ASSESSING NEUROPSYCHOLOGICAL PHENOTYPES OF PEDIATRIC BRAIN TUMOR SURVIVORS: A LATENT PROFILE ANALYSIS

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Abstract: Introduction: Survivors of pediatric brain tumors are at significant risk for both neurocognitive impairments and psychological adjustment difficulties. However, these domains of negative sequelae are primarily examined as distinct sets of symptoms. Thus, the current study aimed to evaluate comprehensive profiles of late effects, across both neurocognitive and psychosocial domains, experienced by young brain tumor survivors. Additionally, several demographic and disease characteristics were evaluated as predictors of late effect profiles. Method: Pediatric brain tumor survivors (N=89) who were assessed in a neuropsychological clinic between May 2009 and May 2018, were diagnosed at least one year prior, and were off-treatment for at least three months, were included. Parent- and teacher-report of psychological symptoms (Child Behavior Checklist and Teacher Report Form), and performance-based measures of neurocognitive functioning (Wechsler Scales, Tower of London-DX-Drexel Version) were examined using latent profile analysis and model fit criterion including the bootstrapped likelihood ratio difference test and the Bayesian Information Criteria. The R3STEP procedure was employed to identify predictors of class membership. Results: Four classes were identified: (1) "Average" (n = 47) characterized by average functioning across all domains, (2) "Cognitive Deficit" (n = 25) characterized by average psychosocial functioning and impaired cognitive functioning, (3) "Social/Cognitive Deficit" (n = 9) characterized by elevated social problems and significant neurocognitive impairments, and (4) "Discrepant" (n = 8), characterized by impaired visual planning and problem-solving and elevated parent-reported psychosocial problems, but average processing speed, working memory, and teacher-reported psychosocial outcomes. Ethnicity, race, treatment with radiation, and the diagnoses of neurofibromatosis 1, hydrocephalus, and posterior fossa syndrome, were all significant predictors of class membership ($ps < 0.05$). Conclusion: Findings were consistent with extant literature, while also shedding light on patterns of relations among neurocognitive and psychosocial domains among survivors. Results show that distinct neuropsychological phenotypes may exist, suggesting the need for closer examination of demographic and illness-related factors that appear to contribute to neuropsychological profiles.

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CHAPTER I

INTRODUCTION

Individuals diagnosed with a brain tumor in childhood or adolescence are known to be at significant risk for a variety of negative sequelae following oncological treatment. Emergence of neuropsychological problems has been documented as early as within the first year after diagnosis, and evidence suggests a persistent and steep decline in functioning during the first few years off-treatment (Embry et al., 2015; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004; Turner, Rey-Casserly, Liptak, & Chordas, 2009). Further, these difficulties appear to be long-lasting, as they relate to reduced independent living and quality of life in later adulthood (Gurney et al., 2009; Maurice-Stam, Grootenhuis, Caron, & Last, 2007; Zebrack et al., 2004). Thus, parallel to the rise in survival rates of pediatric brain tumors, the literature has turned to focus on understanding the long-term outcomes of youth treated for brain tumors (Siegel, Miller, & Jemal, 2016).

Among the most robust findings in the pediatric brain tumor literature is the elevated prevalence of neurocognitive deficits (Glass et al., 2017; Mulhern et al., 2004; Turner et al., 2009). In fact, compared to healthy siblings and survivors of non-central nervous system malignancies, survivors of pediatric brain tumors appear to be at the greatest risk for impairments in global intellectual and cognitive functioning (Duffner, 2004; Ellenberg et al., 2009; Prasad et al., 2015; Ullrich & Embry, 2012; Winick, 2011). Pediatric brain tumor survivors exhibit reduced white matter volume and neural connectivity, which is linked with impairment across multiple neurocognitive

(Conklin et al., 2013; Hardy, Willard, Gioia, Sharkey, & Walsh, 2018; Hardy, Willard, Wigdor, Allen, & Bonner, 2015; Kahalley et al., 2013). Processing speed, working memory, and attentional control appear to be some of the most highly impacted subdomains, and a significant subset of survivors demonstrate deficits in these processes that are well below the performance of healthy age- and gender-matched peers (De Ruiter, Van Mourik, Schouten-Van Meeteren, Grootenhuis, & Oosterlaan, 2013; Mulhern et al., 2004; Reddick et al., 2003).

Declines in general intelligence, potentially driven by underlying difficulties in knowledge acquisition, have been observed among brain tumor survivors (Mulhern et al., 2004; Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013; Spiegler et al., 2004). Specifically, it has been suggested that the mean intelligence quotient (IQ) for pediatric survivors of brain tumors remains well below that of normative samples (Turner et al., 2009). Importantly, these negative outcomes have been documented by multiple informants, including parents, teachers, and the survivors themselves, as well as through performance-based assessments (Hardy et al., 2018; Prasad et al., 2015; Zeltzer et al., 2009). Thus, an increased understanding of potential factors associated with these neurocognitive outcomes is necessary.

In addition to neurocognitive late effects, survivors of pediatric brain tumors are also at significant risk for poor psychological adjustment (Schultz et al., 2007; Turner et al., 2009; Zeltzer et al., 2009). Consistent with neurocognitive findings, the literature on psychosocial outcomes indicates that individuals treated for pediatric brain tumors are at greater risk for internalizing and behavioral difficulties, as compared to healthy peers and survivors of other cancers (Patenaude & Kupst, 2005; Schultz et al., 2007; Zebrack et al., 2004; Zeltzer et al., 2009). Although many studies report great resilience among survivors, it has been noted that approximately 30% of adult survivors of childhood cancers show psychological problems, and that those treated for brain tumors experience considerably more risk (Recklitis, Lockwood, Rothwell, & Diller, 2006). However, reports vary widely across the

literature, suggesting that specific psychological sequelae may be dependent on factors such as age, symptoms assessed, and informant (Fuemmeler, Elkin, & Mullins, 2002).

Nevertheless, the extant literature suggests that pediatric brain tumor survivors are indeed at risk for elevated global distress and reduced quality of life (Zebrack et al., 2004; Zeltzer et al., 2009). More specifically, significant evidence has accrued documenting internalizing symptoms, including increased depressive and anxious symptoms, suicidal ideation, emotion dysregulation, and somatization, which persist through adulthood (Fuemmeler et al., 2002; Prasad et al., 2015; Recklitis et al., 2010; Turner et al., 2009; Zebrack et al., 2004; Zeltzer et al., 2009). Although the research on behavioral problems is more limited, elevated risk is also apparent for externalizing problems among this population (Fuemmeler et al., 2002; Turner et al., 2009). The literature suggests that behavioral problems are prevalent, with both parents and teachers reporting difficulties with aggression, antisocial behaviors, and behavioral regulation at home and at school (Hardy et al., 2018; Holmquist & Scott, 2002; Schultz et al., 2007).

Following from these findings regarding adjustment outcomes, more recent literature has identified social late effects of pediatric brain tumor treatment (Schulte & Barrera, 2010). For instance, one small study suggested that brain tumor survivors experience more social functioning deficits and impairments in social-cognitive skills than typically developing children (Willard, Allen, Hardy, & Bonner, 2017). Another investigation of adolescents found that survivors reported lower social acceptance and reduced self-perception, as compared to adolescents who had just begun oncological treatment (Hardy, Willard, Watral, & Bonner, 2010). It may be that brain tumor survivors have reduced opportunity for social interactions, resulting in the social isolation, victimization, and withdrawal behaviors that have been observed (Salley et al., 2015). Systematic reviews have corroborated these findings, establishing that pediatric brain tumor survivors appear to be at risk for poorer social competency, by both parent- and teacher-report, and are less socially accepted by peers (Fuemmeler et al., 2002; Schulte & Barrera, 2010). Further, adult survivors appear to have reduced

social attainment, including lower rates of marriage and employment, fewer friends, less education, and less independent living, rendering it particularly valuable to evaluate social outcomes among this population (Gurney et al., 2009; Prasad et al., 2015).

Importantly, several key predictors of these neurocognitive and psychosocial late effects have been identified. Demographic characteristics, such as female sex and lower socioeconomic status, as well as disease variables, including tumor location, have been shown to predict greater neurocognitive impairments and psychological adjustment difficulties (Fuemmeler et al., 2002; Moore, 2005; Zebrack et al., 2004). Younger age at diagnosis and greater time since diagnosis also appear to predict greater deficits across domains of functioning (Mulhern et al., 2004; Reimers et al., 2003). Further, medical outcomes, including cerebellar mutism (posterior fossa syndrome) and ventriculoperitoneal shunt placement due to hydrocephalus, have been linked with worse neurocognitive outcomes (Ellenberg et al., 2009; Palmer et al., 2010).

However, treatment variables appear to be the most robust predictors of IQ decline and neurocognitive deficits (Patenaude & Kupst, 2005; Reimers et al., 2003; Turner et al., 2009). The presence and dosage of cranial radiation therapy, specifically larger radiation doses and greater irradiated brain volume, are well-established risk factors for negative neuropsychological outcomes (Kieffer-Renaux et al., 2007; Mulhern et al., 2004). It is important to note that these findings are rarely consistent in the literature, as risk factors vary across informants, age groups, and samples (Ellenberg et al., 2009; Fuemmeler et al., 2002; Mulhern et al., 2004; Turner et al., 2009). Therefore, an interaction likely exists between several disease and demographic characteristics, which may lead, in combination, to the development of both neurocognitive and psychosocial sequelae. Collectively, these findings argue for a more precise understanding of the risk factors for late effects among pediatric brain tumor survivors, and how these risk factors relate to the various domains of sequelae.

Interestingly, research regarding the full constellation of late effects experienced by pediatric brain tumor survivors is quite limited. Most studies seem to examine sequelae as distinct sets of symptoms, such as those concerning neurocognitive impairments (e.g., De Ruiter, Van Mourik, Schouten-Van Meeteren, Grootenhuis, & Oosterlaan, 2013), and those investigating psychosocial outcomes (e.g., Zebrack et al., 2004). Even those studies that examine multiple domains of functioning appear to do so by assessing discrete functions in an independent fashion. For instance, Prasad and colleagues (2015) found elevated risk for adolescent and early young adulthood survivors across psychosocial and neurocognitive domains, but did not examine the pattern of impairment across those domains. Hardy and colleagues (2018) also identified behavioral and neurocognitive difficulties among brain tumor survivors with identified attention deficits, yet correlations among these variables were not reported. Furthermore, several reviews imply that connections exist, but report findings within the context of sections focused on separate domains (Fuemmeler et al., 2002; Turner et al., 2009; Zeltzer et al., 2009). Recent evidence has emerged suggesting a direct link between neurocognitive decline and social deficits among brain tumor survivors, but these findings are limited (Schulte & Barrera, 2010; Willard et al., 2017). Among general populations, a strong association between neurocognitive impairments and psychosocial distress is supported, yet this link is rarely evaluated among pediatric brain tumor survivors, a population at significant risk for impaired functioning in both domains (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Rock, Roiser, Riedel, & Blackwell, 2014).

Thus, the current study aimed to evaluate profiles of neuropsychological late effects experienced by young brain tumor survivors. Specifically, the pattern of impairment across multiple neurocognitive and psychosocial domains was examined among youth who are survivors of pediatric brain tumors. As this study is exploratory in nature, it was hypothesized that unmeasured classes of symptom phenotypes would be identified, and would be characterized by distinct profiles of difficulties across psychosocial and neurocognitive domains, as evidenced by parent- and teacher-report, and

performance-based measures. However, the specific distinctions among profiles could not be anticipated. Additionally, the current study aimed to ascertain if demographic and disease characteristics, including sex, age at diagnosis, and hydrocephalus, show reliable predictive utility of the identified group membership.

CHAPTER II

REVIEW OF LITERATURE

Epidemiology and Treatment of Pediatric Brain Tumors

Pediatric brain tumors are the second most common cancer diagnosis of childhood, following leukemia, for all individuals aged 19 or below (Siegel, Miller, & Jemal, 2016). They account for nearly 26% of all childhood cancers, as well as 20% of cancer diagnoses among older adolescents between the ages of 15 and 19 years old. Thus, they represent the most common diagnosis for the older adolescent age group (Siegel et al., 2016). Since 1975, the incidence rate of childhood cancer has been steadily increasing; meanwhile, mortality rates from pediatric cancers have continuously declined (Siegel et al., 2016). Despite this decline in mortality, it is important to note that pediatric brain tumors continue to be the leading cause of cancer deaths among both children and adolescents. Although any child may experience a brain tumor, it appears that males and children who are Caucasian, Asian, or Pacific Islander may be at a greater risk for a brain tumor diagnosis (Siegel et al., 2016). However, similar to most cancer-related outcomes, the risk for developing a brain tumor varies by tumor type.

Common Brain Tumor Diagnoses

A review of the epidemiology of pediatric brain tumors determined that there are more than 100 histological subtypes of childhood brain tumors (Johnson et al., 2014). The incidence of those that are most common in early childhood, including pilocytic astrocytomas, medulloblastomas, and primitive neuroectodermal tumors, appears to decrease with age whereas, other tumors,

including germ cell tumors appear to peak in adolescence (Kieran, Walker, Frappaz, & Prados, 2010). This suggests an interrelationship with brain growth and development, such that the occurrence of pediatric brain tumors may be connected to maturation process of children's cerebrum.

Gliomas, which are tumors that develop in the glial cells, appear to be the most common among young children between birth and 14-years-old (Johnson et al., 2014). Gliomas tend to result in symptoms including seizures, headaches, and neurologic deficits, due to their primary locations in the central nervous system (Johnson et al., 2014). Gliomas are often categorized into three groups including astrocytomas, ependymomas, and oligodendrogliomas, which each have further subdivisions (Kieran et al., 2010). Pilocytic astrocytomas, one type of astrocytomas, accounts for approximately 17% of all childhood brain tumors (Johnson et al., 2014). Other gliomas, such as oligodendrogliomas, are more common in adults, whereas ependymomas are more rare among both pediatric and adult patients (Kieran et al., 2010). Prognosis also varies greatly across glioma diagnoses, with pilocytic astrocytomas having a very high survival rate, and brain stem tumors having very poor prognoses (Johnson et al., 2014).

Embryonal tumors, which appear to develop in the embryonic cells that remain in the brain after birth, are the second most common pediatric brain tumor diagnosis (Kieran et al., 2010). Embryonal tumors also consist of three main subtypes, including medulloblastomas, primitive neuroectodermal tumors (PNET), and atypical teratoid/rhabdoid tumors (ATRT; Kieran et al., 2010). Medulloblastomas are the most common embryonal tumor and account for more than 20% of childhood brain tumors, whereas the diagnosis is quite rare among adults (Kieran et al., 2010). The 5-year survivorship rate is approximately 80% for children with standard-risk medulloblastomas, but prognosis differs significantly by tumor subtype (Johnson et al., 2014; Kieran et al., 2010). PNET are tumors of the supratentorial region of the brain, or the cerebrum, and are much more commonly diagnosed in early childhood (Johnson et al., 2014; Kieran et al.,

2010). Lastly, ATRT is the most rare embryonal tumor diagnosis, and typically occurs among children younger than three years old (Johnson et al., 2014). Prognosis appears to be significantly related to age, with greater age linked with better outcomes, although research on ATRT is still limited (Johnson et al., 2014).

The third most common group of pediatric brain tumors are germ cell tumors. These tumors typically develop in the midline of the brain, near the pineal gland or suprasellar region, and are most commonly diagnosed in adolescents (Kieran et al., 2010). Thus, the incidence of germ cell tumors is thought to be related to puberty. However, as with all other diagnoses, there is great variability across diagnoses. For instance, certain histologies, such as teratomas, are more common in infancy and early childhood, whereas germinomas and other germ cell malignancies are more common among adolescents (Kieran et al., 2010). Importantly, epidemiological studies aimed at identifying more accurate estimates of tumor incidence and survivorship rates continue to be underway (Johnson et al., 2014; Kieran et al., 2010; Siegel et al., 2016).

Brain Tumor Treatments

Oncological treatments are often complex, with multiple treatment modalities combined to enhance their efficacy. The three most common types of treatments are surgery, chemotherapy, and radiation. These treatments may occur singularly, or in some combination, depending upon a given treatment protocol. Medical organizations, such as the Children's Oncology Group, have developed highly standardized protocols to establish evidence-based guidelines for the best course of treatment per tumor type (Breneman et al., 2018).

Although there are many different types of surgeries performed to diagnose, treat, or relieve symptoms of cancer, the two main forms of oncological surgeries are referred to as curative and debulking (DeSantis et al., 2014). Curative surgery is used to remove all of the cancer when cancerous cells are found in only one discrete part of the body (DeSantis et al., 2014). Thus, the

goal is total resection of the brain tumor; however, this may be complicated by the tumor location and type. Alternatively, the goal of debulking surgery is partial resection, with the goal to only remove some of the cancer. It is used when it would be dangerous too remove an entire tumor, due to the potential damage to adjacent organs or tissues (Bruce & Ogden, 2004). In this case, surgery is frequently used to reduce the amount of cancer in the body, and is then combined with other treatment modalities. In some cases, however, the initial goal of surgery is curative, but only partial resection is accomplished. In these cases, adjuvant therapies often become necessary.

Radiation refers to a treatment that uses high doses of particles or waves to kill or damage cancerous cells (DeSantis et al., 2014). It can be combined with other treatments that cause the cancer cells to be more sensitive to radiation, and it can shrink a tumor prior to surgery (Merchant, Pollack, & Loeffler, 2010). Radiation methods are improving, yet this form of treatment is still problematic due to radiation passing through and potentially damaging healthy cells in the process (DeSantis et al., 2014). To reduce damage to healthy cells, recent advances have led to more focal radiation such as proton therapy, rather than treatments that expose one's entire body to the harmful waves, such photon therapy (Eaton et al., 2016). However, these newer treatments still expose healthy cells to radiation, and may continue to cause detrimental side effects, including neurocognitive impairments (Eaton et al., 2016).

Lastly, chemotherapy refers to the use of drugs that target cancer cells at different phases of the cell cycle in order to destroy or stop the growth of cancerous cells (DeSantis et al., 2014). This treatment is used in a variety of ways, such as to shrink a tumor prior to surgery or to destroy cancer cells that remain following irradiation (Mueller & Chang, 2009). It is particularly useful for treating metastasized cancers or cancers that have spread throughout the body. However, the side effects can be particularly bothersome, since these systemic drugs cannot differentiate between healthy cells and cancer cells, thus attacking and damaging healthy parts of an

individual's body (Mueller & Chang, 2009). Therefore, similar to radiotherapy, there are potentially increased risks for long-term late effects following chemotherapy.

Treatment Approach by Tumor Type

Due to the variability in tumor locations, grades, and types, an array of treatment protocols has been developed, and over time, research has led to the design of more individualistic and tailored plans. For instance, different protocols have been developed to treat each of the most common pediatric brain tumors (Breneman et al., 2018).

For pilocytic astrocytomas, surgery is the frontline form of treatment, with the primary goal of full resection (Dodgshun, Maixner, Hansford, & Sullivan, 2016). For these tumors, gross total resection is related to good prognoses, and subsequent treatments are rarely necessary. When only partial resection is achieved, or if the tumor appears to progress, adjuvant chemotherapy may be implemented (Bonfield & Steinbok, 2015). However, radiation is not recommended for children affected by a pilocytic astrocytoma unless severe progression or relapse occurs. For medulloblastomas, treatment commonly consists of a combination of therapies, including curative surgery, followed by craniospinal radiation and chemotherapy (Kieran et al., 2010). High-risk medulloblastomas require more aggressive forms of chemotherapy and radiation, whereas standard-risk may be treated by less aggressive means. For radiotherapy, photon and proton radiation appear to have similar disease control outcomes following surgery, but it is important to note that proton therapy, as previously mentioned, is thought to be more protective of healthy tissues (Eaton et al., 2016).

Further, cure rates for germinomas are nearly perfect following radiation therapy, but as the current understanding of the late effects of treatment has expanded, arguments for different treatment modalities have been put forth (Kieran et al., 2010). For instance, the addition of chemotherapy to the treatment protocol may reduce the necessary dosage of radiation and may

allow for success with more focal radiation (Kieran et al., 2010). However, treatments are still advancing, and multimodal treatments for more rare, aggressive, or complicated tumors continue to be investigated. Advancements in treatment, as it relates to both effectiveness and minimization of late effects, are constantly occurring (MacDonald, Aguilera, & Kramm, 2011).

Effects of Treatment Approach

Cancer treatments are known to have a significant impact on quality of life in survivorship. Children with brain tumors appear to be at the greatest risk for late effects, as compared to children with other cancers, and this risk may be related to differences in the treatment approaches taken for central nervous system malignancies versus other cancers (Duffner, 2004; Reimers et al., 2003). Specific treatment approaches, or combinations of treatments, appear to result in differential late effects (Kingma et al., 2002; Packer et al., 1989; Peterson et al., 2008). For instance, children treated with surgery and radiation appear to suffer greater losses than those treated with surgery alone (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Packer et al., 1989). Further, the dose of radiation and volume of the brain that was irradiated also relates to outcomes (Kieffer-Renaux et al., 2007; Mulhern et al., 2004). Thus, it is important to consider and assess the variability in outcomes of treatment.

It may be that the differential effects of treatment are variable due to distinct effects on white matter volume. Specifically, research has shown that survivors of pediatric central nervous system malignancies experience significant damage to white matter tracts in their brains, which is related to deficits in neurocognitive functioning, specifically in the domain of processing speed (Aukema et al., 2009). This suggests that young children treated for cancer may have a particular developmental vulnerability. Radiotherapy, which is known to effect white matter volume, has been implicated in these observed impairments. However, one study has shown that white matter damage is observed following surgery, before chemotherapy or radiation, indicating that

oncological treatments may have multifaceted effects on the brain (Glass et al., 2017). As neurocognitive processes are associated with white matter volume and cortical functionality, understanding the unique vulnerabilities of young patients is critical for identifying and intervening with those at risk for a host of difficulties in survivorship.

Neurocognitive Late Effects

It is well-established that oncological treatments affect a variety of cognitive domains and that these effects may vary by disease and demographic characteristics (Fuemmeler, Elkin, & Mullins, 2002; Mulhern et al., 2004; Turner, Rey-Casserly, Liptak, & Chordas, 2009). The most robust evidence documents impairments in processing speed, attentional control, working memory, and especially for brain tumor survivors, intellectual functioning. Overall, findings suggest that a significant subset of survivors exhibit impairments across neurocognitive domains that are well below the performance of healthy age- and gender-matched peers (Mulhern et al., 2004; Reddick et al., 2003).

Processing Speed Impairments

Processing speed, or the ability to quickly and efficiently manage cognitive operations, appear to be particularly important for cognitive functioning, as it underlies domains of higher-order functioning (Kahalley et al., 2013; Palmer et al., 2013). Typically, processing speed improves over the course of childhood and adolescence as neural circuits mature, and it is posited to be closely related to working memory and the development of intellectual functioning (Schatz, Kramer, Ablin, & Matthay, 2000). Notably, research shows that pediatric brain tumor survivors demonstrate lower processing speed than would be expected for their age, and that processing speed may be the cognitive domain with the greatest decline following oncological treatment (Kahalley et al., 2013; Palmer et al., 2013). Interestingly, one study found that an untimed measure of general reasoning ability remained largely intact, suggesting that acquired knowledge

and reasoning abilities may persist relatively intact following oncological treatment, but that declines in processing speed may influence children's functioning and their ability to develop, learn, and achieve (Kahalley et al., 2013).

Consistent impairments in processing speed have been documented through a variety of measurement strategies. Survivors of medulloblastomas tested an average of four years after their diagnosis exhibited deficits in processing speed, as measured by the Processing Speed Index (PSI) from the Wechsler Intelligence Scale for Children (WISC), as well as slowed movement execution (Kieffer-Renaux et al., 2007). Kahalley et al. (2013) found similar results with the PSI from the Wechsler Abbreviated Scale of Intelligence (WASI) for adolescent survivors, noting slower processing speed to be linked with craniospinal irradiation (Kahalley et al., 2013). A study utilizing the Woodcock-Johnson Test of Cognitive Abilities also found that those treated for pediatric medulloblastomas demonstrated decreased processing speed following surgical resection (Glass et al., 2017). Further, an investigation of survivors of medulloblastomas and ependymomas corroborated these findings by employing the Trail Making Test (Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). Decline in performance was estimated to be a loss of one standard deviation every three years, indicating that impairments in processing speed continue to progress as children age over the course of survivorship.

Attentional Control

Attention is a cognitive process that involves being consciously aware of stimuli and the choice of what to focus awareness on (Dennis, Hetherington, & Spiegler, 1998). Attention is a fundamental capacity that supports other cognitive abilities, including working memory and intellectual functioning (Baddeley, 2003). It is also another process that is associated with the prefrontal cortex and white matter volume. However, unlike processing speed, attention is not

directly measured by the Wechsler Intelligence Scales, however, the Digit Span Forward score is sometimes used as an attention measure.

More commonly used to evaluate attentional deficits in pediatric brain tumor survivors is the Conners' Continuous Performance Test (CPT), a computerized test that measures sustained attention, selective attention, reaction time, and impulsivity (Mulhern et al., 2004; Reddick et al., 2003). An investigation of white matter volume and attentional difficulties in pediatric brain tumor survivors also found that seven out of the ten CPT index scores were impaired, compared to age- and gender-matched standard scores (Mulhern et al., 2004). More recently, Glass and colleagues (2017) substantiated this finding and suggested that decreased broad attention was associated with white matter damage. An examination of both brain tumor and leukemia survivors provided further support for the appearance of attention deficits following oncological treatment (Hardy, Willard, Wigdor, Allen, & Bonner, 2015). Specifically, these researchers found that 27.7% of brain tumor survivors, a subsample much larger than standardized norms, met symptom criteria for Attention-Deficit/Hyperactivity Disorder inattentive type (ADHD-I), with the most commonly endorsed symptom being "fails to pay close attention to details."

Interestingly, investigations of attention deficits in pediatric cancer have sparked a great deal of controversy, as some researchers believe that the phenotype of cancer-related attention impairments appears consistent with the deficits exhibited by children with neurodevelopmental ADHD-I (Hardy et al., 2015). However, others argue that there are important differences between neurodevelopmental ADHD and cancer-related cognitive deficits, such that the ADHD model would have clinical limitations if applied to survivors (Alderson & Mullins, 2011). In particular, changes in the expression of ADHD symptomology across childhood, adolescence, and young adulthood, which have not been evidenced in the progression of cancer-related late effects, has been cited as a reason to not employ the ADHD framework (Alderson & Mullins, 2011).

One study has supported this latter view, by demonstrating that an ADHD diagnostic tool could not successfully identify those pediatric cancer survivors who were evidencing difficulties in attention (Kahalley et al., 2011). In contrast, an assessment of an ADHD screening tool's predictive validity suggested that an ADHD framework for understanding cancer-related neurocognitive deficits could be valuable (Hardy et al., 2015). Another study has also demonstrated that brain tumor survivors that have attention difficulties display functional profiles that are similar to children with neurodevelopmental ADHD (Hardy, Willard, Gioia, Sharkey, & Walsh, 2018). Further, these survivors with attention problems appear to experience greater impairments across neurocognitive domains, as compared to those with intact attentional control. This suggests that certain profiles of functioning may be observed among survivors, but greater research is clearly needed to better ascertain the prevalence of attentional difficulties among survivors, as well as the relationship between attention problems and deficits in other areas of neuropsychological functioning.

Working Memory

Working memory encompasses the ability to register, maintain, update, and manipulate information in one's mind (Dennis et al., 1998). It is considered to be a higher-order function, as well as an underlying mechanism of other cognitive capacities, such as intellectual functioning. The prefrontal cortex, along with the dorsal anterior cingulate cortex, are the primary brain regions that appear to be associated with working memory (Robinson et al., 2009). Importantly, these brain regions are continuing to develop throughout adolescence, which may render children particularly vulnerable to the effects of oncological treatments on neurocognitive functioning, including working memory capacity (Robinson et al., 2009).

Working memory impairment has been documented by parent- and teacher-report, and performance-based measures, although concordance among these methods of assessment is often

low (de Vries et al., 2017). The literature suggests that children treated for brain tumors, including posterior fossa tumors and medulloblastomas, show reduced cerebral neuro-connectivity and associated impairments in working memory (Conklin et al., 2013; Law et al., 2011). Working memory deficits, therefore, appear to be highly related to craniospinal irradiation, which is known to damage white matter (Brinkman et al., 2016). Interestingly, recent literature has indicated that children with brain tumors may be at risk for cognitive changes even before treatment begins. In fact, one investigation found that at diagnosis, children with brain tumors had significantly lower working memory performance compared to children with non-central nervous system cancers (Margelisch et al., 2015). Perhaps these early changes account, at least in part, for the significantly higher risk for poor neurocognitive outcomes among brain tumor survivors, as compared to survivors of other pediatric malignancies.

Limited research seems to indicate that pediatric brain tumor survivors experience deficits in multiple cognitive capacities, but that working memory abilities remain intact and are comparable to the abilities of healthy peers (Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Palmer et al., 2013). However, the majority of the literature provides supporting evidence that working memory deficits exist among pediatric brain tumor survivors, and appear to persist well into adulthood with a worsening course (King, Na, & Mao, 2015; Mulhern et al., 2004).

Intellectual Functioning

Although associated with deficits in specific underlying domains of cognitive functioning, pediatric brain tumors also appear to result in impairments in knowledge acquisition and declines in intellectual functioning (Mulhern et al., 2004; Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013; Spiegler et al., 2004). The literature suggests that the mean intelligence quotient (IQ) for survivors of pediatric brain tumors is well below what is found among normative samples (Turner et al., 2009). In fact, one review suggested that following radiotherapy for medulloblastomas,

children lose an average of 2.2-4.3 IQ points per year (Mulhern et al., 2004). Importantly, declines in IQ appear to be directly linked with treatment type. For instance, one study found that proton beam radiation was unrelated to changes in IQ, whereas children treated with photon radiation experienced a decline of 1.1 IQ points per year (Kahalley et al., 2016). Another review found that craniospinal radiotherapy accounted for an average loss of 18 full-scale IQ points among survivors, with a progressive decline in IQ over time (Ullrich & Embry, 2012). Taken together, these findings suggest that children treated for pediatric brain tumors are at significant risk for a variety of neurocognitive impairments, yet there is a lack of specificity in the literature regarding the patterns of difficulties that are observed.

In sum, pediatric brain tumor survivors are at significant risk for reduced neurocognitive functioning. Evidence has accrued suggesting impairments in specific domains, including processing speed, attentional control, and working memory. However, the profile of such deficits is not always consistent in the literature (Conklin et al., 2013; Glass et al., 2017; Kahalley et al., 2013). Research also suggests that pediatric brain tumor survivors may experience declines in intellectual functioning, with disruption in knowledge acquisition and underlying cognitive processes by oncological treatment contributing to the elevated risk (Kahalley et al., 2016; Ullrich & Embry, 2012). However, the lack of a precision in the current understanding of functional profiles among survivors warrants further investigation of the array of neurocognitive difficulties pediatric brain tumor survivors may experience.

Psychosocial Late Effects

In general, pediatric brain tumor survivors appear to experience risk for both reduced health-related quality of life and increased global psychological distress (Macartney, Harrison, VanDenKerkhof, Stacey, & McCarthy, 2014; Zebrack et al., 2004; Zeltzer et al., 2009). Similar to the literature on neurocognitive outcomes, research suggests that children treated for brain tumors

are at the greatest risk for poor psychosocial adjustment when compared to survivors of other cancers and healthy siblings, as documented via multiple informants (Patenaude & Kupst, 2005). Although most pediatric cancer survivors demonstrate resilience and positive coping, the impact of cancer and its treatment on the central nervous system appears to heighten the distress experienced by survivors of pediatric brain tumors (Patenaude & Kupst, 2005). This psychosocial distress may be exhibited in multiple forms, including internalizing symptoms, externalizing symptoms, and social difficulties.

Internalizing Symptoms

Internalizing symptoms, including both depressive and anxious symptoms, have been studied in the context of pediatric brain tumors. For instance, researchers have found that pediatric brain tumor survivors were 1.5 times more likely than their healthy siblings to report depressive or anxious symptoms (Schultz et al., 2007), and that those diagnosed in adolescence and early young adulthood were up to two times more likely to have depressive or anxious symptoms than their healthy siblings (Prasad et al., 2015). However, it is important to note that studies such as these that utilize healthy siblings as a comparison group should be considered with caution, as there is some evidence suggesting that siblings of children with cancer are also at risk for maladjustment (Long et al., 2018). Thus, in the literature utilizing healthy sibling controls, there may be an underestimation of the extent of internalizing symptoms experienced by survivors.

A review of long-term outcomes also found that rates of diagnosed depression and anxiety disorders were higher among pediatric brain tumor survivors than normative samples (Shah et al., 2015). This suggests that not only the prevalence of symptoms, but also the severity of symptoms and related impairment may be greater among pediatric brain tumor survivors, such that psychiatric diagnoses are found at a higher rate. Further evidence also exists for serious consequences of depressive symptomology among survivors, including suicidal ideation and

suicide attempts (Brinkman et al., 2013). Indeed, estimates suggest that between ten and twelve percent of survivors experience suicidal ideation, highlighting the need for a greater understanding of suicidality in the context of pediatric brain tumors (Brinkman et al., 2013; Shah et al., 2015).

Notably, specific forms of anxiety have also been documented among this population. For instance, treatment anxiety and procedural anxiety are reportedly higher among brain tumor survivors as compared to survivors of other cancers (Sato et al., 2014). Across diagnoses, pediatric cancer survivors are also at elevated risk for posttraumatic stress disorder (Stuber et al., 2010). However, those who have received cranial radiation seem to be at particular risk, which indicates that pediatric brain tumor survivors are likely to fall in this high-risk group (Stuber et al., 2010). Although it has been documented that parents report higher levels of posttraumatic stress than survivors, an investigation of youth who have survived a pediatric brain tumor and their parents found that over a third of survivors reported clinically significant posttraumatic stress symptoms (Bruce, Gumley, Isham, Fearon, & Phipps, 2011; Kazak et al., 2004). These symptoms also appear to persist well into adulthood, with one study suggesting that long-term survivors are three times more likely than matched-controls to experience clinically significant posttraumatic stress symptoms (Seitz et al., 2010).

Reviews of the literature have also supported the developmental nature of maladjustment, with adolescent brain tumor survivors at increased risk for internalizing symptoms (Prasad et al., 2015; Turner, et al., 2009). Due to the added social and academic pressures, as well as the increase in independence and responsibility typically obtained during this time, adolescents may be particularly vulnerable to the psychological distress observed among survivors. However, it is important to note that the literature is mixed, and some research seems to suggest that children treated for brain tumors may have minimal risk for internalizing symptoms (Fuemmeler et al., 2002). Some researchers have noted a relative lack of elevated risk in this group, arguing for a

resiliency model among survivors (e.g., Phipps et al., 2014). However, the extant literature also indicates that 30% of adult survivors of childhood cancer show psychological problems, and that the estimate may be even higher for survivors of brain tumors (Recklitis, Lockwood, Rothwell, & Diller, 2006). Therefore, the current literature would suggest that it is likely that a subset of survivors are indeed at risk. However, the literature is difficult to interpret due to variability in the measurement methodologies, definitions of symptomology employed, and characteristics of the samples in which internalizing symptoms are examined (Fuemmeler et al., 2002).

Externalizing Symptoms

Although the literature is much more limited, children treated for brain tumors also appear to exhibit higher rates of externalizing symptoms. Such externalizing problems include more general behavior problems, aggression, and even conduct disorders (Fuemmeler et al., 2002; Holmquist & Scott, 2002; Turner, et al., 2009). A meta-analysis found that the incidence of behavioral problems among brain tumor survivors is approximately 28% (Shah et al., 2015). Per parent and teacher report, behavioral regulation difficulties appear to be prominent both at home and in school, at least for a subset of survivors (Hardy et al., 2018). Parent reports also suggest that survivors of astrocytomas may be more likely to exhibit rule-breaking and aggressive behaviors (Aarsen et al., 2006).

Conversely, other reports suggest that children treated for brain tumors may be at minimal or low risk for externalizing symptoms as compared to normative samples (Fuemmeler et al., 2002). It is suspected that such lowered risk is due to the physical limitations and fatigue associated with brain tumors, which may subsequently reduce the ability of youth to engage in behavioral outbursts (Fuemmeler et al., 2002). It may also be that externalizing problems are harder to identify among youth with certain physical limitations or environmental restrictions. Therefore, due to these mixed findings, it has become increasingly important to evaluate factors that

contribute to the diversity of maladaptive outcomes exhibited by survivors, including predictors of those survivors at risk for externalizing difficulties (Holmquist & Scott, 2002).

Social Problems

More recently, the literature has turned to a focus on a range of social deficits associated with brain tumor survivorship, including difficulties with social competency, antisocial behavior, relationships, and social attainment. Poor social competency appears to be a primary affected area of functioning. This has been strongly supported by systematic reviews, which demonstrate the robust deficits in social competence observed among pediatric brain tumor survivors (Fuemmeler et al., 2002; Schulte & Barrera, 2010). One specific study aimed to identify such differences in competency, and found that children off-therapy for brain tumors report greater concerns regarding social competency than normative samples, and those still in active treatment (Hardy, Willard, Watral, & Bonner, 2010). Survivors have also been found to exhibit greater antisocial behaviors, paired with reduced social competency, as compared to healthy siblings (Brinkman et al., 2012; Schultz et al., 2007). Other investigations have focused on factors that contribute to diminished social competence, such as treatment methodologies and impairments in other domains, including social-cognitive skills (Schultz et al., 2007; Willard, Allen, Hardy, & Bonner, 2017). However, it has been suggested that greater research is needed to better define and evaluate the precise social impairments that are experienced by pediatric brain tumor survivors.

Longitudinal evaluations have also sought to delineate the trajectory of social functioning. The research shows that social competence appears to decline significantly during the first year following treatment and appears to take a worsening course (Brinkman et al., 2012). Pediatric brain tumor survivors are also more likely to report having no close friends, as compared to survivors of other cancers (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005). Relatedly,

they are also likely to be rated as lower in leadership-popularity and higher in sensitivity-isolation and victimization than peers (Salley et al., 2015).

Importantly, as an assessment of the long-term implications of social difficulties following pediatric brain tumor treatment, social attainment outcomes in adulthood have also been investigated. Research suggests that pediatric brain tumor survivors, compared to siblings and survivors of non-central nervous system malignancies, appear to require more special education services, are less likely to attend college, and are more likely to be unemployed and unmarried (Gurney et al., 2009). Evidence has also accrued that indicates pediatric brain tumor survivors exhibit less independent living in adulthood (Kunin-Batson et al., 2011; Maddrey et al., 2005). Overall, the variety of these long-lasting and extensive psychosocial difficulties reported warrant a greater evaluation of the factors that may uniquely contribute to risk for these outcomes.

Predictors of Neuropsychological Late Effects

Across the literature on late effects associated with pediatric brain tumors, numerous predictors of negative outcomes have been identified. The majority of these predictors may be characterized into three primary categories, including demographic variables, disease variables, and treatment variables. Although some have been mentioned thus far, the most salient and robust predictors are summarized below.

Demographic Variables

Age at diagnosis, as well as time since diagnosis, appear to be important predictors of neuropsychological outcomes. In general, it appears that younger age at diagnosis and greater time since diagnosis are associated with worse outcomes (Fuemmeler et al., 2002; Turner, et al., 2009; Zeltzer et al., 2009). In particular, younger age at diagnosis is a salient predictor of impairments across domains of neurocognitive functioning (Spiegler et al., 2004). Since younger children have less neural maturity and are more susceptible to the neurotoxicity of cancer

treatment, it is suspected that they exhibit greater deficits than their older counterparts. These impairments in cognitive functioning may then be exacerbated as the children age and struggle to learn at the same rate as their peers (Spiegler et al., 2004). Further, the rate of decline in IQ appears to be related to age at diagnosis, with those who were diagnosed younger exhibiting greater decline (Mulhern et al., 2004). Overall, a longer time since diagnosis appears to be linked with worse intellectual outcomes (De Ruiter, Van Mourik, Schouten-Van Meeteren, Grootenhuis, & Oosterlaan, 2013). Alternatively, other reports suggest that older age at diagnosis, such as above eleven years old, may be related to worse psychosocial outcomes (Prasad et al., 2015). This indicates that age or time may differentially predict the diverse neuropsychological sequelae experienced by pediatric brain tumor survivors.

Much of the literature also indicates that females are at greater risk for neuropsychological difficulties. Females evidence greater declines in intellectual functioning and processing speed than males following pediatric brain tumor treatment (Von der Weid et al., 2003; Waber et al., 2010; Zebrack et al., 2004). An increased rate of decline in IQ has also been associated with female sex (Mulhern et al., 2004). Specific neuropsychological difficulties, including task efficiency and emotional regulation, have also been found to be related to female sex (Ellenberg et al., 2009). Similar to the general population, female sex also appears to be a risk factor for greater psychological distress (Zebrack et al., 2004). It is possible that female brains have a greater vulnerability to the effects of oncological treatments, due to hormonal differences (Jain, Brouwers, Okcu, Cirino, & Krull, 2009). However, the research is not entirely consistent, such that some investigations have shown that male survivors evidence greater impairments in processing speed, inhibitory control, and working memory (Jain et al., 2009; Kahalley et al., 2013).

Other factors, such as parent education, appear to also have unique patterns of relationships with neuropsychological sequelae. For instance, children of parents with greater education exhibit

greater social competence at diagnosis, but experience a greater decline in competency following treatment (Brinkman et al., 2012). However, Palmer and colleagues (2013) found that parent education was associated with higher baseline neurocognitive functioning, but was unrelated to change in neurocognitive functioning among survivors over time. Further, another study found that parental education was associated with achievement across academic domains for pediatric brain tumor survivors, but was unrelated to the difference observed between survivors and healthy peers (Ach et al., 2013). This may mean that parental education may be related to baseline functioning, but other factors may account for the subsequent declines exhibited by survivors.

Socioeconomic status may have a similar relationship with neuropsychological outcomes. For instance, Ach and colleagues (2013) also found that socioeconomic status was related to cognitive functioning, but was unrelated to the relative deficit experienced by survivors. However, it is important to note that parental education is often used as a proxy for socioeconomic status, thus confounding some of these results (e.g., Reeves et al., 2005). Although, lower levels of socioeconomic status do seem to have a significant association with greater levels of distress among brain tumor survivors, as would be expected given what is known about the general population (Zebrack et al., 2004). Importantly, there may be other mediating relationships with these factors, such that socioeconomic status and parent education relate to other family and patient factors that add to a child's risk for negative outcomes (Copeland, Moore, Francis, Jaffe, & Culbert, 1996).

Disease Variables

Research on the relationship between disease variables or parameters and neuropsychological outcomes in the context of pediatric brain tumors appears to be more well-documented, suggesting that certain medical factors may account for a significant portion of risk for

impairment. For instance, the disease variable of diagnosis is a particularly salient predictor, as the literature consistently demonstrates that survivors of pediatric brain tumors are at the greatest risk for maladjustment and neurocognitive sequelae, as compared to survivors of other cancers (e.g., Duffner, 2004; Macartney et al., 2014; Sato et al., 2014; Zeltzer et al., 2009). At the same time, some studies exist that suggest a lack of relationship between disease characteristics and late effects, indicating that further evaluation of the factors that contribute to different risk profiles is needed (De Ruiter et al., 2013).

Among those disease variables posited to be associated with increased risk is tumor location, with cerebral tumors resulting in greater cognitive deficits (Reimers et al., 2003). It has also been suggested that children treated for infratentorial tumors are at greater risk for neurocognitive deficits, particularly in the domains of inhibitory control and attention (Brinkman et al., 2016; Raghubar et al., 2017). Meanwhile, others have found that supratentorial tumors and those located in the hypothalamic or chiasmatic regions resulted in greater risk for psychosocial adjustment difficulties (Fuemmeler et al., 2002). Interestingly, as tumor type and location vary by age, it is possible that there is an interaction between age and tumor location effecting neuropsychological outcomes (Kieran et al., 2010).

Tumor-associated medical complications are also strong predictors of negative outcomes. For instance, declines in IQ are linked with hydrocephalus, or a build-up of fluid in the brain, which occurs frequently with brain tumor patients (Mulhern et al., 2004). Ventriculoperitoneal shunt placement, due to hydrocephalus, is also linked with poorer neurocognitive functioning (Ellenberg et al., 2009). A more recent investigation supported this finding, indicating that hydrocephalus with shunt placement was related to a 40% increase in risk for impaired intelligence and memory (Brinkman et al., 2016). Cerebellar mutism syndrome, or posterior fossa syndrome, is also strongly related to a host of neurocognitive impairments (Palmer et al., 2010). However, other studies have found no association between late effects and hydrocephalus,

suggesting that it may be a combination of factors that heighten the risk experienced by survivors (De Ruiter et al., 2013).

Treatment Variables

Lastly, multiple treatment-related variables are linked with neuropsychological late effects among pediatric brain tumor survivors. The most robust predictor of negative outcomes is radiotherapy (Fuemmeler et al., 2002; Turner, et al., 2009). The literature has consistently shown that radiation therapy results in the greatest risk for cognitive decline and the most severe impairments (Kingma et al., 2002; Packer et al., 1989; Peterson et al., 2008). Radiation has been shown to result in deficits across working memory and attention tasks, including Digit Span from the WISC and the Stroop Color-Word Test (Harila, Winqvist, Lanning, Bloigu, & Harila-Saari, 2009). When comparing the effects of surgery alone and surgery combined with radiation, children who underwent the combined treatment were the ones who displayed the greatest losses (Packer et al., 1989).

Treatment approach also influences white matter volume. Children treated with chemotherapy-only maintain greater volumes of white matter than those treated with radiation, suggesting that the effects of radiation are long-lasting and pervasive (Reddick et al., 2003). Thus, chemotherapy-only appears to result in fewer and less severe deficits than a combined chemotherapy and radiation protocol (Von der Weid et al., 2003). However, chemotherapy-only is a rare treatment plan for brain tumors; thus, the inclusion of surgery and radiation as treatment modalities may be contributing to the neuropsychological difference between survivors of brain tumors and other cancers. Further, cerebellar mutism syndrome appears to be a complication following certain treatments, suggesting that there may be an interaction between treatment-related and disease-related variables as well (Palmer et al., 2010).

Treatment intensity, including dose of radiation or chemotherapy, is also significantly related to neurocognitive deficits. Larger radiation dose and greater volume of irradiated brain have been identified as risk factors for decline in intellectual functioning (Kieffer-Renaux et al., 2007; Mulhern et al., 2004). Survivors receiving high-dose cranial radiation had significantly more problems with attention, processing speed, memory, and emotion regulation (Zeltzer et al., 2009). Craniospinal irradiation dose also appears to predict worse social functioning among survivors (Brinkman et al., 2012). New advancements in medical treatments have led to more focal irradiation, which is purported to result in improved long-term outcomes for patients. Specifically, research has suggested that children treated with proton radiation show minimal changes in IQ, whereas children treated with photon radiation experience a significant decline (Kahalley et al., 2016). Thus, continued assessment of neuropsychological outcomes is needed in order to parallel the rapidly changing medical landscape.

Relationships Across Domains

Evidently, there is a complex interplay between risk factors for neuropsychological sequelae, which may have varying relationships across domains of neurocognitive and psychosocial functioning. However, the majority of the literature on late effects for pediatric brain tumor survivors appears to present neurocognitive and psychosocial outcomes as distinct sets of symptoms, and rarely are relationships assessed *between* these areas of functioning, despite clear evidence of elevated risk in both domains. Many studies have examined neurocognitive deficits (e.g., Kahalley et al., 2013), whereas other studies investigate the psychosocial impact of pediatric brain tumors and its treatment (e.g., Gurney et al., 2009), without reference to the other areas of potential impairment.

On the other hand, some studies have evaluated both neurocognitive and psychosocial outcomes, yet the different domains are often reported independently. For instance, MaCartney and colleagues (2014) and De Ruiter and colleagues (2013) reported on psychological, social, and cognitive domains of quality of life, but did not evaluate overall profiles of impairment between domains. Schultz and colleagues (2007) reported on the relative risk for outcomes, such as depression, anxiety, and attention difficulties, without examining the potential relationship between these outcomes. Similarly, Prasad and colleagues (2015) utilized the Brief Symptom Inventory and a neurocognitive questionnaire to assess problems across domains of functioning, but neglected to examine correlations across the different measures. Indeed, the authors refer to the intercorrelation between reports of neurocognitive and psychological functioning as a limitation in the study, rather than evaluating and providing interpretations of these relationships. Further, reviews of the literature highlight the significance of both neurocognitive and psychosocial late effects, yet these papers exemplify the clear separation between the domains (e.g., Fuemmeler et al., 2002; Turner et al., 2009).

However, it is important to note that limited research has, to some extent, evaluated the relationship between neurocognitive and psychosocial outcomes. For example, Hardy and colleagues (2018) evaluated the prevalence of parent- and teacher-reported internalizing and externalizing behaviors among brain tumor survivors with and without attention difficulties. Although the direct relationship between these outcomes was not assessed, this study provides preliminary support for a relationship between neurocognitive and psychosocial outcomes. Associations between intellectual functioning and psychological and behavioral symptoms, as well as social deficits and neurocognitive impairments have also been identified among pediatric brain tumor survivors (Poggi et al., 2005; Schulte & Barrera, 2010; Willard et al., 2017). Another recent study has also found correlations between executive functioning and quality of life, but these relationships were dependent on informant (Netson et al., 2016). Other mediating factors,

such as family functioning, have also begun to be investigated as potential links between neurocognitive and psychosocial impairments (Hocking, Hobbie, Deatrick, Hardie, & Barakat, 2015).

Taken together, these findings indicate that relationships do exist between the neurocognitive and psychosocial late effects exhibited by brain tumor survivors. Further, the identification of shared risk factors for a variety of late effects, including child sex, age, and tumor location, suggests that subsets of survivors may have unique risk for certain clusters of impairments that extend across domains (e.g., De Ruiter et al., 2013; Fuemmeler et al., 2002; Zeltzer et al., 2009). However, the literature on these interrelationships is limited, and appears to focus on only specific aspects of functioning, such as quality of life or social competency (e.g., Netson et al., 2016; Schulte & Barrera, 2010). Investigations on associations across domains and predictors of such symptom profiles is clearly lacking. The complex and inconsistent findings regarding specific outcomes and risk factors may indicate that an assessment of the more intricate relationships between outcomes, beyond simple correlations, is needed.

Summary

Brain tumors, which encompass a wide variety of histologies, are the second most common cancer diagnosis among youth (Kieran et al., 2010; Siegel et al., 2016). Advancements in treatment protocols are ever-evolving, facilitating improved prognoses and long-term survival of children treated for pediatric brain tumors (DeSantis et al., 2014; Kieran et al., 2010; MacDonald et al., 2011). However, the robust literature suggests that survivors of pediatric brain tumors experience significant risk for neuropsychological late effects (Fuemmeler et al., 2002; Mulhern et al., 2004; Turner, et al., 2009; Zebrack et al., 2004; Zeltzer et al., 2009). Commonly observed impairments include reduced processing speed and attentional control, declines in intellectual functioning, lowered quality of life, greater depressive and anxious symptoms, increased social

difficulties, and decreased social attainment in adulthood (Barrera et al., 2005; Brinkman et al., 2012; Gurney et al., 2009; Hardy et al., 2015; Kahalley et al., 2013, 2016; Macartney et al., 2014; Shah et al., 2015). The risk for these sequelae appears to vary by child age at diagnosis, child sex, tumor location and type, medical complications, and treatment approach (Ellenberg et al., 2009; Kahalley et al., 2016; Palmer et al., 2010; Prasad et al., 2015; Raghubar et al., 2017; Turner, et al., 2009).

However, risk for the full constellation of late effects that pediatric brain tumor survivors may experience has received limited attention. Difficulties in neurocognitive and psychosocial functioning are often examined discretely in the literature, resulting in little understanding of the global patterns of late effects that are exhibited by survivors (Fuemmeler et al., 2002; Turner, et al., 2009). Thus, the current study aimed to evaluate the neuropsychological profiles of pediatric brain tumor survivors, and to examine predictors of these phenotypes, in an effort to better conceptualize the array of late effects that distinct categories of survivors may experience.

CHAPTER III

METHODOLOGY

Participants and Procedures

Participants are youth (N = 89) who are pediatric brain tumor survivors and were assessed within the pediatric neuropsychology clinic of an academic medical center in the Mid-Atlantic region between May 2009 and May 2018. Participants were eligible if they: (1) had a diagnosis of a brain tumor at or before the age of 18, (2) were diagnosed at least one year prior, and off-treatment for at least three months at the time of assessment, and (3) had a comprehensive evaluation conducted, which included both parent- and teacher-report of symptoms, and performance-based measures. All participants provided informed consent to have their records entered and stored in a database intended to be utilized for research purposes. Institutional review board approval was obtained to abstract demographic, medical, neurocognitive, and psychosocial data from the medical records of brain tumor survivors. All procedures adhered to the American Psychological Association's ethical guidelines.

Measures

Demographic and disease characteristics.

Demographic and disease characteristics were abstracted from the medical records of all brain tumor survivors. Relevant demographic data included child sex, child age at diagnosis, child age at evaluation, child race, and child ethnicity. Family insurance type and other indicators of

socioeconomic status were not consistently reported, and were therefore not abstracted. Relevant disease characteristics included brain tumor diagnosis, time since diagnosis, time since treatment completion, treatment types (i.e., radiation, surgery, chemotherapy), and the diagnoses of hydrocephalus, posterior fossa syndrome, and neurofibromatosis 1 (NF1). Tumor location, radiation dose, and chemotherapy type were not consistently reported, and were therefore not abstracted. For analytic purposes, all demographic and disease variables were dichotomized (e.g., race was dichotomized as Caucasian or non-Caucasian).

Parent and teacher ratings.

Child Behavior Checklist (CBCL) and Teacher Report Form (TRF). The CBCL (Achenbach & Edelbrock, 1991) and TRF (Achenbach & Rescorla, 2001) are parent- and teacher-report measures, respectively. These questionnaires assess the emotional, behavioral, and psychosocial functioning of children between the ages of six and eighteen with Likert scale items and competency ratings. Parent- and teacher-ratings were converted to T-scores, based on the standardization sample of same-aged peers. Higher T-scores suggest a greater degree of impairment, with T-scores above 63 considered to be in the Clinical range and those below considered to be normative. Parent- and teacher-reports of the Internalizing Problems and Externalizing Problems composite scores, as well as the Social Problems subscale score were used for analyses. The CBCL and TRF have shown very high inter-interviewer reliability and test-retest reliability, with good to excellent internal consistency among the scales to be utilized in the current study (Achenbach & Rescorla, 2001).

Performance-based measures.

Wechsler Scales of Intelligence. The Wechsler Scales of Intelligence provide an overall assessment of intellectual functioning, as well as measures of specific intellectual abilities (Wechsler, 2014). As this study included a wide age range of participants evaluated over the

course of a decade, intellectual functioning was assessed using the most recent age-appropriate version of the Wechsler Scales that was available at the time of assessment. The majority of participants completed the *Wechsler Intelligence Scale for Children-Fourth Edition* (*WISC-IV;* 12.36%) or the *Wechsler Intelligence Scale for Children-Fifth Edition* (*WISC-V;* 62.92%). From each version a test of immediate/working memory (Digit Span subtest), and the Processing Speed Index (PSI) were utilized. The Digit Span subtest is standardized to have an average of 10 and a standard deviation of 3, with scores below 6 falling in the "Below Average" range or lower. The PSI is standardized to have an average score of 100, and a standard deviation of 15, with scores below 80 considered to be in the "Below Average" range or lower. The Wechsler scales have demonstrated excellent test-retest reliability and good to excellent internal consistency across subtests and index scores (Wechsler, 2014).

Tower of London-DX-Drexel Version (TOL). The TOL measures visual planning and problem-solving skills among individuals seven-years-old and older, and is employed as a measure of executive functioning (Culbertson & Zilmer, 2005). Raw scores are observed during administration and are converted to normative standard scores. The Total Moves and Total Problem-Solving Time standard scores were used in analyses in the current study and assess skills in visual planning and problem-solving. The TOL has been shown to have acceptable test-retest reliability and internal consistency, as well as strong convergent and divergent validity (Culbertson & Zilmer, 2005).

Overview of Statistical Analyses

Descriptive and summary statistics were first used to detail the prevalence of neurocognitive deficits and clinically significant psychological distress, utilizing standardized cut-off recommendations. Bivariate correlations were conducted to determine if there were detectable relationships between domains of neurocognitive and psychosocial functioning.

Latent profile analysis (LPA), a person-centered data analytic approach, was conducted using Mplus version 8.1 to identify subgroups based on the observed response and performance patterns across the ten neurocognitive and psychosocial indicators (Berlin, Williams, & Parra, 2014). The indicators included both Parent-and Teacher-Reported Internalizing Problems, Externalizing Problems, and Social Problems, child performance on the Total Moves and Total Problem-Solving Time scores from the TOL, the Digit Span subtest from the Wechsler scales and the PSI from the Wechsler scales. Using maximum likelihood estimation with robust standard errors, LPA produces the probability of an individual's membership in each class of symptom profiles and estimates the most likely group membership. The classes consist of individuals with similar means on the ten continuous indicators.

Due to the flexibility and maximal information accounted for by LPA, model fit optimization was evaluated based on substantive theory and model fit criterion. Classes were added iteratively and the feasibility of 1-, 2-, 3-, 4-, and 5-class solutions were examined. Relative model fit was assessed by the Vuong-Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (VLMR), and the parametric bootstrapped likelihood ratio difference test (BLRT; Nylund, Asparouhov, & Muthén, 2007). For these tests, *p*-values less than .05 were assumed to indicate that a model with one additional class was a better fit than a model with one less class. As differences in likelihood ratio tests are likely to arise, preference was given to the BLRT, as it has been shown to produce more consistent results regarding class optimization (Nylund, Asparouhov, & Muthén, 2007).

Entropy and information criteria were also employed to assess model fit optimization. Entropy values closer to one indicate greater accuracy of classification, and thus solutions with higher entropy values were considered preferable (Geiser, 2013). The Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), and Sample Size Adjusted-BIC (SSA-BIC) were also evaluated, with lower values indicating better fit (Geiser, 2013). Additionally, a difference greater than two between the BIC of a model with one additional class and the BIC of a model with one

less class was considered to suggest a sufficient improvement in model fit (Raftery, 1995). If fit indices were discrepant, preference was given to the BIC and SSA-BIC (Henson, Reise, & Kim, 2007; Nylund et al., 2007). Additionally, replication of the best log-likelihood was confirmed for each model to avoid local maxima. The null model log-likelihood for the BLRT was also verified as equivalent to the best log-likelihood value of the model with one less class.

After the optimal class solution was identified, one-way ANOVAs with post-hoc Bonferroni tests were conducted to compare the means of participants' psychosocial and neurocognitive scores between the latent classes, in order to test for independence of samples. Lastly, the R3STEP procedure, which employs multinomial logistic regression, was utilized to assess predictors of class membership (Asparouhov & Muthén, 2015). Specifically, demographic variables including child sex, child race and ethnicity, and disease variables, including age at diagnosis, treatment type, and the presence of hydrocephalus, were tested as predictors of class membership.

CHAPTER IV

FINDINGS

Participants

The final sample included eighty-nine survivors of pediatric brain tumor who were diagnosed at an average age of 6.57 years (SD = 4.53; $M_{\text{age at evaluation}}$ = 12.60, SD = 4.41). The most common diagnosis was pilocytic astrocytoma (28.1%), followed by Medulloblastoma (21.3%), and the majority of the sample were treated with surgery (84.3%) and at least one other treatment type. Patients were primarily Caucasian (71.9%) and nearly half were female (46.1%). Demographic and disease characteristics are detailed in Table 1.

Descriptive statistics demonstrated that, overall, the sample was functioning in the average range (T<63) for psychosocial difficulties, according to both parent- and teacher-report measures. However, psychosocial difficulties were evident for a subset of patients, with 20.5% of parents reporting clinically concerning internalizing symptoms. Neurocognitive impairments were significant across measures of executive functioning, processing speed, and working memory, with nearly 30.00% of the sample demonstrating a deficit in each domain. See Table 2 for descriptive statistics. Bivariate correlations demonstrated some associations between neurocognitive variables and psychosocial outcomes, but the strength of these correlations and significance varied across domains of functioning and informant; thus, the use of LPA was supported (See Table 3 for correlation matrix).

Latent Profile Analysis

Models ranging from one to five classes were identified based on the ten indicators, and the model with four classes was found to have optimal fit. VLMR and BLRT differed in significance, so preference was given to the significant BLRT value ($p < 0.001$). AIC and BIC values both suggested a four-class solution, with a sufficient change in BIC (Raftery, 1995). Entropy was strong for the four-class solution (0.89), and none of the class sample sizes were too small (<5%). Fit statistics can be found in Table 4.

The largest class (n = 47, 52.81%) was termed the "Average" group, and was characterized by average functioning across all domains (i.e., average CBCL and TRF t-scores < 63; TOL and Wechsler scores in the Average range). The second largest class (n = 25, 28.09%) was termed the "Cognitive Deficit" group, as this group was distinguished by average psychosocial functioning (i.e., average CBCL and TRF t-scores < 63), yet evidenced some impairments in neurocognitive functioning (e.g., $M_{PSI} = 78.65$). The third group (n = 9, 10.11%) was characterized by elevated social problems (i.e., average CBCL and TRF Social Problems t-scores > 63) and significant neurocognitive impairments (e.g., $M_{Digit\ Span} = 5.14$; $M_{Total\ Problem\text{-}Solving\ Time} = 70.48$), and was therefore termed the "Social/Cognitive Deficit" group. The final group (n = 8, 8.99%) was termed the "Discrepant" group, as it was characterized by elevated parent-reported Internalizing, Externalizing, and Social Problems (average CBCL t-scores > 63), and difficulties in visual planning and problem-solving (i.e., $M_{Total\ Problem\text{-}Solving\ Time} = 77.20$; $M_{Total\ Moves\ score} = 72.08$). However, it is important to note that the "Discrepant" group demonstrated average processing speed and working memory ($M_{PSI} = 94.56$; $M_{Digit\ Span} = 10.40$). Figure 1 provides a graphical representation of profile means across domains.

Comparisons Between Profiles

All one-way ANOVAs comparing the ten psychosocial and neurocognitive indicators were significant (p's < 0.001), suggesting strong independence of profiles. Post-hoc Bonferroni tests were used with the "Average" group as the reference. Tests showed that the "Average" group scored significantly better (p's < 0.05) than all three of the other profiles across domains, with a few exceptions. The "Average" group did not differ from the "Cognitive Deficit" group (p = 1.00) or the "Social/Cognitive Deficit" group (p = 0.696) on the parent-reported Internalizing Problems scale. Additionally, the "Average" group did not differ from the "Cognitive Deficit" group (p = 0.075) or the "Discrepant" group (p = 1.00) on the Digit Span subtest, and did not differ from the "Discrepant" group on the PSI (p = 1.00). As was previously noted, the "Discrepant" group did not demonstrate deficits in the working memory and processing speed domains.

Predictors of Class Membership

Using the R3STEP Procedure, the "Average" group was chosen as the reference category, since it was the largest class with the highest functioning across measures. See Table 5 for odds estimates.

Demographics. Ethnicity predicted class membership, with those who were Hispanic/Latino less likely to be in the "Cognitive Deficit" group, as compared to the "Average" group (B = -24.03, SE = 1.65, p < 0.001). Those who were Hispanic/Latino were also more likely to be in the "Discrepant" group, as compared to the "Average" group (B = 26.59, SE = 1.65, p < 0.001). Race also predicted class membership, with those who are Caucasian having higher odds of being in the "Discrepant" class than the "Average" class (B = -27.95, SE = 0.00, p < 0.001). Child sex did not predict class membership, relative to the "Average" group.

Treatment Variables. Those treated with radiation had lower odds of being in the "Discrepant" group, as compared to the "Average" group (B = -28.80, SE = 0.00, $p < 0.001$). Chemotherapy and surgery did not significantly relate to class membership, relative to the "Average" group.

Disease Variables. A diagnosis of NF1, hydrocephalus, and Posterior Fossa Syndrome, significantly predicted class membership. Relative to the "Average" group, those with NF1 had higher odds of being in the "Social/Cognitive Deficit" group (B = 25.26, SE = 3.93, $p < 0.001$), the "Cognitive Deficit" group (B = 22.63, SE = 3.11, $p < 0.001$), and the "Discrepant" group (B = 25.24, SE = 0.00, $p < 0.001$). Those with hydrocephalus had lower odds of being in the "Discrepant" class, compared to the "Average" class (B = -23.48, SE = 0.00, $p < 0.001$). Lastly, those with Posterior Fossa Syndrome also had lower odds of being in the "Discrepant" group, relative to the "Average" group (B = -13.89, SE = 0.00, $p < 0.001$). It is important to note that no patient with NF1 had a diagnosis of hydrocephalus and/or Posterior Fossa Syndrome, which may explain why those with hydrocephalus and/or Posterior Fossa Syndrome were unlikely to be members of the "Discrepant" group. Age at diagnosis and time since diagnosis did not significantly predict class membership.

CHAPTER V

CONCLUSION

The current study evaluated psychosocial and neurocognitive functioning among pediatric brain tumor survivors across multiple domains via multi-method assessment, thus providing a comprehensive overview of the broad neuropsychological late effects. Findings were consistent with the extant literature regarding the risk for impairments among survivors, with 20.5% of the current sample demonstrating elevated parent-reported internalizing symptoms, and approximately one-third of the sample showing executive functioning deficits. However, the present study expanded upon these findings by delineating specific phenotypes of psychosocial and neurocognitive outcomes among survivors. By examining observed symptom profiles, these findings shed light on patterns of relations among neuropsychological domains that might have been missed by traditional statistical analyses that rely on correlations alone. Thus, this study is the first to employ this novel approach to understanding the complex and non-linear patterns of symptomology that are experienced in survivorship.

Four distinct profiles of psychosocial and neurocognitive functioning were identified. Approximately half of the sample (52.81%, "Average" class) was found to be functioning within normal limits across both neurocognitive and psychosocial measures, whereas the remaining half demonstrated impairments in at least one domain. The "Average" group may be conceptualized as a resilient group, who did not suffer from treatment-related late effects. However, it may b

that this group represents youth who were functioning in the above average range prior to their brain tumor diagnosis and treatment, and therefore have suffered some treatment-related impairments. Thus, consideration of these profiles in relation to premorbid functioning is necessary, and would be facilitated by future prospective investigations.

Aligned with the robust literature demonstrating neurocognitive difficulties among pediatric brain tumor survivors, the "Cognitive Deficit" class (28.09%) was the second largest class, defined by deficits across performance-based measures of neurocognitive functioning (Glass et al., 2017; Mulhern et al., 2004; Turner et al., 2009). Meanwhile, the "Social/Cognitive Deficit" class (10.11%) was distinguished by additional impairments in social functioning, per parent- and teacher-report. Thus, the distinction of this group is consistent with recent literature suggesting that a significant subset of survivors exhibit impairments, relative to typically developing children, in social competency and specifically in social-cognitive skills that require abilities to process information about others and social situations (Fuemmeler et al., 2002; Schulte & Barrera, 2010; Willard, Allen, Hardy, & Bonner, 2017).

Lastly, the "Discrepant" class (8.99%) demonstrated significantly elevated psychosocial difficulties across domains per parent-report, as well as deficits in visual planning and problem-solving skills. Interestingly, the "Discrepant" class was functioning in the average range, per teacher-report, and did not exhibit impairments in working memory or processing speed. As previous research has shown that reports of psychosocial outcomes often vary based on informant and assessment methodology, it is advantageous that the current study synthesized information from multiple sources to ascertain a more clear pattern of impairments (Ellenberg et al., 2009; Hardy et al., 2018; Kapella et al., 2015; Zebrack et al., 2004). The present finding that parent- and teacher-report of symptomology do not align for the "Discrepant" group highlights the need for data from multiple informants, in order to optimize the benefit of neuropsychological surveillance and develop a more patient-centered understanding of how these diverse reports may relate.

Consistent with the preventative model put forth by Hardy and colleagues (2017), the current study also aimed to identify observable factors that predict specific patterns of neuropsychological functioning. Importantly, the current findings suggest that children with a NF1 diagnosis were disproportionately represented in the "Discrepant" group. Previous research suggests that children with NF1 exhibit uneven neuropsychological profiles, with significant deficits in some domains while other abilities remain intact (Potvin, Hardy, & Walsh, 2015). Further, the literature suggests that psychosocial problems are prevalent, yet teachers appear to report fewer difficulties than parents among this population (Johnson, Saal, Lovell, & Schorry, 1999; Murray et al., 2007). Although the specific pattern of neurocognitive impairment observed in the current study differs from some previous reports, the uneven profiles and higher parent-reported problems exhibited by the "Discrepant" group provides support for the understanding that those with NF1 do indeed evidence a distinct phenotype (Potvin, Hardy, & Walsh, 2015).

Other predictors of class membership included ethnicity, race, treatment with radiation, and diagnoses of hydrocephalus or posterior fossa syndrome. In terms of demographics, it was found that those who were Hispanic/Latino and those who were Caucasian were more likely to be in the "Discrepant" group, compared to the "Average" group. However, it is important to note that variability in race and ethnicity was quite low, suggesting that these differences may not accurately reflect a specific ethnic or racial group's vulnerability to be classified into a certain group. It was also found that those who received radiation treatment were less likely to be in the "Discrepant" group, relative to the "Average" group. At first glance, this result may be surprising as radiation treatment is known to be associated with poorer neurocognitive outcomes (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). However, current research suggests that those with NF1 are at greater risk for radiation-related complications (Grill, Dhermain, & Habrand, 2009). Therefore, current recommendations that caution against the use of radiation among NF1

populations align with the finding that the "Discrepant" group was less likely to receive this form of treatment.

Lastly, those with hydrocephalus or posterior fossa syndrome were less likely to be in the "Discrepant" class, as compared to the "Average" class. This finding may also be surprising, as hydrocephalus and posterior fossa syndrome are medical challenges that are often associated with cognitive impairments. The most parsimonious explanation is that these diagnoses are less common among those with NF1, and thus those with hydrocephalus or posterior fossa syndrome would certainly have lower odds of being members of the "Discrepant" group. Overall, it appeared that these diagnoses did not differentiate between the other three classes, and therefore may not contribute greatly to the experience of a specific symptom profile. Further examination of the extent of medical challenges related to these diagnoses, as well as the treatments utilized, would foster a greater understanding of how hydrocephalus and posterior fossa syndrome may relate to neurocognitive and psychosocial late effects in this population.

Although the current study aimed to identify strong predictors of class membership, the present findings underscore the need for more consistent reporting of demographic and illness-related variables. Understanding the effect of ethnic/racial background and specific diagnoses on neuropsychological profiles is beneficial, yet knowledge of other factors such as tumor location, socioeconomic status, and radiation dose could have added to the clinical utility of the current evaluation. Although these predictors are not modifiable factors, they would likely facilitate targeted screening and subsequent early intervention for those individuals at risk for specific profiles that consist of varying impairments. For instance, knowledge of tumor location may distinguish those youth likely to be in the "Cognitive Deficit" class, from youth with additional risk for social problems (i.e., "Social/Cognitive" class), which could aid in clinical decisions related to further testing and psychological treatment.

The present study adds greatly to the literature on the interrelationships between neurocognitive and psychosocial late effects, yet there are some limitations that necessitate the replication of these findings and subsequent confirmation of the neuropsychological profiles that are delineated here. In particular, confirmatory analyses of these profiles among both larger samples, and more diverse samples is indicated, especially in regard to demographic and disease characteristics. Additionally, replication among more homogenous groups, such as particular age groups or tumor types, is warranted. As the current study consists of a clinic-referred sample, these children may be more economically advantaged, or may be more impaired than the general survivorship population, further necessitating assessment of samples from other referral sources. In addition, it is noted that this preliminary study conducted with a sample size less than 100 should be interpreted with caution when considering generalizability of the findings (Wurpts & Geiser, 2014). However, small sample size was adequately compensated for, as the current sample size was above the minimum necessary (>70), the profiles were shown to have strong independence, and a large number of indicators were utilized.

Prospective evaluations of youth, starting with initial assessments prior to treatment, would also be beneficial, especially as untoward effects of surgery have been documented, even prior to radiotherapy or chemotherapy (Glass et al., 2017). Additionally, the parent- and teacher-report measures, as well as the performance-based assessments, chosen for this investigation were based on the data available due to the standard assessment battery utilized in the neuropsychology clinic. Prospective assessments specifically designed to include a more extensive battery of measures would be advantageous. Future examinations of the change in neuropsychological functioning experienced by these distinct classes will also provide greater insight into the need for targeted screening and intervention. It is also essential that additional predictors of class membership are examined, as this would add to the clinical utility of the observed phenotypes. Specifically, identification of modifiable factors that predict typologies may better facilitate the

design of optimally tailored interventions. Investigation of parent factors, such as parent distress, which are known to relate to child psychological outcomes, may also lead to a greater appreciation for the need for family-centered care (Drotar, 1997). Thus, the current study is a preliminary step toward the future development of effective and efficient assessment and treatment of pediatric brain tumor survivors who are at significant risk for specific patterns of psychosocial and neurocognitive impairment.

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APPENDICES

Table 1. Demographic and illness information of sample ($N = 89$)

Variables	N/M	%/SD
Gender		
Female	41	46.1%
Race/Ethnicity		
Caucasian	64	71.9%
African-American	12	13.5%
Asian	5	5.6%
Native American	1	1.1%
Multi-Racial	2	2.2%
Other	5	5.6%
Hispanic/Latino	8	9.0%
Age at Diagnosis (years)	6.57	4.53
Age at Evaluation (years)	12.60	4.41
Years Since Treatment Completion	4.48	3.41
Diagnosis		
Pilocytic Astrocytoma	25	28.1%
Medulloblastoma	19	21.3%
Ependymoma	11	12.4%
Low-Grade Glioma	8	9.0%
Other	26	29.21%
Treatment Types[†]		
Surgery	75	84.3%
Radiation	53	59.6%
Chemotherapy	65	73.0%
Other Diagnoses		
Posterior Fossa Syndrome	8	9.0%
Hydrocephalus	27	30.34%
Neurofibromatosis 1	7	7.9%

Note. [†]Treatment types are not exclusive, as patients may have received multiple treatment methods.

Table 2. Descriptive Statistics for indicator variables of the entire sample.

Variable Test Measures	Observed Mean (SD)	% Above Clinical Cut-off
Psychosocial Variables		
Internalizing Problems (CBCL parent-report)	54.53 (11.41)	20.5%
Externalizing Problems (CBCL parent-report)	48.50 (11.33)	11.4%
Social Problems (CBCL parent-report)	58.54 (9.13)	27.5%
Internalizing Problems (TRF teacher-report)	50.34 (10.10)	10.9%
Externalizing Problems (TRF teacher-report)	49.11 (8.81)	6.2%
Social Problems (TRF teacher-report)	55.85 (7.77)	16.1%
Neurocognitive Variables		
Total Move Score (TOL)	85.89 (18.01)	33.3%[a]
Total Problem Solving Time (TOL)	85.06 (18.36)	38.9% [a]
Digit Span (Wechsler Scale Subtest)	8.77 (3.15)	33.7%*
Processing Speed Index (Wechsler Scale Index Score)	86.25 (14.87)	33.3%**

Note. CBCL = Child Behavior Check List; TRF = Teacher Report Form; TOL = Tower of London

Note. [a]Cut-off used for TOL scores was the Borderline range (70-79) or below.*Cut-off used for Digit Span was the Below Average range (5-7) or below. **Cut-off used for PSI was the Very Low range (70-79) or below.

Table 3. Bivariate correlations

Variables	1	2	3	4	5	6	7	8	9
1. Internalizing Symptoms (CBCL)	-								
2. Externalizing Symptoms (CBCL)	0.563***	-							
3. Social Problems (CBCL)	0.648***	0.729***	-						
4. Internalizing Symptoms (TRF)	0.178	0.246	0.241	-					
5. Externalizing Symptoms (TRF)	0.216	0.398**	0.354**	0.567***	-				
6. Social Problems	0.041	0.326*	0.328**	0.594***	0.658***	-			
7. (TRF)									
8. Total Moves Score (TOL)	-0.063	-0.329**	-0.192	-0.270	-0.304*	-0.333*	-		
8. Total Problem-Solving Time (TOL)	-0.044	-0.264*	-0.255*	-0.393**	-0.335*	-0.402**	0.625***	-	
9. Digit Span (Wechsler Scales)	-0.088	-0.216*	-0.082	-0.213	-0.137	-0.396**	0.165	0.170	-
10. Processing Speed (Wechsler Scales)	0.423	-0.115	-0.084	-0.159	-0.180	-0.352**	0.151	0.212	0.595***

Note. *p-value < 0.05, **p-value < 0.01, **p-value < 0.001

Table 4. Fit statistics for neurospsychological latent profile analysis.

Classes	BIC[b]	Δ BIC	Sample Size Corrected BIC	AIC[a]	Δ AIC	Bootstrap likelihood ratio different test	P value	Vuong-Lo-Mendell-Rubin test	P value	Entropy
1	5785.859	-	5722.742	5736.086	-	-	-	-	-	-
2	5683.544	102.315	5585.713	5606.396	39.69	-2848.043	<0.001	-2848.043	0.0725	.861
3	5667.461	16.083	5534.917	5562.939	43.457	-2772.198	<0.001	-2772.198	0.4188	.880
4	**5663.890**	**3.571**	**5496.631**	**5531.992**	**30.947**	**-2739.469**	**<0.001**	**-2739.469**	**0.4908**	**.891**
5[c]	-	-	-	-	-	-	-	-	-	-

Note. [a] AIC: Akaike Information Criteria. [b] BIC: Bayesian Information Criteria. [c] An error message about unstable parameter estimates was produced for this model. *Note:* Bold row was chosen model.

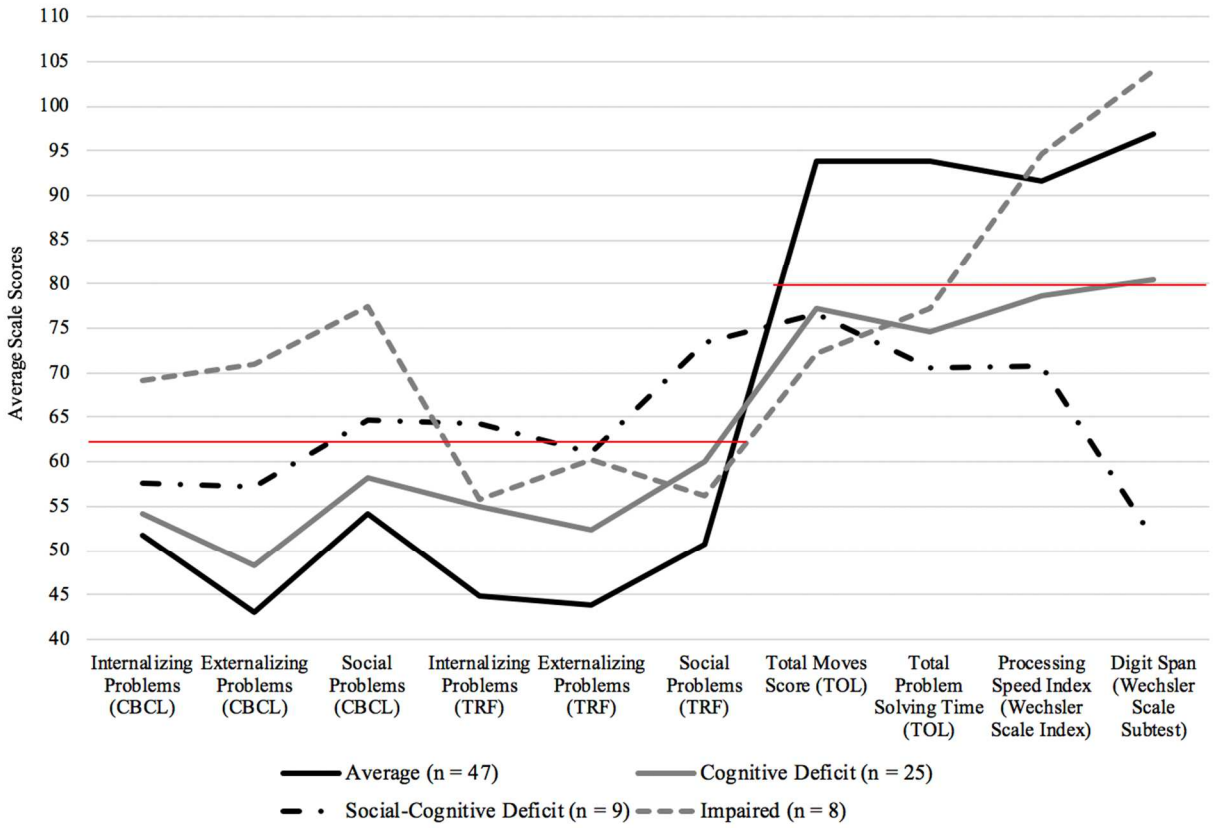

Figure 1. Psychosocial and neurocognitive domain scores by latent profile.
Note. To improve visual depiction of scores, average Digit Span scores were multiplied by 10.
Note. Red lines indicate clinically concerning cut-offs (i.e., CBCL and TRF t-scores > 63; TOL and Wechsler scale scores < 80).

Table 5. Multinomial logistic regression for four class latent profile model using the R3STEP procedure.

	Cognitive Deficit Class			Social/Cognitive Deficit Class			Discrepant Class		
	Log Odds	**S.E.**	***p***	**Log Odds**	**S.E.**	***p***	**Log Odds**	**S.E.**	***p***
Predictors									
Child Age at Diagnosis	-0.030	0.109	0.785	-0.237	0.163	0.146	-0.218	0.201	0.278
Years Since Diagnosis	-0.004	0.136	0.975	-0.178	0.261	0.495	0.421	0.436	0.334
Child Sex	-0.355	0.843	0.673	-0.925	1.152	0.422	1.974	1.556	0.204
Child Ethnicity	-24.030	1.646	0.000	-0.652	1.881	0.729	26.594	1.646	0.000
Child Race	0.155	0.782	0.843	1.466	1.898	0.440	-27.945	0.000	0.000
Radiation	-2.140	1.459	0.142	0.219	2.206	0.921	-28.803	0.000	0.000
Chemotherapy	0.849	1.142	0.457	1.739	2.699	0.519	-4.537	2.888	0.116
Surgery	-1.519	1.125	0.177	1.234	1.218	0.311	-2.985	3.283	0.363
Hydrocephalus	-0.251	0.953	0.792	-0.652	1.429	0.648	-23.475	0.000	0.000
Posterior Fossa Syndrome	3.148	3.674	0.392	3.433	2.142	0.109	-13.888	0.000	0.000
Neurofibromatosis 1	22.633	3.107	0.000	25.245	3.933	0.000	25.243	0.000	0.000

Note. ‘‘Average class” is the reference category for latent classes. Log odds = estimate for categorical latent variable multinomial logistic regressions. S.E.= standard error.

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