in slope on the MCI (95% Confidence Interval = 1.27-2.75). The odds of being in the High Externalizing Problems class (versus Low Externalizing Problems class) increase by 1.87 times for every one-unit increase in slope on the MCI (95% Confidence Interval = 1.16-3.00). For the WJ-III COG, none of the clusters (i.e., Broad Attention, Executive Processes, Processing Speed, and Working Memory) were predictive of Externalizing Problems class.

Three classes for the Total Problems index were found via LGMM, so a multinomial
regression was applied (See Table 7). For the BRIEF, the odds of being in the Medium Total Problems class (versus Low Total Problems class) increase by 1.68 times for every one-unit increase in slope on the BRI (95% Confidence Interval = 1.01-2.79). The odds of being in the High Total Problems class (versus Low Total Problems class) increase by 3.33 times for every one-unit increase in slope on the BRI (95% Confidence Interval = 1.91-5.81). The odds of being in the Medium Total Problems class (versus Low Total Problems class) increase by 1.61 times for every one-unit increase in slope on the MCI (95% Confidence Interval = 1.02-2.53). The odds of being in the High Total Problems class (versus Low Total Problems class) increase by 2.75 times for every one-unit increase in slope on the MCI (95% Confidence Interval = 1.66-4.56). The odds of being in the Medium Total Problems class (versus Low Total Problems class) decrease by 0.76 times for every one-unit increase in slope on the WJ-COG III Executive Processes cluster (95% Confidence Interval = 0.58-1.00). The odds of being in the Medium Total Problems Class (versus the Low Total Problems class) decrease by 0.79 times for every one-unit increase in slope on the WJ-COG III Processing Speed cluster (95% Confidence Interval = 0.65-0.95).

Two classes were found via LGMM for Social Competence, so a logistic regression was applied (See Table 8). For the BRIEF, the odds of being in the High Social Competence class (versus the Moderate Social Competence class) decrease by 0.57 times for every one-unit increase in BRI slope (95% Confidence Interval = 0.39-0.82). The odds of being in the High Social Competence class (versus Moderate Social Competence class) decrease by 0.60 times for every one-unit increase in MCI slope (95% Confidence Interval = 1.42-0.85). For the WJ-III COG, the odds of being in the High Social Competence class (versus the Moderate Social Competence class) increase by 1.21 times for every one-unit increase in Broad Attention cluster
slope (95% Confidence Interval = 1.01-1.455). The odds of being in the High Social Competence class (versus Moderate Social Competence class) increase by 1.28 times for every one-unit increase in Executive Processes cluster slope (95% Confidence Interval = 1.02-1.60). The odds of being in the High Social Competence class (versus Moderate Social Competence class) increase by 1.22 times for every one-unit increase in Processing Speed slope (95% Confidence Interval = 1.04-1.43). The Working Memory cluster was not predictive of Social Competence.
CHAPTER 4
DISCUSSION

The aim of the current study was to examine the relationship between EF and psychosocial outcomes among survivors of pediatric brain tumors. The first phase of data analysis involved investigation of the presence of latent classes based on longitudinal trajectory within multiple measures of psychosocial functioning (e.g., Internalizing Problems, Externalizing Problems, Total Problems, and Social Competence) over time. In the second phase, change over time in several aspects of EF (e.g., Behavior Regulation, Metacognition, Broad Attention, Executive Processes, Processing Speed, Working Memory) was evaluated. Finally, change in EF over time was investigated as a predictor of psychosocial outcomes. This multifaceted approach to analysis was crafted to provide a more nuanced understanding of the relationship between EF and psychosocial outcomes and to better identify survivors of childhood brain tumors who are at risk for psychosocial difficulties.

Psychosocial Trajectories. Longitudinal growth mixture modeling revealed the presence of three latent classes for Internalizing Problems, Externalizing Problems, and Total Problems. For each of these scales, a High, Medium, and Low class was found. Two classes were found for Social Competence: Moderate and High Social Competence. Originally, it was hypothesized that
latent classes would be reflective of changes over time in psychosocial outcomes (e.g., who gets worse, improves, or stays the same); however, these findings suggested only slight change over time. Thus, latent classes seemed more appropriately interpreted to reflect general levels of distress rather than change in level of distress over time.

For the Internalizing Problems cluster, only the High Internalizing Problems class demonstrated impairment within the borderline to clinically significant range. Both the Medium and Low Internalizing Problems classes were well below the clinical cutoff. The High Internalizing Problems class is comprised of approximately one-third of the sample; mean scores were within the clinically significant range at baseline and remained elevated over time. Findings suggest that most survivors of pediatric brain tumor do not exhibit clinically significant difficulties with internalizing problems; however, a small subset does. For this class, their functioning is likely to remain impaired up to five years from diagnosis.

For Externalizing Problems, the Medium and Low Externalizing Problems classes were well below clinical significance. The High Externalizing Problems class evidenced mean scores within normal limits at baseline, but scores increased slightly at two and three years post-diagnosis, suggesting a worsening course. The High Externalizing Problems class is made up of 17.3% of the sample. While it is promising that the overwhelming majority of this sample did not exhibit externalizing pathology at baseline or across the five year follow-up period, a small subset did report difficulty that was generally maintained over time.

Total Problems provides a summary indicator of the number and severity of problems faced by survivors of pediatric brain tumor. As with the other problem scales, the Medium and Low Total Problems classes did not exhibit clinically significant concerns. However, the High Total Problems class (32.7% of the sample) demonstrated mean scores at or slightly above the
borderline significant range at two and three years post-diagnosis, suggesting that some survivors do experience psychosocial problems worthy of clinical attention.

These findings among pediatric patients are similar to those observed among adult survivors in that some, but not all, survivors suffer psychosocial morbidities secondary to disease and treatment (Zebrack et al., 2004; Zebrack et al., 2007; Zeltzer et al., 2008; Brinkman et al., 2013). Further, results of the current study indicate that those at risk for psychosocial difficulties at baseline are likely to continue to experience difficulties up to five years after diagnosis. In a longitudinal examination of adult survivors of childhood cancer, Brinkman and colleagues (2013) demonstrated persistent distress throughout the course of survivorship, including an increase in psychosocial distress that emerged well after diagnosis. However, in a review of 20 studies evaluating the psychological consequences of childhood cancer and subsequent treatment, Eiser, Hill, and Vance (2000) found that survivors generally did not exhibit greater impairments in depression and anxiety than those found among peers or matched controls. Zebrack and Seltzer (2003) found that childhood cancer survivors did not experience higher levels of depression than those expected among the general population. Regardless, while most survivors in the current study are psychologically well-adjusted, some demonstrate levels of internalizing and/or externalizing problems worthy of clinical intervention.

In terms of social functioning, two latent classes were found among the current sample. Both the Moderate Social Competence and High Social Competence classes exhibited mean longitudinal trajectories well within the expected range; no borderline or clinically significant social difficulties were found. While it is reassuring that survivors did not report concerns related to social competence, this finding is somewhat inconsistent with literature examining social outcomes among this population. For example, Willard, Conklin, Wu, and Merchant (2015)
investigated behavioral outcomes among a sample of 80 survivors of low-grade glioma. Findings showed problems with social difficulties at baseline and up to five years post diagnosis and longitudinal trajectory of social concerns was stable over time. Vanatta, Gartstein, Short, and Knoll (1998) found that childhood brain tumor survivors are nominated less by peers as a best friend and are more socially isolated. Hardy, Willard, Watral, and Bonner (2010) demonstrated that off-treatment survivors evidence greater social impairment than those on active-treatment and a normative sample. Additionally, adult survivors of childhood cancer often attain typical social milestones (e.g., marriage, employment) at lower rates and at a later time than healthy peers (Gurney et al., 2009), indicating that social functioning among survivors is discrepant from their peers.

Measurement of social outcomes among survivors of pediatric brain tumors is notably difficult (Barrera & Schulte, 2009). It is possible that the measure included in the current study is not sensitive to the social difficulties experienced by survivors due to emphasis on more global indicators of social skill (e.g., number of friends, weekly social engagements, and ability to get along with others). In fact, Vance, Eiser, and Horne (2004) found that the social difficulties of survivors of childhood brain tumor are often more subtle; parents reported that their child struggled with skills such as finding their place with peers and awareness of social expectations. Perhaps this was also the case among our sample.

**Change in Executive Function Over Time**

Participants in the current study evidenced statistically significant declines in specific domains of EF over time, as captured by both performance-based and parent-report measures, consistent with original hypotheses and extant literature (Knight et al., 2012; Palmer et al., 2013). On the BRIEF, parent-report indicated that survivors’ ability to regulate their behavior
and engage in metacognitive processes worsened by 0.86 and 1.10 points per year, respectively. On the WJ-III COG, survivors’ broad attention and working memory worsened by 1.53 and 1.33 points per year, respectively. This is unsurprising, given that problems with attention are one of the most commonly reported difficulties among survivors of childhood cancer (Mabbot, Snyder, Penkman, & Witol, 2009). No significant change over time was found for Executive Processes. Interestingly, and in contrast to previous reports (Palmer et al., 2013), there was no significant change in processing speed over the 5-year follow-up period. Current findings also highlight the importance of parent-report of executive function, as our sample experienced increases in problems with behavioral regulation and metacognition over the 5-year follow-up period. As noted by Howarth and colleagues (2013) parent-report and performance-based measures of executive function provide similar but perhaps different information; both are useful in the investigation of EF.

**Prediction of Psychosocial Latent Class Trajectories**

The third phase of the current study investigated the role of EF in psychosocial outcomes. Consistent with original hypotheses, change in EF over time was generally found to be predictive of psychosocial outcomes. Broadly, parent-reported difficulties with aspects of EF were most predictive of psychosocial difficulties. However, selected performance-based indices were predictive as well. On the BRIEF, greater impairment in both behavior regulation and metacognition predicted membership in both the Medium and High classes for Internalizing Problems. Performance-based indices from the WJ-III COG were not. A similar pattern was observed for Externalizing Problems; greater difficulties in behavior regulation and metacognition were predictive of both Medium and High Externalizing Problems latent class membership. For both internalizing and externalizing difficulties, greater EF impairment is
associated with greater psychosocial impairment.

With respect to Total Problems, the relationship is less clear. On the BRIEF, greater impairment in both behavior regulation and metacognition was predictive of membership in Total Problems latent classes, with greater EF impairment associated with greater total problems. For the WJ-III COG, however, greater impairment in executive processes and processing speed was predictive of membership in the Medium Total Problems class, but not the High Total Problems class. Broad Attention and Working Memory were not predictive of Total Problems latent class membership. These findings make interpretation of the importance of EF to Total Problems less straightforward.

The level of social competence demonstrated among the current sample is reassuring in that average social functioning for this cohort remained within the normal range. Despite this, a strong relationship between change in EF over time (via both parent-report and performance-based measures) and social competence was found. On the BRIEF, greater impairment in both behavioral regulation and metacognition was predictive of reduced social competence. On the WJ-III COG, greater impairment in broad attention, executive processes, and processing speed were predictive of reduced social competence; working memory was not predictive. These findings demonstrate the EFs are foundational cognitive skills necessary for navigation of social relationships.

**Strengths**

The longitudinal nature of the current study allowed for data collection at prospectively planned time points and represents the largest dataset of its kind at present, making it particularly amenable to the data analysis strategies utilized. Latent growth mixture modeling of psychosocial functioning provides a more nuanced understanding of the psychosocial trajectory
for survivors of pediatric brain tumor. As such, this study provides increased understanding of which patients are at risk for psychosocial difficulties thereby allowing for identification of those in need of intervention. Interestingly, change in EF over time was predictive of psychosocial trajectory suggesting that EF may constitute an appropriate target for intervention.

Limitations

Within the context of the current findings, study limitations are acknowledged. The current study was limited by the constraints of the larger study within which it was designed. While the measures included were designed to answer the questions in the current study, perhaps there are more sensitive measures that would more accurately capture the nuances of psychosocial and executive functioning among survivors of pediatric brain tumor (e.g., specific measures of social functioning). Additionally, no control group was included that would allow for comparison to a matched sample. The current study utilized comparisons via normative data provided by the included measures and only included one rater of psychosocial functioning and the everyday aspects of EF. Enhanced understanding may be achieved with the inclusion of multiple raters (e.g., teacher and/or self-report). Finally, while this study represents the largest dataset of its kind to date, the sample size is still considerably small.

Future Directions

With these limitations in mind, future directions include use of measures providing observations from multiple informants (e.g., parent-, self-, and teacher-report) is suggested. Further, longitudinal studies that investigate functioning beyond five years post-diagnosis would be helpful for providing understanding of longer-term outcomes. Inclusion of a matched control group (e.g., sibling or community-based) would allow for examination of practice effects and provide a more ecologically valid point of comparison. Inclusion of more participants, to the
extent possible, might allow for an even greater understanding of survivors functioning over time. For example, it would be interesting to look at distinct tumor types independently (i.e., medulloblastoma, ATRT) to examine the possibility for divergent outcomes. Utilization of alternative measures of social functioning (e.g., the Social Problems scale from the CBCL/6-18) as compared to the Social Competence scale included in the current study would be interesting. Measurement of social skills among survivors of pediatric brain tumors is notably challenging and examination of the most appropriate measures to capture this domain is of great importance. Additionally, consideration of demographic and clinical characteristics as well as performance at baseline that might suggest which specific survivors are at risk for diminished functioning would be helpful to more accurately determine who is in need of targeted intervention.

The treatment process for childhood cancer is long and involves multiple inpatient and outpatient visits over the course of several years. Not surprisingly, many families are hesitant to continue multiple visits to providers once their child finishes treatment. Interventions that provide empirically supported benefit for late effects, but do not pose increased demand on family resources are preferred. Trials investigating the use of pharmacologic intervention for cognitive late effects demonstrated generalization to teacher-reported psychosocial functioning, providing further support for the relationship between cognitive and psychosocial functioning (Conklin et al., 2010). Cogmed, a remotely-administered working memory training program has been shown to be both feasible and efficacious for remediating cognitive late effects among pediatric brain tumor survivors (Cox et al., 2015; Conklin et al., 2015). Building upon the findings of the current study regarding the relationship between cognitive and psychosocial functioning, it would be interesting to evaluate the efficacy of Cogmed for improving psychosocial functioning.
Conclusions

Findings from the current study support the foundational role of EF in psychosocial outcomes among survivors of pediatric brain tumor. Executive function predicts psychosocial trajectory, highlighting the necessity of EF for navigating psychosocial well-being in the survivorship period. The findings of this study are consistent with previous reports that show EF as an underlying process for psychosocial function (Moyer et al., 2012; Willard, Allen, Hardy, & Bonner, 2016). Of note, parent-reported EF was a better predictor of internalizing and externalizing trajectory for this sample. Generally, results suggest that as EF becomes more impaired, psychosocial functioning (e.g., internalizing and externalizing problems) diminishes as well.
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BIBLIOGRAPHY


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APPENDIX
<table>
<thead>
<tr>
<th>Assessment time point</th>
<th>Measures completed</th>
<th>Participating institutions</th>
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<tbody>
<tr>
<td>Baseline</td>
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<td>SJCRH</td>
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<tr>
<td>Post diagnosis 60 months</td>
<td>WJ-III Cognitive, CBCL</td>
<td>SJCRH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Collaborating sites</td>
</tr>
</tbody>
</table>
Table 2. Participant Characteristics

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>102 (61.45%)</td>
</tr>
<tr>
<td>Female</td>
<td>64 (38.55%)</td>
</tr>
</tbody>
</table>

Mean age at diagnosis

<table>
<thead>
<tr>
<th>Standard Deviation</th>
<th>3.25 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>3-18</td>
</tr>
</tbody>
</table>

Race

<table>
<thead>
<tr>
<th>Race</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>126 (75.90%)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>18 (10.84%)</td>
</tr>
<tr>
<td>Asian</td>
<td>8  (4.82%)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1  (0.60%)</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>1  (0.60%)</td>
</tr>
<tr>
<td>Other</td>
<td>7  (4.22%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5  (3.01%)</td>
</tr>
</tbody>
</table>

Clinical Characteristics

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>139 (83.72%)</td>
</tr>
<tr>
<td>Primitive Neuroectodermal Tumor (PNET)</td>
<td>8  (4.82%)</td>
</tr>
<tr>
<td>Atypical Teratoid Rhabdoid Tumor (ATRT)</td>
<td>11 (6.63%)</td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td>8  (4.82%)</td>
</tr>
</tbody>
</table>

Risk Arm

<table>
<thead>
<tr>
<th>Risk Arm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>125 (75.30%)</td>
</tr>
<tr>
<td>High</td>
<td>41  (24.70%)</td>
</tr>
</tbody>
</table>

Posterior Fossa Syndrome

<table>
<thead>
<tr>
<th>Posterior Fossa Syndrome</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31 (18.67%)</td>
</tr>
</tbody>
</table>

Treating Institutions

<table>
<thead>
<tr>
<th>Treating Institutions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Jude Children’s Research Hospital (Memphis, Tennessee)</td>
<td>114 (68.67%)</td>
</tr>
<tr>
<td>Lady Cliento Children’s Hospital (Brisbane, Australia)</td>
<td>20  (12.05%)</td>
</tr>
<tr>
<td>Hospital for Sick Children (Toronto, Canada)</td>
<td>17  (10.24%)</td>
</tr>
<tr>
<td>Duke University Medical Center (Durham, North Carolina)</td>
<td>9   (5.42%)</td>
</tr>
<tr>
<td>Children’s Hospital of Philadelphia (Philadelphia, Pennsylvania)</td>
<td>3   (1.81%)</td>
</tr>
<tr>
<td>Texas Children’s Hospital (Houston, Texas)</td>
<td>2   (1.20%)</td>
</tr>
<tr>
<td>Royal Children’s Hospital (Melbourne, Australia)</td>
<td>1   (0.60%)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Number of Latent Classes</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Internalizing Problems</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Externalizing Problems</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Total Problems</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Social Competence</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

*Generally, lower AIC and BIC absolute values indicate greater fit (Ram & Grimm, 2009). For entropy, higher values (>0.80) suggest that individuals can be confidently classified to specific groups and there is considerable separation between groups (Ram & Grimm, 2009). Vuong-Lo-Mendell-Rubell (VLMR) Likelihood Ratio Tests is used to evaluate whether the current model was a good fit in comparison to a reduced model where the number of latent classes is reduced by 1.
Table 4. Modeling Executive Function Change Over Time

| Outcome               | Effect       | Parameter Estimate | Standard Error | T-Value | Probability <\(|t|\) |
|-----------------------|--------------|--------------------|----------------|---------|-----------------|
| Working Memory*       | Intercept    | 95.00              | 3.83           | 24.81   | < 0.0001        |
|                       | Year\(^\text{a}\) | -1.33              | 0.26           | -5.08   | < 0.0001        |
|                       | Risk         | 0.07               | 2.88           | 0.02    | 0.98            |
|                       | Age at Diagnosis | 0.53              | 0.38           | 1.37    | 0.17            |
| Broad Attention*      | Intercept    | 93.36              | 4.06           | 23.00   | < 0.0001        |
|                       | Year         | -1.53              | 0.31           | -5.00   | < 0.0001        |
|                       | Risk         | -0.37              | 3.03           | -0.12   | 0.90            |
|                       | Age at Diagnosis | 0.16              | 0.41           | 0.39    | 0.70            |
| Executive Processes* | Intercept    | 95.98              | 3.66           | 26.20   | < 0.0001        |
|                       | Year         | 0.06               | 0.26           | 0.24    | 0.81            |
|                       | Risk         | -0.57              | 2.75           | -0.21   | 0.84            |
|                       | Age at Diagnosis | -0.11             | 0.37           | -0.31   | 0.76            |
| Processing Speed*     | Intercept    | 83.29              | 4.79           | 17.39   | < 0.0001        |
|                       | Year         | 0.18               | 0.33           | 0.54    | 0.59            |
|                       | Risk         | 2.69               | 3.65           | 0.74    | 0.46            |
|                       | Age at Diagnosis | -0.19             | 0.48           | -0.40   | 0.69            |
| Behavioral Regulation Index* | Intercept | 45.83              | 1.98           | 23.09   | < 0.0001        |
|                       | Year         | 0.86               | 0.21           | 4.16    | < 0.0001        |
|                       | Risk         | -1.18              | 1.43           | -0.82   | 0.41            |
|                       | Age at Diagnosis | 0.05              | 0.20           | 0.28    | 0.78            |
| Metacognition Index*  | Intercept    | 49.54              | 2.20           | 22.56   | < 0.0001        |
|                       | Year         | 1.10               | 0.22           | 5.12    | < 0.0001        |
|                       | Risk         | -1.27              | 1.59           | -0.80   | 0.42            |
|                       | Age at Diagnosis | -0.22             | 0.22           | -1.04   | 0.30            |

*Measures from the WJ-III COG include Working Memory, Broad Attention, Executive Processes, and Processing Speed. Measures from the BRIEF include: Behavioral Regulation Index, and Metacognition Index.
\(^\text{a}\) Year = time point
\(^\text{b}\) Risk = risk arm (average or high)
<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Class</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; Chi-Square</th>
<th>Odds Ratio Estimate</th>
<th>95% Confidence Limit for Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.06</td>
<td>0.24</td>
<td>0.07</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI Estimate</td>
<td>2</td>
<td>0.55</td>
<td>0.26</td>
<td>4.65</td>
<td>0.03</td>
<td>1.74</td>
<td>(1.05, 2.88)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>-0.74</td>
<td>0.29</td>
<td>6.31</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI Estimate</td>
<td>3</td>
<td>1.15</td>
<td>0.27</td>
<td>17.96</td>
<td>&lt; 0.0001</td>
<td>3.17</td>
<td>(1.86, 5.41)</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>-0.07</td>
<td>0.27</td>
<td>0.06</td>
<td>0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI Estimate</td>
<td>2</td>
<td>0.53</td>
<td>0.23</td>
<td>5.17</td>
<td>&lt; 0.0001</td>
<td>3.17</td>
<td>(1.08, 2.66)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>-0.87</td>
<td>0.33</td>
<td>6.86</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI Estimate</td>
<td>3</td>
<td>1.01</td>
<td>0.25</td>
<td>16.20</td>
<td>&lt; 0.0001</td>
<td>3.17</td>
<td>(1.68, 4.51)</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.14</td>
<td>0.25</td>
<td>0.30</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA Estimate</td>
<td>2</td>
<td>-0.17</td>
<td>0.11</td>
<td>2.22</td>
<td>0.14</td>
<td>0.85</td>
<td>(0.68, 1.05)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>0.08</td>
<td>0.25</td>
<td>0.09</td>
<td>0.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA Estimate</td>
<td>3</td>
<td>-0.09</td>
<td>0.12</td>
<td>0.61</td>
<td>0.44</td>
<td>0.91</td>
<td>(0.73, 1.15)</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.40</td>
<td>0.20</td>
<td>4.21</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP Estimate</td>
<td>2</td>
<td>-0.22</td>
<td>0.14</td>
<td>2.56</td>
<td>0.11</td>
<td>0.81</td>
<td>(0.62, 1.05)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>0.22</td>
<td>0.20</td>
<td>1.20</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP Estimate</td>
<td>3</td>
<td>-0.11</td>
<td>0.14</td>
<td>0.64</td>
<td>0.43</td>
<td>0.90</td>
<td>(0.68, 1.18)</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.42</td>
<td>0.20</td>
<td>4.43</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS Estimate</td>
<td>2</td>
<td>-0.15</td>
<td>0.09</td>
<td>2.60</td>
<td>0.11</td>
<td>0.86</td>
<td>(0.71, 1.03)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>0.23</td>
<td>0.21</td>
<td>1.23</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS Estimate</td>
<td>3</td>
<td>-0.07</td>
<td>0.10</td>
<td>0.54</td>
<td>0.46</td>
<td>0.93</td>
<td>(0.77, 1.12)</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.14</td>
<td>0.31</td>
<td>0.19</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WM Estimate</td>
<td>2</td>
<td>-0.19</td>
<td>0.18</td>
<td>1.03</td>
<td>0.31</td>
<td>0.83</td>
<td>(0.58, 1.19)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>0.13</td>
<td>0.31</td>
<td>0.17</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WM Estimate</td>
<td>3</td>
<td>-0.06</td>
<td>0.19</td>
<td>0.08</td>
<td>0.77</td>
<td>0.95</td>
<td>(0.65, 1.38)</td>
</tr>
</tbody>
</table>

Scales from the BRIEF include the Behavior Regulation Index (BRI) and Metacognition Index (MCI). Scales from the WJ-III COG include the Broad Attention (BA), Executive Processes (EP), Processing Speed (PS), and Working Memory (WM) clusters. Bold text in the body of the chart connotes statistical significance ($p < 0.05$).
Table 6. Modeling Externalizing Problems Using Individual Time Coefficients

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Class</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; Chi-Square</th>
<th>Odds Ratio Estimate</th>
<th>95% Confidence Limit for Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept BRI Estimate</td>
<td>2</td>
<td>-0.87</td>
<td>0.25</td>
<td>12.01</td>
<td>0.0005</td>
<td>3.08</td>
<td>(1.82, 5.22)</td>
</tr>
<tr>
<td>Intercept BRI Estimate</td>
<td>3</td>
<td>-2.71</td>
<td>0.43</td>
<td>39.37</td>
<td>&lt; 0.0001</td>
<td>6.66</td>
<td>(3.49, 12.70)</td>
</tr>
<tr>
<td>Intercept MCI Estimate</td>
<td>2</td>
<td>-0.79</td>
<td>0.27</td>
<td>8.33</td>
<td>0.00</td>
<td>1.87</td>
<td>(1.27, 2.75)</td>
</tr>
<tr>
<td>Intercept MCI Estimate</td>
<td>3</td>
<td>-1.58</td>
<td>0.36</td>
<td>19.43</td>
<td>&lt; 0.0001</td>
<td>6.66</td>
<td>(3.49, 12.70)</td>
</tr>
<tr>
<td>Intercept BA Estimate</td>
<td>2</td>
<td>-0.18</td>
<td>0.22</td>
<td>0.66</td>
<td>0.42</td>
<td>0.97</td>
<td>(0.80, 1.17)</td>
</tr>
<tr>
<td>Intercept BA Estimate</td>
<td>3</td>
<td>-1.23</td>
<td>0.30</td>
<td>16.25</td>
<td>&lt; 0.0001</td>
<td>0.97</td>
<td>(0.80, 1.17)</td>
</tr>
<tr>
<td>Intercept EP Estimate</td>
<td>2</td>
<td>-0.92</td>
<td>0.17</td>
<td>0.53</td>
<td>0.47</td>
<td>0.92</td>
<td>(0.73, 1.16)</td>
</tr>
<tr>
<td>Intercept EP Estimate</td>
<td>3</td>
<td>-0.92</td>
<td>0.17</td>
<td>0.53</td>
<td>0.47</td>
<td>0.92</td>
<td>(0.73, 1.16)</td>
</tr>
<tr>
<td>Intercept PS Estimate</td>
<td>2</td>
<td>-0.13</td>
<td>0.17</td>
<td>0.53</td>
<td>0.47</td>
<td>0.98</td>
<td>(0.83, 1.15)</td>
</tr>
<tr>
<td>Intercept PS Estimate</td>
<td>3</td>
<td>0.91</td>
<td>0.22</td>
<td>17.24</td>
<td>&lt; 0.0001</td>
<td>0.98</td>
<td>(0.83, 1.15)</td>
</tr>
<tr>
<td>Intercept WM Estimate</td>
<td>2</td>
<td>-0.26</td>
<td>0.22</td>
<td>0.93</td>
<td>0.33</td>
<td>0.92</td>
<td>(0.74, 1.14)</td>
</tr>
<tr>
<td>Intercept WM Estimate</td>
<td>3</td>
<td>-1.28</td>
<td>0.36</td>
<td>12.53</td>
<td>0.0004</td>
<td>0.92</td>
<td>(0.74, 1.14)</td>
</tr>
</tbody>
</table>

Scales from the BRIEF include the Behavior Regulation Index (BRI) and Metacognition Index (MCI). Scales from the WJ-III COG include the Broad Attention (BA), Executive Processes (EP), Processing Speed (PS), and Working Memory (WM) clusters. Bold text in the body of the chart connotes statistical significance ($p < 0.05$).
<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Class</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; Chi-Square</th>
<th>Odds Ratio Estimate</th>
<th>95% Confidence Limit for Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.30</td>
<td>0.24</td>
<td>1.56</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI Estimate</td>
<td>2</td>
<td>0.52</td>
<td>0.26</td>
<td>3.97</td>
<td>0.05</td>
<td>1.68</td>
<td>(1.01, 2.80)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>-0.79</td>
<td>0.31</td>
<td>6.45</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI Estimate</td>
<td>3</td>
<td>1.20</td>
<td>0.28</td>
<td>18.05</td>
<td>&lt; 0.0001</td>
<td>3.33</td>
<td>(1.91, 5.81)</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.18</td>
<td>0.27</td>
<td>0.46</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI Estimate</td>
<td>2</td>
<td>0.47</td>
<td>0.23</td>
<td>4.22</td>
<td>0.04</td>
<td>1.61</td>
<td>(1.02, 2.53)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>-0.87</td>
<td>0.35</td>
<td>6.29</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI Estimate</td>
<td>3</td>
<td>1.01</td>
<td>0.26</td>
<td>15.28</td>
<td>&lt; 0.0001</td>
<td>2.75</td>
<td>(1.66, 4.56)</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.30</td>
<td>0.25</td>
<td>1.44</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA Estimate</td>
<td>2</td>
<td>-0.21</td>
<td>0.12</td>
<td>3.37</td>
<td>0.07</td>
<td>0.81</td>
<td>(0.64, 1.01)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>-0.03</td>
<td>0.27</td>
<td>0.01</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA Estimate</td>
<td>3</td>
<td>-0.18</td>
<td>0.12</td>
<td>2.20</td>
<td>0.14</td>
<td>0.83</td>
<td>(0.66, 1.06)</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>0.62</td>
<td>0.20</td>
<td>9.66</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP Estimate</td>
<td>2</td>
<td>-0.28</td>
<td>0.14</td>
<td>3.98</td>
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<td>0.25</td>
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<td>-0.13</td>
<td>0.15</td>
<td>0.74</td>
<td>0.39</td>
<td>0.88</td>
<td>(0.66, 1.17)</td>
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<tr>
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<td>0.10</td>
<td>6.02</td>
<td>0.01</td>
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<td>(0.65, 0.95)</td>
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<tr>
<td>Intercept</td>
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<td></td>
</tr>
<tr>
<td>PS Estimate</td>
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<td>-0.09</td>
<td>0.10</td>
<td>0.88</td>
<td>0.35</td>
<td>0.91</td>
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<td>0.75</td>
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<td>-0.25</td>
<td>0.19</td>
<td>1.80</td>
<td>0.18</td>
<td>0.78</td>
<td>(0.54, 1.13)</td>
</tr>
<tr>
<td>Intercept</td>
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<td>-0.02</td>
<td>0.33</td>
<td>0.00</td>
<td>0.96</td>
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<tr>
<td>WM Estimate</td>
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<td>-0.19</td>
<td>0.20</td>
<td>0.86</td>
<td>0.35</td>
<td>0.83</td>
<td>(0.56, 1.23)</td>
</tr>
</tbody>
</table>

Scales from the BRIEF include the Behavior Regulation Index (BRI) and Metacognition Index (MCI). Scales from the WJ-III COG include the Broad Attention (BA), Executive Processes (EP), Processing Speed (PS), and Working Memory (WM) clusters. Bold text in the body of the chart connotes statistical significance ($p < 0.05$).
<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Class</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; Chi-Square</th>
<th>Odds Ratio Estimate</th>
<th>95% Confidence Limit for Odds Ratio</th>
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<td>0.06</td>
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<td>EP Estimate</td>
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<td>5.94</td>
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<td>(1.04, 1.43)</td>
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<td>0.25</td>
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<td>0.16</td>
<td>3.29</td>
<td>0.07</td>
<td>1.33</td>
<td>(0.98, 1.81)</td>
</tr>
</tbody>
</table>

Scales from the BRIEF include the Behavior Regulation Index (BRI) and Metacognition Index (MCI). Scales from the WJ-III COG include the Broad Attention (BA), Executive Processes (EP), Processing Speed (PS), and Working Memory (WM) clusters. Bold text in the body of the chart connotes statistical significance ($p < 0.05$).
VITA

Lauren Elizabeth Cox, M.A.

EDUCATION

University of Mississippi  Anticipated Spring 2016  Ph.D. (Clinical Psychology)
University, MS  APA Accredited
Advisor: Karen A. Christoff, Ph.D.
Dissertation: Survivors of Pediatric Brain Tumor: Psychosocial Outcomes and Executive Function

University of Mississippi  December 2012  M.A. (Clinical Psychology)
University, MS  APA Accredited
Advisor: Karen A. Christoff, Ph.D.
Thesis: The Applicability of Video Self-Monitoring for Adults with Developmental and Intellectual Disabilities

Harding University  May 2009  B.A. (Psychology)
Searcy, AR  Cum Laude

PROFESSIONAL EXPERIENCE

Texas Child Study Center  2015 - 2016  Predoctoral Internship
Dell Children’s Medical Center  Pediatric Psychology
University of Texas at Austin  APA Accredited
Training Director: Jane Gray, Ph.D.

HONORS AND AWARDS

Best Graduate Oral  University of Mississippi Conference on Psychological Science  2014
Presentation  University of Mississippi Graduate School  2013, 2012
Research Travel Grant  Mississippi Academy of Sciences  2010
Best Graduate Poster  Harding University, Department of Behavioral Sciences  2009
Outstanding Psychology Student  Harding University, Department of Behavioral Sciences  2007
Psi Chi, Vice President

PROFESSIONAL LICENSURE

Examination for Professional Practice in Psychology  Passed at Ph.D. level  08/2014

CLINICAL EXPERIENCE

Position: Predoctoral Psychology Intern
Dates: July 2015 - December 2015
Location: Children’s Blood and Cancer Center
Conducted comprehensive neuropsychological assessment for oncology and hematology patients, including battery selection, measure administration, scoring, report writing, and feedback.

**Position:** Predoctoral Psychology Intern  
**Dates:** July 2015 - December 2015  
**Location:** Concussion Clinic, Pediatric Neurology  
**Supervisors:** Michael Reardon, M.D., Puja Patel, Ph.D.  
**Duties:** Participated in multidisciplinary team to manage pediatric concussion patients, including initial evaluation, screening and treatment for post concussive symptoms, and brief mental health intervention. Assisted with the design of a clinic-based research study to examine predictors of protracted recovery from concussion.

**Position:** Predoctoral Psychology Intern  
**Dates:** July 2015 - December 2015  
**Location:** Collaborative Abdominal Pain Program, Pediatric Gastroenterology  
**Supervisors:** David Heckler, Ph.D., Puja Patel, Ph.D., Anees Siddiqui, M.D.  
**Duties:** Conducted intake evaluations for patients with chronic abdominal pain. Facilitated multidisciplinary intervention using cognitive behavioral therapy (CBT) for chronic abdominal pain. Assisted in the design of program materials, including intake and patient information paperwork, modular-based CBT interventions, and psychological assessment of outcomes.

**Position:** Predoctoral Psychology Intern  
**Dates:** July 2015 - December 2015  
**Location:** Children’s Blood and Cancer Center  
**Supervisor:** Puja Patel, Ph.D.  
**Duties:** Co-facilitated cognitive remediation group, including trial of Lumosity, for survivors of pediatric brain tumors, leukemia, and sickle cell disease. Provided brief psychological interventions for inpatient and outpatient hematology/oncology patients.

**Position:** Predoctoral Psychology Intern  
**Dates:** July 2015 - December 2015  
**Location:** Internalizing Disorders Clinic  
**Supervisors:** Jane S. Gray, Ph.D., David Heckler, Ph.D., Janie Black, Ph.D.  
**Duties:** Provided individual CBT for patients with internalizing disorders. Utilized evidence-based interventions for children and adolescents including
MATCH-ADTC and DBT. Conducted intake evaluations for new patients including psychodiagnostic assessment, documentation, and triage.

**Position:** Predoctoral Psychology Intern  
**Dates:** January 2016 – June 2016 (anticipated)  
**Location:** Emergency Department  
Dell Children’s Medical Center  
**Supervisor:** Janie Black, Ph.D.  
**Duties:** Suicide and homicide risk assessment for pediatric patients and families. Development of safety plans and assessment for appropriate level of care, Assistance with patient triage and support for families in crisis following accidental trauma.

**Position:** Predoctoral Psychology Intern  
**Dates:** January 2016 – June 2016 (anticipated)  
**Location:** Consultation/Liaison Service  
Dell Children’s Medical Center  
**Supervisors:** Janie Black, Ph.D., Kevin Stark, Ph.D.  
**Duties:** Assessment and consultation with pediatric patients, including management of psychiatric emergencies. Brief cognitive behavioral therapeutic interventions (e.g., behavioral medicine techniques, coping skills training, and family support) as needed.

**Position:** Predoctoral Psychology Intern  
**Dates:** January 2016 – June 2016 (anticipated)  
**Location:** Medical Coping Clinic  
Texas Child Study Center  
**Supervisors:** Jane Gray, Ph.D., David Heckler, Ph.D., Lynn Monnat, Ph.D.  
**Duties:** Provide evidence-based outpatient psychotherapy for children with chronic medical conditions. Collaborate with medical team, family, and school as needed for optimal patient care.

**Position:** Graduate Extern  
**Dates:** August 2013 – May 2015  
**Location:** Department of Psychology, Section of Neuropsychology  
St. Jude Children’s Research Hospital, Memphis, TN  
**Supervisors:** Jane E. Schreiber, Ph.D., Lisa M. Jacola, Ph.D.  
**Duties:** Administer brief neuropsychological assessments (test administration, scoring, interpretation, and report-writing) to screen neurobehavioral functioning in patients with sickle cell disease between the ages of 8-18. Conducted comprehensive neuropsychological assessments based on clinical referral for children and adolescents.

**Position:** Mental Health Consultant  
**Dates:** August 2011 – May 2015  
**Location:** ICS/HeadStart Mississippi, Holly Springs, MS
Supervisor: Alan Gross, Ph.D.
Duties: Classroom observation and behavioral support for preschool teachers and students. Conducted teacher and parent conferences as needed.

Position: Graduate Therapist
Dates: August 2010 – May 2015
Location: Psychological Services Center, University of Mississippi, University, MS
Supervisors: Karen A. Christoff, Ph.D., John Young, Ph.D., Danielle Maack, Ph.D.
Duties: Provided evidence-based outpatient psychological services for adults and children.

Position: Graduate Examiner
Dates: August 2012 – May 2013
Location: Psychological Assessment Clinic, University of Mississippi, University, MS
Supervisor: Scott A. Gustafson, Ph.D.
Duties: Administered comprehensive psychodiagnostic assessments (test administration, scoring, interpretation, report-writing, and feedback) based on clinical referral for adults and children.

Position: Graduate Student Intern
Dates: January 2012 – August 2012
Location: Autism Center of Tupelo, Tupelo, MS
Supervisor: J. Scott Bethay, Ph.D.
Duties: Implemented one-on-one behavioral intervention for children with DD/ID using Verbal Behavior procedures. Consulted with special education departments in area schools regarding appropriate behavioral and educational supports. Conducted parent and teacher trainings for school districts on behavioral support for students with DD/ID.

Position: Verification Specialist
Dates: January 2012 – May 2012
Location: Office of Student Disability Services, University of Mississippi, University, MS
Supervisor: Scott A. Gustafson, Ph.D.
Duties: Evaluated documentation for academic accommodation qualification and conducted student interviews.

Position: Therapist, Adult Services
Dates: August 2011 – December 2011
Location: Region IV Community Mental Health Center, Hernando, MS
Supervisor: Priscilla Roth-Wall, Ph.D.
Duties: Provided individual outpatient psychotherapy with caseload of approximately 40 clients. Utilized evidence-based treatment protocols and assessment measures to monitor treatment progress.

Position: Intern
**Dates:** June 2010 – June 2011  
**Location:** Education and Research, The Baddour Center, Senatobia, MS  
**Supervisor:** Shannon Hill, Ph.D.  
**Duties:** Provided individual and group psychotherapy and skills training, functional behavior assessments, and behavior support plans. Conducted brief psychological assessments for adults with DD/ID.

**Position:** Undergraduate Behavioral Health Intern  
**Dates:** July 2008 – August 2008  
**Location:** Cook Children’s Medical Center, Ft. Worth, TX  
**Supervisor:** Lena Zettler, M.A.  
**Duties:** Assisted with a summer program for children with severe attention problems and behavioral disturbance. Observed intake evaluations, diagnostic interviews, group psychotherapy sessions, and psychological assessment.

**RESEARCH EXPERIENCE**

**Position:** Graduate Research Assistant, Dissertation project  
**Dates:** May 2014 - Present  
**Location:** Department of Psychology, Section of Neuropsychology  
St. Jude Children’s Research Hospital, Memphis, TN  
**Supervisors:** Jane E. Schreiber, Ph.D., Karen A. Christoff, Ph.D.  
**Description:** Examines longitudinal trajectory of psychosocial outcomes and executive function among pediatric medulloblastoma survivors.  
**Duties:** Project conceptualization, data analysis, and dissemination of results. Participated in weekly lab meetings.

**Position:** Graduate Research Assistant  
**Dates:** September 2012 – August 2014  
**Location:** Department of Psychology, Section of Neuropsychology  
St. Jude Children’s Research Hospital, Memphis, TN  
**Supervisor:** Heather M. Conklin, Ph.D. (Principal Investigator)  
**Description:** Investigated efficacy of a computerized working memory training program to ameliorate neurocognitive late effects among survivors of pediatric cancer. (NCT01217996)  
**Duties:** Neuropsychological testing, data analysis and dissemination of results. Participated in weekly lab meetings.

**Position:** Principal Investigator, Thesis project  
**Dates:** June 2010 - September 2012  
**Location:** The Baddour Center, Senatobia, MS  
**Supervisors:** Karen A. Christoff, Ph.D., Shannon Hill, Ph.D.  
**Description:** Investigated the use of video self-modeling for adults with DD/ID.  
**Duties:** Project conceptualization, data collection, data analysis, dissemination of results.

**TEACHING EXPERIENCE**
Position: Adjunct Instructor
Dates: August 2014 – December 2014
Location: Harding School of Theology, Counseling Program, Memphis, TN
Supervisor: Edward A. Gray, Ed.D.
Course: Marriage and Family Therapy 5772: Testing and Assessment in Counseling
Duties: Responsible for teaching 12 graduate students the basics of testing and assessment for counselors including psychometrics, types of measures, administration, scoring, report writing, and interpretation. Developed syllabus and course curriculum.

Position: Graduate Instructor
Dates: August 2014 – May 2015
Location: Department of Psychology, University of Mississippi, University, MS
Supervisor: Karen A. Christoff, Ph.D.
Course: Psychology 201: Introduction to Psychology
Duties: Responsible for teaching 80 undergraduates. Developed syllabus and course curriculum.

Position: Teaching Assistant
Dates: August 2008 – May 2009
Location: Department of Behavioral Sciences, Harding University, Searcy, AR
Supervisor: Kenneth Hobby, Ph.D.
Course: Psychology 325: Undergraduate Statistics
Duties: Conducted class in professor’s absence, assisted in preparation and grading of examinations, completed various office-related tasks.

GRANTSMANSHIP
Dates: May 2012 – December 2012
Title: PEERS Program for Adolescents with Autism Spectrum Disorders
Investigators: Lauren E. Cox, M.A., Sharon D. Boudeaux, M.A.T., J. Scott Bethay, Ph.D
Role: Developed application materials and project design.
Description: Manualized protocol for teaching middle and high school students essential skills to make and keep friends.
Funding Source: Mississippi Council on Developmental Disabilities
Award: $34,000

PROFESSIONAL MEMBERSHIPS & SERVICE
Student Member Diversity Committee, Texas Child Study Center
Student Member Association for Behavioral and Cognitive Therapies (ABCT)
Student Member American Psychological Association (APA)
Division 54, Society of Pediatric Psychology
Division 53, Society of Child Clinical Psychology
Student Member International Neuropsychological Association (INS)
Student Member Mississippi Psychological Association (MPA)

PEER-REVIEWED PUBLICATIONS

POSTER PRESENTATIONS


ACADEMIC PRESENTATIONS


Cox, L. E. (2013, August). *The Feasibility and Applicability of a Computerized Intervention to Mitigate Neurocognitive Late Effects among Childhood Cancer Survivors*. Presented at Psychology Rounds, St. Jude Children’s Research Hospital, Memphis, TN.


