ACADEMIC FLUENCY IN PEDIATRIC BRAIN TUMOR SURVIVORS TREATED WITH PROTON BEAM RADIATION THERAPY VERSUS PHOTON RADIATION THERAPY

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Amanda E. Child

June 2018

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Abstract

Brain and central nervous system (CNS) tumors are the most common tumor type in children and adolescents, and are often treated with a combination of surgery, chemotherapy, and radiation therapy. Historically, most pediatric brain tumor patients have received photon radiation therapy (XRT). However, this treatment is associated with negative long-term neurocognitive and academic effects due to unavoidable irradiation of healthy brain tissue. In an effort to minimize radiation exposure to healthy tissue, proton beam radiation therapy (PBRT) was developed due to its ability to maximize radiation administered to the tumor and minimize radiation to normal tissue. This therapy is becoming an increasingly popular treatment for children, as scientists theorize that decreased irradiation of healthy brain tissue will correspond to relatively improved long-term cognitive and academic outcomes. However, very little research has explored outcomes in children treated with PBRT. The present study compared long-term cognitive (i.e., working memory, processing speed, vocabulary, attention, shifting, and fine motor) and academic (i.e., reading, math, and writing fluency) outcomes in pediatric brain tumor survivors treated with XRT versus PBRT, and evaluated the degree to which group differences in academic fluency are mediated by cognitive ability. Results revealed that PBRT patients outperformed XRT patients on multiple cognitive measures (vocabulary, processing speed, shifting, working memory) as well as all fluency measures (reading, writing, math fluency). In addition, vocabulary and processing speed fully mediated relations between group and all three fluency outcomes. Working memory also mediated relations between group and math fluency. Findings suggest that academic fluency interventions that are effective for typically developing children with learning disabilities may also ameliorate fluency difficulties in brain tumor survivors,

although modifications would likely be needed due the significant processing speed difficulties that are unique to this population.

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Academic Fluency in Pediatric Brain Tumor Survivors Treated with Proton Beam Radiation Therapy versus Photon Radiation Therapy

Brain and CNS tumors are the most common cancer type in children and adolescents, with an annual incidence of 5.57 per 100,000 individuals (Ostrom et al., 2015). While brain and CNS tumors remain the second most common cause of cancer mortality in this age group (Ostrom et al., 2015), treatment advances have resulted in substantially improved 5-year survival rates, from 59% in 1979 to 75% in 2009 (Ward, Desantis, Robbins, Kohler, & Jemal, 2014). Correspondingly, current research focuses on long-term quality-of-life outcomes following cancer treatment. Unfortunately, this research documents significant impairment in a variety of domains. Specifically, long-term survivors of childhood brain tumors have global psychosocial deficits, with notable difficulty living independently, driving, holding employment, dating, and participating in a typical education (Gurney et al., 2009; Maddrey et al., 2005), in addition to exhibiting social competence deficits (Schulte & Barrera, 2010) as well as long-term risk of psychiatric hospitalization (Ross et al., 2003).

Of significant relevance to school-aged children, in particular, are the significant negative effects of cancer treatment on cognitive as well as academic functioning (i.e., Mabbott et al., 2005; Mulhern et al., 2005), both of which predict functional outcomes such as employment (Benz, Yovanoff, & Doren, 1997; Nybo & Koskiniemi, 1999; Rivera-Batiz, 1992). The current study considers cognitive and academic outcomes in pediatric brain tumor survivors, with particular emphasis on assessing if recent advances in radiation treatment correspond to increased preservation of cognitive and academic functioning, as currently theorized (Merchant et al., 2008).

Mechanism of Action for Photon Beam Radiation Therapy

Radiation therapy damages and often kills cells that are actively dividing by directly or indirectly causing breaks in DNA. Since cancerous cells typically divide much more quickly relative to normal cells, resulting in out-of-control growth, these cells are more susceptible to damage via radiation treatment relative to normal, non-cancerous cells. However, radiation also damages normal cells that are in the process of dividing, resulting in unwanted side effects (Baskar, Dai, Wenlong, Yeo, & Yeoh, 2014). Of note, the rate at which tissue types grow is proportional to the rate at which they die following radiation treatment; specifically, faster-growing tissues (i.e., intestines) are quickly affected by radiation treatment, but slow-growing tissues (i.e., brain tissue) often experience cell death months or years after radiation therapy (Stone, Coleman, Anscher, & McBride, 2003). Most neurogenesis occurs prenatally, so gray matter loss after radiation therapy is subtle or negligible in most brain areas (Nieman et al., 2015). However, neurogenesis within the subventricular zone continues into adulthood, and these neurons later migrate to the olfactory bulb and hippocampus (Houston, Herting, & Sowell, 2014). Correspondingly, children who have undergone radiation therapy show reduced hippocampal volume despite minimal gray matter changes in the rest of the brain (Riggs et al., 2014).

In contrast to its subtle effects on gray matter, radiation treatment causes significant and widespread impaired development or loss of white matter (Mulhern et al., 2001). These white matter changes are thought be attributable to radiation effects on astrocytes, microglia, oligodendrocytes, vascular endothelial cells, and their interactions with one another. However, it remains unclear precisely how these cells’ responses to radiation therapy influence white matter (i.e., by causing white matter loss or by preventing future white matter development) and eventually lead to radiation-induced late effects (Greene-Schloesser et al., 2012). In a normally developing brain, axonal myelination begins in the 3rd or 4th month of gestation and continues until around age 40, with the most rapid myelination occurring during childhood and slower rates of myelination from adolescence to adulthood (Lebel et al., 2012; Miller et al., 2012). Radiation therapy can negatively affect myelination, though, resulting in toxic leukoencephalopathy (Filley & Kleinschmidt-DeMasters, 2001) or, in more severe cases, radiation necrosis (Keime-Guibert, Napolitano, & Delattre, 1998). In addition, radiation appears to have permanent effects on white matter integrity, with white matter abnormalities evident even in adult survivors of pediatric brain tumor (Brinkman et al., 2012).

There are multiple types of radiation therapy, and the conventional approach to radiation uses photons (or x-rays) to target tumor tissue. Photon radiation therapy (commonly abbreviated XRT, for External Beam Radiation Therapy) was first introduced as a method of treating cancer in the late 19th century (Connell & Hellman, 2009). During XRT, photons travel through all tissue in their path without stopping, thus irradiating healthy tissue both in front of and behind the clinical target tissue (i.e., the tumor). The maximum XRT dose is deposited within the first few centimeters of entrance into the tissue, and deposited dose lessens exponentially across the radiation field (Hoffman & Yock, 2009). Ultimately, achieving the desired clinical dose at the target requires substantial irradiation of surrounding healthy tissue.

Irradiation of healthy tissue is particularly problematic for structures that are more susceptible to the effects of radiation due to vulnerability of cells still undergoing neurogenesis (i.e., the hippocampi; Greene-Schloesser et al., 2012) or sensitivity to free radicals produced during radiation (i.e., the cochlea; Wong & Ryan, 2015). Fortunately, in the 1990s, novel CT imaging techniques were developed to allow 3-dimensional visualization of tumors and surrounding healthy structures (Hoffman & Yock, 2009). This, in turn, allowed physicians to develop methods of more precisely targeting tumors with radiation, as well as avoiding sensitive structures. 3-D conformal radiation therapy techniques apply static radiation fields from different angles, and each radiation field is weighted in accordance to with regard to the amount of radiation administered. All radiation fields converge on the target treatment zone so as to provide a maximal additive radiation dose at the tumor and tumor bed (Hoffman & Yock, 2009). However, to achieve this clinical radiation dose at the target, healthy tissue immediately surrounding the tumor bed also receives a substantial dose of irradiation. In addition, structures that are very sensitive to the effects of radiation (i.e., the cochlea or hippocampi) may be irradiated as well.

Intensity Modulated Radiation Therapy, or IMRT, developed in the 2000s, has allowed for further sparing of sensitive structures. Specifically, this allows radiation oncologists to vary and customize the amount of radiation delivered across a radiation beam. For example, physicians often wish to minimize irradiation of the cochlea. Thus, with IMRT, the dose resulting from the area of the radiation beam impacting the cochlea can be minimized, while the rest of the beam can deliver greater dose to the target. The outcome of this approach is that the tumor can receive the desired clinical dose, while surrounding tissue receives less and vulnerable structures receive minimal dose.

Neurocognitive Effects of XRT

Effects of central nervous system radiation are observed in three stages: acute (0-2 months after radiation therapy), subacute (2-6 months after RT), and late effects (> 6 months;

Moore, 2005). Changes seen during or soon after radiation treatment are often attributed to sudden and significant neurological deterioration or effects related to the tumor, chemotherapy, or surgical treatment (Moore, 2005). Effects of radiation therapy, in contrast, typically emerge over time and are associated with gradual and persistent neurocognitive declines in many domains, including processing speed, attention, working memory, language, executive functions, and fine motor functioning (i.e., Edelstein et al., 2011; Mabbott et al., 2005, 2011). Of note, even modern approaches to radiation therapy aimed at reducing dose to healthy tissue (i.e., IMRT) are associated with neurocognitive decline in processing speed, working memory, and academic skills (Kahalley et al., 2013; Mulhern et al., 2005; Schatz, Kramer, Ablin, & Matthay, 2000). Importantly, these declines in scores over time represent a failure to gain skills at the same rate as their typically developing peers; typically, there is no *loss* of function, as raw scores on these measures tend to increase over time (Mulhern, Hancock, Fairclough, & Kun, 1992; Palmer et al., 2001).

In general, it is thought that white matter damage (rather than gray matter damage) or impaired white matter development contribute to long-term neurocognitive effects seen in pediatric brain tumor survivors (Khong et al., 2006; Rueckriegel et al., 2010). These results are consistent with findings that younger age at radiation therapy is associated with reduced normal-appearing white matter (Reddick et al., 2006) as well as poorer neurocognitive outcomes (Mulhern et al., 2001). Neuropsychological correlates of white matter disruption in pediatric brain tumor survivors include slowed processing speed (Aukema et al., 2009; Scantlebury et al., 2016) as well as memory, problem solving, and attention difficulties (Keime-Guibert et al., 1998; Mulhern et al., 2001).

Mechanism of Action and Neurocognitive Effects of PBRT

Charged particle therapies (i.e., proton beam radiation therapy, or PBRT) were developed fairly recently to reduce radiation exposure to healthy tissue. These therapies act by ionizing molecules and atoms in cells, leading to DNA double-strand breaks and, consequently, tumor cell death (Wang, 2015). In contrast to photon beams, which deposit most of their energy almost immediately after entering tissue and continue to deposit energy along their entire path, proton beams deposit maximum radiation dose at the maximum penetration depth, with almost no exit dose to tissues beyond this point (Loeffler & Durante, 2013). Thus, when the maximum dose is deposited at the target tissue, almost no healthy tissue beyond the target tissue is irradiated. There is still an entrance dose, however, since protons lose energy along their trajectory, although the amount of radiation deposited is generally lower than the entrance dose of photon beams (Wang, 2015).

This ability to minimize radiation dose to healthy brain tissue while maximizing radiation dose to the tumor may have important clinical advantages, including minimizing effects on brain development in children. For example, one advantage of PBRT is that it allows physicians to more precisely distribute radiation to the target, avoid sensitive structures such as the cochlea, pituitary gland, and temporal lobes (Kim & Park, 2015), and minimize additional radiation dose to areas immediately surrounding the target. It is important to note that early findings suggest 6-year overall and recurrence-free survival rates are comparable in children treated with PBRT vs. XRT (Eaton et al., 2016), suggesting adequate disease control and affirming its potential as a suitable treatment modality. Side effect profiles are also improved with PBRT, including low rates of audiological effects (see Chapman & Ermoian, 2017 for review).

While there are medical advantages to PBRT relative to XRT, only a few published articles have explored if PBRT is in fact associated with improved neuropsychological outcomes relative to XRT. This is not surprising, however, given that PBRT is a new (although rapidly proliferating) technology. In 2009, only four proton centers in the country treated pediatric brain tumors. There are currently 25 active proton radiation centers, and pediatric brain and CNS tumors are the most common pediatric cancer; however, the incidence rate of pediatric brain tumors is still very low (5.57 per 100,000 individuals, or less than 0.0006% of children; Ostrom et al., 2015). Thus, it takes a great deal of time to accumulate enough patients for systematic study, particularly given that this type of research requires long-term follow-up to assess for late cognitive effects.

Two of the first published open-PBRT studies considered changes in overall IQ and its scales in patients treated with PBRT. Results showed declines in processing speed over time in this treatment group (Pulsifer et al., 2015; Yock et al., 2016), with some evidence for verbal comprehension declines as well (Yock et al., 2016). Additional studies with individuals treated with PBRT have also shown processing speed difficulties (Antonini et al., 2017; Ventura et al., 2018) in addition to difficulties with switching (Antonini et al., 2017), but with preserved intelligence, attention, and executive function skills (Ventura et al., 2018). In addition, one study has compared children treated with PBRT to those treated with XRT in a sample different from the current study. This found significant IQ declines in children treated with XRT, but not in those treated with PBRT; however, there was no significant difference between the IQ slopes between PBRT and XRT groups, possibly due to lack of power or insufficient sensitivity of using a global IQ measure to detect cognitive change (Kahalley et al., 2016). While this study has already made notable contributions to elucidating the true effects of PBRT as compared to XRT, further research will allow for better characterization of the long-term neurocognitive effects of this treatment.

Radiation Effects on Academic Functioning

While research has begun to explore global cognitive functioning in individuals treated with PBRT, only one study to date has considered academic functioning in individuals treated with this relatively novel form of radiation therapy: This found evidence for preserved basic academic skills in individuals treated with PBRT assessed 1.0 to 8.9 years following treatment (i.e., word reading, numerical operations, spelling; Ventura et al., 2018). A greater number of studies have explored academic functioning following brain tumor treatment with XRT. Long-term academic effects of XRT typically include poorer performance on reading, math, and spelling measures relative to controls (i.e., Anderson, Godber, Smibert, Weiskop, & Ekert, 2000; see Robinson et al., 2010 for meta-analysis), although some studies have found comparable performance between radiation treatment and control groups (Mabbott et al., 2011). In addition, declines in academic functioning are observed over time in long-term brain tumor survivors, with greater declines in reading and math in patients diagnosed at a younger (<7 years old) versus older age (Mabbott et al., 2005; Mulhern et al., 2005).

The aforementioned studies have focused on basic untimed academic skills (i.e., word reading, basic math skills, spelling). However, from typically developing children, it is known that the *automaticity* of these basic academic skills (i.e., academic fluency) is a critical precursor for more advanced academic tasks, such as reading comprehension, math word problems, and written expression (Fuchs, Gilbert, et al., 2016; Fuchs, Fuchs, Hosp, & Jenkins, 2001; Limpo, Alves, & Connelly, 2017; Little et al., 2017), particularly beyond the earliest grades. Importantly, processing speed (Kail, 2000) as well as basic academic skills (Hudson, Pullen, Lane, & Torgesen, 2008; Petrill et al., 2012) contribute to increased academic fluency as development progresses. Since radiation therapy has significant negative effects on processing speed (Kahalley et al., 2013; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008), it is particularly important to consider academic fluency outcomes in pediatric brain tumor survivors. However, only one known study explored academic fluency outcomes specifically in this population. Results indicated that academic fluency performance was actually poorer relative to basic academic skills in survivors of pediatric medulloblastoma (Holland, Hughes, & Stavinoha, 2015), affirming that academic fluency skills are particularly vulnerable to XRT. Findings from other clinical populations suggest that brain injuries sustained while skills are still being acquired result in significant deficits, while later injuries are generally associated with relatively preserved skills (Barnes, Dennis, & Wilkinson, 1999). Thus, it is likely that children undergoing brain tumor treatment at an earlier age will have relatively worse academic fluency outcomes, while children who are older during treatment will be somewhat less affected.

In addition to limited research on academic fluency skills, only two known studies of pediatric brain tumor survivors have considered cognitive predictors of academic functioning more broadly. One study found that the relation between white matter integrity and word reading outcomes in adult survivors of childhood brain tumors was mediated by processing speed (Smith et al., 2014), while another found that attentional functioning (as measured by the Conners' Continuous Performance Task, or CPT) accounted for relations between white matter and reading, writing, and spelling (Reddick et al., 2003). Still, additional research is needed to understand the effect of long-term cognitive changes on academic outcomes in children treated with XRT vs. PBRT. Knowing which cognitive changes are most detrimental to academic outcomes will help inform interventions for these children, who have notoriously high rates of academic difficulties (Maddrey et al., 2005; Mulhern et al., 1992).

What also remains unstudied is whether long-term development of cognitive and academic fluency skills in survivors of pediatric brain tumors differs by the type of radiation therapy they received (i.e., PBRT vs. XRT). Scientists are hopeful that PBRT's relative sparing of healthy brain tissue, as compared to XRT, will correspond to improved cognitive and academic outcomes; however, very few studies have compared long-term cognitive outcomes between the two groups, and none have looked at academics. Furthermore, if differences in academic fluency performance do exist, elucidating the cognitive deficits that are driving these differences (i.e., using a mediation model) would aid our understanding of academic difficulties in this population as well as inform potential academic interventions.

Assessment of Academic Outcomes

Similar to literature exploring academic performance in children with brain tumors, academic functioning in typically developing children is also most commonly assessed with untimed measures (e.g., Branum-Martin, Fletcher, & Stuebing, 2013; Catts, Gillispie, Leonard, Kail, & Miller, 2002; Compton, Fuchs, Fuchs, Lambert, & Hamlett, 2012). Thus, while the broad literature within each academic domain is reviewed below, the present study will focus on fluency outcomes.

Reading. Cognitive processes relating to basic reading skills (i.e., untimed word reading) have been thoroughly examined within the broader literature of academic skills. Domain-specific cognitive skills that are important for word reading include basic language processes, particularly phonological awareness (i.e., ability to discern the sound structure of spoken language; Dickinson, McCabe, Anastasopoulos, Peisner-Feinberg, & Poe, 2003; Wolf & Bowers, 1999; Wolf et al., 2002), rapid naming (Wolf et al., 2002; Wolf & Bowers, 1999), and vocabulary (Dickinson et al., 2003; Swanson, Trainin, Necoechea, & Hammill, 2003). Particular emphasis has been placed on phonological awareness and rapid naming (i.e., double deficit hypothesis of reading; Wolf & Bowers, 1999; Wolf et al., 2002). However, studies have found that phonological awareness and vocabulary correlate moderately with each other ($r = 0.51$; Dickinson et al., 2003) and relate equally strongly to reading skills (Dickinson et al., 2003; Swanson et al., 2003).

Domain-general processes also contribute significantly to word reading outcomes, albeit typically to a lesser degree than language-related variables. Processing speed, for example, describes the ability to process information quickly with reasonable accuracy and relates to reading outcomes (Shanahan et al., 2006; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005; Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008), in part because processing speed affects the speed and accuracy with which words can be retrieved from long term memory (Christopher et al., 2012). However, the role of processing speed is unclear because people define it in different ways, and researchers who have found relations between processing speed and reading sometimes use RAN as a measure of processing speed (Shanahan et al., 2006).

Working memory tasks require participants to hold information in immediate memory while engaging in an interference task or manipulating the information in some way. Performance on verbal working memory tasks has been linked to word reading as well as reading comprehension skill (Jacobson et al., 2011; Locascio, Mahone, Eason, & Cutting, 2010; Moll, Göbel, Gooch, Landerl, & Snowling, 2014; Swanson & Jerman, 2006, 2007;

Willcutt et al., 2013), as the ability to hold and manipulate verbal information in short term memory enables readers to identify and combine phonemes within novel words, ascertain the meaning of new words from context as they read, and comprehend text. Shifting ability has also been linked to word reading skill (Bull, Espy, & Wiebe, 2008); this skill allows students to shift fluidly between mental sets or operations (e.g., Monsell, 1996).

Attentional skills also contribute to reading ability (Jacobson et al., 2011; Moll et al., 2014; Swanson & Jerman, 2006, 2007; Willcutt et al., 2013), for the simple reason that problems paying attention make it difficult to learn. For example, attention difficulties make it hard for the child to focus on what the teacher is saying or what they are reading, thus making it less likely they will be able to focus on and comprehend passages, learn new words, or read quickly. However, attention is operationalized in many ways: Some studies focus on behavioral measures of attention (i.e., parent questionnaires) while others assess attention via cognitive tasks (i.e., auditory attention span tasks). While continuous performance tasks are not commonly used to assess attention in academic literature, they are more frequently employed (i.e., Mabbott et al., 2008; Reeves et al., 2006), and are impaired in (Reeves et al., 2006), the pediatric brain tumor literature. However, not all skills are associated with reading. For example, fine motor skills are not typically associated with reading ability (Berninger, Nielsen, Abbott, Wijsman, & Raskind, 2008).

Research exploring cognitive prediction of academic fluency outcomes is relatively limited; however, there is evidence that fluency outcomes are generally predicted by the same cognitions that relate to untimed academic outcomes reviewed above (i.e., Wolf & Katzir-Cohen, 2001). Specifically, reading fluency has been shown to be related to processing speed (Camarata & Woodcock, 2006; Schatschneider, Fletcher, Francis, Carlson,

& Foorman, 2004), vocabulary (Wolf & Katzir-Cohen, 2001), working memory (Jacobson et al., 2011), shifting (van der Sluis, de Jong, & van der Leij, 2007), and attention (Mabbott, Penkman, Witol, Strother, & Bouffet, 2008), with no significant role of fine motor functioning (Barnes, Dennis, & Hetherington, 2004).

Writing. Writing is a complex skill that requires the integration of many cognitive processes. For example, when writing a sentence, children need to generate ideas and transform them into a language format, attend to and manipulate this information so it can be recorded on the page in a manner consistent with grammatical and syntactic rules, and then transcribe the words on the page (Berninger, Winn, MacArthur, Graham, & Fitzgerald, 2006). Given that both reading and writing are heavily language-based skills, the same suite of predictors critical for reading are likely also relevant for writing. Unsurprisingly, vocabulary (in combination with world knowledge) was the strongest predictor of basic writing as well as written expression ability across ages in a study by Floyd et al. (2008). Consistent with reading, studies have also found that working memory ability (Berninger, Cartwright, Yates, Swanson, & Abbott, 1994; DeBono et al., 2012; Swanson & Berninger, 1996) as well as shifting skills are linked to writing composition skill (Hooper, Swartz, Wakely, de Kruif, & Montgomery, 2002). In addition, the ability to process information quickly and to retrieve information from long-term storage efficiently contributes to writing skill, as basic processing speed skills are predictive of basic writing skills (i.e., spelling) and written expression across childhood and adolescence (DeBono et al., 2012; Floyd, McGrew, & Evans, 2008).

Links between attention skill and writing outcomes are inconsistent, with some studies failing to find significant relations between behavioral attention and writing (DeBono et al., 2012) and others finding significantly poorer writing outcomes in individuals with attention problems (Graham, Fishman, et al., 2016). Fine motor skills also inconsistently relate to writing outcomes, with some studies finding links between fine motor skills and handwriting (Abbott & Berninger, 1993) or composition (Berninger et al., 1992) while others found no contribution of fine motor ability to composition skills (Berninger et al., 1994; DeBono et al., 2012).

The physical ability to write efficiently is particularly important for speeded writing tasks, as evidenced by a study that found dominant-hand fine motor skills predict compositional fluency (Berninger et al., 1994). Verbal working memory (Berninger et al., 1994), attention (Kent, Wanzek, Petscher, Otaiba, & Kim, 2014; Graham, Fishman, et al., 2016), and processing speed (DeBono et al., 2012; Williams, Zolten, Rickert, Spence, & Ashcraft, 1993) have also been shown to predict writing fluency. Shifting is also expected to contribute to writing fluency. Extant studies have not found a relation of vocabulary to writing fluency (Kent et al., 2014; Nagy, Berninger, Abbott, Vaughan, & Vermeulen, 2003).

Math. Math, like reading and writing, is predicted by a range of domain-specific and domain-general variables. However, given that skills that relate specifically to math (i.e., numerosity, subitizing) tend not to relate to either reading or writing, these were not included in the present study. Domain-general process that are consistently linked to math outcomes include working memory (Barnes et al., 2014; Willcutt et al., 2013) and processing speed (Bull & Johnston, 1997; Fuchs et al., 2006; Willcutt et al., 2013). Processing speed can affect the rate at which well-learned math problems can be pulled from long-term memory (Christopher et al., 2012) as well as the rate at which less familiar problems can be solved (Fuchs et al., 2008; Geary, 1993), while working memory allows individuals to coordinate and monitor each step while solving arithmetic problems (Fürst & Hitch, 2000; Imbo & Vandierendonck, 2007; Imbo, Vandierendonck, & De Rammelaere, 2007). Shifting skills also predict math performance in children (Bull, Johnston, & Roy, 1999; Bull & Scerif, 2001; McLean & Hitch, 1999; van der Sluis, de Jong, & van der Leij, 2004). Like reading, attention is also related to math performance, likely due to the effects that distractibility can have on learning as well as inhibiting irrelevant information when solving problems (Fuchs et al., 2005). In addition, while typically conceptualized as primarily being related to reading, vocabulary and overall verbal comprehension skills have been linked to math skills or difficulties in school-aged children (Martin, Cirino, Sharp, & Barnes, 2014; Willcutt et al., 2013), likely due to the role of language abilities in learning math skills in language-heavy classroom settings (Robinson, Menchetti, & Torgesen, 2002). Math skill is also linked to ability to switch between strategies (Bull et al., 1999; Bull & Scerif, 2001).

Interestingly, the development of early math skills also relies on one’s mental finger representations due to young children’s reliance on fingers to represent numerosity as well as to count. These relations between fine motor skills and math ability persist later into childhood when math skills are more advanced (Barnes et al., 2005), with evidence suggesting that finger gnosia and finger tapping predict knowledge of the number system which, in turn, account for variance in math calculation skill (Penner-Wilger et al., 2007; Wasner, Nuerk, Martignon, Roesch, & Moeller, 2016).

Researchers have found significant contributions to math fluency from processing speed (Camarata & Woodcock, 2006; Fuchs et al., 2006), attention (Fuchs, Fuchs, Compton, et al., 2006; Fuchs, Geary, et al., 2011), and fine motor functioning (Raghubar et al., 2015). Findings are mixed, however, regarding the contribution of language variables (i.e., vocabulary or phonological awareness; Barnes et al., 2014; Fuchs, Geary, Fuchs, Compton, & Hamlett, 2016; Lefevre et al., 2009; Locuniak & Jordan, 2008; Martin et al., 2014) and working memory (Fuchs et al., 2006; Fuchs, Geary, et al., 2016; Locuniak & Jordan, 2008) to math fluency outcomes. Math fluency has previously not been related to shifting skill (Clark, Pritchard, & Woodward, 2010).

Summary and Current Study

As reviewed above, relations between cognitive skills and academic outcomes are well known in typically developing children, with evidence for many cognitive skills contributing to reading, math, and writing fluency outcomes. However, this predictor and outcome set remains unstudied in children treated with radiation therapy for brain tumors. Skills and abilities associated with academic achievement are relevant across the continuum of academic skill, whether or not children meet criteria for a learning disability (i.e., Branum-Martin et al., 2013). Thus, there is no reason to expect that a different set of abilities would account for academic fluency skills in children who struggle academically following radiation therapy. However, given that some cognitive skills (i.e., processing speed) tend to be more strongly affected by radiation treatment relative to others (i.e., language), we expect that these cognitions would most strongly mediate relations between radiation group and academic fluency, as difficulties in these cognitive domains would likely limit the degree to which children could become proficient academically.

Given the above, the present study will examine cognitive mediators and academic fluency in two subgroups of childhood cancer survivors. First, we will examine the relationship of the aforementioned cognitive domains in the prediction of fluency outcomes in pediatric brain tumor survivors. Then, we will determine if the two treatment groups

(PBRT vs. XRT) differ in their performance on cognitive as well as academic measures. Finally, we will assess if the cognitive variables mediate group differences in academic outcomes.

Hypotheses

1. **Children treated with PBRT have better cognitive or academic performance than those treated with XRT.**
    a. Children treated with XRT are expected to have relatively poorer performance on all cognitive tasks relative to children treated with PBRT.
    b. In addition, children treated with XRT are hypothesized to have relatively poorer performance on all academic fluency tasks relative to children treated with PBRT.
2. **Neurocognitive variables are associated with academic outcomes in pediatric brain tumor survivors treated with radiation therapy.**
    a. We expect that reading fluency will be predicted by processing speed and vocabulary, followed by working memory, shifting, and attention, with no significant role of fine motor functioning. Attention will likely be less predictive of reading fluency relative to other predictors.
    b. We expect writing fluency to be predicted by processing speed, followed by working memory, attention, shifting, and fine motor skills. Vocabulary is not expected to significantly contribute to writing fluency.
    c. Similar to reading fluency, math fluency is expected to be strongly predicted by processing speed, followed by working memory and attention. Fine motor skills are also expected to predict math fluency, albeit to a lesser degree than

the other domains. Vocabulary and shifting are not expected to predict math fluency.

3. **Cognitive ability mediates the relationship between radiation treatment type and academic fluency performance.**
    a. When cognitive variables (i.e., processing speed, working memory, attention, fine motor, vocabulary, shifting) are included as mediators in the model relating radiation group to academic outcomes, it is expected that group differences in academic performance will become nonsignificant. This is because cognitive deficits are hypothesized to drive increased academic fluency deficits in children treated with XRT relative to PBRT.

Methods

Participants and Procedures

Eighty-two participants (54 PBRT, 29 XRT) were included in this study. Patient characteristics are described in Table 1. Fifty-four participants are male (65%). The most common tumor type was medulloblastoma/PNET (*n* = 32), followed by low-grade glioma/astrocytoma (n = 18), germ cell tumor (*n* = 13), ependymoma (*n* = 11), and other tumor types (*n* = 9) (Table 1).

--Insert Table 1 here--

Participants were part of a larger ongoing study exploring long-term outcomes in pediatric brain tumor survivors. With approval from the Baylor College of Medicine Institutional Review Board (IRB), eligible participants were identified via review of medical charts and were approached for enrollment during medical appointments at Texas Children's Hospital. Parents/guardians provided written consent and children provided written or verbal assent prior to beginning participation in the study. The parent study was originally designed as a cross-sectional study comparing neurocognitive outcomes at a single time point between patients previously treated with XRT vs. PBRT, but it was later expanded to include longitudinal surveillance of participants in survivorship. The proposed study is cross-sectional, examining outcomes at a single time point.

The present study examined data from participants between 5.59 and 31.36 years old at the time of evaluation (Table 1) with a history of a brain tumor. Participants in the XRT group were treated between 2001-2007, and participants in the PBRT group were treated between 2006-2013. Patients treated with XRT after 2007, when PBRT became standard of care for most pediatric brain tumors at this institution, were excluded from the study to minimize possible treatment selection bias. Given that many patients had undergone multiple evaluations as part of the longitudinal component of the overall study, we used data from the earliest evaluations for XRT patients and the latest evaluations for PBRT patients, so that groups would be as close to equivalent as possible with regard to time since radiation. In addition, patients with high-grade gliomas, atypical teratoid/rhabdoid tumors, and brain stem gliomas were excluded due to characteristically poor prognoses that are incompatible with the study's focus on long-term outcomes. Data were excluded from the current analyses for patients that experienced progressive disease/death (n=6), were unable to complete testing due to profound cognitive impairment or visual deficits (n=5), or were tested in Spanish (n=5).

Cognitive Variables

Vocabulary represented language skills and served as a domain-specific predictor of reading outcomes. This will be assessed with the WISC-IV (ages 6-16; Wechsler, 2003) or WAIS-IV (ages > 17; Wechsler, 2008) Vocabulary subtest. For both subtests, children were asked to verbally define a series of words. Each definition was scored as a 0, 1, or 2, based on the quality of the response per guidelines provided in the manual. Scaled scores (normative M = 10, SD = 3) were used in analyses. Reliability across ages is 0.89 for the WISC-IV and 0.94 for the WAIS-IV (Wechsler, 2003, 2008b).

Processing speed was assessed with the WISC-IV or WAIS-IV Processing Speed Index (Wechsler, 2003; Wechsler, 2008). For both the WISC-IV and WAIS-IV, this composite included the Symbol Search and Coding subtests. For Symbol Search, participants were provided with rows of symbols. Each row contained one (ages 6-7) or two (ages 8 and up) target symbols next to a set of 3 (ages 6-7) or 5 (ages 8 and up) search symbols. They were asked to mark a search symbol if it matched a target symbol, or mark a “No” box if none of the search symbols matched a target symbol. They were given 2 minutes to complete the task. For the Coding subtest, participants were provided with a key that paired symbols with shapes (ages 6-7) or symbols with numbers (ages 8 and up) as well as a series of empty shapes or numbers over empty boxes. Participants were required to draw the appropriate symbol inside the empty shape or under the number. They were given 2 minutes to complete the task. The Processing Speed Index standard score (normative $M = 100$, $SD = 15$) was used in analyses. Reliability across ages is 0.88 for the WISC-IV and 0.90 for the WAIS-IV, and subtests intercorrelated 0.53 for the WISC-IV and 0.65 for the WAIS-IV (Wechsler, 2003, 2008b).

Verbal working memory was assessed with the WISC-IV or WAIS-IV Working Memory Index (Wechsler, 2003; Wechsler, 2008). All participants (i.e., administered either the WISC-IV or WAIS-IV) completed the Digit Span subtest, which required them to listen to and subsequently repeat increasingly long series of numbers in forward or backward order.

WISC-IV participants also completed the Letter Number Sequencing subtest, where participants listened to increasingly long groups of letters and numbers. They subsequently repeated the letters and numbers back to the examiner starting with the numbers in smallest to largest order, then the letters in alphabetical order. Points were awarded regardless of if they listed numbers or letters first, provided they remembered all items and they were listed in the correct order. WAIS-IV participants also completed the Arithmetic subtest, where examiners read a brief math word problem aloud which participants mentally solved. Participants had 30 seconds to orally provide an answer. The standard score from the Working Memory Index (normative $M = 100$, $SD = 15$) was used in analyses. Reliability was 0.92 across ages for the WISC-IV and 0.94 for the WAIS-IV. Subtests intercorrelated 0.49 for the WISC-IV and 0.60 for the WAIS-IV (Wechsler, 2003, 2008b).

Sustained attention was assessed with the Conners Continuous Performance Test-2nd Edition (CPT-II; Conners, 2000), which is a computerized attention measure. Letters appeared on the computer screen one at a time and subjects were asked to press the space bar following every letter except for X. The length of time between stimuli varied across trials (1, 2, or 4 seconds), and the task was about 14 minutes long with 360 trials in total. For analyses, we used the detectability (d') variable (normative $M = 50$, $SD = 10$), a T-score that describes the subject's ability to differentiate between target (i.e., all letters except X) and non-target (i.e., X) stimuli. This is an index of attentiveness that has previously been shown to be deficient in childhood medulloblastoma survivors (Reeves et al., 2006). Test-retest reliability is 0.76 for d' (Conners, 2000)

Fine motor functioning was assessed with the Grooved Pegboard subtest. For this task, subjects placed grooved pegs one at a time into a pegboard using their dominant hand.

The task was then repeated for their nondominant hand. The amount of time required to place the first 10 pegs (ages 6-8) or all 25 pegs (ages 9 and up) was recorded. Due to significant skew, logarithmically transformed raw scores were used in analyses. Test-retest reliability ranged from 0.72 (dominant hand) to 0.74 (nondominant hand) in adults (Ruff & Parker, 1993), and 0.80 (dominant hand) to 0.81 (nondominant hand) in children (Knights & Moule, 1968).

Shifting skills were assessed with the Verbal Fluency Switching subtest of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001). Subjects verbally listed as many items as they can from two categories in alternating fashion (i.e., they name a fruit, a piece of furniture, a fruit, etc.). They had one minute to name as many items as possible. The variable we used in analyses was category switching accuracy, a scaled score of the number of times the subject accurately switched between categories (normative M = 10, SD = 3). Test-retest reliability is 0.53 for 8-19 year olds, and 0.24 for 20-49-year-olds (Delis et al., 2001).

Academic Fluency Variables

Academic fluency was assessed with the reading, writing, and math fluency subtests of the Woodcock Johnson-III (Woodcock, McGrew, & Mather, 2001). Reading fluency requires children to read simple sentences and indicate if each sentence is true or false. Participants were given 3 minutes to complete as many items as possible. Raw scores were computed by subtracting number of incorrect items from number of correct items. Writing fluency provides participants with a series of pictures, each accompanied by three words. Participants then wrote a short sentence about each picture incorporating all three words. The words could not be altered, and children had 7 minutes to write as many sentences as possible. Participants received one point for each sentence that used all three words, and raw scores were a sum of all accumulated points. Regarding math fluency, children were provided with a series of basic addition, subtraction, multiplication, and division problems. They completed as many problems as possible within 3 minutes. Raw scores were calculated by adding together the number of correctly completed items. Standard scores were used in analyses. Median reliability across ages is 0.95 for Reading Fluency, 0.98 for Math Fluency, and 0.83 for Writing Fluency (McGrew & Woodcock, 2001).

Analyses

We used multiple mediated regression models to assess relations between radiation treatment group, cognitive variables, and academic fluency variables, including: group differences in academic functioning between XRT and PBRT treatment groups (Hypothesis 1); relations between cognitive and academic fluency variables across treatment groups (Hypothesis 2); and the degree to which cognitive variables mediate the relation between treatment group (XRT vs. PBRT) and academic fluency outcomes (Hypothesis 3).

In order for cognitive mediation of group effects on achievement outcomes to occur, there must be cognitive variables that relate both to group as well as academic functioning (Little, Card, Bovaird, & Crandall, 2007). We compared relations between treatment group and academic fluency outcomes before and after we controlled for the effects for each of the cognitive variables. Specifically, we first determined direct effects, which are direct relations between radiation treatment group and academic fluency outcome. Then, we determined indirect effects, which are relations between radiation treatment group and academic fluency *through* a particular mediator variable (mathematically, this is the product of beta values from treatment group to mediator and mediator to fluency variable). Total indirect effects were the sum of all indirect effects, and total effects were the sum of all indirect *and* direct effects. For all three fluencies, we assessed whether the relation between radiation group and fluency outcomes was partially mediated (significant total and total indirect effects, as well as remaining significant direct effects) or fully mediated (significant total and total indirect effects, but nonsignificant direct effects).

We used bootstrapping to assess statistical significance. Bootstrapping involves repeatedly selecting N sample datasets (with replacement) from the overall dataset and estimating the indirect effects from each sample dataset. By resampling thousands of times, the sampling distribution of the indirect effect can be estimated. Bootstrapping yielded a point estimate for each indirect effect as well as 95% confidence intervals. If these confidence intervals did *not* include zero, the variable was a significant mediator of the relation between group and fluency (Little, Card, Bovaird, & Crandall, 2007; Preacher & Hayes, 2008). This method does not assume normal distribution of errors, which is particularly useful given that the standard errors of indirect effects are typically highly skewed, except in very large samples. We ran the models in MPLUS (Muthén & Muthén, 2017), and used 10,000 bootstrap samples to generate the results presented here, given recommendations that thousands of samples be used (Preacher & Hayes, 2008). Of note, this model is "just identified," so by definition there are 0 degrees of freedom and the model fit is perfect. Thus, we do not provide model fit statistics. Utilizing a just identified model primarily allows us to simultaneously assess the individual parameters/relations between radiation group, cognitive variables, and academic fluency variables, which are of primary interest in this study.

In order to determine covariates to consider in analyses, we first assessed correlations between potential covariates and outcomes, as well as group differences on potential covariates (assessed with chi square analyses for categorical covariates, or t-tests for continuous covariates). Previous research has found academic performance differences based on demographic variables such as age, sex, and race/ethnicity (Kao & Thompson, 2003; Ladson-Billings & Madison, 1997; Lubienski, 2002; McGraw, Lubienski, & Strutchens, 2006; Tate, 1997), so we assessed whether or not these characteristics contributed to variability in academic fluency outcomes. SES variables (household income, patient insurance source, etc.) were also considered, given links between SES and academic skills in the literature (Foster, Lambert, Abbott-Shim, McCarty, & Franze, 2005; Tate, 1997). Regarding medical variables, existing literature has not found associations between radiation dose or tumor location and cognitive outcomes (Kahalley et al., 2016; Mabbott et al., 2005a). However, PBRT is still a novel form of radiation with largely unexplored cognitive/academic effects, so we assessed whether or not these variables contributed to academic fluency performance. Age at treatment and time since treatment were also considered, as there is strong evidence in the literature that both of these variables are related to cognitive outcomes (Barnes et al., 1999; Palmer et al., 2001). Lansky/Karnofsky scores, which are general indications of level of functioning following surgery that range from 0 (unresponsive) to 100 (normal), were also considered. In addition, children treated with XRT will have had longer time since treatment by virtue of the study design (i.e., no children who received XRT after 2007 are eligible for the present study), so time since radiation treatment was an important variable to consider within this sample in particular. Of note, in order to minimize group differences in the amount of time since treatment, we examined data from the earliest evaluation available for each child treated with XRT and data from the latest evaluation available for each child treated with PBRT.

Variables that most significantly differed between groups included age at evaluation, follow-up interval, and Lansky/Karnofsky ratings (Table 1). Variables that significantly correlated with all three academic fluency outcomes included follow-up interval, radiation therapy field (CSI vs. focal radiation), and Lansky/Karnofsky ratings (Table 2). Correlations between cognitive/academic variables and the four covariates that differed between groups or correlated with fluency outcomes are shown in Table 3. All variables listed above were explored within the full mediation model, and relations between covariates and each of the other variables in the model were explored (i.e., covariate to group, covariate to each cognitive variable, and covariate to each fluency variable). Results did not change with any of the covariates included in the model. Time from radiation to evaluation was the only covariate that significantly related to academic fluency outcomes when included in the mediation model; thus, this was the only covariate considered in analyses. However, results did not change with or without this variable, so results presented below do not include this covariate in the model in order to minimize the number of variables used and maximize power.

--Insert Table 2 here--—

--Insert Table 3 here--

For all analyses, the variables were assumed to be linearly related and have normally distributed residuals within groups. In addition, homoscedasticity of the data and homogeneity of variance are assumed across groups. In order to test these assumptions, variable distributions were examined in order to assess for anomalies. In addition, Shapiro-

Wilk tests of normality were consulted to test for normal distribution of the variables, as were Q-Q plots. For all variables except for Grooved Pegboard, these assumptions were met. Grooved Pegboard was significantly positively skewed due to a number of patients requiring a long time to complete the task, however, so the Grooved Pegboard raw score was logarithmically transformed prior to being used in analyses.

Outliers were determined by considering univariate as well as multivariate diagnostics. Regarding univariate outliers, no variables had observations >3SD from the sample mean (Tabachnick & Fidell, 2001). For multivariate outliers, Cook's d and dffits were used to ascertain high-influence outliers (Tabachnick & Fidell, 2001). Seven individuals were above threshold on both indices, and analyses were conducted with and without these outliers. Because the pattern of results did not change except where noted below, outliers were included in all analyses.

We also explored variance inflation and tolerance statistics in order to assess for multicollinearity. These were within normal limits for all cognitive variables across academic fluency outcomes (Tabachnick & Fidell, 2001). However, vocabulary and working memory were highly correlated with one another ($r(82) = 0.78$, $p < 0.0001$), so we also explored collinearity diagnostics and found evidence for collinearity between vocabulary and working memory with all three fluency outcomes. We decided to retain vocabulary and conduct analyses with/without working memory because these two measures likely overlap due to a strong shared language component, and vocabulary is a more pure measure of language skill. However, both sets of analyses are presented in figures/tables and discussed below.

Results

Zero-Order Correlations

Table 4 shows zero-order correlations among all variables for all patients, and Table 5 shows zero-order correlations divided by radiation treatment group, means and standard deviations for cognitive and academic tasks for each group, and proportion of each group that performed below the 8th percentile (in the Very Low or Extremely Low ranges; Wechsler, 2003). Within the entire sample, correlations between academic fluency variables were strong and significant, $r(79) = 0.83$ to $r(80) = 0.88$; $p < 0.0001$. Correlations between cognitive variables and academic fluency variables were also significant, $r(77) = -0.24$, $p = 0.04$ to $r(79) = 0.81$, $p < 0.0001$, with the exception of the correlation between attention and math fluency, $r(77) = -0.16$, $p = 0.16$. When divided by treatment group, zero-order correlations between academic fluency variables as well as between cognitive variables and academic fluency variables were similar across groups and exhibited a comparable pattern to zero-order correlations within the overall sample, although were generally weaker due to reduced sample sizes (i.e., correlations between academic fluency outcomes ranged from $r(29) = 0.79$, $p = < 0.0001$ to $r(29) = 0.87$, $p < 0.0001$ for XRT, and $r(51) = 0.75$, $p <0.0001$ to $r(51) = 0.86$, $p <0.0001$ for PBRT). Across tasks, larger proportions of individuals in the XRT group performed below the 8th percentile relative to individuals in the PBRT group.

--Insert Table 4 here--

--Insert Table 5 here--

Multiple Mediation Model

Tables 5 and 6 present multiple mediation model results with and without working memory included in the model, respectively. Total effects for each fluency outcome were significant (Reading Fluency: $\beta = .40$, $p = <.001$; Writing Fluency: $\beta = .34$, $p = <.001$; Math

Fluency: β = .43, p = <.001), indicating that the sum of the direct and indirect effects was significant for each outcome and, consequently, significant group differences in fluency outcomes. The sections below detail findings for each portion of the model (i.e., group to cognitive variable, group to academic fluency variable, cognitive variable to academic fluency variable). This is followed by a summary of the overall model findings.

Group Differences in Cognitive and Academic Fluency Performance. When comparing the two groups directly, results were generally consistent with our hypothesis that individuals treated with PBRT would outperform the XRT group on all cognitive and academic measures. Indeed, individuals treated with PBRT performed significantly better relative to individuals treated with XRT on nearly all cognitive tasks, as indicated by significant effects from radiation therapy type to most cognitive measures (see Figures 1b & 2b; β = .31, p < .01 to β = .42, p <.001), with the exception of attention and fine motor skills (β = -.15, p = 0.17 and β = -.22, p = 0.06, respectively). Significant group differences were also found for all academic fluency outcomes, with the PBRT group outperforming XRT, as indicated by significant total effects for each fluency outcome displayed in Figures 1a and 2a as well as Tables 5 and 6 (Reading Fluency: β = .40, p < 0.001; Writing Fluency: β = .34, p < 0.001; Math Fluency: β = .43, p < 0.001).

Cognitive Prediction of Academic Fluency Outcomes. Reading, writing, and math fluency were significantly predicted by processing speed and vocabulary, as indicated by significant effects from processing speed and vocabulary to fluency outcomes (Figure 1b; β = .22, p = .02 to β = .50 , p < .001). Math fluency was also significantly predicted by working memory (Figure 1b; β = .26, p < .01), but this effect became nonsignificant when the full set of 7 outliers was removed from the model (β = .13 p = .14). In models with working memory removed (Figure 2b), all three fluency outcomes were again predicted by processing speed and vocabulary (Figure 2b; β = .39, *p* <.001 to β = .56 , *p* < .001).

Overall Model. Full mediation model results are presented in Table 6 and Figure 1 (with working memory) and Table 7 and Figure 2 (without working memory). As mentioned above, total effects for each fluency outcome were significant (Figure 1a, Table 6; Reading Fluency: β = .40, *p* < .001; Writing Fluency: β = .34, *p* < .001; Math Fluency: β = .43, *p* < .001) indicating significant group differences in reading, writing, and math fluency. Total indirect effects were also significant for each fluency outcome (Table 6; Reading Fluency: β = .37, *p* < .001; Writing Fluency: β = .37, *p* < .001; Math Fluency: β = .35, *p* < .001), indicating that at least one cognitive variable significantly mediated the relation between group and fluency outcome. Further, the total direct effects were not significant after accounting for all indirect effects for each of the three outcomes (Table 6; Reading Fluency: β = .03, *p* = .54; Writing Fluency: β = -.03, *p* = .73; Math Fluency: β = .08, *p* = .22), affirming that the model was fully mediated and significant mediators fully accounted for group differences in fluency outcomes.

Contrary to hypotheses, however, significant indirect effects were only found for vocabulary and processing speed across all outcomes (Table 6; β = .07, *p* = .06 to β = .21, *p* < .001). Working memory was also a significant mediator for the math fluency model (Table 6; β = .08, *p* = .03), prior to its removal. Of note, β values for indirect effects are the product of β values for each component of the path. To illustrate, the β for the indirect effect from RT to reading fluency via vocabulary is .16 (Table 6), or .34 (β for RT to vocabulary; Figure 1) multiplied by .48 (β for vocabulary to reading fluency; Figure 1). These findings affirm that vocabulary and processing speed fully account for group differences in reading, writing, and math fluency outcomes.

--Insert Table 6 here--

--Insert Figure 1 here--

--Insert Table 7 here--

--Insert Figure 2 here--

Discussion

The aim of this study was to elucidate if PBRT is associated with improved long-term cognitive and academic fluency outcomes relative to conventional XRT, as well as if cognitive skills mediate the relation between radiation treatment and academic fluency skills in pediatric brain tumor survivors. Because PBRT is a relatively new form of radiation treatment, thus far, research considering long-term effects of PBRT has been limited and primarily focused on broad cognitive indices (i.e., IQ). Further, only one study has directly compared cognitive skills in children treated with PBRT relative to XRT (Kahalley et al. 2016), and none have considered academic fluency outcomes, despite evidence for impaired fluency skills in brain tumor survivors (Holland et al., 2015). Results from the present study broadly suggest that children treated with PBRT have better cognitive and academic fluency outcomes relative to children treated with XRT. In addition, better performance on all three forms of academic fluency in the PBRT group relative to the XRT group appears to be attributable to relatively preserved vocabulary and processing speed skills.

Group Differences in Cognitive and Academic Fluency Performance

Broadly consistent with hypotheses, the PBRT group performed significantly better on most cognitive (vocabulary, working memory, processing speed, switching) and all academic fluency tasks relative to children treated with XRT. These findings lend support to theories asserting that XRT corresponds with depressed functioning on a wide range of cognitive and academic skills, with particular impact on fluid, “on-line” skills such as processing speed, working memory, executive functions, and academic fluency (Edelstein et al., 2011; Holland et al., 2015; Mabbott et al., 2005b, 2011). This also supports the theory that decreased irradiation to healthy tissue in children treated with PBRT versus XRT corresponds to improved long-term functional outcomes across a broad range of skills (Harrabi et al., 2016).

While we did not include a control group (i.e., surgery-only patients or age-matched children without brain tumor), we can broadly comment on performance in the two groups relative to the normative population (see Table 5). For cognitive measures, it is notable that while the average scores across measures for children treated with PBRT were below the normative average of 100, these scores were still within the average range (defined here as standard scores from 90-109; Wechsler, 2003), with 4 to 39% of individuals performing in the very low or extremely low ranges (defined as standard scores below 79, or below the 8th percentile; Wechsler, 2003). The exceptions to this were performance on processing speed and fine motor tasks, where the average scores for individuals within the PBRT group were in the low average range (defined as standard scores from 80-89; Wechsler, 2003), with 41 to 44% of individuals performing in the very low or extremely low ranges. In contrast, individuals treated with XRT performed in the extremely low (standard scores below 70; Wechsler, 2003) to low average range on all measures except the CPT, where performance was average. Correspondingly, between 52 and 79% of the XRT group performed in the very low or extremely low ranges across tasks, with 14% performing in this range for the CPT.

Similar findings were observed with academic fluency, where children in the XRT group exhibited very low performance (standard scores from 70-79; Wechsler, 2003) on average, with 69% performing in the very low or extremely low ranges across tasks, while individuals in the PBRT group performed in the low average range, with 24 to 31% performing in the very low or extremely low ranges.

Consistent with hypotheses, both groups demonstrated a relative processing speed weakness, with particularly impaired scores found in the XRT group relative to PBRT. This is consistent with previous studies that have found significant decline in processing speed over time in pediatric brain tumor survivors treated with XRT (Kahalley et al., 2013; Mulhern et al., 2005; Schatz, Kramer, Ablin, & Matthay, 2000) as well as emerging indications of processing speed vulnerability in survivors treated with PBRT (Pulsifer et al., 2015; Yock et al., 2016). Because poor processing speed outcomes are thought to reflect white matter disruption following radiation therapy (Aukema et al., 2009; Scantlebury et al., 2016), present findings suggest that white matter may be less impacted, although not entirely unaffected, in PBRT relative to XRT. This would need to be verified directly, but the present results warrant further study with neuroimaging techniques.

As expected, PBRT patients performed in the low end of the average range on working memory measures, which was significantly higher than XRT survivors, who exhibited very low performance on working memory tasks (Table 4). Similarly, shifting skills were average for PBRT patients, but fell in the low average range for XRT patients, again with significant differences between RT groups. These findings are consistent with the XRT literature and the theory that fluid skills are particularly vulnerable to radiation treatment (Butler & Mulhern, 2005; Maddrey et al., 2005).

Of note, vocabulary scores were average for patients who had received PBRT, and low average for patients treated with XRT; thus, vocabulary was not a significant deficit, even in patients treated with XRT. However, group differences in vocabulary performance (even when controlling for time since radiation) do suggest an adverse effect of XRT in particular on language skill. This is consistent with a meta-analytic study, which also found significantly lower language performance (albeit less impaired than other domains) in children with brain tumors relative to the normative population, moderated by whether the children were treated with XRT versus no radiation therapy (Robinson et al., 2013). While basic language skills (i.e., vocabulary, syntax, lexicon) are conceptualized as being relatively robust to brain injury (Chapman & McKinnon, 2000; Vas, Chapman, & Cook, 2015) and some studies have found no evidence of language deficits following XRT (Mabbott et al., 2011; Moxon-Emre et al., 2014), Butler and Mulhern (2005) conceptualized two layers of neurocognitive deficits in children treated with radiation therapy. First, *core deficits* represent fluid skills (i.e., processing speed, working memory) that exhibit earlier and more significant deficits. Next, *secondary deficits* represent crystallized skills (i.e., vocabulary) that are eventually negatively impacted due to downstream effects of the initial core symptoms. While we did not explore this possibility in our model (i.e., testing if group differences in processing speed predict vocabulary, in turn predicting academic fluency differences), it is possible that group differences in vocabulary skill manifested because the participants in this study were relatively far removed from radiation therapy, and so may represent secondary deficits, particularly in XRT patients. Unlike other cognitive skills, no group differences were found in attention and fine motor functioning. In addition, attention skills were in the average range for both groups. It is very unlikely that attention skills are simply not impacted by either type of radiation therapy, given consistent evidence that XRT leads to attention difficulties (Kiehna, Mulhern, Li, Xiong, & Merchant, 2006; Mabbott et al., 2005a; Reddick et al., 2006), as well as broad associations between white matter damage and attention difficulties (Mulhern et al., 2004; Reddick et al., 2006). Thus, it is worth considering if this may be an effect of using the CPT to measure attention. While the CPT is a widely used clinical measure of attentional skill, there is some question regarding its sensitivity and specificity for predicting clinically significant attention problems (Edwards et al., 2007; McGee, Clark, & Symons, 2000). Further, although the CPT is almost exclusively used to assess attention in brain tumor survivors, performance on this measure (including the d' variable) has inconsistently been impaired in this population (Merchant et al., 2002; Reddick et al., 2006; but see Mulhern et al., 2004). Indeed, given average performance on this task in PBRT and XRT survivors, it may be the case that the CPT d' variable is not sensitive to attention difficulties following radiation therapy.

Regarding fine motor skills, survivors performed in the extremely low and low average for XRT and PBRT groups, respectively, with a difference of 14 standard score points between group averages. However, group differences were not significant within the context of the multiple mediation model, suggesting that PBRT has similarly negative effects on fine motor functioning relative to XRT. This may be an effect of tumor location and associated treatment. Specifically, in this study, both groups were composed of about 50% infratentorial tumors and received comparable radiation doses to the tumor. Given the role of the cerebellum in fine motor activity (Mendoza & Foundas, 2008) and the link between degree of fine motor deficit and radiation dose (Kieffer-Renaux et al., 2000), it is possible that the lack of group difference in fine motor skill simply reflects an effect of tumor location and treatment that does not vary significantly based on radiation type. However, children did exhibit significant group differences on the fine motor task in preliminary t-tests; this effect simply disappeared in the model when we controlled for other cognitive skills. Thus, significant overlap in variance between grooved pegboard and other cognitive measures (i.e., processing speed, which also requires speeded fine motor skills) may also account for the lack of group difference when all other cognitive skills were also included in the model.

Cognitive Prediction of Academic Fluency Outcomes

Within the context of the broad mediation model, all three fluency outcomes were predicted by processing speed and vocabulary. The significant processing speed findings were consistent with hypotheses as well as literature in typically developing children (Camarata & Woodcock, 2006; DeBono et al., 2012; Fuchs et al., 2006; Schatschneider et al., 2004) and neurodevelopmental populations (Cirino et al., 2018), and were not surprising, given the timed nature of the academic fluency outcomes. Further, correlations *between* academic fluency outcomes were very strong and higher than what is typically seen in typically developing individuals, which is also consistent with findings in neurodevelopmental populations, including spina bifida (Cirino et al., 2018). While we did not hypothesize that vocabulary would predict math and writing fluency (only reading fluency), the importance of language in writing as well as math skill development may explain this finding (Cirino et al., 2018; Floyd et al., 2008; Martin et al., 2014).

We hypothesized a greater number of significant mediators for each outcome than we found, however, and the fact that we only found two significant mediators is likely due to a few factors. First, vocabulary was very highly correlated with working memory, raising concerns for multicollinearity and rendering it less likely that we would find a significant unique effect of working memory in the context of vocabulary. Regardless of multicollinearity between vocabulary and working memory, however, shifting, attention, and fine motor skills were nonsignificant predictors across outcomes. This was unexpected, given that we had hypothesized that attention would predict all three outcomes, shifting would predict reading fluency and writing fluency, and fine motor would predict writing fluency and math fluency. As mentioned above, CPT as an attention variable (particularly the d' variable) may be insensitive to attention problems in this population. Indeed, CPT d' (which measures attentiveness, or ability to distinguish between target and non-target items) was average for both groups, and exhibited the lowest zero-order correlations of all the variables, only yielding significant (and low) correlations with processing speed, reading fluency, and writing fluency. This may be because survivors are able to attend, and respond appropriately, to target versus non-target items, but struggle in other domains of attention, such as vigilance or sustained attention. If this is the case, it is possible that other CPT variables may be a more sensitive to the types of attention problems in brain tumor survivors (i.e., errors of omission over time or hit reaction time by interstimulus interval; Kahalley et al., 2010; Reeves et al., 2006). Alternatively, parent- or teacher-report measures (i.e., Child Behavior Checklist, Conners' Rating Scales) are also commonly used to assess attention problems at home and school, and may better capture post-treatment attention difficulties (Willard, Conklin, Boop, Wu, & Merchant, 2014), particularly in conjunction with other indices of attention (Netson et al., 2011). Overall, however, better characterization of post-radiation therapy attention difficulties is needed. In contrast to attention, shifting and fine motor exhibited strong correlations with all three fluency outcomes; however, they also correlated highly with other cognitive variables, suggesting that shifting and fine motor contributed no unique effects for academic fluency above and beyond the effects of the other cognitive skills included within the model.

Overall Model, Implications, and Future Directions

Our findings suggest that children treated with PBRT relative to XRT have better long-term academic fluency skills, which are associated with relatively preserved language (vocabulary) and speeded (processing speed) skills. These findings are among the first to suggest improved long-term functional outcomes in individuals treated with PBRT versus XRT. In addition to informing radiation treatment recommendations at the time of diagnosis (in conjunction with medical considerations, such as survival rates, potential side effects, etc.), these results also have implications for academic assessment and intervention. While it has already been suggested that survivors treated with XRT should undergo neurocognitive evaluation and academic monitoring in order to ensure academic success (Nathan et al., 2007), results from this study further suggest that survivors treated with PBRT should also be closely monitored. PBRT survivors broadly performed better than XRT survivors on cognitive and academic measures; however, average academic fluency skills were still below the normative average. In addition, there was a wide range of variability on academic fluency performance in PBRT survivors, affirming that many children in the PBRT group struggled with speeded academic tasks and would likely benefit from assessment, intervention, and accommodations in a school setting.

All academic fluency skills are closely related to their untimed achievement skill counterparts (Fuchs, Gilbert, et al., 2016; Schwanenflugel et al., 2006), and improved academic fluency and automaticity of basic skills (i.e., reading simple words, solving basic facts, writing simple sentences) frees cognitive resources for more advanced academic skills (i.e., reading comprehension, solving complex math problems, written expression; Fuchs, Gilbert, et al., 2016; Fuchs et al., 2001; Limpo et al., 2017; Little et al., 2017). Thus, it is critical to identify and intervene with fluency difficulties early in a child’s academic career, given the downstream effects that fluency problems can have on academic performance as they progress through school. While academic fluency interventions have not been studied in this population, the fact that group differences in academic fluency were mediated by vocabulary and processing speed skills in brain tumor survivors has implications for the potential role of these cognitive skills in interventions as well as the likelihood that interventions will be effective in survivors.

Regarding the role of vocabulary in fluency interventions, meta-analytic findings affirm that vocabulary interventions in typically developing children are associated with increases in vocabulary knowledge by an average of 1 standard deviation (Marulis & Neuman, 2010), and work best when explicit (i.e., teaching definitions associated with words) strategies are combined with implicit ones (i.e., teaching words in the context of an activity, such as reading a story). Correspondingly, research in reading fluency interventions in typically developing children suggests that in addition to repeated reading or use of audiobooks to assist reading, combining reading fluency intervention with vocabulary or reading comprehension instruction is most effective in improving reading fluency skill (see Stevens, Walker, & Vaughn, 2017, for review). Thus, incorporating vocabulary intervention into a reading fluency intervention may similarly benefit survivors struggling with fluent reading, particularly given vocabulary’s relation to reading fluency skill in this group.

There is very little research exploring writing fluency interventions (Hier & Eckert, 2014), and none incorporating a vocabulary element into a writing fluency intervention.

However, given links between vocabulary and writing fluency in this population, and the fact that knowing more words likely makes generating written text faster, it is reasonable to expect that addressing vocabulary weaknesses within an established writing fluency intervention (i.e., providing specific performance feedback during writing exercises; Hier & Eckert, 2014) may also improve writing fluency. This effect may be specific to brain tumor survivors, however, since vocabulary has not related to writing fluency in typically developing children (Kent et al., 2014; Nagy et al., 2003).

Vocabulary also significantly related to math fluency in this study; however, it is unlikely that vocabulary intervention would directly impact math fluency performance. Indeed, math fluency interventions studied in typically developing children primarily emphasize frequent practice with solving basic math facts, sometimes in conjunction with teaching explicit strategies for solving basic math problems (i.e., Math Flash and Pirate Math; Fuchs, Fuchs, Powell, et al., 2008; Schutte et al., 2015). It may be the case, though, that weak vocabulary skills make it more difficult to learn in a highly verbal classroom environment, so early monitoring and intervention of vocabulary skills may function to prevent later difficulty with acquiring math fluency skills.

Processing speed also played a significant role in all academic fluency outcomes, but its potential role as an intervention target is less well supported relative to vocabulary. Various researchers have explored the potential efficacy of interventions/training to improve processing speed skills in children as well as adults. While some findings support the efficacy of training in improving processing speed (i.e., Mackey, Hill, Stone, & Bunge, 2011), these improvements typically do not generalize beyond improvements in the same, or very similar, tasks that were used in the training (i.e., near transfer; see Takeuchi &

Kawashima, 2012, for review). Lack of evidence for generalizability to less closely related tasks (i.e., far transfer; see Takeuchi & Kawashima, 2012, for review) suggests that general processing speed training would likely not result in corresponding improvements in academic fluency unless students were trained specifically on academic fluency tasks, which is already a core element in current academic fluency interventions. Instead, intervention efforts should instead be focused on other empirically-supported methods, and should accommodate, rather than attempt to intervene, at the level of basic processing speed. For example, brain tumor survivors who are known to struggle with processing speed and academic fluency would likely benefit from a fluency intervention with adequate time to complete assignments when learning new skills, frequent practice to develop fluency, brief and clear instructions, and frequent check-ins to ensure comprehension.

In general, it is worth noting that while academic fluency interventions have improved academic fluency skills to the average range in typically developing children, not all children benefit from these interventions (Fuchs et al., 2005; Fuchs, Fuchs, Powell, et al., 2008), and it is often more difficult to improve fluency skills relative to untimed academic skills, such as word reading (Fuchs et al., 2005; Wolf & Katzir-Cohen, 2001). In addition, there is no literature exploring these interventions in brain tumor survivors. Thus, while we are hopeful that interventions would improve fluency skills, it is difficult to predict how much improvement should be expected following intervention. One important difference between children with learning disabilities (who are the typical targets for academic interventions) and our population of brain tumor survivors is the level of processing speed difficulty. While children with learning disabilities have been shown to have significantly lower scores on processing speed measures relative to non-learning disabled peers, processing speed performance still typically falls within the average range (i.e., Compton et al., 2012; Shanahan et al., 2006; Willcutt et al., 2005), which are much less severe deficits than what we found in the current study. In addition, fluency difficulties in typically developing children are often driven by difficulties with basic academic skills (in conjunction with other cognitive skills; i.e., Fuchs, Gilbert, et al., 2016; Schwanenflugel et al., 2006), while basic academic skills are relatively preserved in brain tumor survivors (Holland et al., 2015; Mabbott et al., 2005a). This implies that interventions currently used in children with learning disabilities may be less effective when applied to brain tumor survivors, given that speeded skills (which are the primary deficit in brain tumor survivors) are difficult to improve with intervention, as noted above. However, it is still possible that adapting existing interventions to account for processing speed difficulty will nevertheless allow for some academic fluency improvement in brain tumor survivors. Specifically, incorporating more sessions to complete the intervention and including even more repeated practice (i.e., 15 minutes of repeated word reading, math fact solving, or sentence writing, when 5 minutes might be recommended for a child with learning disability) may still help build fluency skills in survivors. Future studies should explore the efficacy of academic fluency interventions in this population, particularly with modifications to account for processing speed difficulties.

Limitations

While we are encouraged by the findings presented here, it is worth noting the study's limitations. First, the study had a relatively small sample size. While 82 participants is sizable for a medical population, it limits power to detect significant effects, particularly in the present model with many mediators and covariates to consider. However, it is worth noting the difficulty in following brain tumor survivors for extended periods of time post-treatment, so obtaining large sample sizes for a long-term outcomes study would be very challenging. Also, given the small sample size, it was not possible to divide the population into as many groups as we may have liked (i.e., examining separate mediation models based on histology, tumor location, CSI vs. focal radiation, etc.), or consider associations between treatments (i.e., if patients who receive CSI are also more likely to receive chemotherapy). While we did consider many medical variables as covariates, more extensive exploration of medical factors is needed in larger-scale future studies, including (for example) the possibility that chemotherapy is more commonly given to patients who receive CSI. This study was also cross-sectional rather than longitudinal, so we could not definitively determine causation (i.e., if processing speed skill predicted later academic fluency skill), which should be addressed in future studies as well. Further, while race did not differ by group or relate to fluency outcomes, it is possible that bilingual individuals may have performed differently on these measures, particularly if their primary language was not English. Future studies should explore effects of radiation in bilingual populations specifically.

The study may be vulnerable to cohort effects, given that XRT patients received radiation between 2001 and 2007 and PBRT patients received radiation between 2006 and 2013, although we controlled for time from radiation to evaluation to minimize these effects as much as possible. Specifically, it is possible that the standard of care for surgery and chemotherapy were different for the XRT group versus the PBRT group, which may have also affected long-term cognitive and academic outcomes. We also ultimately removed working memory from the mediation models due to collinearity between vocabulary and working memory. In future studies, it would still be beneficial to explore the role of working memory skills in the relation between radiation and academic fluency. This could be achieved by using a different working memory measure, such as a visuospatial working memory measure that would be less likely to correlate highly with vocabulary. Further, it is possible that mood contributed to some of the processing speed difficulties observed across both groups (although it is highly unlikely that patients in both groups do not have processing speed difficulties). Thus, future studies should explore the degree to which mood symptoms may be exacerbating poor performance on processing speed measures.

It is also worth noting that relatively impaired vocabulary skills in the XRT group may have been attributable to disproportionate occurrence of cerebellar mutism following surgery in individuals with medulloblastoma or other infratentorial tumors. Cerebellar mutism is not well characterized, but is broadly associated with inability to speak, hypotonia, ataxia, and irritability immediately following surgery (Wibroe et al., 2017), as well as long-term motor speech deficits (Huber, Bradley, Spiegler, & Dennis, 2006) and non-motor language difficulty (Robertson et al., 2006). This seems unlikely in our sample, however. There is no reliable way to retroactively determine which patients exhibited cerebellar mutism following surgery for medulloblastoma, as physicians at Texas Children's Hospital do not adhere to specific diagnostic criteria and do not reliably assess for cerebellar mutism in the medical chart. However, Lansky/Karnovsky scores documented at the first post-operative outpatient visit indicate level of functioning (including speech and motor functioning) following surgery and are routinely recorded in medical charts. Thus, these scores can be used to approximate whether or not cerebellar mutism occurred. While there were group differences on Lansky/Karnovsky scores, including these scores as a covariate in the multiple mediation model did not negate the group differences in vocabulary, suggesting that group differences in vocabulary are likely not primarily due to higher rates of functional impairment (encompassing cerebellar mutism) in XRT patients versus PBRT. Future studies should more directly explore the potential contribution of cerebellar mutism to long-term vocabulary and fluency difficulties.

Additional considerations related to vocabulary include the possibility that our vocabulary measure may be less indicative of vocabulary skills *specifically*, and more indicative of broad crystallized skills, language skills in general, or expressive language skills. Future studies would benefit from including a wider range of language and crystallized skills in order to elucidate if vocabulary specifically contributes to academic fluency skills, and thus should certainly be targeted as part of a fluency intervention, or if broad language or crystallized ability skills are primarily driving fluency skills.

Future directions also include considering a broader range of cognitive and academic skills, as well as exploring the same cognitive/academic skills with different measures to affirm generalizability of the findings. Further, it is strongly worth considering other functional and quality-of-life outcomes, such as social, psychiatric, or occupational outcomes. In addition, the wide variability in performance on cognitive and fluency measures was noteworthy; future studies would also benefit from considering factors that promote resilience to PBRT and XRT, in addition to factors that render an individual more susceptible to their effects.

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Table 1

Demographics and group differences

	XRT		PBRT		*p*
	n	%	*n*	%	
Total *n*	29	34.94	54	65.06	
Gender (% M)	22	75.86	35	64.81	0.30
Tumor types:					0.70
Glioma	5	17.24	13	24.07	
PNET	13	44.83	19	35.19	
Ependymoma	5	17.24	6	11.11	
Germ cell tumor	3	10.34	10	18.52	
Other	3	10.34	6	11.11	
Infratentorial (versus supratentorial) tumor	17	58.62	26	48.15	0.55
Craniospinal (versus focal) radiation therapy	12	41.38	29	53.70	0.67
Race					0.80
White	16	55.17	29	53.70	
Black	4	13.79	6	11.11	
Hispanic/Latino	8	27.59	14	25.93	
Other	1	3.45	5	9.26	
Government Assistance	9	31.03	19	35.19	0.74
	Mean $\pm$ *SD*	*Range*	*Mean* $\pm$ *SD*	*Range*	
Age at end of treatment	7.03 + 4.11	1.65 - 16.39	8.19 + 4.09	1.65 - 16.39	0.22
Age at evaluation	16.22 + 5.34	8.52 - 31.36	13.23 + 4.04	5.59 - 21.55	**0.01**
Follow-up interval	9.19 + 2.90	3.96 - 15.31	5.05 + 2.45	1.15 - 8.71	**<0.0001**
Lansky/Karnofsky	75.50 + 15.04	50 - 100	85.42 + 13.83	50 - 100	**0.01**
	Median	*Range*	*Median*	*Range*	
Total RT dose, Gy	54.0	30.6 – 59.4	54.0	45.0 – 59.4	0.75

Average Household Income, median income bracket (range)	\$60,000 - \$80,000	<\$10,000 - >\$200,000	\$60,000 - \$80,000	<\$10,000 - >\$200,000	0.81

Note. *P* values refer to group differences in each variable, as determined by *t*-tests or Chi-square analyses. *P* values less than 0.05 were bolded to indicate significance. Total RT dose, Gy, indicates total amount of radiation administered to the tumor/tumor bed.

Table 2
Zero-order correlations between covariates and academic fluency variables

	Reading Fluency	**Writing Fluency**	**Math Fluency**
Gender	0.17	0.21	0.07
Tumor type	0.11	0.05	0.03
Tumor level	-0.19	-0.26*	-0.20
Craniospinal (versus focal) radiation therapy	**-0.41*** **	**-0.44*** **	**-0.37*** **
Total RT dose	0.06	-0.08	0.06
Age at end of treatment	0.18	0.21	0.21
Age-at-evaluation	-0.02	0.00	-0.12
Follow-up interval	**-0.25* **	**-0.27* **	**-0.43*** **
Race	0.04	-0.04	0.03
Government Assistance	-0.14	-0.21	-0.16
Lansky/Karnofsky	**0.31* **	**0.39** **	**0.36** **
Average Household Income	0.22	0.16	0.15

Note. RT = radiation therapy. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 3
Zero-order correlations between covariates considered in analyses, academic fluency variables, and cognitive variables

	Craniospinal (versus focal) radiation therapy	**Age at Evaluation**	**Follow-up Interval**	**Lansky/Karnofsky**
Reading Fluency	-0.41***	-0.02	-0.25*	0.31*
Writing Fluency	-0.44***	0.00	-0.27*	0.38**
Math Fluency	-0.37***	-0.12	-0.43***	0.36**
Vocabulary	-0.40***	0.10	-0.23*	0.17
WM	-0.38***	0.83	-0.31**	0.19
PS	-0.37***	-0.14	-0.38***	0.35**
Attention	0.11	-0.14	0.01	-0.14
Fine motor	0.33**	0.20	0.23*	-0.36**
Switching	-0.13	-0.05	-0.36**	0.14

Note. WM = working memory; PS = processing speed. Most measures were scaled such that higher scores corresponded with better performance; however, for attention and fine motor, higher scores corresponded with poorer performance. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 4

Zero-order correlations, means, and standard deviations of cognitive and academic measures

	Vocabulary	**WM**	**PS**	**Attention**	**Fine Motor**	**Switching**	**RF**	**WF**	**MF**
Vocabulary									
WM	0.78***								
PS	0.64***	0.62***							
Attention	-0.20	-0.21	-0.28*						
Fine Motor	-0.49***	-0.39***	-0.61***	0.18					
Switching	0.47***	0.43***	0.49***	-0.11	-0.30**				
RF	0.81***	0.70***	0.81***	-0.24*	-0.63***	0.51***			
WF	0.76***	0.70***	0.77***	-0.28*	-0.53***	0.49***	0.88***		
MF	0.75***	0.74***	0.81***	-0.16	-0.53***	0.46***	0.83***	0.82***	

Note. WM = working memory; PS = processing speed; RF = reading fluency; WF = writing fluency; MF = math fluency. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Most measures were scaled such that higher scores corresponded with better performance; however, for attention and fine motor, higher scores corresponded with poorer performance.

Table 5

Zero-order correlations, means, and standard deviations of cognitive and academic measures by radiation treatment group

	Vocabulary	WM	PS	Attention	Fine Motor	Switching	RF	WF	MF
Vocabulary	---	0.72***	0.55***	-0.13	-0.42**	0.26	0.75***	0.69***	0.68***
WM	0.81***	---	0.52***	-0.11	-0.42**	0.30*	0.65***	0.62***	0.66***
PS	0.63***	0.64***	---	-0.23	-0.63***	0.44**	0.80***	0.75***	0.74***
Attention	-0.19	-0.23	-0.20	---	0.28*	-0.10	-0.19	-0.30*	-0.13
Fine Motor	-0.46*	-0.25	-0.51**	-0.04	---	-0.24	-0.64***	-0.49***	-0.50***
Switching	0.51**	0.40*	0.25	0.02	-0.23	---	0.31*	0.35*	0.36*
RF	0.82***	0.64***	0.70***	-0.15	-0.56**	0.52**	---	0.86***	0.78***
WF	0.80***	0.75***	0.69***	-0.07	-0.52**	0.43*	0.85***	---	0.75***
MF	0.73***	0.77***	0.77***	-0.01	-0.48**	0.29	0.79***	0.87***	---
XRT									
Mean	82.24	78.69	68.83	104.12	66.72	80.86	69.14	71.28	67.93
SD	18.01	20.28	13.41	19.90	24.46	18.72	17.64	17.05	16.83
% Below 8th Percentile	66	52	72	14	69	79	69	69	69
PBRT									
Mean	95.66	91.38	83.08	98.71	80.08	96.41	87.94	87.50	85.57
SD	15.67	17.73	14.44	22.03	27.20	15.28	18.60	20.76	16.10
% Below 8th Percentile	39	20	44	4	41	31	24	35	31

Note. WM = working memory; PS = processing speed; RF = reading fluency; WF = writing fluency; MF = math fluency. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Correlations for the PBRT group are located in the top right of the matrix, and correlations for the XRT group are in the bottom left. Most measures were scaled such that higher scores corresponded with better performance; however, for attention and fine motor, higher scores corresponded with poorer performance. All means and standard deviations are presented in standard score format (population mean = 100, SD = 15) to facilitate comparison across measures. These were also the scores used in analyses with the exception of the fine motor measure, where logarithmically transformed raw scores were used (including in the above correlation matrix). "% Below 8th percentile" refers to percentage of individuals in each group who performed below the 8th percentile (in the Very Low and Extremely Low ranges).

Figure 1
Multiple mediation model with working memory

Figure 1a
Path estimates for the total effect of group on reading, writing, and math fluency

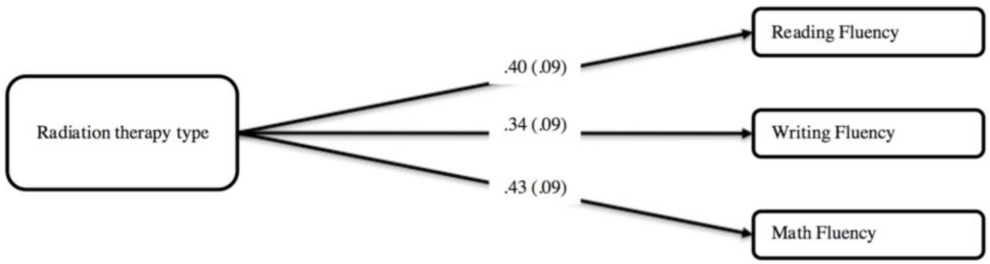
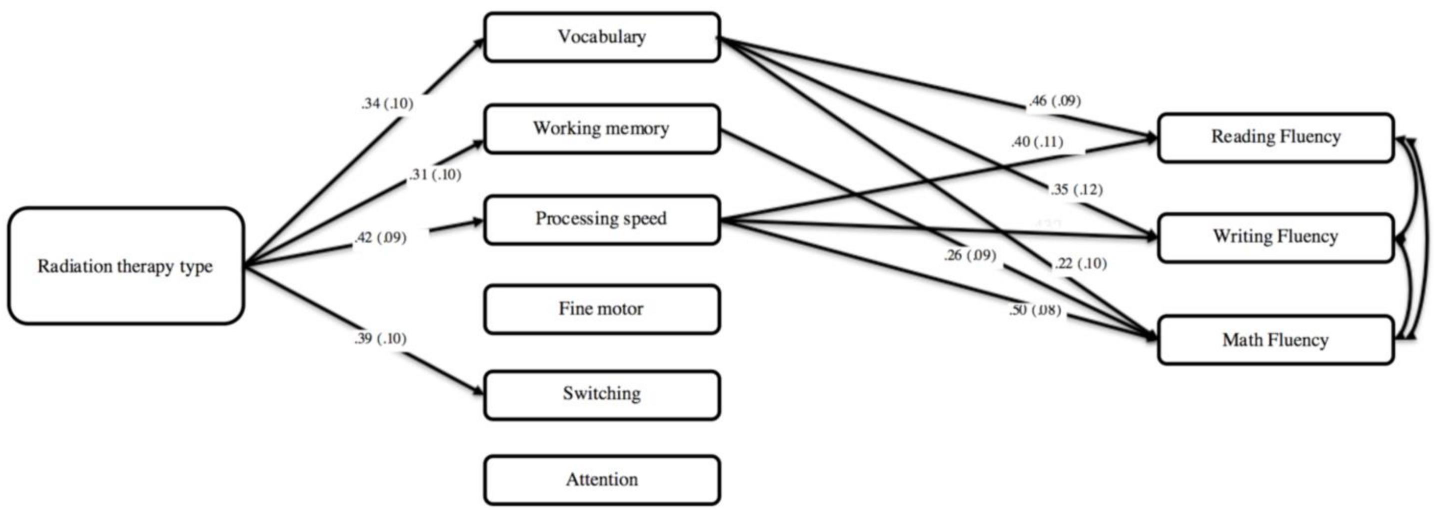


Figure 1b
Full mediation of the relation between group and reading, writing, and math fluency



Note. Data presented are standardized estimates (standard error). Only significant effects are displayed ($p < 0.05$).

Table 6

Bootstrap analyses of direct and indirect effects with working memory.

	Independent variable	Mediator variable	Dependent variable	Mean indirect/direct effect (beta)	SE	*p*	95% CI
Total Effects	RT		RF	0.40	0.09	<0.001	**[.22, .57]***
Total Indirect Effects	RT		RF	0.37	0.09	<0.001	**[.20, .54]***
Direct Effects	RT		RF	0.03	0.06	0.54	[-.09, .14]
Specific Indirect Effects	RT	Vocabulary	RF	0.15	0.06	0.01	**[.06, .28]***
	RT	WM	RF	0.01	0.03	0.75	[-.06, .07]
	RT	PS	RF	0.17	0.06	<0.01	**[.07, .29]***
	RT	Attention	RF	0.00	0.01	0.04	[-.02, .03]
	RT	Fine motor	RF	0.02	0.03	0.47	[-.02, .08]
	RT	Switching	RF	0.02	0.03	0.56	[-.04, .09]
Total Effects	RT		WF	0.34	0.09	<0.001	**[.15, .51]***
Total Indirect Effects	RT		WF	0.37	0.09	<0.001	**[.19, .55]***
Direct Effects	RT		WF	-0.03	0.07	0.73	[-.18, .11]
Specific Indirect Effects	RT	Vocabulary	WF	0.12	0.05	0.02	**[.04, .24]***
	RT	WM	WF	0.04	0.03	0.14	[.00, .11]
	RT	PS	WF	0.18	0.06	<0.01	**[.08, .31]***
	RT	Attention	WF	0.01	0.01	0.56	[-.01, .05]
	RT	Fine motor	WF	0.01	0.03	0.81	[-.04, .07]
	RT	Switching	WF	0.01	0.04	0.73	[-.06, .10]
Total Effects	RT		MF	0.43	0.09	<0.001	**[.24, .58]***
Total Indirect Effects	RT		MF	0.35	0.09	<0.001	**[.16, .51]***
Direct Effects	RT		MF	0.08	0.07	0.22	[-.04, .21]
Specific Indirect Effects	RT	Vocabulary	MF	0.07	0.04	0.06	**[.02, .18]***
	RT	WM	MF	0.08	0.04	0.03	**[.02, .18]***
	RT	PS	MF	0.21	0.06	<0.001	**[.11, .33]***
	RT	Attention	MF	-0.01	0.01	0.34	[-.05, .00]
	RT	Fine motor	MF	0.01	0.02	0.72	[-.02, .06]
	RT	Switching	MF	-0.01	0.03	0.67	[-.07, .04]

Note. RT = radiation type; WM = working memory; PS = processing speed; RF = reading fluency; WF = writing fluency; MF = math fluency. Beta and SE values are standardized estimates.

Figure 2
Multiple mediation model without working memory

Figure 2a
Path estimates for the total effect of group on reading, writing, and math fluency

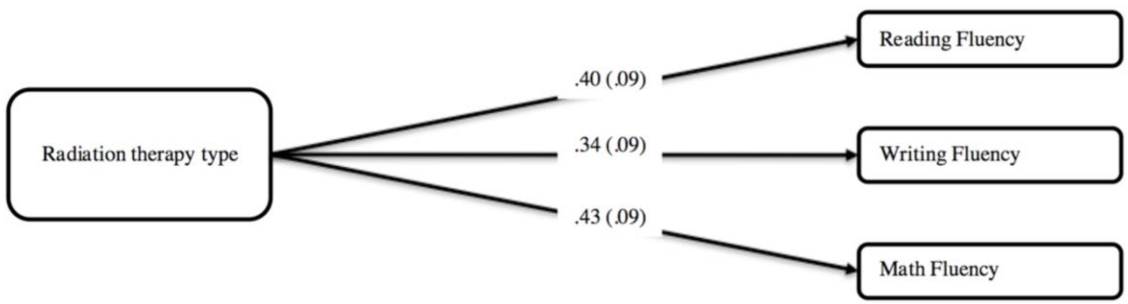
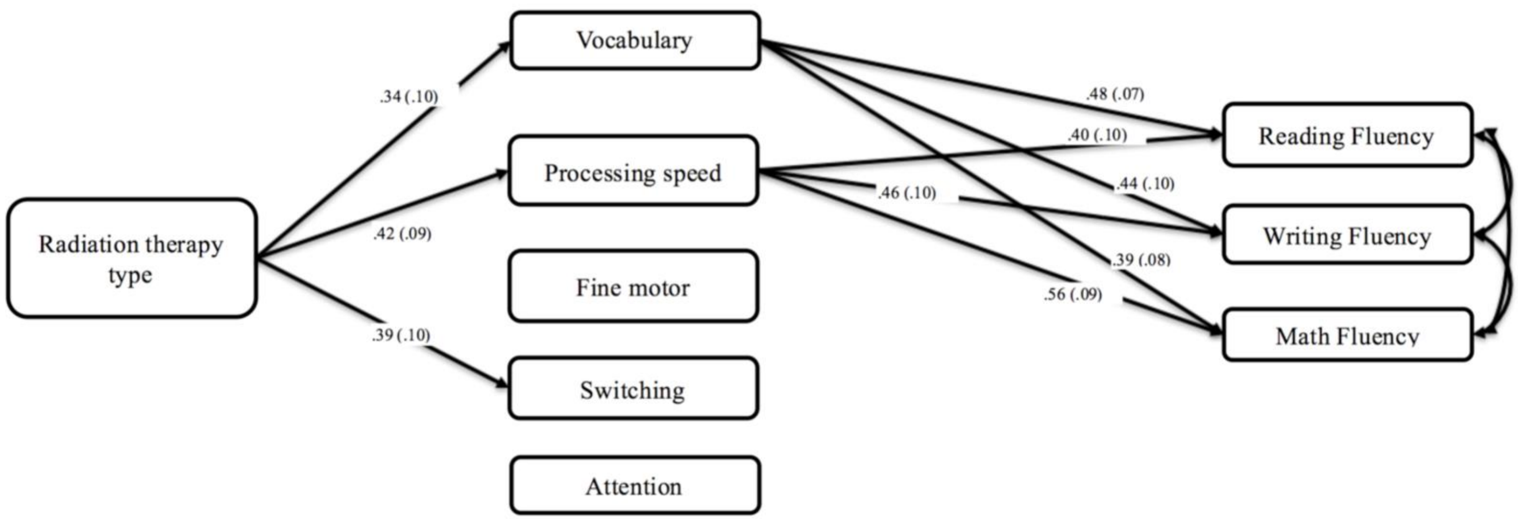


Figure 2b
Full mediation of the relation between group and reading, writing, and math fluency



Note. Data presented are standardized estimates (standard error). Only significant effects are displayed ($p < 0.05$).

Table 7
Bootstrap analyses of direct and indirect effects without working memory

	Independent variable	**Mediator variable**	**Dependent variable**	**Mean indirect/direct effect (beta)**	**SE**	***p***	**95% CI**
Total Effects	RT		RF	0.40	0.09	<.001	**[.21, .57]***
Total Indirect Effects	RT		RF	0.37	0.09	<.001	**[.20, .54]***
Direct Effects	RT		RF	0.04	0.06	0.53	[-.08, .14]
Specific Indirect Effects	RT	Vocabulary	RF	0.16	0.05	<.01	**[.07, .27]***
Specific Indirect Effects	RT	PS	RF	0.17	0.06	<.01	**[.07, .30]***
Specific Indirect Effects	RT	Attention	RF	0.00	0.01	0.92	[-.02, .03]
Specific Indirect Effects	RT	Fine motor	RF	0.02	0.03	0.48	[-.02, .08]
Specific Indirect Effects	RT	Switching	RF	0.02	0.03	0.54	[-.03, .09]
Total Effects	RT		WF	0.34	0.09	<.001	**[.15, .51]***
Total Indirect Effects	RT		WF	0.37	0.09	<.001	**[.19, .55]***
Direct Effects	RT		WF	-0.03	0.07	0.72	[-.18, .11]
Specific Indirect Effects	RT	Vocabulary	WF	0.15	0.05	0.01	**[.07, .27]***
Specific Indirect Effects	RT	PS	WF	0.19	0.06	0.00	**[.09, .32]***
Specific Indirect Effects	RT	Attention	WF	0.01	0.01	0.54	[-.01, .05]
Specific Indirect Effects	RT	Fine motor	WF	0.01	0.03	0.86	[-.05, .07]
Specific Indirect Effects	RT	Switching	WF	0.02	0.04	0.67	[-.06, .10]
Total Effects	RT		MF	0.43	0.09	<.001	**[.23, .58]***
Total Indirect Effects	RT		MF	0.35	0.09	<.001	**[.17, .51]***
Direct Effects	RT		MF	0.08	0.07	0.28	[-.06, .22]
Specific Indirect Effects	RT	Vocabulary	MF	0.13	0.05	0.01	**[.05, .24]***
Specific Indirect Effects	RT	PS	MF	0.23	0.06	<.001	**[.13, .36]***
Specific Indirect Effects	RT	Attention	MF	-0.01	0.01	0.38	[-.06, .00]
Specific Indirect Effects	RT	Fine motor	MF	0.00	0.02	0.90	[-.03, .05]
Specific Indirect Effects	RT	Switching	MF	-0.01	0.03	0.85	[-.07, .05]

Note. RT = radiation type; WM = working memory; PS = processing speed; RF = reading fluency; WF = writing fluency; MF = math fluency. Beta and SE values are standardized estimates.