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Executive Functions and Cardiorespiratory Fitness in Survivors of Pediatric Posterior Fossa Tumor

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ABSTRACT

As survival rates for pediatric posterior fossa tumor have improved, issues related to survivorship have become increasingly important. Foremost among these are cognitive difficulties, particularly in the domain of executive functions. The first manuscript reports on a systematic, comprehensive literature review of studies examining executive deficits in survivors of pediatric posterior fossa tumor, including the intervention studies that have attempted to ameliorate these difficulties. The second manuscript establishes the safety and feasibility of peak cardiorespiratory fitness testing in a cohort of pediatric posterior fossa tumor survivors. Survivors had lower fitness than typically developing children and children with cystic fibrosis, and similar fitness levels as children with chronic heart disease, according to published normative data. The third manuscript reports on the neural substrates recruited by pediatric posterior fossa tumor survivors to accomplish a working memory task, which were quite similar to those recruited by typically developing children and adults in the literature. Higher cardiorespiratory fitness was related to better executive functioning across measures. Aerobic exercise may be an effective intervention strategy to address executive function deficits in pediatric posterior fossa tumor survivors; future intervention studies should further explore this possibility.

Keywords: Pediatric brain tumor; Executive functions; Working memory; Cardiorespiratory fitness; Neuropsychology; Cranial radiation therapy.

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INTRODUCTION

The research project described in this document is a comprehensive investigation of the relationship between executive functions and cardiorespiratory fitness in survivors of pediatric posterior fossa tumor. We begin by synthesizing the extant literature describing executive deficits in this population and its neural underpinnings. Next, we report original data on cardiorespiratory fitness of a cohort of pediatric posterior fossa tumor survivors. Then, we describe functional magnetic resonance imaging (fMRI) data of working memory, an area of executive functions, in pediatric posterior fossa tumor survivors. Additionally, we report on the relationships between behavioral and neural measures of executive functions and cardiorespiratory fitness in our cohort of pediatric posterior fossa tumor survivors.

I. Pediatric Posterior Fossa Tumor

Brain tumor is the second most common type of childhood cancer, accounting for approximately 20% of all diagnoses (Kaatsch, 2010). Brain tumors vary widely according to location, size, and histological composition, with tumors arising in the posterior fossa being the most common type of childhood brain tumor (Crawford, MacDonald, & Packer, 2007). The advent of multimodal treatment has significantly increased survival rates in the past few decades, even up to 90% for average-risk pediatric medulloblastoma, the most common posterior fossa tumor in children (Crawford et al., 2007). As a result, survivorship issues have become increasingly important. The consequent long-term morbidities of multimodal treatment (termed "late effects") may be severe and include endocrine, neurological, hearing/visual, and especially cognitive dysfunction (Anderson, 2005). While survivors of childhood posterior fossa tumor treated with surgical resection alone have also been noted to show cognitive difficulties (Ronning et al., 2005), multimodal therapy including cranial radiation therapy (CRT) is typically associated with the most notable cognitive decline (Spiegler et al., 2004). For example, a recent national trial reported average IQ declines of 4.3 points per year in pediatric medulloblastoma survivors, in spite of decreases in CRT dosage (Ris et al., 2001). These cognitive deficits are thought to result from a failure to learn at an age-appropriate rate, rather than the loss of already-encoded knowledge (Palmer et al., 2001), and attempts to address these deficits through cognitive and pharmacological intervention have yielded mixed results (Butler et al., 2008; Thompson et al., 2001). Current literature indicates that CRT directly impacts the neuroanatomical substrates of executive functions such as attention and working memory, which over time results secondarily in decreased IQ and academic achievement scores (Butler & Mulhern, 2005; Palmer 2008).

II. Executive Functions

Executive functions can be conceptualized in four main components: (1) volition; (2) planning (e.g., working memory, organization); (3) purposive action (e.g., inhibition, set-shifting); and (4) effective performance (e.g., self-monitoring; Lezak, 2004). The beginnings of executive functions have been studied in infants and toddlers (e.g., Marcovitch & Zelazo, 2009), and they are widely considered to continue developing into young adulthood (Luna et al., 2001). Historically, the prefrontal cortex has been implicated as the mediator of executive functions such as working memory, selective attention, and response inhibition (Goldman-Rakic, 1987; Fuster 1989, Diamond, 1988).

Lesion studies and studies using electrophysiological and neuroimaging measures have corroborated the importance of prefrontal areas for accomplishing working memory tasks (Tsuchida & Fellows, 2009; Voytek & Knight, 2010; Kessels, Postma, Wijnalda, & de Haan, 2000). This has been shown across development, with a cohort of children ages 9-11 showing similar patterns of activation as adults during an fMRI working memory task (Casey et al., 1995). Executive functions continue to develop across adolescence and into adulthood (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). This corresponds with neuroanatomical changes seen in late childhood and adolescence; for instance, the linear increase in white matter volume and the substantial decreases in synaptic connections resulting in increased neural efficiency (Woo et al., 1997; Barnea-Goraly et al., 2005; Giedd et al., 1999). Thus, the development of executive functions appears to co-occur with increasing myelination (white matter), particularly in the frontal lobes.

Although whole brain CRT results in equal amounts of radiation to all parts of the brain, the frontal lobe may be more susceptible to radiation-induced injury. One diffusion tensor imaging (DTI) study examined fractional anisotropy (FA), a marker of white matter integrity, in pediatric medulloblastoma survivors and found that frontal lobe FA was more significantly reduced compared with parietal lobe FA, although they had received the same dose of radiation (Qiu et al., 2007). In addition, decreased normal appearing white matter volume in the bilateral prefrontal cortices has been shown to correlate with multiple indices of sustained attention in survivors of malignant brain tumor treated with CRT (Mulhern et al., 2004). In a longitudinal structural imaging study, pediatric medulloblastoma survivors ages 6-12 years who had undergone whole-brain CRT with a boost to the posterior fossa region were compared with healthy control subjects (Reddick et al., 2005). Not only did the medulloblastoma survivors have reduced white matter volume, but they also showed relative decreases in white matter over time, while the control group showed a normal rate of increase in white matter over time.

The susceptibility of white matter to CRT-induced injury may be related to reduced vasculature density in white matter compared to grey matter (Reinhold et al., 1990). In adults, positron-emission tomography (PET) studies have noted the cerebral blood flow to be lower in the frontal lobe compared with temporal, parietal, and occipital lobes (Ito et al., 2003). As a result, the frontal lobe may be especially prone to insufficient perfusion after CRT-induced white matter damage (Qiu et al., 2007). Because the myelination process continues throughout adolescence and young adulthood, particularly in the frontal lobes (Ullen, 2009), the neuroanatomical substrates of executive functions may have increased vulnerability to injury and delayed development after receiving CRT in childhood.

III. Exercise and Cognition

While much literature has chronicled the neurocognitive sequelae of diagnosis of and treatment for pediatric brain tumor, the few studies attempting to remediate these deficits have been met with somewhat limited success, particularly in the domain of executive functioning. Physical exercise has been linked with various physiological benefits, including improvements in cardiovascular and metabolic functioning; it has also been associated with improved cognitive outcomes in some populations such as older adults (see Colcombe & Kramer, 2003 for a meta-analysis). The relationship between exercise and cognition has been examined at various levels including translational and human research throughout development, and suggests an as-yet-unexplored potential intervention for executive deficits in survivors of pediatric brain tumor.

Translational models using rodents have suggested that exercise increases brain availability of several types of growth factors: Brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial-derived growth factor (VEGF). These growth factors modulate such outcomes as angiogenesis, neurogenesis, and improved learning, all associated with exercise (Cotman et al., 2007). One likely mechanism through which exercise affects these growth factors is by reducing the circulation of pro-inflammatory cytokines, which impair circulation of BDNF and IGF-1 (Tong et al., 2005).

Voluntary exercise has been shown to improve performance on cognitive tasks and increase BDNF in cortically injured rats (Griesbach et al., 2008). Furthermore, the improved cognitive performance was dependent upon increases in BDNF (Griesbach et al., 2009). Particularly relevant to childhood cancer survivors is a study that examined the effects of voluntary running on neurogenesis after irradiation of the young mouse brain (Naylor et al., 2008). Mice who were allowed access to a running wheel showed restored precursor cell and neurogenesis levels, and in fact, the CRT-induced structural damage to neurons in the hippocampus was reversed by exercise. These changes were seen on a behavioral level as well, with irradiated mice that were allowed to exercise performing on a similar level to non-irradiated mice, while the irradiated mice that did not exercise performed far worse.

Translational research has examined the relationship between neurogenesis and exercise in the hippocampus due to the similarities between rodent and human hippocampi. However, investigating executive functions in rodents is difficult due to the anatomical and functional differences between rodents' and humans' frontal lobes. In addition, as the magnitude of executive functions in humans far outweighs that of rodents, a mouse model may not be sufficient for a comprehensive examination of the effects of exercise on executive functions. Nevertheless, reports of the neurochemical cascade of events resulting from exercise in translational research can inform and enhance our understanding of cognition and exercise research in human subjects.

Findings across studies of cognition and exercise in aging humans have yielded equivocal results (Smiley-Oyen, 2008). However, this may be due to the use of cognitive outcomes not particularly sensitive to the effects of exercise. In a landmark meta-analysis, Colcombe & Kramer (2003) found that across studies with older adults, the strongest effect of exercise was found for executive control tasks, as opposed to knowledge-based, visuospatial, or speed tasks. These findings supported Kramer and colleagues' (1999) "selective improvement" hypothesis, which suggests that aerobic exercise leads to select, rather than generalized, cognitive benefits, specifically in executive functions.

Cardiorespiratory fitness is a relatively long-term, stable trait, and its effect on executive functions has been shown to be independent from, and stronger than, that of acute aerobic exercise in adolescents (Stroth et al., 2009). In preadolescent, typically developing children, greater cardiorespiratory fitness has been associated with better performance on all three conditions of the Stroop task (i.e., word reading, color naming, and incongruent color naming), independent of IQ and other personal and health demographic information (Buck, Hillman, & Castelli, 2008).

A number of intervention studies have attempted to isolate the effects of aerobic exercise training programs on cognitive abilities in young people, with varying success. In a compilation of the findings of such studies (Tomporowski et al., 2007), a pattern emerged similar to Colcombe & Kramer's (2003) meta-analysis of exercise studies in older adults, such that executive function outcome measures were more often improved by exercise interventions than were other cognitive outcome measures. This review concluded that executive functions are the most likely cognitive domain to benefit from aerobic exercise programs in young people, as has been hypothesized in the aging population.

IV. Specific Aims

Specific Aim 1: Describe nature and extent of executive function deficits reported in studies with pediatric posterior fossa tumor survivors. This was accomplished through the first paper, which synthesizes extant studies reporting on executive functions within this population. In addition, this paper presents a conceptual model, derived from the literature, representing contributing factors to executive deficits in pediatric posterior fossa tumor survivors as well as intervention studies to address these deficits.

Specific Aim 2: Examine the physical fitness of a cohort of pediatric posterior fossa tumor survivors who received CRT, and compare their fitness levels with published norms. This was accomplished through the second manuscript, which reports on VO_2max, or peak cardiorespiratory fitness, testing with this population. We employed a standardized protocol using a cycle ergometer, obtaining data regarding heart rate, lung capacity, and cardiorespiratory fitness for each participant. The safety and feasibility of this type of fitness testing with pediatric posterior fossa tumors was established, and their fitness levels were found to be below expected levels compared to published norms for typically developing children and some pediatric chronic illness populations.

Specific Aim 3: Examine the brain responses associated with executive functions, specifically working memory, in pediatric posterior fossa tumor survivors, and investigate the relationship between cardiorespiratory fitness and working memory in this population. This was accomplished through the third paper, which presents fMRI data from a working memory task in our cohort of pediatric posterior fossa tumor survivors. This paper also demonstrates evidence that cardiorespiratory fitness was related to executive functioning in pediatric posterior fossa tumor survivors across neural, behavioral, and parent-report measures.

Through the studies reported here, we hope to establish the rationale, although from preliminary data, for a randomized controlled trial to examine the impact of aerobic exercise on executive functions in pediatric brain tumor survivors.

EXECUTIVE DYSFUNCTION IN PEDIATRIC POSTERIOR FOSSA TUMOR SURVIVORS: A SYSTEMATIC REVIEW OF NEUROCOGNITIVE DEFICITS AND INTERVENTIONS

by

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Abstract

Improved medical therapies have increased survivorship rates for children with posterior fossa tumors; resultantly, morbidities associated with survivorship, such as executive function deficits, have become increasingly important to identify and address. Executive dysfunction can impact academic achievement as well as functional outcomes. We summarize studies describing executive functioning deficits in pediatric posterior fossa tumor survivors who received cranial radiation therapy and intervention studies that have targeted executive functioning deficits. Previous theoretical models describing the etiology of these deficits are reviewed, and a new, more comprehensive model is proposed. Future research should move towards incorporating neuroimaging, longitudinal designs, and multiple informants.

Introduction

Childhood brain tumors, the second most common type of childhood cancer, account for approximately 20 percent of the pediatric oncology population (Kaatsch, 2010). The overall incidence of pediatric brain tumor is approximately 4.5 in 100,000, with males comprising about 57 percent of the population (CBTRUS, 2008). Medulloblastoma, a tumor arising in the posterior fossa (PF), is the most commonly occurring brain tumor in childhood (Crawford, MacDonald & Packer, 2007). Other tumors typically occurring in the PF include ependymoma and astrocytoma. Surgical resection is standard treatment for all types of malignant PF tumors, and cranial radiation therapy (CRT) is considered standard for most medulloblastoma and ependymoma patients over the age of three years (Muzamdar & Ventureyra, 2010). By its very nature, a PF tumor can have a profound impact on children's neurocognitive status given its location within the brain. Evidence of this has been substantiated by studies showing neurocognitive deficits in PF tumor survivors treated with surgical resection only (Levisohn et al., 2000; Riva & Giorgi, 2000; Steinlin et al., 2003; Ris et al., 2008; Zuzak et al., 2008). Secondary effects may also occur, compounded with those related to surgical resection, when CRT is a part of the treatment regimen.

Improved medical technology including CRT has resulted in increased five-year survival rates for children diagnosed with PF tumors, and heightened the importance of functional outcomes and quality of life after completion of treatment (American Cancer Society, 2007). Nonetheless, pediatric PF tumor survivors experience significant treatment-related late effects across multiple domains of functioning including neurological, endocrinologic, motor, and neurocognitive difficulties (Anderson, 2005;

Aarsen et al., 2009; Gurney et al., 2003). These late effects are generally chronic in nature and tend to worsen over time. The repercussions of these late effects often leave PF tumor survivors unable to manage their complex health problems independently and to function autonomously in society (Ellenberg et al., 2009).

Of particular concern following CRT is the impact of neurocognitive deficits in the domain of executive functions (Riva & Giorgi, 2000; Aarsen et al., 2004; Maddrey et al., 2005). Executive functions are a diverse set of cognitive processes broadly conceptualized according to four primary domains: volition, planning (e.g., working memory, organization), purposive action (e.g., inhibition, set-shifting), and effective performance (e.g., self-monitoring; Lezak, 2004). However, most neurocognitive tests of executive functions focus on the domains of attention, working memory, processing speed, and "general executive functions," a term encompassing planning, metacognition, and problem-solving abilities. Developmentally these processes have been studied in infants and toddlers (e.g. Marcovitch & Zelazo, 2009), and are widely considered to continue developing into young adulthood (Blakemore & Choudhury, 2006; Luna et al., 2001).

Neuroanatomically, the prefrontal cortex has been implicated in the principal component processes of executive function, such as working memory, attention, and response inhibition (Goldman-Rakic, 1987; Fuster, 1989; Diamond, 1988). In fact, in one investigation children ages 9 to 11 years exhibited similar patterns of prefrontal neural activation as an adult group on a working memory task (Casey et al., 1995). Comparable activation patterns in the prefrontal cortex on a response inhibition task have also been observed in children between the ages of 7-12 years and adults, although children had more widely distributed activation overall (Casey et al., 1997). Such distributed patterns of activation in children may be related to the maturation of executive function processes. Development of these processes corresponds with neuroanatomical changes seen in late adolescence, such as the proliferation and subsequent pruning of synaptic connections during puberty (McGivern et al., 2002).

Histological studies of monkey prefrontal cortices have shown synapse proliferation in the subgranular layers of the prefrontal cortex just before puberty. A plateau phase is postulated to occur during puberty with subsequent synaptic pruning and reorganization (Woo et al., 1997). Structural imaging comparing children with adolescents has found larger volume of grey matter in the frontal and parietal cortices during childhood, which declines during adolescence and is replaced by greater volume of white matter in these regions (Sowell et al., 1999). White matter volume has been shown to increase linearly over time during late childhood and adolescence (Barnea-Goraly et al., 2005; Giedd 2008). These findings align with a study showing that the behavioral performances of 11-17 year-olds on tasks of selective attention, working memory, and problem-solving improved linearly across the age span with older participants performing better (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). Additional studies have substantiated improvements in executive functions during the course of adolescence in tasks of inhibition (Luna et al., 2004), working memory (Luciana, Conklin, Cooper, & Yarger, 2005), and processing speed (Luna et al., 2004). Thus, the development of executive functions appears to co-occur with increasing myelination (i.e., white matter), particularly in the frontal lobes.

A growing body of literature has examined neurocognitive sequelae status post completion of CRT for childhood PF tumor survivors. Whole brain CRT results in equal amounts of radiation to all parts of the brain; however, the frontal lobe is more susceptible to radiation-induced injury. One study examined white matter fractional anisotropy (WMFA), a marker of white matter integrity, in pediatric medulloblastoma survivors and found that frontal lobe WMFA was more severely reduced compared with parietal lobe WMFA, although all parts of the brain had received the same dose of radiation (Qiu et al 2007). In addition, decreased normal appearing white matter volumes in the bilateral prefrontal cortices and right frontal cortex has been shown to correlate with multiple indices of sustained attention in survivors of malignant brain tumor treated with CRT (Mulhern et al., 2004a). A longitudinal structural imaging study, comparing pediatric medulloblastoma survivors ages 6-12 years who had received whole-brain CRT plus a boost to the posterior fossa region with healthy control subjects (Reddick et al., 2003), indicated that the survivors had reduced white matter volume. In fact, they showed relative white matter decreases of -1.1% per year, while the control group showed a normal rate of white matter growth at 5.4% per year. Interestingly, the cohort of medulloblastoma survivors who were 12 years and older at the time of radiation showed white matter volume and growth trajectories comparable to the age-matched healthy control group. This suggests that white matter development is particularly susceptible to radiation during childhood, and may not be as vulnerable when exposed after age 12 years.

The susceptibility of white matter to CRT-induced injury may be related to reduced vasculature density in white matter compared to grey matter (Reinhold et al., 1990). In normal adults, positron-emission tomography (PET) studies have noted cerebral blood flow to be lower in the frontal cortices compared with temporal, parietal, and occipital cortices (Ito et al., 2003). As a result, the frontal lobe may be especially prone to insufficient perfusion after CRT-related white matter damage (Qiu et al., 2007). Because the myelination process continues throughout adolescence and young adulthood, particularly in the frontal lobes (Ullen, 2009), the neuroanatomical substrates of executive functions may have increased vulnerability to injury and delayed development after irradiation.

In addition to the effects of CRT, injury of the PF including a tumor and its resection may be associated with cerebellar cognitive affective syndrome (CCAS) which can involve language disturbances, blunting of affect, disinhibited behavior, spatial cognition deficits, and particularly executive function deficits (Schmahmann & Sherman, 1998). Several studies have found marked executive function deficits in survivors of PF tumor treated with surgical resection only (e.g. Levisohn et al., 2000). The pathophysiology of these executive deficits remains unclear; however, a recent neuroimaging investigation found decreased cerebral perfusion in frontal areas of the brain following PF tumor resection (De Smet et al., 2009). Thus, it is plausible that the resection of a PF tumor and subsequent CRT may additively exacerbate hypoperfusion in the frontal lobes. The exact etiology of CCAS, however, has yet to be defined.

In addition to treatment variables, neurocognitive function post completion of treatment is also impacted by other child-specific risk factors. For example, female gender and younger age at treatment have been associated with poorer outcomes (Mulhern et al., 2004a; Mulhern et al., 2001; Maddrey et al., 2005; Ellenberg et al., 2009). Few studies have had the statistical power to adequately investigate the impact of various child-specific factors on executive function deficits, however. Clearly, this is an area that warrants further study.

Several studies have designed interventions to ameliorate executive deficits in pediatric brain tumor survivors, only one specific to PF tumor survivors, but with limited success. Extant literature describing both deficits and interventions will be delineated in the present review. Following the literature review, we describe two published theoretical models of executive function deficits in pediatric brain tumor survivors who received CRT. The limitations of these models are addressed through a new proposed model, incorporating the findings of the present review, that provides a more comprehensive explanation of the neuroanatomical, neurocognitive, and contextual factors affecting the executive functions of pediatric PF tumor survivors who have received CRT.

Methods

Literature searches were first conducted within PubMed, PsychInfo, and the Cochrane Controlled Trials databases using all possible combinations of the following search terms: "pediatric" or "childhood" + "brain tumor" or "posterior fossa tumor" + "executive function" or "neurocognitive" or "cognitive" or "attention". Inclusion criteria for studies were: (1) Examined some aspect of executive functions in pediatric brain tumor survivors or intervention to improve executive functions, with "executive functions" being defined as attention, working memory, processing speed, or general executive functions (e.g. planning, problem-solving); (2) Inclusion of only PF tumor survivors who had received CRT, or analyzed a cohort of PF survivors who all received

CRT separately from other diagnoses and treatment types (except in intervention articles due to limited number of studies); (3) Study included original data; and (4) Inclusion of only participants that were off-treatment.

Initial searches using the aforementioned combinations of search terms yielded 260 peer-reviewed scientific articles. Of these, 14 met all inclusion and no exclusion criteria. The bibliographies of these 14 articles were subsequently perused and potential articles of interest not found in the initial search stage were examined. Resultantly, three additional articles were found to meet inclusion criteria. In total, 17 articles are analyzed in the present review (See Tables 1-5). Articles will be summarized by the domain of executive functions examined. Limitations inherent to each study may be found in the corresponding tables. When we list "small sample size," we refer to a study's overall number of participants as being below the typical rule for adequate statistical power given the analyses utilized. When we list "heterogeneity in terms of treatment/age at diagnosis/tumor type/etc." it means that the cohort differed amongst themselves on this variable, and thus it is a potential confounding variable in assessments. Other limitations, such as "no control group," "unequal group sizes," or "missing data" are unambiguous.

Literature Review

Attention

Attention is a cognitive task involving allocating processing resources in order to selectively focus on one aspect of the environment while ignoring others (Anderson, 2004). Various models have been proposed to describe this multidimensional construct. Mirsky's original model (Mirsky et al., 1991), as one example, included such abilities as focus/execute, sustain, encode, and shift. Attention is key for performing most tasks in daily life, and is particularly relevant to children because it is crucial for learning. Since subsequent learning-related processes such as permanent encoding and recall cannot take place without basic attentional processes, children with attention problems may miss important information in the classroom and consequently do poorly in school. This may affect not only their immediate academic progress but also their friendships, self-esteem, and future educational achievement. Attention deficits have been well documented in pediatric PF tumor survivors who received CRT, with the majority of studies documenting significant attention deficits (Table 1). In one such study, Ronning, Sundet, Tonnessen, Lundar, and Helseth (2005) compared the attentional abilities of 11 childhood medulloblastoma survivors treated with surgery, chemotherapy, and CRT (whole brain = 27.0-35.0 Gy; with posterior fossa boost = 45.0-47.0 Gy) with 12 childhood astrocytoma survivors who had received surgical resection only. While both groups performed well below the normative means, the medulloblastoma group performed more poorly on all three measures. Given the small sample size, and corresponding low statistical power, this finding is particularly noteworthy and suggests greater impairment in attentional processes for PF tumor survivors to be associated with CRT.

In another study, Mabbott, Snyder, Penkman and Witol (2009) specifically examined selective attention, or the ability to attend to particular stimuli while filtering out irrelevant information (Pashler, 1988). A cohort of PF tumor survivors who received CRT (whole brain = 0-3600 cGY, and 5110-5580 cGY to the PF) was compared with a group of PF tumor survivors who were treated with surgical resection only, with a non-CNS tumor group, and with a healthy control group. Overall, both PF tumor groups performed worse than the non-CNS tumor and healthy control groups on tasks of selective attention. Further analysis showed that both the PF tumor groups as well as the non-CNS tumor group had slower reaction times compared to the healthy control groups. Additionally, the PF tumor group treated with CRT showed increased error rates when a target was present compared to the non-CNS tumor and healthy control groups, but did not differ from the PF tumor group treated with surgery only. As most studies in this area have investigated sustained attention in this population, Mabbott et al.'s study of selective attention adds to the body of literature finding global attention impairments to frequently present in pediatric PF tumor survivors, particularly those who have received CRT.

A few studies have examined the neuroanatomical and neurocognitive effects of CRT on attention in childhood brain tumor survivors. Mulhern and colleagues (2001) explored the relationships between normal appearing white matter (NAWM), age at CRT, and sustained attention performance in 42 childhood medulloblastoma survivors who had received whole brain CRT (23.4-36.0 Gy) with a boost to the PF (total dose of 49-54 Gy). Younger age at CRT was associated with both lower performance on a measure of sustained attention, and decreased NAWM. This study contributed to converging evidence that younger age at CRT is likely a moderating factor of worse cognitive outcomes, an important finding that has prompted investigations of the efficacy of lower doses of CRT (e.g. Thomas et al., 2000).

Table 1

Studies Examining Attention

Reference	N, Population, Design	Time since Treatment	Treatment Regimen	Results	Limitations
Mabbott et al. (2008)	60 survivors of PF tumor; 10 non-CNS tumor control subjects; Cross-sectional	Mean since diagnosis: PF group = 5.4y; non-CNS tumor group = 5.9y	PF group: 32/60 received CRT; 28/62 received surgery only; Non-CNS group received chemo + surgery	No differences in sustained attention were found between PF groups and/or healthy control group.	Heterogeneity in type of treatment received; Unequal group sizes.
Mabbott et al. (2009)	22 survivors of MDB; 17 survivors of low-grade PF glioma; 15 survivors of non-CNS tumor; 10 healthy controls; Cross-sectional	MDB group: Mean = 4.9y (SD=0.55y)	MDB group received CRT + surgery, 10/22 also received chemo.	Overall, both PF groups performed worse on selective attention tasks than the non-CNS and control groups. MDB group who received CRT, had more errors and slower reaction times compared to non-CNS and control groups.	Potentially confounded by MDB group having 18% with residual complications of tumor (0% in all other groups); Unequal group sizes.
Maddrey et al. (2005)	16 long-term survivors of MDB; Cross-sectional	Mean = 14.6y (SD = 3.5y)	All received surgery + CRT	The majority were impaired on measures of attention.	Small sample size; No control group.
Mulhern et al. (2001)	42 MDB survivors; Cross-sectional	Mean = 4.9y; Range (1.8-11.0y)	All received surgery + CRT; 29/42 also received chemo	Cohort showed deficits in selective attention; these were linked to younger age at time of CRT.	No control group; Heterogeneity of treatment.
Reeves et al. (2006)	38 MDB survivors; Cross-sectional	Time since diagnosis: Mean= 1.9y; Range (0.1-4.7y)	Surgery and CRT: 25/38; Surgery, CRT, and chemo: 13/38	8/11 attention variables were significantly below sample mean; omission errors associated with lower reading and math.	No control group; Wide range of time since treatment.
Ronning et al. (2005)	23 survivors of MDB (n=11) or astrocytoma (n=12); Cross-sectional	Mean = 15.9y, Range (10.2-20.8y)	MDB: Surgery, CRT + chemo; Astroctyoma: Surgery	Both groups performed below the mean; MDB group performed worse than astrocytoma group in attention.	Small sample size; No control group.

Note. MDB = medulloblastoma; PF = posterior fossa; Y = years; SD = standard deviation; CRT = cranial radiation therapy; chemo = chemotherapy; CNS = Central Nervous System

While neurocognitive studies often divide cognition into discrete and separable domains of functioning, it is likely that a deficit in one domain may have a significant impact on other domains, and vice versa. For example, if a child has an attentional deficit, her visuomotor skills may also be impaired because of decreased thoughtful planning and organization while drawing or taking notes. In one study seeking to investigate the interconnectedness between deficits in various cognitive domains, Reeves and colleagues (2006) examined the relationship between attention and academic achievement among 38 childhood medulloblastoma survivors, who had received whole brain CRT and a boost to the PF (total dose = 55.8-59.4 Gy). When compared to normative scores, medulloblastoma survivors scored more poorly on eight of 11 attention variables, and inattention predicted worse performance in reading and mathematical reasoning. By examining the relationships between attention and academic achievement, Reeves et al. emphasized the importance of interconnections between different domains of cognition, suggesting the need for addressing cognitive sequelae in pediatric cancer survivors at a global level since performance in one domain may likely affect performance in others.

Because longitudinal studies are often costly and labor intensive, long-term follow-up studies of brain tumor survivors also shed light on late sequelae of diagnosis and treatment. In one such study, Maddrey and colleagues (2005) investigated executive functioning in 10-year survivors of pediatric medulloblastoma, all of whom had received CRT (37.9 Gy to the whole brain and a 15.5 Gy boost to the PF) and found the majority of participants demonstrated marked deficits in attention. More specifically, 78% of participants were classified as impaired (≥1.5 SD below the mean) on a computerized sustained attention task, and 90% were considered to be impaired on a motor-based attention task. The high prevalence of attentional deficits in this group of long-term survivors is concerning, particularly because the radiation dosages are not significantly greater than many of the other, more recent studies described here. Thus, the deficits observed in these long-term survivors may foreshadow what is to come for cohorts of more recently treated survivors.

In a single study finding no impairments in attentional abilities, Mabbott et al. (2008) examined attention in 60 survivors of posterior fossa tumor, 32 of whom had received CRT (0 – 36.0 Gy to the whole brain and a total of 51.1 – 55.8 Gy to the PF). Subjects were compared with 10 non-CNS tumor controls. No differences were found on indices of attention between groups, and all groups performed within the normal range. It is possible that since approximately one-third of the CRT cohort received radiation only to the PF tumor bed, this may have conserved some attentional functioning. Mabbott et al.'s findings are encouraging for the preservation of attentional functioning in some PF tumor survivors; future research will need to tease apart the various protective factors that may influence the manifestation of attentional deficits in this population.

In sum, in PF tumor survivors who received CRT, attentional deficits have been widely noted. These are possibly related to the CCAS, decreased white matter, and decreased perfusion of frontal lobe areas. Further research in this area should continue to utilize neuroimaging methods to investigate mechanisms of deficits, and move towards using longitudinal or prospective designs to characterize changes in white matter over time and how those changes relate to attentional abilities.

Working Memory

Working memory is typically conceptualized as a temporary mental workspace, lasting 30 seconds or less, in which information is either maintained or manipulated (Mesulam, 2000). Because the manipulation component of working memory is more difficult than simply maintaining information in mind for a period of time, studies have utilized tasks that demand the participant to comprehend information, perform some mental operation(s) on it, and then formulate a correct response. Working memory is crucial for many aspects of academic learning, for example, mental mathematical operations, reading comprehension, and remembering the last few words said by the teacher until they can be written down. A couple of studies have investigated working memory deficits in survivors of pediatric PF tumor (Table 2).

Table 2.

Studies Examining Working Memory

Reference	Population, N, Design	Time since Treatment	Treatment Regimen	Outcome	Limitations
Mabbott et al. (2008)	62 survivors of PF tumor; 10 non-CNS tumor control subjects; Cross-sectional	Mean since diagnosis: PF groups = 5.4y; non-CNS group = 5.9y	PF group: 31/62 received CRT; 31/62 received surgery only; Non-CNS group received chemo + surgery	No differences were found between PF CRT, PF Surgery, and non-CNS tumor groups on working memory.	Heterogeneity in type of treatment received; Unequal group sizes.
Spiegler et al. (2004)	34 survivors of pediatric posterior fossa tumor; Longitudinal.	Range (0-10y)	Surgery + CRT: 10/34; Surgery, CRT, + chemo: 24/34	Working memory declined by 1.86 standard points per year; with worse declines just after treatment.	Heterogeneity in treatment received and complications; No control group; Missing data;

Note. PF = posterior fossa; CNS = central nervous system; Y = years; CRT = cranial radiation therapy; chemo = chemotherapy.

As with attention deficits, the long-term nature of working memory deficits in childhood brain tumor survivors is still unclear. Spiegler et al. (2004) utilized growth curve analyses to predict change in working memory abilities over time after treatment for posterior fossa tumor including CRT of 23.4-36.0 Gy to the whole brain and up to 45.0-55.8 Gy to the PF. Working memory declined by 1.86 standard score points per year after diagnosis. Interestingly, the greatest decline was seen immediately following treatment, followed by a gradual decline over time. This was a relatively young sample (M=6.08 years, SD=2.73), and thus it may not be representative of cognitive trajectories in childhood cancer survivors diagnosed as adolescents. As the neural substrates of working memory are known to involve areas of the frontal cortex, such as the dorsolateral prefrontal cortex (DLPFC; Casey et al., 1995), and the myelin of the frontal lobes is particularly sensitive to the harmful effects of CRT as it is still forming throughout childhood and adolescence, progressive failure to develop normal myelination over time may help explain the worsening deficits in working memory observed in this study. Rather than a loss of already acquired skills, these deficits are likely to reflect instead a failure to develop cognitive abilities at expected rates (Palmer, 2008). Spiegler et al.'s study suggests that cognitive interventions for working memory might be most effective when implemented during treatment or immediately post completion of medical therapy.

One study of working memory in pediatric PF tumor survivors who received CRT did not find deficits. Mabbott et al. (2008) found that both cohorts who received CRT (doses described above) and who received surgery only scored within the normal range on three measures of working memory, and did not differ significantly from non-CNS tumor control subjects. As previously mentioned, the lack of deficits noted may be related to one-third of Mabbott et al.'s CRT cohort not receiving whole-brain irradiation; alternatively, protective factors yet to be directly examined may have been present in this cohort.

In conclusion, one major study of childhood PF tumor survivors receiving CRT has noted deficits in working memory. Moreover, these deficits were shown to worsen over time and to predict poorer educational and social outcomes in adulthood. Studies examining survivors of other types of pediatric brain tumor who received CRT have also noted deficits in working memory (Briere et al., 2008; Scott et al., 2001; Waber et al., 2006). Future research should focus on substantiating the presence of working memory deficits in PF tumor survivors and elucidating their mechanisms and moderators, particularly whether they are related to changes in NAWM.

Processing Speed

Processing speed is typically conceptualized as the rapidity with which one can perform relatively automatic mental tasks. Processing speed interacts with other cognitive functions, for example faster processing speed places less demand on maintaining information in working memory. Slow processing speed can affect comprehension of verbally presented information at school, as children may be struggling to keep up with what the teacher is explaining. Outside the classroom, children may have difficulty keeping up with conversations or may spend hours longer on homework than their classmates to do the same amount of work. Several studies have examined processing speed deficits in pediatric PF tumor survivors (see Table 3).

Ribi et al. (2005) investigated processing speed and attention (combined into one factor score) in 16 pediatric medulloblastoma survivors, all of whom had received 23.4-36.0 Gy of CRT and a total of 48.0-55.0 Gy to the PF. Eleven subjects showed deficits on this composite factor; however, interpretation of specific deficits is difficult due to the lack of reporting separate scores for attention and processing speed.

Table 3.

Studies Examining Processing Speed

Reference	Population, N	Time since Treatment	Treatment Regimen	Outcome	Limitations
Aukema et al. (2009)	6 medulloblastoma survivors; Cross-sectional	Median = 3.5y since diagnosis	All had surgery, chemo + CRT	Medulloblastoma group scored worse on processing speed, had lower WMFA	Small sample size; No control group
Mabbott et al. (2008)	62 survivors of PF tumor; 10 non-CNS tumor control subjects; Cross-sectional	Mean since diagnosis: PF group = 5.4y; non-CNS tumor group = 5.9y	PF group: 31/62 received CRT; 31/62 received surgery only; Non-CNS group received chemo + surgery	PF-CRT group had lowest processing speed scores, followed by PF-surgery group. Non-CNS tumor group had best scores.	Heterogeneity in type of treatment received; Unequal group sizes.
Ribi et al. (2005)	16 medulloblastoma survivors; Cross-sectional	Mean age at diagnosis: 6.8y; Mean age at assessment: 18.9y	Surgery + CRT: 4/18; Surgery + Chemo: 12/18; Chemo only: 2/18	11/16 showed deficits in attention/processing speed factor	Heterogeneity in treatment; No control group; Small sample size.
Spiegler et al. (2004)	32 posterior fossa tumor survivors; Longitudinal	Range (0-10y)	Surgery + CRT: 10/34; Surgery, CRT, + chemo: 24/34	Processing speed declined steadily after treatment.	Heterogeneity in treatment; No control group; Missing data.

Note. Y = years; chemo = chemotherapy; CRT = cranial radiation therapy; WMFA = white matter fractional anisotropy; PF = posterior fossa; CNS = central nervous system.

Mabbott et al. (2008) investigated processing speed in 62 survivors of posterior fossa tumor, half of whom had received CRT (doses described above). Subjects were compared with a non-CNS tumor control group. A between-group effect was found such that the group that had received CRT had the lowest scores in processing speed, followed by the surgery-only posterior fossa group, and the non-CNS tumor control group had the highest scores. Additionally, processing speed was found to predict IQ after accounting for treatment type in a multiple regression model. The authors proposed that reduced processing speed may be a critical mechanism for intellectual deficits in pediatric brain tumor survivors.

Few studies have examined the longitudinal course of processing speed deficits in childhood posterior fossa tumor survivors. Spiegler et al. (2004) found that processing speed declined by about two standard score points per year for participants who received CRT (doses reported above), the steepest decline across all factor scores. When only subjects observed from baseline were considered, the estimated decline was even steeper at about three standard score points per year. These reported trends warrant additional long-term studies to validate or correct these estimates.

Speed of cognitive processing relies on connections between various areas of the brain, particularly white matter tracts (e.g. Turken et al., 2008). Thus, imaging techniques such as diffusion tensor imaging (DTI) that examine the structural integrity of white matter in the brain have been utilized in an effort to establish whether reduced processing speed in childhood brain tumor survivors is directly linked to reduced white matter integrity. Aukema et al. (2009) compared childhood medulloblastoma survivors, who had received 25.2-34.5 Gy whole brain CRT and a total of 53.3-55.4 Gy to the PF, with childhood acute lymphocytic leukemia (ALL) survivors who had received high-dose or low-dose intrathecal chemotherapy, and age-matched healthy controls. Medulloblastoma survivors had slower cognitive processing speed than both the high-dose and low dose ALL groups, as well as the healthy controls. Furthermore, the medulloblastoma group had lower WMFA when compared to the high-dose ALL group and age-matched controls. Reduced WMFA in the splenium was specifically related to slower processing speed. As intrathecal chemotherapy crosses the blood-brain barrier, it has been shown to affect cognition (Mennes et al., 2005). However, the results of this study suggest that intrathecal chemotherapy did not affect white matter as strongly as did the CRT. Additional factors to consider include the effects of a solid tumor such as medulloblastoma in the cerebellar region, which may have also impacted processing speed.

In sum, pediatric PF tumor survivors have shown deficits in processing speed when compared to survivors of other types of cancer as well as healthy controls. The longitudinal course of these deficits appears bleak, with progressive decline shown in one study. White matter integrity has been examined as a candidate mechanism for processing speed deficits in childhood brain tumor survivors, and reduced WMFA was associated with slower processing speed in one cohort. Further study of the mechanisms and moderating factors of processing speed deficits should be undertaken in the future, utilizing neuroimaging methods. Additionally, further longitudinal studies are necessary to validate or modify the current information regarding worsening of deficits over time.

General Executive Functions

Although attention, working memory, and processing speed are often considered parts or necessary companions of global executive functions in a conceptual framework, assessment tools may vary in the specific domains they assess. Consequently, "general executive functions" is a catch-all term encompassing other aspects of executive functions not included in the more commonly assessed domains already discussed. This category includes planning, metacognition, organization, reasoning, and problem-solving; all components of executive functions that are closely related to daily living, coping, interpersonal, and academic skills (Baron, 2004). Several studies have examined these abilities in survivors of pediatric PF tumor (Table 4).

Table 4.

Studies Examining General Executive Functions

Reference	Population, N	Time since Treatment	Treatment Regimen	Outcome	Limitations
Maddrey et al. (2005)	16 MDB survivors; Cross-sectional	Mean age at diagnosis: 7.2y; Mean age at assessment: 22.2y	Surgery + CRT: 16/16; Surgery, CRT + chemo: 9/16	79% and 85% found to be impaired on measures of EF	Small sample size; No control group; Heterogeneity of treatment.
Ronning et al. (2005)	23 survivors of MDB (n=11) or astrocytoma (n=12); Cross-sectional	Mean = 15.9y, Range (10.2-20.8y)	MDB: All had surgery, chemo, + CRT; Astroctyoma: All had surgery only	Both groups performed below the mean on measures of EF	Small sample size; No control group.
Spiegler et al. (2004)	32 brain tumor survivors; Longitudinal	Range (0-10y)	Surgery + CRT: 10/34; Surgery, CRT, + chemo: 24/34	EF was within average range at first evaluation, but declined over time	Heterogeneity in treatment received and complications; No control group; Missing data.

Note. MDB = medulloblastoma; y = years; CRT = cranial radiation therapy; chemo = chemotherapy; EF = executive function.

Ronning et al. (2005) compared a cohort of young adults treated for childhood astrocytoma with surgery only, and young adult survivors of medulloblastoma treated with surgery, chemotherapy, and CRT (27.0 – 35.0 Gy to the whole brain, and 45.0-57.0 Gy to the PF). While both groups performed below the mean on a measure of executive functions, the groups' scores did not significantly differ. This study reinforces the deleterious outcomes that can be associated with surgical resection even in the absence of subsequent CRT.

Characterizing the long-term course of executive function deficits following treatment for PF brain tumor in childhood is an important step towards addressing these deficits comprehensively. Maddrey and colleagues (2005) investigated executive functioning in 10-year survivors of pediatric medulloblastoma, all of whom had received CRT (doses reported above). In this sample, 79-85% showed deficits on tests of planning and cognitive set-shifting. Performance on these tests of executive abilities correlated with age at diagnosis, with younger age being linked to worse performance. This finding is supported by the literature documenting the importance of waiting as long as possible to administer CRT (e.g. Mulhern et al., 2001).

Spiegler et al. (2004) examined problem solving, fluency, and cognitive flexibility over time in survivors of childhood PF tumor, all of whom received CRT (doses reported above). Significant negative slopes were noted for all three domains, indicating worsening performance over time when compared to same-age peers. For measures of problem solving, a decline of approximately one standard deviation every five years was observed.

In conclusion, deficits in general executive functions have been found in PF tumor survivors who received CRT, and worse scores were related to younger age at treatment. Longitudinal data indicates that these general executive deficits worsen over time. Future research should investigate neuroanatomical mechanisms of these general executive deficits using neuroimaging methods and standardize which aspects of general executive functions (e.g. planning) are most important to assess in this population.

Interventions and Treatment-Related Studies

There is a well-established body of literature delineating the multifaceted deficits in executive functions experienced by pediatric PF tumor survivors. Not surprisingly therefore, the focus has recently shifted to developing interventions to ameliorate the documented deficits. A few focal avenues for treatment have been studied including modification of medical treatment protocols, pharmaceutical interventions, and cognitive training programs (see Table 5).

Table 5.

Intervention Studies

Reference	Study Design	Population, N	Intervention	Domain(s) Assessed	Outcome	Limitations
Butler et al. (2008)	Randomized (2:1); Tested before, after, and 6 mo. post; Wait-list control group	161 childhood cancer survivors that had CNS treatment	20 2-hour sessions over 4-5 mo focused on cognitive training	5 indices: Academics, brief attention, WM, memory, vigilance	Improvements found in academics & parent report attention after intervention compared to control group.	Moderate compliance; No long-term follow-up; Wide variation in cancer diagnoses and treatment types.
Conklin et al. (2007)	Double-blind, crossover in clinic testing sessions; Subjects served as own controls	122 survivors of BT or ALL with attention problems	Received either MPH (60 mg) or placebo before testing	NP battery, focused on attention, and processing speed	Improvements in selective attention, impulsivity, cognitive flexibility, and processing speed, but not sustained attention.	Combined ALL and BT groups; Heterogeneous treatment types.
Conklin et al. (2010)	12-month, open-label MPH trial. If participants declined medication or were not classified as responders, they were in control group	122 survivors of BT or ALL (control group = 58) with attention problems.	After 3-week trial, those who responded well to MPH continued taking it for 12 mo. Pre- and post-NP testing occurred.	IQ, achievement, attention, and behavior indices	Improvements in attention through objective, parent-report, teacher-report, and self-report measures, as well as parent-report social skills and behavior problems.	Groups not randomized; MPH group biased towards those who responded to MPH initially; Heterogenous treatment types; Combined BT and ALL participants for analyses.
Hardy et al. (2011)	Tested at baseline, post-intervention, and three months post intervention	Nine survivors of childhood cancer, including six PF tumor survivors	Computerized, home-based, 12-week cognitive training intervention	Attention, working memory	Working memory and parent-reported attention scores improved from baseline to post-assessment	Combined ALL and BT groups; Small sample size; Variable compliance.

Jain et al. (2008)	Cross-sectional data comparing standard CRT with IMRT; Standard treatment control group	25 survivors of medulloblastom a	Treated with either standard CRT or IMRT, and were evaluated afterwards	IQ, visuomotor, and processing speed indices.	No differences between IMRT and standard CRT group on any NP variables; both groups performed below norms on processing speed.	Small sample size; Not randomized into groups; No long-term follow-up.
Mulhern et al. (2004b)	Randomized, 3-week, double-blind, crossover study; Subjects were own controls	83 long-term survivors of childhood ALL (n=40) or BT (n=43)	Received low-dose MPH, moderate-dose MPH, and placebo for one week each	Social skills and attention (both teacher & parent report)	Significant improvement with MPH compared to placebo; no effect for high-dose over low-dose MPH.	Combined ALL and BT groups; No long-term follow-up; Wide range of ages at treatment.
Patel et al. (2009)	Pre/post testing, intervention in between; No control group	12 survivors of childhood cancer w/CNS involvement (9-CNS tumors)	15 sessions focused on learning strategies and problem solving	IQ, attention, memory, academics, social skills, and behavior indices	Gains were seen in all attention scores, though none statistically significant	Small sample size; No control group; Wide range of ages and diagnoses; Moderate compliance.
Thompson et al. (2001)	Baseline testing, then repeat next day after receiving MPH or placebo; Used placebo control group	32 survivors of childhood ALL (n=7) or BT (n=25)	Baseline NP testing; then randomly assigned to MPH or placebo, did NP tests again.	Baseline: IQ, achievement, attention, and memory. MPH/Placebo: Attention, and memory	Improvements for MPH over placebo noted in overall attention and omission indices.	Small sample size; Combined ALL and BT groups; No long-term follow-up.

Note. Mo = months; CNS = central nervous system; BT = brain tumor; ALL = acute lymphoblastic leukemia; MPH = methylphenidate; NP = neuropsychological; IMRT = intensity-modulated radiation therapy; and CRT = cranial radiation therapy.

Modifying treatment protocols.

Given the well-documented negative effects of radiation therapy on cognitive functions, various techniques to modulate these repercussions while retaining treatment efficacy have been examined in recent years. One such technique is intensity-modulated radiation therapy (IMRT), which is able to precisely deliver radiation to the target tissue with relative sparing of the surrounding tissue. Unfortunately, the only study using cognitive outcome measures after treatment with IMRT found equivocal results. Jain and colleagues (2008) found no differences on two measures of processing speed in children treated for medulloblastoma with IMRT compared with traditional CRT. Although the mean scores for the IMRT cohort were generally higher than the CRT cohort, no conclusions can be drawn for cognitive sparing of IMRT given the lack of statistically significant differences in this study. Further studies should compare IMRT with traditional CRT using larger sample sizes and examining additional domains of executive functions. Using proton beam radiotherapy instead of conventional radiation is another up-and-coming avenue for sparing maximal healthy tissue and potentially preserving cognitive functioning; however, cognitive outcomes after proton beam radiotherapy have yet to be published.

Cognitive intervention.

Most cognitive interventions currently available in childhood cancer focus on treating deficits in long-term survivors. In a seminal multi-center randomized clinical trial, Butler and colleagues (2008) evaluated the efficacy of the "Cognitive Remediation Program," a collection of cognitive training modules based on the principles of pediatric traumatic brain injury, cognitive rehabilitation, educational psychology, and child clinical psychology, with childhood cancer survivors who received CNS treatment. Findings from this labor-intensive intervention revealed improvements in learning strategies, parents' perceptions of cognitive problems and attention, and in all academic domains except reading comprehension.

The efficacy of the "Cognitive Remediation Program" for survivors of childhood cancer was also tested by Patel and colleagues (2009). While significant improvements were only noted in tests of social skills and writing achievement, the small sample size of this pilot study (N=12) likely contributed to difficulty finding statistical significance. Improvements in scores approaching statistical significance included measures of focused and sustained attention, memory, and externalizing behavior. The lack of a control group limits findings, particularly since Butler et al.'s (2008) study showed significant improvements over time in the wait-list control group on some measures of attention.

More recently, Hardy et al. (2011) tested the efficacy of a computerized, home-based, 12-week intervention. Nine survivors of childhood cancer including six PF tumor survivors completed the program, entitled "Captain's Log". Overall working memory scores showed a trend (p=.07) towards improvement from baseline to three months post-intervention; this finding may have been statistically significant with a larger cohort. Changes in working memory abilities were associated with greater time spent training. Additionally, parent-reported attention problems decreased from baseline to post-assessment. As the first published intervention to examine change in working memory in childhood cancer survivors over time, Hardy et al. set an important precedent to include executive function outcome measures other than those pertaining to attention, as working memory, processing speed, and general executive functions may benefit as well from these intervention programs.

Pharmacological intervention.

In addition to cognitive remediation programs, a few studies have endeavored to test the effects of methylphenidate (MPH), an effective psychostimulant in the traditional treatment of attention deficit disorders (*Committee on Children with Disabilities and Committee on Drugs: Medication for children with attention disorders*, 1996), for attentional difficulties in childhood cancer survivors. The first study to investigate this hypothesis found significant improvements for MPH over placebo in omission and overall attention indices (Thompson et al., 2001). While the sample size in this study was relatively modest for a clinical trial (N=32), the results nonetheless provided encouraging support for the effectiveness of MPH for attention problems and established rationale for future, larger studies exploring the efficacy of MPH in this population.

In a more recent, larger investigation, Conklin and colleagues (2007) found significant improvements associated with taking MPH on one index of executive functioning. No measures of attention were shown to improve with MPH over placebo. It is unclear why MPH did not improve attention in this study; perhaps it was dose-related, or perhaps MPH had positive effect for some subjects, but not others, and so the overall group effect was washed out. Regardless, in a recently published follow-up to this original study, Conklin et al. (2010) found more promising effects, noting improvements in sustained attention, parent-report, teacher-report, and self-report attention, and parent ratings of social skills and behavioral problems. The control group only improved on parent ratings of social skills and attention.

In another study investigating the efficacy of MPH in childhood cancer survivors, Mulhern et al. (2004b) found that teachers (but not parents) reported improvements in overall social skills and academic competence in both moderate-dose and low-dose MPH groups, and improvements in problem behaviors for the moderate-dose MPH group. No relative benefit was found for moderate doses of MPH compared with low doses. Although the efficacy of MPH for attentional difficulties observed by teacher report is encouraging, the short-term nature of this study makes it difficult to extrapolate findings regarding long-term clinical effectiveness. The authors mention future plans to follow up with the participants who chose to continue using MPH after the study ended. This will be enlightening, as Conklin et al. (2010) is currently the only long-term study of the effects of MPH on cognition, social skills, and achievement.

Not specifically discussed in this section were ecological interventions, for example special education services in schools and classroom accommodations. These interventions are certainly vital to the academic success of pediatric brain tumor survivors; however, as they do not aim to directly address primary cognitive deficits, their specifics are outside the scope of the present review. Overall, while interventions directed at modifying treatment protocols have not been definitively shown to be efficacious, cognitive training programs and pharmacological intervention techniques have shown efficacy in addressing attentional deficits in some pediatric brain tumor survivors. However, a theoretical model describing the relationships between contextual, neurocognitive, and neuroanatomical factors is the next step towards designing more comprehensive interventions to effectively address executive function deficits in this population.

Existing Conceptual Models

Seminal models of executive function deficits in pediatric brain tumor survivors include those of Reddick et al. (2003) and Palmer (2008). While Reddick et al.'s model focuses on neural substrates to understand only attention deficits, Palmer's model employs a broader conceptualization of executive function and includes both child and treatment variables.

Reddick et al.'s (2003) model incorporated data from structural neuroimaging, positing that reductions in NAWM affect attention negatively and these deficits in turn affect IQ and academic achievement. Direct links between deficits in attention and academic achievement were also proposed in the final model. A main contribution of Reddick et al.'s model is how it related the neurocognitive deficits back to underlying neuroanatomical substrates. However, as the model did not include executive functions other than attention, nor child risk factors or treatment-related variables, it may not be a comprehensive description of executive function deficits in pediatric brain tumor survivors.

Palmer's (2008) model suggested that both the brain tumor diagnosis and its associated treatment affect processing speed, attention, and working memory, potentially leading to lower IQ and academic achievement. These effects are moderated by idiopathic factors, such as the age of the patient. This model took into account multiple contextual and neurocognitive factors in explaining executive functions in pediatric brain tumor survivors. Furthermore, it indicated areas for future study, particularly in the domain of interventions. Limitations of this model, however, include no mention of general executive functions such as planning and metacognition, and not including the neuroimaging literature that has linked deficits in executive functions with underlying white matter deficiencies.

Each model makes a viable contribution but has limitations. What is needed is a more comprehensive approach taking into account contextual (e.g. patient gender, age, brain tumor, and treatment type), neurocognitive (e.g. executive functions), and neuroanatomical (e.g. white matter) factors. Such a model will not only sum up the existing body of literature, but also delineate future directions for research. In particular, a comprehensive model will give inspiration and focus for new targets of intervention strategies.

A New Model

The proposed model (Figure 1), derived from the literature review, aligns with and expands upon aspects of previously published models from Palmer (2008) and Reddick et al. (2003). Unique contributions of the new model include incorporating executive functions as an important neurocognitive subdomain and revising the targets of published interventions. As in previous models, the tumor and its treatment negatively impact white matter (Reddick et al., 2003) and this effect may be moderated by the child's age, gender, and/or stage of neurodevelopment (Palmer 2008). Decrements in white matter negatively affect executive functions; this has been documented in attention (Mulhern et al., 2004a) and processing speed (Aukema et al., 2009), and it is likely that working memory and general executive functions are also affected similarly. Future research should examine this hypothesis. Deficits in core executive functions over time lead to decreased intellectual functioning and academic achievement. Recent modifications in delivery of CRT (e.g. intensity-modulated radiation therapy) may preemptively impact the effects of the brain tumor and treatment on NAWM (Jain et al., 2008). In contrast to this treatment-related approach most other interventions have focused on ameliorating the deficits in core executive functions for survivors, mostly in attention, through pharmacological aids or cognitive training (Conklin et al., 2007; Thompson et al., 2001; Butler et al., 2008; Patel et al., 2009; Hardy et al., 2011).

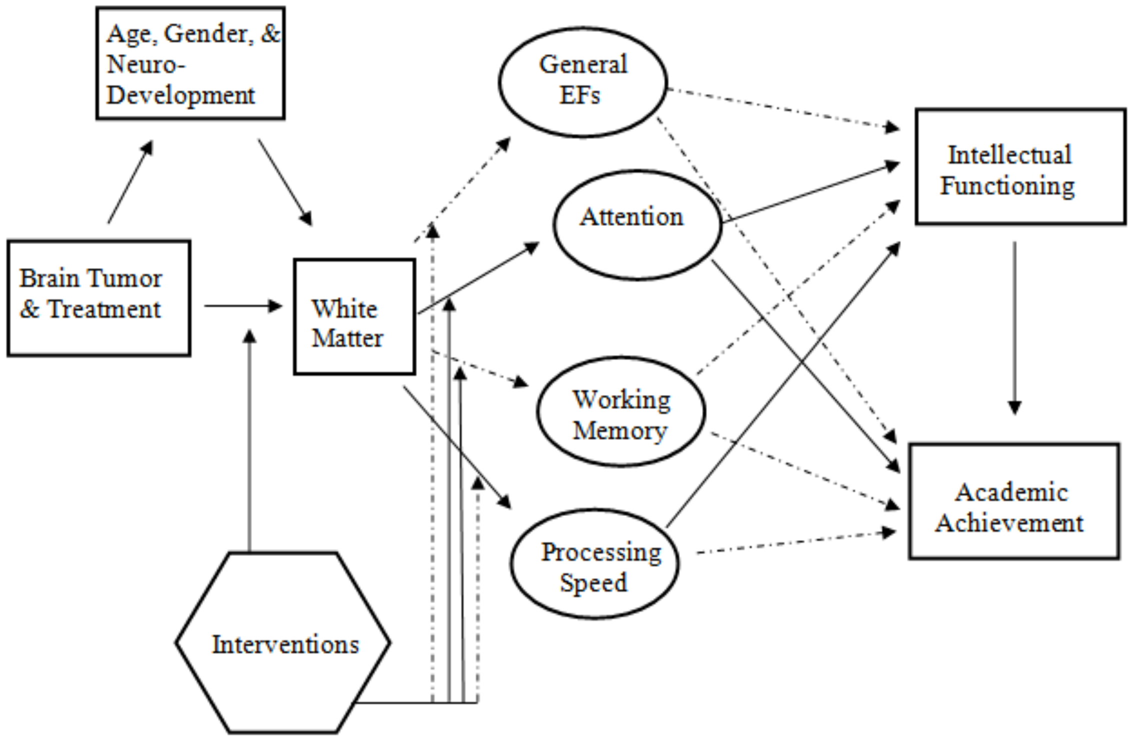

Figure 1. A theoretical model of the effects of pediatric brain tumor and its treatment on intellectual functioning and academic achievement. Solid lines represent findings from studies with pediatric brain tumor survivors. Dotted lines represent relationships that are theoretically plausible but have yet to be investigated in the literature.

By expanding previous models, our model outlines the current state of knowledge regarding the relationships between factors from contextual, neurocognitive, and neuroanatomical levels which interact to produce executive function deficits in pediatric brain tumor survivors. While the majority of the extant literature focuses on characterizing deficits in executive functions, fewer studies have examined the relationships between these deficits and other variables that certainly impact the presence and severity of executive dysfunction. Importantly, comprehensive intervention strategies should be designed to address multiple levels of factors contributing to deficits. For example, delaying CRT in very young children addresses a contextual variable; modified treatment protocols that ameliorate white matter damage focus on neuroanatomical factors; and cognitive training programs soon after completion of therapy address neurocognitive variables. Clearer understanding of the multifaceted contributing factors to executive dysfunction, and the ways in which they are interrelated in pediatric brain tumor survivors, will produce more creative, comprehensive and effective intervention strategies.

Conclusions and Future Directions

There is a substantial body of literature documenting the executive function deficits in pediatric PF tumor survivors who received CRT. Executive abilities including attention, working memory, processing speed, and general executive functions (e.g. planning and metacognition) are often negatively impacted by both the brain tumor diagnosis and its associated treatment. Additional documented risk factors include younger age at treatment, gender (female), and longer time post completion of treatment. Recent neuroimaging research has begun to link these neurocognitive deficits to reduced white matter integrity in the brains of survivors. Knowledge of these factors is important for researchers as they strive to decrease neurocognitive toxicity while maintaining treatment effectiveness.

As we move forward in this field, studies from multiple disciplines that provide convergent evidence of deficits and their contributing mechanisms will become increasingly important. Emphasis is shifting towards neuroimaging research, such as functional and structural magnetic resonance imaging, and psychophysiological tools, such as electroencephalography. These objective and non-invasive measures add another important dimension to our appreciation of the nature of executive function deficits, and flesh out our understanding of why they occur. In spite of the potential artifacts in neuroimaging or vascular abnormalities due to the tumor itself, functional and structural neuroimaging afford opportunities to compare the neural substrates of cognitive abilities in childhood brain tumor survivors to those of typically developing children, and both the similarities and differences found will be meaningful for developing new targets for cognitive intervention.

Because neurocognitive deficits from CRT may not be evident until years after treatment, longitudinal studies of childhood brain tumor survivors are important to fully characterize enduring morbidities; including a longitudinal component should be seriously considered in all future studies in this area. When longitudinal studies are not feasible due to financial or time constraints, long-term follow-up cross-sectional studies should be considered as a snapshot of how survivors are functioning long after the completion of treatment. Also, while objective neurocognitive tests may provide an empirical account of abilities, self-report and proxy-report questionnaires reveal an ecologically valid perspective on how the patient is functioning in real life, and should be included more often.

As this review has documented, there have been several smaller-scale studies that described executive function deficits in pediatric brain tumor survivors and the various factors that can affect these deficits. A potential next step for research in this area will be to collaborate in larger-scale studies that will provide sufficient statistical power for analyzing the relative contributions of both idiopathic and treatment-related variables, as well as accurately characterizing the mechanisms underlying these deficits. The Childhood Cancer Survivors Study (CCSS; Ellenburg et al., 2009) is an excellent example of the potential afforded by larger-scale studies to draw meaningful conclusions regarding a large number of variables. A limitation of the CCSS, however, was the lack of objective neurocognitive test scores. Large-scale studies with objective neuropsychological data will be best accomplished by standardization of neuropsychological testing protocols across treating medical centers. This has already been established for some Children's Oncology Group protocols, but is often not done for children who are being medically treated off-study. Regardless of whether a child is treated on-study or off-study, the neuropsychological time points and test batteries should be uniform. If centers can collaborate with this standardized data, it would afford an incredible opportunity for large-scale research in this specialized population. A major limitation of studies in this area is the heterogeneity of neurocognitive tests utilized to assess these domains of executive functions, as it impedes the interpretation of inter-study comparisons. Therefore, a first step in this direction would be to standardize testing protocols, including the exact measures to be utilized, across childhood cancer treating centers. Computerized screening batteries may be particularly well-suited for this endeavor, as they tend to be more economical than one-on-one testing and ensure a high level of consistency across administrations.

On the vanguard of research in this area are interventions designed to address these executive function deficits in pediatric brain tumor survivors. Three avenues of intervention that have shown promise are: 1) modifying treatment protocols to reduce or become more precise with radiation dosages, 2) cognitive interventions similar to those used with brain-injured populations, and 3) stimulant medication trials. However, these approaches to intervention are still nascent, with accompanying limitations. For instance, the only study examining cognitive outcomes after IMRT did not show benefits over and above traditional CRT. Proton beam radiotherapy shows promise for a new technique that may spare maximal healthy tissue; however, cognitive outcomes after its use have yet to be established. Cognitive training interventions are both time and labor-intensive, requiring many sessions and often one-on-one training, which may not be feasible for widespread dissemination. Finally, although pharmacological trials using MPH have shown encouraging results, particularly over longer periods of time, the side effects of this medication may be prohibitive for some pediatric PF survivors.

While the current literature on intervention is promising, further research is necessary to explore for whom these interventions are effective and by what mechanisms. Future studies should move towards incorporating neuroimaging and psychophysiological measurement tools in their outcome measures to provide additional insight into the mechanisms behind observed changes. For example, do cognitive training programs play a significant role in white matter connectivity, or in functional activity in relevant brain areas? In addition, while current interventions such as cognitive training seem to affect endpoints such as academic achievement, the evidence for their effect on core deficits (i.e. attention, working memory, processing speed and general executive functions) is less clear. Future interventions should focus on targeting those core impairments.

The importance of pursuing effective interventions for executive function deficits in pediatric brain tumor survivors cannot be overstated, as these deficits have been shown to affect other cognitive abilities, academic achievement, and social functioning. As larger-scale studies using multiple measurement modalities are able to parse out the effects of idiopathic and treatment-related variables on executive function deficits in pediatric brain tumor survivors, directions for effective intervention strategies will become increasingly clearer, and the interventions themselves, progressively more effective.

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CARDIORESPIRATORY FITNESS IN SURVIVORS OF PEDIATRIC POSTERIOR FOSSA TUMOR

by

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Abstract

Advances in medical therapies have greatly improved survivorship rates in children diagnosed with brain tumor; as a result, morbidities associated with survivorship have become increasingly important to identify and address. In general, pediatric posterior fossa tumor survivors tend to be less physically active than peers. This may be related to late effects of diagnosis and treatment, including cardiovascular, endocrine, psychological, and neurocognitive difficulties. Exercise has been shown to be effective in improving physical functioning, mood, and even cognitive functioning. Consequently, the benefits of physical exercise need to be explored and incorporated into the daily lives of pediatric posterior fossa tumor survivors. The primary aim of the present study was to establish the feasibility and safety of cardiorespiratory fitness testing in pediatric posterior fossa tumor survivors who had received cranial radiation therapy. Additionally, comparing our cohort to previously published data, we found that pediatric posterior fossa tumor survivors tended to be less fit than children with pulmonary disease as well as healthy controls, and approximately as fit as children with chronic heart disease and survivors of other types of childhood cancer. The importance of cardiorespiratory fitness in pediatric posterior fossa tumor survivors is discussed along with implications for future directions.

Key words: Pediatric posterior fossa tumor, Cardiorespiratory fitness, VO_2max testing, Pediatric brain tumor

Introduction

Childhood brain tumors, the second most common type of childhood cancer, account for approximately 20 percent of the pediatric oncology population.[1] Brain tumors vary widely according to location, size, and histological composition. In a recent epidemiological review, males comprised about 57% of the pediatric brain tumor population. The overall incidence of pediatric brain tumor is approximately 4.5 in 100,000;[2] however, various types of tumors peak in incidence at different points of development.

Late Effects

Survivors of pediatric brain tumor tend to be less active than their same-age peers.[3] This is likely related to the myriad of late effects that survivors often experience related to the tumor and treatment, including physical complications. In a large, multi-center study, 18% of pediatric brain tumor survivors reported having one or more cardiovascular conditions, and 43% reported having one or more endocrine conditions.[4] These cardiovascular conditions (e.g., shortness of breath or angina-like symptoms) and endocrine conditions (specifically growth hormone deficiency) might negatively affect cardiorespiratory fitness in this population. While few late effects were observed for those survivors receiving only surgical resection, the risk level was elevated for those treated with cranial radiation therapy and adjuvant chemotherapy.

Multi-modal medical treatment has also been associated with increased late effects across several other domains of functioning. For example, studies of cognitive sequelae from pediatric brain tumor and its treatment consistently document that individuals treated with radiation and chemotherapy have poorer neurocognitive outcomes relative to youth treated with only surgical resection across domains of IQ, executive function, memory, and processing speed.[5,6,7] Additionally, a systematic literature review of studies assessing psychological outcomes in pediatric brain tumor survivors noted that receipt of radiation therapy was associated with internalizing (e.g., anxiety, depression) and externalizing (e.g., acting out, aggression) disorders across several studies.[8]

Tumors arising in the posterior fossa are the most common type of childhood brain tumor.[9] Cerebellar tumors may lead to a number of additional difficulties because of their location within the brain, including poor balance[10] as well as difficulty regulating thoughts and emotions secondary to cerebellar cognitive affective syndrome (CCAS).[11] Additionally, standard treatment for medulloblastoma and ependymoma, two of the most common cerebellar tumors in children, typically involves radiation therapy and sometimes adjuvant chemotherapy.[9,12] Thus, survivors of pediatric medulloblastoma and ependymoma are at increased risk for late effects across domains of functioning given the tumor location and treatment received.

Survivors are Less Physically Active

These physical, cognitive, and psychological late effects may be related to the decreased functional performance abilities noted in pediatric brain tumor survivors, who report more difficulties with completing routine activities and attending work or school relative to survivors of any other type of cancer.[13] Pediatric brain tumor survivors are also more likely to be underweight and less overweight than population norms. Being underweight has been associated with lower social competence, lower verbal IQ, and higher internalizing behaviors in this population.[3] In addition to the multi-domain late effects, children diagnosed with a brain tumor are often not physically active while on treatment due to fatigue, pain, and general malaise. Thus, they are likely at greater risk to develop sedentary habits than healthy peers, a pattern which may continue into survivorship and manifest as lower rates of exercise and thus lower cardiorespiratory fitness. Neurological late effects such as poorer balance due to cerebellar injury may also contribute to lower rates of exercise in pediatric posterior fossa tumor survivors. It is likely that these late effects interact with one another across domains. For example, cognitive difficulties might include low initiation, which could contribute to depression, both of which might result in less frequent physical activity. Overall, survivors of pediatric brain tumor experience more barriers to physical activity than survivors of other types of childhood cancer and typically developing peers.[13]

Physical exercise has shown benefits across various areas of health, improving emotional, physical, and cognitive functioning.[14,15] Thus, it follows that exercise would be of great importance for survivors of pediatric posterior fossa tumor, given their documented difficulties across these domains. However, feasibility and safety of vigorous physical exercise has yet to be shown for this population, and is of particular concern given the aforementioned physical complications that may present. Survivors of pediatric posterior fossa tumor might not be as capable of reaching peak aerobic capacity due to the late effects of the tumor and treatment. Principal concerns with aerobic exercise with this population would include the possibility of adverse cardiac events (e.g., shortness of breath, angina-like symptoms), lightheadedness, or general malaise. Thus, the purpose of the present pilot study was to determine the preliminary feasibility and safety of cardiorespiratory fitness testing in survivors of pediatric posterior fossa tumor who had undergone surgical resection and radiation therapy, with or without adjuvant chemotherapy. A secondary aim was to compare the body composition variables from youth in this sample with normative means, and the physical fitness variables with those previously reported in healthy and other childhood chronic illness samples. We hypothesized that cardiorespiratory fitness testing would be feasible and safe with this population. Additionally, we expected that our cohort of pediatric brain tumor survivors would have lower cardiorespiratory fitness compared with typically developing youth, and comparable fitness with other childhood chronic illness samples, because of the various cognitive, emotional, and physical late effects associated with the tumor and its treatment.

Materials and Methods

Participants

Participants were consecutively recruited from the Neuro-Oncology clinic at an urban children's hospital in the southern United States. Inclusion criteria were youth ages 11-18 years, who had survived a posterior fossa tumor, received cranial radiation therapy as part of their medical treatment regimen, were at least 2-years post completion of therapy, and had a Modified Lansky score of $\geq$ 70. The Lansky score is a play performance scale in children who have or have been treated for cancer, indicating their functional abilities (e.g., to sit down on the floor, walk independently, etc.).[16] Exclusion criteria included child residence outside of primary caregiver's home, disabilities that prohibited child or primary caregiver from completing measures, and the child or caregiver not being English-speaking. The final sample included 14 posterior fossa tumor survivors, who were grossly similar to the national pediatric posterior fossa survivor population in terms of male gender predominance, younger ages at diagnosis, and that they were treated with standardized Children's Oncology Group protocols. No eligible participants that were approached to take part in this study declined participation.

Procedures

Eligible survivors were identified through patient databases of children and adolescents treated in the UAB Division of Pediatric Hematology and Oncology Neuro-oncology clinic at Children's Hospital of Alabama since 1993. Medical records were reviewed to determine eligibility. Eligible participants were recruited during regular clinic follow-up visits or by phone. Informed consent and assent were obtained when the participant came for the study in accordance with the approval of the UAB Institutional Review Board. The parent/caregiver completed a demographics questionnaire, and the survivor completed a self-report seven-day recall of physical activity and the cardiorespiratory fitness testing. Following completion of fitness testing, the caregiver was given a $10 incentive, and the survivor a $50 incentive.

Measures

VO_2max Testing. Maximum oxygen uptake, or VO_2max, testing was completed on a Monark stationary cycle ergometer using a standardized protocol. We chose to use the cycle ergometer instead of the more traditional treadmill test because of the problems in balance often experienced by pediatric posterior fossa tumor survivors. Heart rate (HR) data was captured using a POLAR Vantage XL HR monitor (Gays Mills, WI, USA). Subjects warmed up by cycling at 25 Watts for 4 minutes. Those subjects with a heart rate of greater than 110 beats/minute after 4 the minute warm-up increased workload 12.5 Watts/minute throughout the rest of the test. Those subjects with a HR of less than 110

beats/minute after the 4 minute warm-up increased workload 25 Watts/minute throughout the rest of the test. Oxygen uptake and carbon dioxide production were measured continuously using a Physiodyne Instrument Corporation, MAX-II Cart (Quogue, NY, USA). Gas analyzers were calibrated with certified gases of known concentrations. Subjects were encouraged to maintain work output for as long as they could and the test was terminated when subjects could no longer maintain the prescribed work level. Standard criteria for HR, respiratory exchange ratio (RER), and plateauing were used to assess achievement of VO_2max.[17] Specifically, two of the following three criteria had to be met in order for the subject to have achieved a true VO_2max: (1) HR > 85^{th} percentile of age-predicted maximum; (2) RER > 1.0; and (3) Observable plateau of VO_2 uptake.

Physical Activity Questionnaire. Participants also completed the age-appropriate version of the Physical Activity Questionnaire (PAQ), a self-report 7-day recall of physical activity in the past week. The psychometric properties of the two versions of this measure (i.e., the PAQ-C for older children and the PAQ-A for adolescents) have been well established.[18,19] The means and standard deviations of published normative data for the PAQ-A[20] and PAQ-C[21] were used to convert participants' data into z-scores standardized by age and gender.

Body Mass Index. The body mass index (BMI) of each participant was calculated from his or her weight and height (kg/m^2). Body composition indices (i.e. percent body fat and percent fat free mass) were calculated by measuring skin folds at the tricep, chest, abdomen, suprailium, and thigh. These skin folds were then used to estimate body density[22,23] and percent body fat was calculated from body density.[24]

Late Effects Severity Score (LESS). We utilized Benesch and colleagues'[25] system for quantifying physical late effects in pediatric medulloblastoma survivors entitled the Late Effects Severity Score (LESS). This involved rating the late effects experienced by each survivor in the domains of neurology, endocrinology, visual/auditory, and other symptoms. In each domain, survivors received 0 points for no late effects, 1 point for one late effect in that area that did not require medical intervention (e.g., hearing loss not requiring correction with hearing aids), or 2 points for one or more late effects in that area requiring intervention (e.g., growth hormone replacement therapy). Thus, the maximum overall score would be 8, with a maximum score of 2 for each domain. All information for LESS ratings was found in the survivor's medical chart.

Data Analysis

BMI values were examined with regards to cutoffs from the CDC for underweight, overweight, and obese.[26] Relationships between physical fitness variables, treatment variables, LESS scores, and demographic variables were examined using correlational analyses. In order to put our cohort's VO_2max scores in broad context compared with other chronic illnesses or healthy controls, brain tumor survivors' VO_2max scores were compared to those reported in a previous study by Groen and colleagues,[27] who used a very similar cycle ergometry protocol to obtain VO_2max scores from cohorts of older children and adolescents with cystic fibrosis (CF), with chronic heart disease (CHD), and a healthy control cohort. These comparisons were done using one sample two-tailed *t*-tests.

Studies assessing VO_2max with other pediatric oncology survivor populations have been published; however, they have used treadmill testing which consistently produces VO_2max scores that are consistently about 11% higher than those obtained through cycle ergometry protocols.[28] Therefore, in order to broadly compare the scores from our brain tumor survivor cohort with those of childhood cancer survivors (excluding brain tumor survivors), we multiplied the obtained VO_2max scores of our sample by 1.11 to obtain the estimated VO_2max scores for a treadmill protocol. We then compared these scores to the mean VO_2max scores reported by De Caro and colleagues[29] for childhood cancer survivors using one sample two-tailed *t*-tests. Significance was set at less than 0.05 for all analyses. While this was a somewhat less exact comparison due to the different measurement methods utilized, we felt it important to compare the aerobic fitness of our brain tumor survivors with survivors of other types of childhood cancer, because the two groups often experience quite different late effects.

Results

The main results of this study are as follows: 1) VO_2max testing was shown to be feasible and safe for a small cohort of survivors of pediatric posterior fossa tumor; 2) Survivors' self-reported physical fitness and objectively recorded VO_2max scores were lower than published norms for typically-developing children; 3) More severe neurological late effects were related to lower levels of cardiorespiratory fitness; and 4) Survivors' VO_2max scores were lower than those published for children with cystic fibrosis, but no different from the published VO_2max scores of children with chronic heart disease or other types of childhood cancer.

Thirteen participants were able to participate in the VO_2max testing with no adverse incidents such as a cardiovascular event, lightheadedness, or general malaise. The one participant that did not complete the test had a very strong gag reflex, and thus we were unable to adequately insert the mouthpiece in order to measure intake and expiration of gases. Self-report physical activity was collected for this participant, so he is included in those analyses.

Table 1. Participant characteristics

Demographic	M (SD)	Min	Max
Age	14.41 (1.86)	11.5	17.25
Age at brain tumor diagnosis	5.59 (2.89)	1.16	9.00
Male/Female	12/2	--	--
Caucasian/African-American	12/2	--	--
Medulloblastoma/ependymoma	10/4	--	--
Received radiation therapy;	14	--	--
Average dose in Gy[§]	54.8 (9.1)	54.0	55.8
Received adjuvant chemotherapy	11	--	--
Received surgical resection	14	--	--
Weight (kg)	44.28 (10.51)	28.34	65.31
Fat free mass (kg)	39.70 (9.33)	26.22	55.43
Height (in)	59.54 (3.08)	54.00	63.00
BMI	19.20 (3.38)	14.50	25.50
BMI Percentile	40.84 (33.83)	1.00	87.00

Note. [§]Radiation dose reported is total dose including boost to posterior fossa.
M = mean, SD = standard deviation, Gy = Gray, BMI = body mass index.

Participant characteristics are presented in Table 1. BMIs ranged widely, from the 1^{st} to the 87^{th} percentiles. Although none of our participants had a BMI that met CDC criteria for the obese range (>95^{th} percentile), 3 were in the overweight range (>85^{th}

percentile), and 3 were classified as being underweight (<5th percentile). All participants received very similar doses of cranial radiation therapy (54.0-55.8 Gy), and none received any radiation to the heart. Fitness variables including VO_2max, RER, ventilation (VE), maximum HR (HRmax) and self-report physical activity are presented in Table 2. Twelve of 13 participants reached VO_2max according to the aforementioned criteria. On average, participants reported almost a standard deviation less physical activity than their same age peers, though this ranged widely. LESS domain and overall scores are also presented in Table 2.

Table 2. Fitness test and self-report physical activity results

Fitness Measure	N	M (SD)	Min	Max
VO_2max (ml·kg^{-1}·min^{-1})	12	31.8 (7.2)	22.6	44.0
VO_2max /FFM (ml·kg FFM^{-1}·min^{-1})	12	35.3 (5.8)	28.6	45.8
HRmax (beats·min^{-1})	13	187.0 (11.2)	164.0	205.0
RER	13	1.2 (0.1)	0.9	1.4
VEmax	13	50.8 (18.0)	18.4	75.3
PAQ z-score	14	-0.8 (0.9)	-2.3	1.1
LESS Overall Score	14	3.8 (1.8)	0	7
LESS Neurology Score	14	0.5 (0.5)	0	1
LESS Endocrinology Score	14	1.6 (0.7)	0	2
LESS Visual/Auditory Score	14	0.9 (0.9)	0	2
LESS Other Score	14	0.7 (0.9)	0	2

Note. VO_2max = peak oxygen uptake; VO_2/FFM = peak oxygen uptake relative to fat-free mass; HRmax = maximum heart rate; RER = respiratory exchange ratio; VEmax = maximum ventilatory threshold; PAQ = physical activity questionnaire (age-appropriate version). LESS = Late Effects Severity Score.

As would be anticipated, VO_2max was found to be related to percent body fat. Therefore, we calculated VO_2max using only fat-free body mass (VO_2max/FFM) to investigate its relationship with other demographic variables. Using two-tailed partial correlations, z-scores of self-report physical activity were related to VO_2max/FFM after accounting for age (Table 3; $p<0.05$). VO_2max/FFM was not related to gender, which is unusual but likely relates to the unequal numbers of males and females in our cohort. VO_2max/FFM was also not related to receipt of chemotherapy, age at diagnosis, or race. In examining the relationship between fitness and late effects, greater neurological late effects were related to lower VO_2max/FFM scores. Cardiorespiratory fitness was not related to any other LESS domain scores or the overall LESS score.

In single sample two-tailed *t*-test comparisons to Groen et al.'s reported values[27] (Table 4), in order to grossly estimate a comparison between the cardiorespiratory fitness of pediatric brain tumor survivors compared to typically developing peers and other chronic illness control groups, brain tumor survivors' VO_2max scores were lower than those of healthy controls ($p<0.001$) as well as children with CF ($p<0.001$). No differences were found between brain tumor survivors and children with CHD on VO_2max. Brain tumor survivors had higher HRmax values than children with CHD. No differences among RER were found.

Table 3. Partial correlations between VO_2max (ml·kg $FFM^{-1}·min^{-1}$) and descriptive demographic/self report variables after accounting for age at evaluation

Descriptive Variable	VO₂max Partial Correlation	
	df	Partial *r*
PAQ z-score[1]	9	0.70*
Received chemotherapy[2]	9	0.03
Age at diagnosis[1]	9	-0.20
Gender[2]	9	-0.50
Race[2]	9	-0.39
LESS[3] Total	9	-0.24
LESS Neurology	9	-0.69*
LESS Endocrinology	9	0.03
LESS Visual/Auditory	9	0.29
LESS Other	9	-0.42

Note. VO_2max = peak oxygen uptake calculated using only fat-free body mass; PAQ = physical activity questionnaire (age-appropriate version); LESS = Late Effects Severity Score
*p<0.05
[1] Pearson correlation coefficient reported. Higher scores on the PAQ indicate more reported exercise.
[2] Point-biserial correlation coefficient reported. Received chemotherapy: 0 = no, 1 = yes. Gender: 0 = male, 1 = female. Race: 0 = Caucasian, 1 = African-American.
[3] Pearson correlation coefficient reported. Higher LESS scores indicate more severe late effects.

After adjusting our sample's VO_2max levels up by 11% to obtain estimated treadmill VO_2max scores, no differences were noted in VO_2max or HRmax between brain tumor survivors and other types of childhood cancer survivors using single sample two-tailed *t*-tests (Table 5). The brain tumor survivor cohort also had higher RER values than the childhood cancer cohort.

Table 4. Comparison of our cohort of brain tumor survivors with healthy controls and other chronic illness groups from Groen and colleagues[25]

Fitness Variable	BTS	Healthy	CF	CHD
VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)	31.8 (7.2)	49.3 (7.9)***	42.5 (6.8)***	33.7 (8.9)
HRmax ($beats \cdot min^{-1}$)	187 (11)	193 (7)	188 (10)	164 (28)***
RER	1.2 (0.1)	1.16 (.07)	1.19 (.06)	1.19 (.15)

Note. VO_2max = peak oxygen uptake; HRmax = maximum heart rate; RER = respiratory exchange ratio; BTS= brain tumor survivors; CF=cystic fibrosis; CHD = chronic heart disease. All values are mean (SD). Single sample *T*-test comparisons with the BTS cohort: ***$p<0.001$

Table 5. Comparison with other childhood cancer survivors from De Caro, et al.[27]

Fitness Variable	BTS	CCS
VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)	35.3 (7.9)§	38.1 (8.4)
HRmax ($beats \cdot min^{-1}$)	187 (11)	191 (14)
RER	1.2 (0.1)	1.1 (0.1)*

Note. § Estimated treadmill test value (equal to the cycle ergometer value multiplied by 1.11). VO_2max = peak oxygen uptake; HRmax = maximum heart rate; RER = respiratory exchange ratio; BTS = brain tumor survivors; CCS= childhood cancer survivors (excluded brain tumor survivors). All values are mean (SD). Single sample *T*-test comparisons with the BT cohort: *$p<0.05$

Discussion

Our preliminary findings suggest that VO_2max testing is feasible and safe to perform with survivors of pediatric brain tumor. Although 1 participant was unable to complete the testing due to a sensitive gag reflex, this is unlikely to be related to his tumor or treatment. In fact, posterior fossa syndrome, which can occur after resection of a posterior fossa tumor, may be associated with bulbar palsy, which includes loss of gag reflex[30]. Of the 13 participants who did complete VO_2 testing, 12 were able to reach a true VO_2max. This percentage of over 92% achieving a true VO_2max compares quite favorably with the 82% reported for healthy children in prior studies.[31,32] Though this was essentially a pilot study with a small sample size, our findings suggest that most pediatric brain tumor survivors are able to exercise to the point of maximum respiratory capacity as well as most healthy children.

Pediatric brain tumor survivors reported levels of exercise that were almost one standard deviation lower than normative means. This is consistent with previous studies reporting low levels of physical activity in this population[33]. The validity of self-report levels of exercise in this population was supported by the fact that lower self-reported physical activity was related to lower objective cardiorespiratory fitness scores. Additionally, greater neurological late effects were related to lower fitness scores in our cohort. The main specific neurological late effects included cranial nerve palsies and balance difficulties. While each of our participants was able to ride a stationary bicycle with little difficulty, it is likely that these neurological impairments contribute to lower rates of exercise in daily life.

Comparison with control subjects reported elsewhere[27] indicated that cardiorespiratory fitness in pediatric brain tumor survivors is lower than that in healthy peers. Of note, the peak oxygen uptake scores of Groen and colleagues' cohort on the cycle ergometer may be somewhat elevated as this study was conducted in the Netherlands, where bicycle riding is more prevalent than in the United States[34]. However, pediatric brain tumor survivors' cardiorespiratory fitness was also poorer compared to that of children with pulmonary disease (Cystic Fibrosis), and was comparable to that of children with chronic heart disease in the Netherlands. The causes of reduced cardiorespiratory fitness in pediatric brain tumor survivors are not clear; it is likely due to a combination of tumor and treatment sequelae (including cardiovascular, endocrine, and functional problems) as well as lower rates of physical exercise. The reduced cardiorespiratory fitness in our sample was not due to fat mass, as none of our participants were labeled obese and in fact almost one-fourth were classified as being underweight. Additionally, female adolescents tend to have lower cardiorespiratory fitness scores than males[35], and as our sample only contained 2 females, it might actually represent a slight overestimation of the cardiorespiratory fitness of the brain tumor survivor population as a whole.

Finally, our pediatric brain tumor survivor cohort's cardiorespiratory fitness, adjusted to estimate values obtained using a treadmill protocol, was not significantly different from that of survivors of other types of childhood cancer.[29] Notable, however, is that the childhood cancer survivor cohort tended to be obese (31% had BMIs > 95th percentile), which certainly reduced their cardiorespiratory fitness. Despite our pediatric brain tumor survivor cohort not being obese, their values were still comparable to that of the childhood cancer survivor cohort, indicating that other limiting factors are present for the brain tumor cohort. These might include growth hormone deficiency, depression, or balance problems that limit or inhibit participation in physical activity. Nonetheless, the brain tumor survivors in our study were able to push themselves to their respiratory capacities, as their RER values were equal to or greater than those reported in other studies, with no adverse events occurring.

The principal weakness of this study is the small sample size, which makes it difficult to draw definitive conclusions regarding the safety and feasibility of maximum capacity aerobic exercise for all survivors of pediatric posterior fossa tumor.

Additionally, our statistical analyses comparing findings across published studies provide broad estimates of the fitness of our cohort compared to other pediatric healthy and chronic illness cohorts, not exact comparisons. Although we used a small cohort and compared findings across published studies, our data reports on the feasibility and safety of cardiorespiratory fitness testing on a novel population, which encourages further research in this area. Future studies should examine the cardiorespiratory fitness of survivors of other types of pediatric brain tumor, since we only included posterior fossa tumor survivors, to compare the effects of tumor location and treatment regimen across cohorts. Future studies should use larger sample sizes to more definitively establish the safety of vigorous exercise in this population, in addition to examining other factors that might contribute to reduced rates of exercise, including psychological and cognitive factors.

Regular exercise is important for various domains of health, including physical, emotional, and cognitive development. Pediatric posterior fossa tumor survivors are known to often have difficulties in all three of those areas. The pediatric posterior fossa tumor survivors in our study reported exercising less often than their peers, and had lower cardiorespiratory fitness scores than healthy and chronic illness samples from other published studies. However, the majority of our cohort demonstrated no impairments in the ability to reach peak respiratory capacity during exercise, indicating that physical exertion is likely a safe and feasible activity to include in their daily lives. This study lays groundwork for exercise interventions with pediatric brain tumor survivors, many of whom are in need of increased physical activity in their daily lives.

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AN FMRI INVESTIGATION OF WORKING MEMORY AND ITS RELATIONSHIP WITH CARDIORESPIRATORY FITNESS IN PEDIATRIC POSTERIOR FOSSA TUMOR SURVIVORS WHO RECEIVED CRANIAL RADIATION THERAPY

by

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Abstract

Objectives: The present study investigated the relationship between cardiorespiratory fitness and executive functioning in pediatric brain tumor survivors who received cranial radiation. This population is known to show executive dysfunction and lower rates of aerobic exercise compared to peers.

Method: Nine adolescent survivors of pediatric posterior fossa tumor completed a working memory task during a functional MRI scan, and cardiorespiratory fitness testing on a cycle ergometer.

Results: Neuroimaging findings indicated typical activation patterns associated with working memory, mainly in the frontal-parietal network. Higher cardiorespiratory fitness was related to better performance on parent-report and behavioral measures of executive functions, and more efficient neural functioning.

Conclusions: This study provides preliminary evidence that exercise may be an effective intervention for executive functions, particularly working memory, in pediatric brain tumor survivors. Descriptions of the brain regions recruited for working memory by pediatric brain tumor survivors may be used to inform future interventions or indicators of treatment efficacy.

Introduction

Brain tumor is the second most common type of childhood cancer, accounting for approximately 20% of all diagnoses (Kaatsch, 2010). In a recent epidemiological review, males composed about 57% of the pediatric brain tumor population, and the overall incidence of pediatric brain tumor was approximately 4.5 in 100,000 (Central Brain Tumor Registry of the United States, 2007-2008). Pediatric brain tumor is hardly a unitary construct, as tumor type, location, histology, and age at diagnosis may all have a significant impact on medical therapies, survival rates, and late effects associated with survivorship. Tumors occuring beneath the posterior fossa are the most common tumors in childhood (Crawford, MacDonald, & Packer, 2007).

The advent of multimodal treatment in pediatric posterior fossa tumor has significantly increased survival rates in the past few decades, even up to 90% for average-risk pediatric medulloblastoma (Crawford et al., 2007). Consequently, survivorship issues have become increasingly important. Late effects from the tumor and treatment may be severe and include endocrine, neurological, hearing/visual, and especially cognitive dysfunction (Anderson, 2005). Recent studies have found substantial evidence for impairment in executive functioning in survivors of childhood posterior fossa tumor, including specific deficits in working memory (see Wolfe, Madan-Swain, & Kana, 2012, for a systematic literature review). However, attempts to address these deficits through cognitive and pharmacological intervention have yielded mixed results (Butler et al., 2008; Hardy, Willard, & Bonner, 2011). While a tumor in the posterior fossa region would not necessarily be expected to produce deficits in working memory, current literature indicates that cranial radiation therapy (CRT) directly impacts the neuroanatomical structures underlying core executive functions, such as working memory, which over time results secondarily in decreased IQ and academic achievement scores (Butler & Mulhern, 2005; Palmer, 2008). Deficits in working memory and other domains of executive functions affect many aspects of life, including social, adaptive, academic, and career outcomes (Wolfe et al., 2012).

Historically, the prefrontal cortex has been considered the epicenter of executive functions such as working memory (Goldman-Rakic, 1987). The n-back working memory task is a classic paradigm in which the subject is asked to monitor a series of stimuli and indicate whether the current stimulus presented is the same as the one seen *n* trials previously (n is usually 0, 1, 2 or 3; Kirchner, 1958). The n-back task places demands on a number of components of working memory, including monitoring, updating, and manipulating short-term storage of information, and is arguably considered the gold standard paradigm for measuring working memory (Conway et al., 2005). In a meta-analysis of n-back studies in adults using functional magnetic resonance imaging (fMRI) techniques, robust activation was noted across studies in frontal poles, dorsolateral and ventrolateral prefrontal cortices, lateral premotor cortex, dorsal cingulate and medial premotor cortex, and medial and lateral posterior parietal cortices (Owen, McMillan, Laird, & Bullmore, 2005). Thus, consistent patterns of frontal-parietal activation were significant in accomplishing n-back working memory tasks in adults. While there are fewer fMRI working memory studies in child and adolescent populations, findings have been largely consistent with adult studies, namely finding frontal and parietal activation in children as young as 8 years of age (Nelson et al., 2000; Casey et al., 1995).

While there is an abundance of literature documenting the neurocognitive sequelae associated with brain tumor diagnosis and treatment, there are relatively few studies attempting to remediate these deficits. Results of intervention studies including pharmacological and cognitive interventions have been equivocal, particularly in the domain of executive functioning (Wolfe et al., 2012). An as-yet unexplored avenue for improving executive functioning in survivors of pediatric brain tumor may be physical exercise. Aerobic exercise has been linked with various physiological benefits, including improvements in cardiovascular and metabolic functioning. Recent data indicates that exercise interventions also have been associated with improved cognitive outcomes in studies with both aging adults and children (Colcombe & Kramer, 2003; Tomporowski, Davis, Miller, & Naglieri, 2008). Cross-sectional studies have found correlations between cardiorespiratory fitness and higher cognitive functioning in children and adolescents (Buck, Hillman & Castelli, 2008; Themanson, Pontifex, & Hillman, 2008; Aberg et al., 2009; Stroth et al., 2009). The cognitive benefits of exercise may be particularly relevant for youth with disability, such as survivors of pediatric brain tumor, as they often experience more barriers to physical activity than typically developing peers (Ploughman, 2008). The relationship between exercise and cognition has been examined at various levels including translational and human research throughout development, and has unexplored potential as an intervention for executive deficits in survivors of pediatric brain tumor.

The present study was designed to investigate the neural responses to an n-back working memory task in adolescent survivors of pediatric posterior fossa tumor who received CRT, as well as to investigate the relationships between behavioral and neural measures of executive functioning and cardiorespiratory fitness in this population. We hypothesized that our sample would show essentially typical patterns of activation in response to this task, including frontal and parietal activation (Owen et al., 2005). We also hypothesized that improved cardiorespiratory fitness in our sample would be associated with improved scores on parent-report and behavioral measures of executive functioning, with more "typical" (i.e. similar to that reported in the literature) patterns of neural activation in response to the n-back task, and with greater functional connectivity between neural areas during the n-back task. This is one of the first studies to utilize functional magnetic resonance imaging (fMRI) techniques to study neural activation patterns in pediatric brain tumor survivors. In doing so, we provide insight into the brain regions recruited for working memory by pediatric posterior fossa tumor survivors, an area of commonly-noted deficits in this population. These data may be used in future studies as targets for intervention or as indicators of treatment efficacy.

Methods

Participants

Survivors of posterior fossa tumor were recruited consecutively from the neuro-oncology clinic at an urban children's hospital in the United States. Eligible survivors were identified through medical records and approached for recruitment either during regular clinic follow-up visits or by phone if no clinic appointment was scheduled. All participants who were approached agreed to participate in the study. Fourteen participants were eligible to participate and provided informed assent along with their caregivers' informed consent in accordance with the protocol approved by the Institutional Review Board. Four participants wore oral braces, which although safe for the scanner, rendered the imaging unusable. One participant could not begin the VO_2max testing due to a strong gag reflex, as he was unable to wear the mouthpiece. Thus, nine participants completed the study protocol successfully (see Table 1 for descriptive data).

Table 1. Participant characteristics

Demographic	Mean (SD)	Min	Max
Age (years)	14.89 (1.9)	11.50	17.25
Age at brain tumor diagnosis (years)	5.00 (2.7)	1.33	8.00
Male/Female	8/1	--	--
Caucasian/African-American	8/1	--	--
Medulloblastoma/ependymoma	6/3	--	--
Received cranial radiation therapy	9	--	--
Average radiation dose in Gy[§]	54.62 (0.9)	54.00	55.80
Received adjuvant chemotherapy	7	--	--
Received surgical resection	9	--	--
VO_2max /FFM (ml·kg FFM^{-1}·min^{-1})	33.87 (3.7)	29.26	40.42
WASI Full-Scale IQ	85.30 (10.8)	70	109
BRIEF GEC	57.20 (8.6)	42	68

SD = standard deviation; min = minimum value; max = maximum value; VO_2max /FFM = peak oxygen uptake calculated using fat-free mass; WASI = Wechsler Abbreviated Scale of Intelligence; BRIEF GEC = Behavior Rating Inventory of Executive Function Global Executive Composite.

[§]Radiation dose reported is total dose including boost to posterior fossa. Gy = Gray.

Inclusion criteria for participation included (a) Posterior fossa tumor survivors at least two years post-completion of medical therapy; (b) Received cranial radiation therapy as part of treatment; (c) Between the ages of 11-18 years; (d) Full-Scale IQ $\geq$ 70, so as to be able to comprehend and fully participate in the working memory task; (e) Right-handed, due to the neuroimaging component; (f) English speaking; and (g) Lansky score ≥ 70, in order to ensure ability to pedal the cycle ergometer (Lansky, List, Lansky, Ritter-Sterr, & Miller, 1987). Additionally, as this study involved fMRI, exclusionary criteria included any individuals with metal or other implants that were unsafe for the scanner, or participants who were claustrophobic. Participants received a small monetary compensation for participating in the study.

Demographic and Psychological Measures

IQ screening was performed using the *Wechsler Abbreviated Scale of Intelligence (WASI;* Wechsler, 1999). Handedness was assessed through self-report and caretaker-report, and confirmed using the Edinburgh Handedness Inventory, a brief questionnaire assessing dominant handedness (Oldfield, 1971). Lansky scores were assessed through examiner observation. Each participant's parent or caretaker completed several paper-and-pencil measures, including a demographics questionnaire and the *Behavior Rating Inventory of Executive Function (BRIEF)*, an ecologically-valid measure of real-world executive function behaviors (Gioia, Isquith, Guy, & Kenworthy, 2000) that has been widely used with pediatric brain tumor survivors (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002). Summary scores obtained from the *BRIEF* for analyses included the Global Executive Composite (GEC), Metacognition Index (MI) and Behavioral Regulation Index (BRI).

Data Acquisition

Brain activation and synchronization associated with working memory and increased cognitive demand were examined using fMRI. Structural images were first acquired during an anatomical scan using high resolution T1-weighted scans using a 160 slice 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo) volume scan with a TR = 200 ms, TE = 3.34 ms, flip angle = 7, FOV = 25.6cm, 256 X 256 matrix size, and 1 mm slice thickness. To record functional imaging data, a single-shot gradient-recalled echo-planar pulse sequence was used which offers the advantage of rapid image acquisition (TR = 1000 ms, TE = 30 ms, flip angle = 60 degrees, FOV = 24 cm, matrix 64 x 64). This sequence covers most of the cortex (17 slices, 5mm thick, with a 1 mm gap were acquired in an oblique-axial orientation) in a single cycle of scanning (1 TR) with an in-plane resolution of 3.75 x 3.75 x 5mm. All tasks were completed in a single fMRI session per participant lasting about 60 minutes conducted on a Siemens 3T Allegra MRI scanner (Siemens Corporation, Erlangen, Germany). While in the scanner, E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA) was used to present the stimuli. An IFIS interface (Integrated Functional Imaging System, Invivo Corporation, Orlando, FL) projected the data onto a screen behind the participant's head, who viewed it through a mirror. Responses to the stimuli were recorded using fiber-optic button boxes, which indicated performance accuracy and response time.

Experimental Stimuli

During the functional imaging scan, participants completed an n-back working memory task, a paradigm that has been used in a multitude of previous studies with both children and adults (Owen et al., 2005; Casey et al., 1995; Koshino et al., 2005). In this task, a randomized series of letters of the alphabet was presented, and participants were asked to press a button during three separate conditions: Whenever they saw the letter "x" (0-back condition), whenever they saw the same letter twice in a row (1-back condition), or whenever the letter they saw was the same as two before (2-back condition). Letters were presented for 500 ms each, with a 1500 ms inter-stimulus interval during which the participant could still respond. In each condition, 40 letters were presented, with eight targets. Presentation of conditions was counterbalanced such that participants performed each condition twice, but in reverse order (i.e., 0-back, 1-back, 2-back, 2-back, 1-back, 0-back). Participants were given ample opportunity to practice the task on a laptop computer prior to entering the scanner, and were given one truncated practice run of each condition using different stimuli while inside the scanner before beginning the task.

Cardiorespiratory Fitness Testing

Maximum oxygen uptake, or VO_2max, testing was completed on a Monark stationary cycle ergometer. A standardized protocol was employed to help each participant achieve his or her maximum aerobic capacity. We chose to use the cycle ergometer instead of the more traditional treadmill test because of the problems in balance often experienced by pediatric posterior fossa tumor survivors (Schoch, Konczak, Dimitrova, Gizewski, Wieland, & Timmann, 2006). Heart rate data was captured using a POLAR Vantage XL heart rate (HR) monitor (Gays Mills, WI, USA). Participants warmed up by cycling at a rate of 25 Watts for 4 minutes. For participants with a heart rate of greater than 110 beats/minute after the 4-minute warm-up, workload was increased by 12.5 Watts/minute throughout the rest of the test. For participants with a heart rate of less than 110 beats/minute after the 4-minute warm-up, workload was increased by 25 Watts/minute throughout the rest of the test. Very similar protocols have been used extensively in exercise science literature (e.g., Dzurenkova, Marcek, & Hajkova, 2011; Loftin, Sothern, Warren, & Udall, 2004; Takken, Henneken, van de Putte, Helders, & Engelbert, 2007). Oxygen uptake and carbon dioxide production were measured continuously using a Physiodyne Instrument Corporation, MAX-II Cart (Quogue, NY, USA). Gas analyzers were calibrated with certified gases of known concentrations. Participants were encouraged to maintain work output for as long as they could and the test was terminated when participants could no longer maintain the prescribed work level.

Standard criteria for HR, respiratory exchange ratio (RER), and plateauing were used to assess achievement of VO_2max (Rowland, 1996). Cardiorespiratory fitness variables obtained for behavioral data analyses included VO_2max/FFM, or maximum oxygen uptake in relation to fat-free body mass (since adjusting VO_2 for body mass would be confounded by fat mass); RER, or respiratory exchange ratio (ratio of oxygen to carbon dioxide; a measure of physical exertion); maximum HR; and maximum ventilation (VE), a measure of lung capacity.

Data Analysis

Behavioral and cardiorespiratory fitness data were analyzed using SPSS version 11.5 for Windows. Scores on the *BRIEF* and *WASI* were standardized according to age and gender. Because of the smaller sample size and thus decreased statistical power, analyses were limited to bivariate or partial correlations and paired *t*-tests.

The fMRI data were pre- and post-processed, and statistically analyzed using SPM8 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Images were corrected for slice acquisition timing, motion corrected, spatially realigned, normalized to the Montreal Neurological Institute template and spatially smoothed with an 8-mm Full Width Half Maximum filter. Statistical analyses were performed on individual data using the general linear model, while group analyses were performed using a random-effects model. Regions of interest (ROIs) with statistically significant activation were identified using a t-statistic on a voxel by voxel basis. To correct for multiple comparisons, a spatial clustering operation was performed in AFNI using AlphaSim with 10,000 Monte Carlo simulations taking into account the entire functional matrix, with a map-wise false-positive probability of $p<0.05$.

Functional connectivity (synchronization of the time-course of activation across spatially remote brain areas) was computed for each participant by correlating the average time course of signal intensity of all the activated voxels within the functionally-defined ROIs. The activation time course extracted for each participant over the activated voxels within each ROI originated from the normalized and smoothed images, which were high-pass filtered and had the linear trend removed. Correlation coefficients were calculated by comparing the time courses across ROIs. A Fisher's r to z transformation was applied to the correlation coefficients for each participant before averaging and conducting the statistical comparison of the two experimental conditions.

Results

Descriptive and Behavioral Data

All participants who began the fitness test achieved a VO_2max score during cardiorespiratory fitness testing; further details of the feasibility of physical fitness testing and the physical fitness of this cohort compared to published normative data are described elsewhere, as they are outside the scope of the present paper (Wolfe et al., personal communication). IQ screening on the *WASI* and parent report on the *BRIEF GEC* indicated wide ranges of cognitive and executive function abilities, respectively (Table 1).

Analysis of performance accuracy and reaction time on the fMRI task across subjects indicated their active participation in the task. Average reaction times increased across conditions as the task demand (working memory load) increased. A paired sample two-tailed *t*-test revealed significant changes in reaction time from 0-back to 1-back, $t(10) = -2.67$, $p<0.05$, and from 0-back to 2-back, $t(10) = -2.31$, $p<0.05$, with reaction times becoming longer as the difficulty increased. As hypothesized, performance accuracy tended to decrease linearly across conditions as task difficulty increased, with poorer accuracy in 2-back condition compared to both 0-back ($t[10] = 4.26$, $p<0.01$), and 1-back ($t[10] = 4.08$, $p<0.01$), conditions.

Neural Activation Patterns

Group analysis of activation for all three working memory conditions combined versus fixation (0back + 1back + 2back vs. fixation) showed patterns of frontal-parietal activation ($p<0.001$, with cluster threshold = 72 contiguous voxels determined by Monte Carlo Simulation using AlphaSim). Specifically, seven clusters of significant activation were noted in: right inferior frontal gyrus (RIFG), supplementary motor area (SMA), left insula (LINS), right insula (RINS), left inferior parietal lobule (LIPL), right inferior parietal lobule (RIPL), and right middle occipital gyrus (RMOG; see Figure 1). Previous studies have implicated IFG and IPL in mediating different aspects of working memory (IFG: phonological storage; IPL: visual rhyming; Baldo & Dronkers, 2006). Therefore, the recruitment of IFG and IPL to perform this n-back task suggests a grossly typical working memory cortical network in this group of pediatric brain tumor survivors.

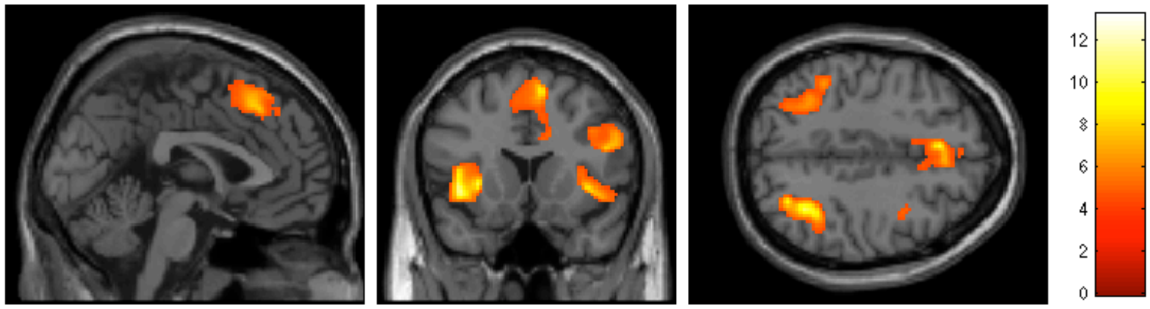

Figure 1. Group combined activation across conditions compared with fixation baseline (0-back + 1-back + 2-back – Fixation).
Clusters of activation are noted primarily in frontal and parietal areas.

Executive Functioning and Cardiorespiratory Fitness

Hypothesis-driven one-tailed partial correlations between *BRIEF* summary scores and fitness variables, controlling for age, indicated that higher RER values were related to better executive functioning on the *BRIEF GEC* (*pr* = -0.62, $p<0.05$) and the *BRIEF MI* (*pr* =-0.63, p<0.05). Thus, better parent-reported executive functions, specifically metacognitive skills, corresponded with achieving higher rates of respiratory exertion on the fitness test (see Figure 2).

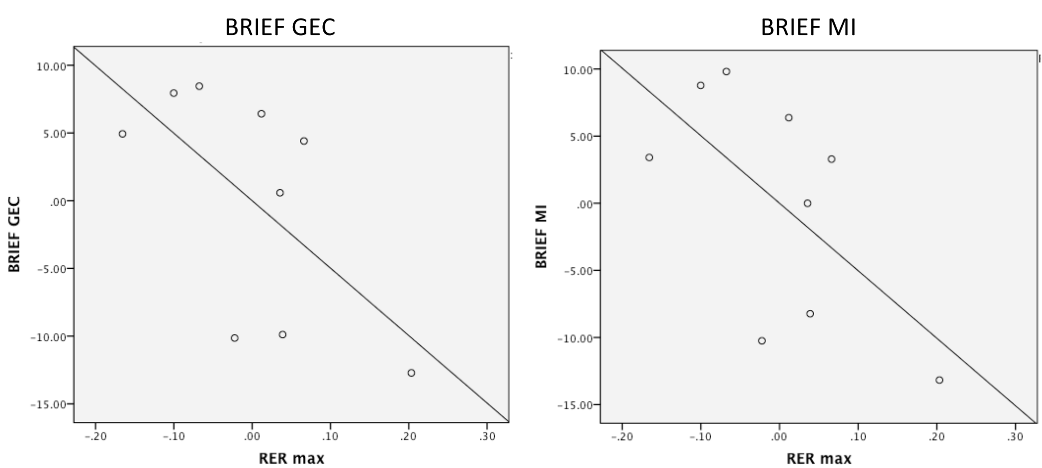

Figure 2. Partial correlations between RERmax and BRIEF summary scores after accounting for age at evaluation.
BRIEF = Behavior Rating Inventory of Executive Functions; GEC = Global Executive Composite; RER max = maximum Respiratory Exertion Rate; MI = Metacognition Index

Behavioral data including accuracy and reaction time were collected from the working memory task. Participants' VEmax, or maximum lung capacity, was related to reaction time across 0-back ($pr = -0.74$, $p<0.05$), 1-back ($pr = -0.69$, $p<0.05$), and 2-back ($pr = -0.71$, $p<0.05$) conditions after controlling for age, such that participants with greater cardiorespiratory lung capacity showed faster reaction times in all conditions of the working memory task (see Figure 3).

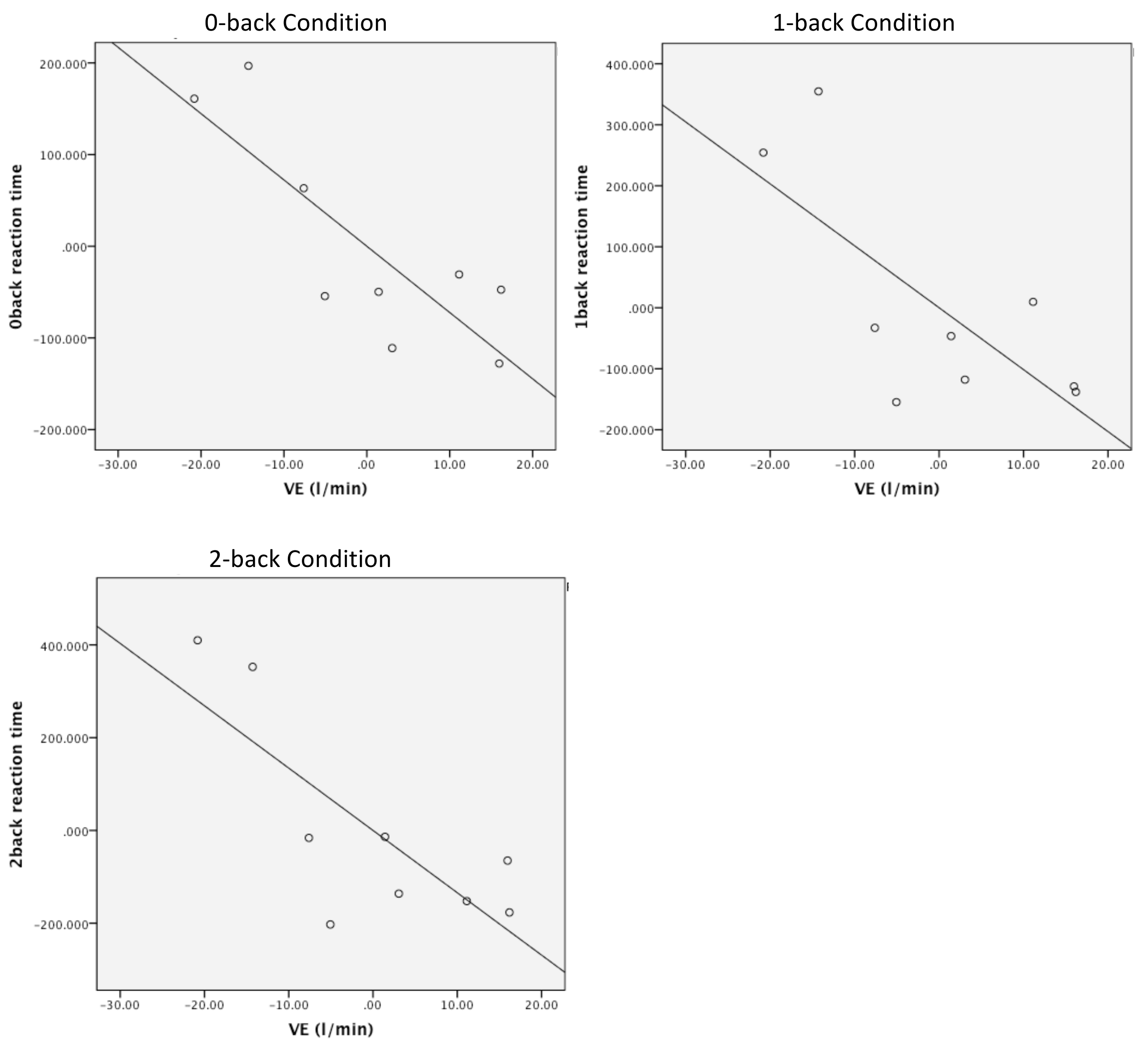

Figure 3. Partial Correlations between 0-back, 1-back, and 2-back condition reaction times and VE max after accounting for age at evaluation.
VE = Ventilation (a measure of respiratory capacity); l/min = liters per minute (units of VE).

As an index of brain response, the number of activated voxels was counted from ROIs mentioned above across all participants. Two-tailed paired samples *t*-tests were conducted to assess differences in activated voxel count by condition; however, no significant differences across conditions were found. We hypothesized that an interaction might be the underlying cause of this lack of linear differences in voxel count. To test this, we obtained two-tailed partial correlations between activated voxel counts across ROIs and VO_2max/FFM scores, accounting for age. An interaction was found such that higher cardiorespiratory fitness scores were correlated with lower activation in the 0-back condition compared against baseline across ROIs ($pr = -0.88$, $p<0.01$) after accounting for age at the time of participation in the study. However, in the 2-back condition compared against baseline, higher cardiovascular fitness scores correlated with *greater* activation across ROIs ($pr = 0.71$, $p<0.05$). We did not find any significant correlation between VO_2max/FFM scores and active voxel counts in any ROI in the 1-back condition compared to baseline. Thus, the activation patterns of higher-fit participants appeared to be more efficient in that they showed less brain activation during the easier task, and were able to recruit additional voxels during the more difficult task (see Figure 4). The strength of these correlations is notable, and indicates that cardiorespiratory fitness may be associated with more efficient neural processing in survivors of pediatric brain tumor.

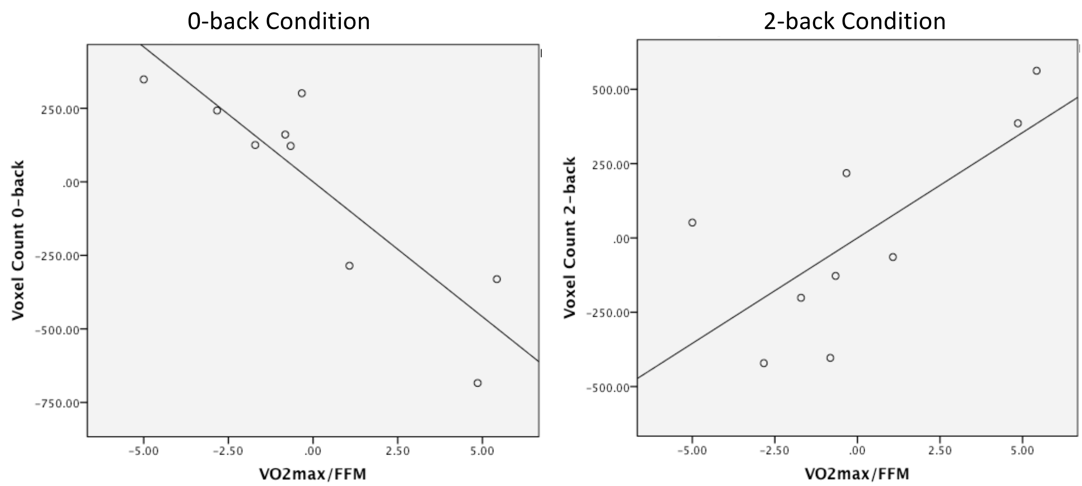

Figure 4. Partial correlations between VO_2max/FFM and voxel count activation in 0-back and 2-back conditions, after accounting for age at evaluation.
Participants with greater fitness showed a more efficient neural pattern, activating fewer voxels to accomplish the easier, 0-back condition, and more to accomplish the more difficult, 2-back condition. VO_2max/FFM = Peak oxygen uptake after accounting for fat mass.

Overall functional connectivity across ROIs was obtained to assess the relationship between neural synchronization and cardiorespiratory fitness. Functional connectivity approached a relationship with VO_2max/FFM scores using hypothesis-driven one-tailed correlations (r=0.51, p<0.10) such that higher cardiorespiratory fitness was related to greater functional connectivity. The low statistical power in our study due to small sample size is likely a factor in this result not quite reaching significance.

Discussion

The present study is unique given its multidimensional investigation spanning, cognitive, behavioral, and neural aspects of working memory along with cardiorespiratory fitness in pediatric posterior fossa tumor survivors. Hence, the findings provide valuable insights into how a variable like physical exercise may have a significant impact on improving cognitive and neural functioning in this population.

Perhaps the most interesting finding of our study was that higher cardiorespiratory fitness was associated with better executive functioning across several measures in this study. Higher RER, or respiratory exertion, scores were related to fewer parent-reported problems on several *BRIEF* summary scores, with regards to overall executive function and particularly metacognition, or regulation of one's own thoughts and behaviors. VEmax, or the maximum amount of air each participant was able to move in and out of the lungs, was related to quicker responding across 0-back, 1-back, and 2-back conditions. Peak cardiorespiratory fitness after accounting for fat mass (VO_2max/FFM) correlated with more efficient neural response patterns, such that higher fit participants showed fewer activated voxels across ROIs in response to the 0-back condition, and greater number of voxels activated during the 2-back condition, with no differences in overall accuracy between groups. Coefficients of variability indicated that over 50% of variance in voxel counts across 0-back and 2-back conditions was accounted for by aerobic fitness, and in several variables over 90% of variance was accounted for by aerobic fitness, after controlling for age. Additionally, greater functional connectivity, or synchronization of activation across neural areas of interest, approached significance for explaining approximately 50% of variance in cardiorespiratory fitness in our population, with greater connectivity relating to higher levels of fitness. These strong relationships are remarkable given the myriad of factors that can affect VO_2max, executive functions, and neural activation measures.

In humans, physical exercise has been shown to benefit executive functions in elderly, adult, adolescent, and child populations. Colcombe and Kramer (2003) examined 18 randomized controlled trials of aerobic exercise using cognitive outcome measures with adults ages 55-80 years. The strongest effect size for exercise was found in executive function measures ($g = 0.68$); findings support Kramer and colleagues' "selective improvement" hypothesis, which posits that aerobic exercise leads to selective, rather than generalized, cognitive benefits, specifically in executive functions (Kramer et al., 1999). This aligns with a systematic literature review of exercise interventions in children by Tomporowski and colleagues (2008) demonstrating that executive function measures showed the most consistent improvements in response to exercise intervention. Cross-sectional studies of children and adolescents also have found cardiorespiratory fitness to be related to better executive functions (Buck et al., 2008; Stroth et al., 2009). In addition, a recent fMRI study in people with Alzheimer's disease found that greater functional connectivity mediated the relationship between higher cardiorespiratory fitness and better cognitive functioning (Voss et al., 2010).

Cardiorespiratory fitness is a function of both genetic predisposition as well as activity level. It is possible that a common genetic predisposition underlies the relationship between aerobic fitness and cognitive function, i.e., those individuals who have a genetic predisposition towards higher aerobic fitness also have a genetic predisposition towards higher cognitive functioning. An alternate explanation for these relationships would be that a more active lifestyle enhanced both aerobic fitness and cognitive functioning for some participants in this group of pediatric posterior fossa tumor survivors. Given the very high coefficients of variability reported, it is quite possible that both lifestyle and genetic factors may have influenced the reported relationships between working memory and cardiorespiratory fitness. Regardless, these results warrant further study involving exercise training with this population examining working memory outcomes.

This fMRI study also found that pediatric survivors of posterior fossa tumor showed typical activation patterns in response to n-back working memory demands, recruiting mainly frontal and parietal lobe areas. Performing this task involved the participation of regions such as the RIFG, SMA, LINS, RINS, LIPL, RIPL, and RMOG, as shown across measures of activation. This is consistent with the implication of prefrontal, supplementary motor, and inferior parietal areas in previous studies of working memory demand in healthy adult populations (Owen et al., 2005). While our study involved adolescents, previous fMRI studies comparing neural response to working memory tasks between adolescents and adults found broadly similar patterns, with young adolescents recruiting the same neural areas as adults (Casey et al., 1995).

Different roles for inferior frontal and inferior parietal cortices in working memory tasks have been proposed, with inferior frontal areas associated mainly with articulatory rehearsal, and inferior parietal areas implicated in digit span, rhyming, and repetition tasks (Baldo & Dronkers, 2006). The Brodmann's area (47) corresponding to the locations of bilateral INS clusters of activation is shared with ventrolateral prefrontal cortex (vlPFC). Activation in vlPFC was identified as a common finding across n-back working memory tasks in adults and in a spatial working memory task in adolescents (Owen et al., 2005; Schweinsburg et al., 2005). The recruitment of RMOG also is consistent with previous neuroimaging studies of working memory in both adults and children, and has been posited to show increased activity during visual tasks that require focused attention (Nelson et al., 2000; Courtney, Ungerleider, Keil & Haxby, 1997; Beauchamp, Cox, & DeYoe, 1997).

Therefore, our findings indicate that survivors of pediatric posterior fossa tumor recruit similar areas as typically developing individuals to perform working memory tasks, even though they are at increased risk for cognitive deficits in the domain of working memory. These areas may be employed in future studies, for example linking neurocognitive deficits to neural functioning or assessing the direct effects of working memory interventions on neural functioning.

Several limitations to the present study should be discussed, including the cross-sectional nature of our analyses. As this was not a longitudinal or intervention study, we cannot assume that higher cardiorespiratory fitness necessarily caused better executive functioning in this sample. For example, it might be the case that a survivor's better executive functioning resulted in more frequent exercise and thus higher aerobic fitness. Alternatively, a third variable may better explain this relationship, such as depression, which might negatively impact both executive functioning and motivation to exercise. Additionally, while our sample size is reasonable for fMRI analyses, it is small for behavioral analyses and thus the results should be interpreted with caution.

In conclusion, results of the present study are the first to document neural patterns of working memory, an often-found area of deficit, in pediatric posterior fossa tumor survivors who received CRT. Overall, the brain regions our participants recruited to perform this task were largely consistent with functional neuroimaging literature documenting neural responses to n-back and other working memory tasks in typical adult, adolescent, and child populations. This is consistent with studies positing that the neural activation patterns of youth are quite similar to those of adults in executive function tasks (Casey et al., 1995). These neural areas may be useful in future studies as targets for intervention or as indicators of treatment efficacy for working memory interventions in pediatric posterior fossa tumor survivors. In our sample, higher cardiorespiratory fitness across measures was related to indices of parent-report executive function behaviors, behavioral response time data, neural activation, and functional connectivity measures. While our small sample size and lack of control group limit our ability to generalize these findings to pediatric brain tumor survivors as a whole, we have certainly laid groundwork for further study as to the efficacy of exercise as a method of improving executive functioning in this population. Exercise is a low-cost, easily-disseminated intervention that promotes physical and emotional health as well, and is thus likely to benefit pediatric brain tumor survivors in multiple areas. Intervention studies, including randomized controlled trials, will be the next step to substantiate or contradict the potential benefits of aerobic exercise for executive functioning in pediatric posterior fossa tumor survivors.

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CONCLUSIONS

Long-term survivors of pediatric posterior fossa tumor are at increased risk for deficits in executive functions. Executive deficits may lead to difficulties in academic, intellectual, social, and vocational outcomes. Demographic and treatment-related variables also affect the relationship between tumor and long-term cognitive outcomes. The impact of CRT on cognitive functions has been established, in that those who received CRT tend to have greater long-term executive difficulties than those who were treated with surgery and/or chemotherapy alone.

Aerobic exercise has been documented to positively impact executive functions more than any other area of cognition in children, adolescents, and aging adults. We established the safety and feasibility of maximum effort cardiorespiratory exertion for survivors of pediatric posterior fossa tumor, finding that survivors were able to attain maximal effort as well as typically-developing children. Pediatric posterior fossa tumor survivors reported daily physical activity levels almost one standard deviation lower than normative means. Additionally, their cardiorespiratory fitness was below that of published norms for typically-developing children and children with cystic fibrosis, and posterior fossa tumor survivors' fitness was on par with that of children with chronic heart disease. The physical fitness of our pediatric posterior fossa tumor survivors did not differ from previously published data of survivors of other types of childhood cancer, though the childhood cancer cohort tended to be obese, and our brain tumor cohort tended to be underweight. Although it is safe and physically feasible for these survivors to engage in high-intensity aerobic exercise, most are not doing so in their everyday lives.

Working memory is a component of executive functions, involving a "temporary workspace" where information is held for a short time before encoding or discarding it. The fMRI data reported in this document, acquired during a working memory task, indicated that survivors of pediatric posterior fossa tumor utilized typical frontal-parietal brain regions for performing this task, similar to the findings from neuroimaging studies of n-back memory tasks in typically-developing populations. This implies that although survivors may have difficulty with working memory tasks, they recruit similar brain areas as typically developing individuals to perform the tasks. However, since we were unable to compare our cohort with a typically developing control group, it is not clear whether these brain areas are responding to the same degree in survivors as in typically-developing children. If differences are found, these neural areas may be used as targets for treatment or indicators of treatment efficacy, as the intervention literature for executive deficits in pediatric brain tumor survivors continues to grow.

As cognitive demand increased, survivors tended to recruit additional brain regions to perform the task. Additionally, functional connectivity (synchronization of activated brain areas across time) increased with cognitive demand, indicating the need for more neural resources to cope with increased difficulty. With regards to the primary aim of this consortium of studies, cardiorespiratory fitness was found to be related to improved working memory and broader executive functioning across neural, behavioral, and parent-report measurements. Thus, preliminary support for future intervention studies using exercise with executive function outcome measures was provided.

Deficits in working memory, among other executive function deficits, may be particularly detrimental for social, academic, and career outcomes. Unlike difficulties with one particular subject matter (e.g., math) that can be tutored and eventually steered away from as a career choice, executive functions are necessary to succeed across domains in life. Carrying on a conversation, for instance, involves attending to what the other is saying, holding that information in working memory, searching one's own memory for relevant information, formulating a coherent response, and following social cues to determine the correct time to respond aloud. Organization, another aspect of executive functions, is crucial in the workplace as well as at home with one's own finances, plans, and possessions. Decision-making is a complex process involving weighing the pros and cons of various options, and selecting the best option based upon one's goals. This requires working memory, inhibition, and initiation abilities, among others.

Studying the human brain *in vivo* through neuroimaging techniques has revolutionized the way we conceptualize neuroscience questions. As the field of neuropsycho-oncology moves forward, incorporating structural and functional imaging techniques as well as psychophysiological tools (e.g., electroencephalography) will be important in augmenting our understanding of the neurobiological mechanisms behind cognitive deficits in pediatric posterior fossa tumor survivors, and for creating meaningful targets for intervention. In addition, as this is a relatively rare population, standardization of neuropsychological test batteries across sites will be crucial for conducting studies with adequate statistical power to parse out the effects of various demographic and treatment-related variables on cognitive outcomes.

While extant intervention studies have documented some efficacy in addressing attention deficits through stimulant medications (Thompson et al., 2001) and in addressing executive function deficits through cognitive training programs (Butler et al., 2008), the generalizability of these findings to the broader population of pediatric brain tumor survivors, as well as the generalizability of reported gains to real-life functioning, is unclear. Future research should explore additional methods of improving executive functions in this population.

Given the importance of executive functions across settings in everyday life, establishing effective interventions for executive dysfunction in children treated for brain tumors is of utmost importance. Based on the findings of the present study, the next step in this line of research is a randomized controlled trial of aerobic exercise in this population, using executive function outcome measures. Exercise is a feasible, easily-disseminable intervention that can be customized for individual tastes; the important factor seems to be elevating one's heart rate to high levels of aerobic exertion, whether that occurs through swimming, cycling, dancing, running, and so on. As the benefits of exercise for executive functions have been shown across the lifespan in typically developing populations, as well as in adults with Alzheimer's disease or dementia, it is certainly possible, though not taken for granted, that positive effects would be noted in survivors of pediatric brain tumor as well. This finding could carry tremendous applications for the field of childhood cancer survivorship research, as well as have a positive impact on the lives of thousands of long-term childhood brain tumor survivors.

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APPENDIX A

IRB APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on October 26, 2010. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines.

Principal Investigator:	ROSS, KELLY A
Co-Investigator(s):	HUNTER, GARY R KANA, RAJESH KUMAR MADAN-SWAIN, AVI REDDY, ALYSSA T
Protocol Number:	**F100805002**
Protocol Title:	*Cognitive and Neural Correlates of Cardiorespiratory Fitness in Pediatric Posterior Fossa Tumor Survivors*

The IRB reviewed and approved the above named project on 8/25/2010. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 8/25/2010

Date IRB Approval Issued: 9/22/10

Identification Number: IRB00000726

Julius Linn, MD
Julius Linn, M.D.
Acting Chair of the Institutional
Review Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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Principal Investigator:	ROSS, KELLY A
Co-Investigator(s):	HUNTER, GARY R KANA, RAJESH KUMAR MADAN-SWAIN, AVI REDDY, ALYSSA T
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This project received FULL COMMITTEE review.

IRB Approval Date: 9/14/2011

Date IRB Approval Issued: 9-16-11

Identification Number: IRB00000726

Ferdinand Urthaler, MD/RC

Ferdinand Urthaler, M.D.
Chairman of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

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APPENDIX B

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