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The Mediating Role of Processing Speed in Reading-Related White Matter Tracts and Word Reading Skills of Adult Survivors of Childhood Brain Tumor

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THE MEDIATING ROLE OF PROCESSING SPEED IN READING-RELATED WHITE MATTER TRACTS AND WORD READING SKILLS OF ADULT SURVIVORS OF CHILDHOOD BRAIN TUMOR

by

KRISTEN M. SMITH

Under the Direction of Dr. Tricia King

ABSTRACT

The purpose of this study was to investigate the relationship between word reading and white matter (WM) integrity in the reading system and test a theory-based moderated mediation model such that relationship of WM integrity with word reading is mediated by processing speed and indirect effect is moderated by group. Thirty-seven adult survivors of childhood brain tumor and typically developing adults participated (mean age=24.19(4.51) years, 62% female). Tractography identified the WM tract for three reading system connections. Fractional anisotropy of the IFOF and PT-OT tracts were significantly correlated with word reading in survivors (r=.55, .46, respectively; p<.05) and controls (r=.59, p<.01 IFOF). The moderated mediation model was significant for IFOF and PT-OT, such that the indirect effect of processing speed was only present for survivors (CI: 2.88, 28.33). Results suggest the occipitotemporal area is a critical component of the reading system in adults. Results align with the developmental cascade model.

INDEX WORDS: DTI, White matter, Reading, Childhood brain tumor survivors, Long term, Processing speed

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KRISTEN M. SMITH

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1 INTRODUCTION

The incidence of brain tumors in children is about 4 cases annually per 100,000 (Legler et al., 1999; Miltenburg, Louw, & Sutherland, 1996). Treatment related advances in childhood brain tumors have greatly increased the survival rate to an estimated 70% at 5 years post diagnosis (Bleyer, 1999). With survival rates on the rise, the focus of research has turned to the long-term cognitive outcomes of survivors of childhood brain tumors.

1.1 GENERAL COGNITIVE OUTCOME

Cognitive dysfunction is considerable and 40 to 100 percent of long term survivors experience some sort of cognitive dysfunction (Glauser & Packer, 1991; Mulhern & Palmer, 2003). However, cognitive difficulties are not always apparent immediately after treatment. In fact, many deficits do not appear until years after treatment is completed. Longitudinal studies have shown that survivors progress more slowly than their peers in verbal, nonverbal, and general intelligence and this effect increases over time since diagnosis (Palmer, 2008). These learning difficulties appear to be due to a reduced rate of skill acquisition rather than a loss of previously learned skills (Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Palmer et al., 2001). Therefore, a survivor may continue to learn and incorporate new information, albeit at a slower rate and hence, the performance of the survivor relative to same age peers grows increasingly different.

1.2 ACHIEVEMENT OUTCOME

Much of the work on outcomes in brain tumor survivors has focused on general intelligence. Although measures of intelligence provide an adequate measure of general cognition, more research is needed on specific functional impairments that affect everyday life in order to plan relevant interventions. Academic achievement is an important measure of learning and school performance. Achievement measures have higher ecological validity than intelligence measures because they are a direct measure of skills learned in the school environment (Mabbott et al., 2005). Research has shown that survivors experience significant difficulties in academic achievement (Mabbott et al., 2005; Mulhern et al., 2005; Palmer, 2008). In one study, survivors utilized special education services more than a sibling comparison group (Mitby et al., 2003). Those younger at the time of diagnosis had the highest percentage of receiving special education services. Survivors of brain tumors also were less likely than survivors of non-CNS cancer to complete high school regardless of whether they had ever received special education services. In longitudinal studies, after diagnosis children exhibited progressively slower learning in each academic skill tested: math, spelling, and reading (Mabbott et al., 2005). Standard scores decreased over time compared to healthy peers reflecting slower paced learning of new skills in survivors.

1.3 READING OUTCOME

Reading achievement appears particularly vulnerable to disease and treatment risk factors in brain tumor survivors. Several studies have found reading decoding scores for real words below normative values post treatment (Beebe et al., 2005; Kieffer-Renaux et al., 2000; Reddick et al., 2003; Reeves et al., 2006; Robinson et al., 2010). In a group of survivors of medulloblastoma treated with surgery and radiation who were an average of 8 years of age at treatment and an average of 2 years since the initiation of radiation treatment, Reeves et al. (2006) observed decoding scores significantly below the standardization sample (M=92.50, SD=15.28). Beebe et al. (2005) also observed a higher rate of reading decoding scores below the 25th percentile in survivors of cerebellar astrocytoma treated with surgery only, average of 108 days since treatment, tested at an average of 8.5 years of age, though these average scores were not statistically significantly below the population mean. In a group with a variety of tumor pathologies treated with radiation and a wide range of time since treatment (3-15 years) and age at treatment (2-15 years), reading decoding was on average, below the test norms (Reddick et al., 2003). Kieffer-Renaux et al. (2000) found that regardless of radiation dose, medulloblastoma survivors, an average of 4 years since treatment, and 6-26 years at examination exhibited impaired reading decoding. Furthermore, longitudinal data indicate slow reading progress in survivors over time signifying that survivors have more difficulty learning at the same rate as their peers. In general, as time since diagnosis increased, survivors remained behind their peers and progressed more slowly in mastering decoding skills. For posterior fossa tumor survivors treated with radiation, an average of 7 years at diagnosis, median time since treatment of 4 years, standard scores of reading decoding started in the average range but declined over time indicating that the survivors did not learn at the same rate as their peers (Mabbott et al., 2005). This effect attenuated over time such that the rate of standard score decline decreased with increased time since diagnosis, suggesting that this effect becomes weaker over time. In another study, medulloblastoma survivors 0-6 years since diagnosis, 3-20 years at the time of diagnosis, exhibited a slow progression of decoding skills over time, which was slower for those younger at diagnosis (Mulhern et al., 2005). The most recent study to observe slow learning of reading decoding in survivors (Conklin, Li, Xiong, Ogg, & Merchant, 2008) found that while standard scores for reading declined over time (median follow up time of 60 months), scores for spelling and math achievement remained on par with peers. This reading decline was particularly evident for those younger than 5 years at treatment. This group of survivors of ependymoma brain tumors treated with radiation treatment, 1-18 years at treatment (tested at baseline, 6 months post treatment and annually up to 99.7 months since treatment), illustrated that reading was more prone to difficulties than other areas of achievement during this follow up period. Much of the aforementioned research examined short term outcome or short and long term survivors combined to one group. Relatively little data are available on reading skills in long term survivors greater than 15 years since diagnosis. Overall, the significant reading difficulties experienced by survivors with various tumor pathologies and treatment modalities indicate that reading can be a problematic skill for survivors to develop and master. Reading outcomes may be related to difficulty with core cognitive skills integral to reading ability.

1.4 CORE COGNITIVE FUNCTION AND ENCOMPASSING MODEL

Understanding why survivors tend to struggle with learning and advancing reading skills may be related to the development of core cognitive abilities that can impact reading acquisition. In her model of the neurodevelopmental impacts of brain tumors, Palmer (2008) proposed disease and treatment risk factors along with age at diagnosis to be associated with academic achievement and intelligence through core cognitive functions. Yet the achievement and cognition relation aspect of the model has not been adequately studied. Multiple studies have looked at the relationship between intelligence and core cognitive difficulties; however few studies have looked at the association of reading and cognition in survivors. In survivors, academic achievement is considered a distal marker of underlying deficits in core cognitive skills such as processing speed, attention, and memory (Mabbott et al., 2005; Mulhern et al., 2005; Palmer, 2008). Two studies have observed a relationship between reading and attention in short-term survivors (Reddick et al., 2003; Reeves et al., 2006). In a recent study, reading skill in long term survivors was related to information processing speed but not related to working memory (K. M. Smith, King, Morris, & Krawiecki, 2011). Moreover, processing speed in particular may be related to complex cognitive processes, such as reading, as processing speed is a foundational construct for a broad range of basic and advanced cognitive functions.

Information processing speed refers to the efficiency of processing simple cognitive or perceptual information (Palmer, 2008). In brain tumor survivors, difficulties in processing speed are observed in individuals who received treatment with surgery only, treatment with radiation, or radiation dose (Kieffer-Renaux et al., 2000; Ronning, Sundet, Due-Tonnessen, Lundar, & Helseth, 2005). Although findings with survivors who were treated with surgery only are more variable with some studies showing impairment in processing speed and other studies finding processing speed in the average range (Kieffer-Renaux et al., 2000; Mabbott et al., 2008; Ronning et al., 2005). Processing speed has been found to be further impaired when surgery was accompanied by treatment with radiation or shunt placed for hydrocephalus, and may also be affected by age at treatment (Mabbott et al., 2008; Ronning et al., 2005). A long-term outcome study with survivors 12-21 years post treatment, found poor speed in addition to poor neurocognitive performance in attention and executive function (Ronning et al., 2005). This study in particular highlights the persistence of cognitive difficulties in survivors. However, speed has been shown to be slow even when attention and working memory deficits were not found (Briere, Scott, McNall-Knapp, & Adams, 2008; Mabbott et al., 2008). In addition, information processing speed has been identified as a possible precursor to broader cognitive dysfunction in survivors (Palmer, 2008). It is hypothesized to be the first deficit to arise after treatment (Mabbott et al., 2008).

Our research team found that slower processing speed was significantly associated with poor reading achievement in long term survivors (Kohl, Wendell, King, Morris, & Krawiecki, 2010). Consistent with this finding, it appears that in the general population, reading difficulties are often accompanied by slower processing speed (Catts, Gillispie, Leonard, Kail, & Miller, 2002; Shanahan et al., 2006). Children with reading difficulties tended to have slower nonlinguistic, perceptual processing speed (Catts et al., 2002; Plaza & Cohen, 2005). In addition, processing speed contributed uniquely to reading achievement after accounting for IQ and phonological awareness (Catts et al., 2002). In children with traumatic brain injury of varying severities (40% in the severe range), decoding skills were lower than a comparison group (Barnes, Dennis, & Wilkinson, 1999). Even when matched for decoding skills, the children with traumatic brain injury remained slower on average. Therefore a processing speed component was evident in this group in addition to difficulty decoding words.

1.5 WHITE MATTER INTEGRITY

Structural brain changes also may underlie reading ability in survivors of childhood brain tumors. White matter (WM) in the brain represents myelinated axons, which carry neuronal impulses, facilitating communication across brain regions. WM development and proliferation takes place from birth to young adulthood in which WM increases with age. Therefore, neurological insult in childhood, can negatively impact the development of white matter. In addition, differences in white matter structure have correlated with cognitive function (Cascio, Gerig, & Piven, 2007).

Diffusion tensor imaging (DTI) is a noninvasive, in vivo technique to measure the quality of white matter structure. DTI is sensitive to changes in WM due to injury, damage or development (Assaf & Pasternak, 2008). DTI characterizes WM by measuring the diffusion of water within tissue. Among bundles of myelinated axons, water diffuses along the direction of the axon in an anisotropic manner (Cascio et al., 2007). Fractional anisotropy (FA) is the most commonly used DTI index, which is a normalized measure of directional diffusion. High anisotropy indicates fast water diffusivity parallel to the fibers, and slow diffusivity perpendicular to the fibers (Assaf & Pasternak, 2008). In areas that have similar water diffusion in all directions, such as gray matter and cerebral spinal fluid, FA will be close to zero (Assaf & Pasternak, 2008). Low FA is generally interpreted to indicate less myelination, and higher FA, greater myelination; however, it could also be related to axonal size and pathway complexity (Ben-Shachar, Dougherty, & Wandell, 2007; Frye et al., 2010). Mean diffusivity (MD) is another commonly reported index of DTI that is the average of the three diffusivities or eigenvalues (λ_1, λ_2, λ_3) in three directions- axial or parallel, radial and perpendicular to axonal fibers (Nagesh et al., 2008). Low MD is generally interpreted to reflect greater WM integrity, and high MD, less white matter integrity. MD can help to further characterize white matter fibers by measuring displacement of water molecules (Nagesh et al., 2008).

1.6 READING AND WHITE MATTER

In order to understand how white matter pathways may relate to reading ability, one must take note of the functional brain system involved in reading. Learning to read is a complex cognitive skill involving the coordination of multiple regions of the brain. Functional MRI studies of word decoding have established a reliable network of left hemisphere brain regions responsible for skilled reading. This network consists of an anterior region in the inferior frontal gyrus (IFG) including Broca’s area, a dorsal posterior region in the parietotemporal area (PT), and a ventral posterior region in the occipitotemporal area (OT) consisting of the visual word form area in the fusiform gyrus (Pugh et al., 2001; B. A. Shaywitz et al., 2002). The inferior frontal gyrus has been found to be active with word analysis including: articulation, phonological recording, silent reading, and naming, and general speech production (Pugh et al., 2001). Functions of the parietotemporal area also include word analysis. The parietotemporal region in particular appears work in concert with the IFG to command early development of word decoding (Booth et al., 2001; Pugh et al., 2010), while further learning is facilitated by the occipitotemporal area and IFG interaction. The occipitotemporal area becomes central as proficiency in word decoding increases and this area is particularly attuned to skilled and fluent reading (B. A. Shaywitz et al., 2007; S. E. Shaywitz & Shaywitz, 2008). Processing speed may serve a primary role in this region.

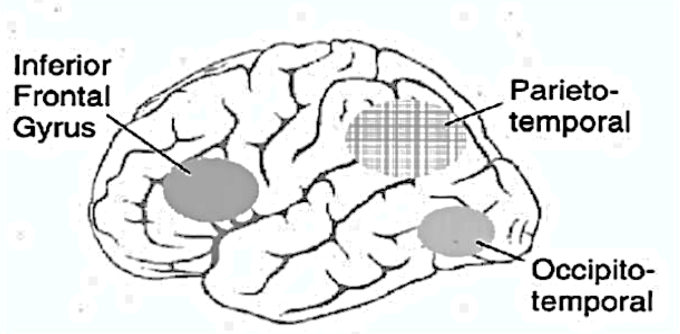


Figure 1. *Model of functional reading-related brain regions (B. A. Shaywitz et al., 2002)*

Functional activation during reading tasks becomes more left lateralized with age and increased reading skill in nonimpaired readers. The functional activation of reading in poor readers looks consistently different from nonimpaired readers. Poor readers have a disruption of the left hemisphere posterior systems (PT & OT), presenting as underactivation (B. A. Shaywitz, Lyon, & Shaywitz, 2006). Compensatory activation in poor readers includes overactivation of the left anterior system, and additional activation of the right hemisphere in the inferior frontal gyrus and right occipitotemporal area (B. A. Shaywitz et al., 2006). Weaker connectivity between the anterior region (IFG) and the posterior regions (PT & OT) may be related to this pattern of compensatory activation in poor readers (Paulesu et al., 1996).

Several studies have examined the relationship between white matter structure and reading ability. These studies have looked at WM differences in the functional reading network and corpus callosum differences relating to lateralization of skill. Studies of white matter in the reading network, have found support for the disruption of posterior reading systems in poor readers. Klingberg et al. (2000) looked at the correlation of whole brain white matter and both word identification and pseudoword decoding in adults with both poor reading and average reading skill. Both reading measures correlated positively with FA in one cluster of WM that overlapped the parietotemporal area. This correlation was significant for both poor readers and nonimpaired readers. Fifty-six percent of the voxels in this region were oriented in the anterior-posterior direction. They hypothesized that this area was part of a tract connecting the parietotemporal region and frontal reading regions. Bealieu et al. (2005) extended the relationship between the left parietotemporal area and reading to a sample of children of average reading level. They found 5 clusters in which FA correlated with word identification with the largest cluster located in the parietotemporal region, left posterior limb of the internal capsule. However, in contrast to Klingberg et al. (2000), the tract direction was estimated to be in an inferior-superior orientation. Another study in children also found similar results with children using a predefined volume of interest in the parietotemporal region. Several reading measures including word identification and pseudoword decoding correlated with FA in the left parietotemporal region. Similar to Bealieu et al. (2005), the majority of the voxels were oriented in the inferior-superior direction (Deutsch et al., 2005). Niogi and McCandliss (2006) investigated 5 a priori ROIs and also found that word identification correlated positively with FA in the left centrum semioval and left superior corona radiata, part of the parietotemporal region. Again, tracts were oriented primarily in the inferior-superior direction. Studies of the corpus callosum have generally found increased WM integrity in poorer readers in the corpus callosum, which is hypothesized to be due to less lateralization of reading function which is in contrast to skilled readers who exhibit left lateralization of cortical reading networks.

Ben-Schachar et al. (2007) hypothesized that lower FA found in the parietotemporal area may be due to increased fibers in the splenium which cross in the parietotemporal area. Further studies have found support for this hypothesis. In a study with 50 nonimpaired readers, reading measures, including pseudoword decoding, correlated positively with radial diffusivity and negatively with FA in a segment of the corpus callosum that intersects with temporal lobe tracts, which the authors posit is due to a higher proportion of large axons in nonimpaired readers (Dougherty et al., 2007). Another study found that decoding was negatively associated with FA and axial diffusivity (AD) in the splenium in two groups of adult readers (Frye et al., 2008). They suggest that this decreased organization of splenium fibers in nonimpaired readers is a result of increased specialization of reading to the left hemisphere. Odegard (2009) found both a positive correlation between reading and FA in a parietotemporal area (left superior corona radiata in the superior-inferior direction), and a negative correlation between FA and reading in the posterior corpus callosum.

These studies found consistent differences between reading groups in both adults and children in the parietotemporal posterior reading system and the corpus callosum. However, the fibers in the parietotemporal area appear to be in the superior-inferior direction, which do not commonly connect the three areas in the functional reading system. The ability to more directly examine connections between these cortical functional reading related regions in the brain will be crucial to identify possible area(s) of poor communication within the reading system.

Advances in technology now allow us to track and measure connections between brain regions using DTI tractography (Mori & van Zijl, 2002). Studying the connections between each of the functional reading areas (IFT, PT, & OT) can allow us to compare white matter tracts involved in the cortical reading system for a potential breakdown in communication, where the structure may not be as strong. This will allow a more direct examination of white matter connections in the functional reading system.

A model proposed by Reddick et al. (2003) suggests that white matter structural changes likely work through core cognitive deficits to affect broader cognitive function and achievement including reading. He found evidence for this model in survivors who received radiation, between 7 and 19 years at exam, between 2 and 15 years at irradiation and a median of 5.7 years since irradiation, and a range of tumor pathology. In his model, cognitive function, specifically attention, mediated the relationship between whole brain white matter volume and intelligence and academic achievement (Reddick et al., 2003). In one study that specifically looked at reading ability and white matter in survivors, FA was associated with reading ability in survivors in several regions of the cortex including: the left and right posterior limb of the internal capsule, left temporal occipital, right knee of the internal capsule, right occipital lobe, left inferior parietal, and mid-cingulate (Palmer et al., 2010). However, relatively little research has sought to test this model by examining empirically driven white matter tracts related to core cognitive functions such as processing speed and to reading achievement. Exploring the cognitive mechanisms by which white matter is associated with reading vulnerability in survivors, may allow better identification of survivors at risk for reading difficulties. This study aims to examine the structure of white matter tracts connecting the primary cortical regions involved in skilled reading: inferior frontal gyrus to parietotemporal (IFG- PT), inferior frontal gyrus to occipitotemporal (IFG-OT), and parietotemporal to occipitotemporal (PT-OT) in accordance with word reading in adult survivors of childhood brain tumors. Processing speed may particularly mediate the relationship between white matter integrity and reading decoding for the white matter connections between the inferior frontal gyrus and occipotemporal region (IFG-OT) involved in fluent reading.

1.7 POTENTIALLY CONFOUNDING VARIABLES

In survivors of childhood brain tumors, multiple factors may play a role in shaping reading outcome including: age at diagnosis, treatment type (i.e., radiation therapy, chemotherapy, & surgery), age at diagnosis, time since diagnosis, and presence of hydrocephalus, and treatment with seizure medication. In addition, there could be a cumulative effect of multiple treatments and medical complications (Micklewright, King, Morris, & Krawiecki, 2008) on reading outcome. In survivors, hydrocephalus has been associated with poorer academic achievement with a trend toward poorer reading skill (Mabbott et al., 2005). In multiple studies, younger age at diagnosis or treatment has been associated with poorer reading outcome compared to those who were older at the time of diagnosis (Conklin et al., 2008; Mabbott et al., 2005). Time since radiation treatment has also been significantly associated with reading skill. These disease and treatment variables are predicted to affect reading outcome through their effect on neurodevelopment. This is highlighted in Palmer's (2008) neurodevelopmental model in which disease and treatment factors affect the neurodevelopment of the patient, which affect core cognitive factors, and finally affect intellectual and achievement outcome. Demographic variables also could affect reading skill in the survivor and comparison groups. This includes such factors as: level of education, socioeconomic status, age, ethnicity, and sex. To control for the effects of these variables on reading outcome, the two groups will be carefully matched on demographics. As potentially confounding variables may misconstrue the true relationship between white matter structure, processing speed, and reading between groups as measured in this study, demographic variables will be included in analyses as covariates if significantly different between groups and associated with the dependent variable.

1.8 SPECIFIC AIMS

The purpose of this study was to investigate the relationship between word reading skill and white matter integrity of tracts in the reading system, and test a model incorporating processing speed in long term survivors of childhood brain tumors. The proposed study examined long-term survivors of childhood brain tumors and a healthy comparison sample.

Aim One was to explore the relationship between reading skill and white matter integrity associated with the tracts connecting the three primary functional reading brain regions (inferior frontal gyrus, parietotemporal area, & occipitotemporal area). White matter quality was be measured using Fractional Anisotropy and Mean Diffusivity.

Aim Two was to investigate the relation between integrity of the white matter connection (FA) between the anterior reading area (IFG) and the ventral posterior reading area (OT), and reading achievement as mediated by processing speed in each group. The effect of speed was only expected for the survivor group given previous research, therefore, the indirect effect of processing speed was proposed to be moderated by group (Figure 2).

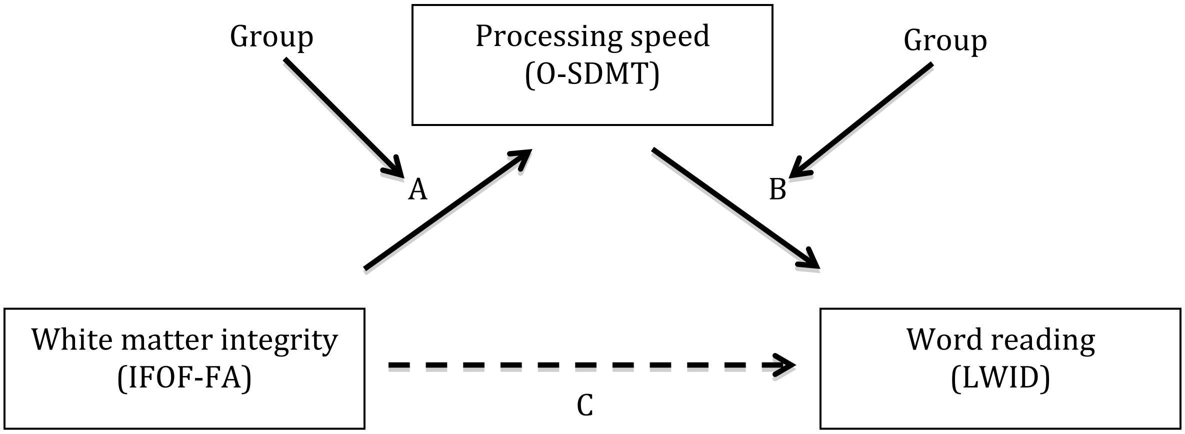


Figure 2. *Hypothesized moderated mediation model in which the relationship between white matter integrity and word reading is mediated by processing speed, and the indirect effect (paths a & b) are moderated by group.*

1.9 HYPOTHESES

With respect to **Aim One**, we hypothesized that both the survivor group and the healthy comparison group would have significant positive relationships between white matter integrity in each of the three measured tracts and word reading skill.

With respect to **Aim Two**, we hypothesized that information processing speed would partially mediate the relationship between white matter integrity and reading skill in survivors and that the indirect effect of processing speed would be moderated by group membership.

2 METHOD

2.1 PARTICIPANTS

Thirty-eight participants were involved in this archival study and were recruited as part of a larger parent study of long-term neuropsychological outcome of survivors of childhood brain tumors (American Cancer Society, Principal Investigator: T.Z. King, #RSGPB-CPPB-114044).

The current study used data gathered as part of this larger study and did not involve any additional visits or measures that were not part of the larger study. This study was approved by the Georgia State University Institutional Review Board (IRB: H03177 & H08323) Georgia State University/Georgia Institute of Technology Joint Center for Advanced Brain Imaging (IRB: H09157) where the assessment and scanning were completed. All participants signed informed consent. Brain tumor survivors were recruited from two sources: 1) a previous longitudinal study, in which they participated as children, and 2) opt-in letters mailed to survivors identified by physicians on the study. Twelve survivors were excluded for the following criteria: left hemisphere DTI data was distorted due to shunt or metal artifact (n=8), not a native English speaker (n=1), incomplete DTI data (n=1), severely enlarged ventricles (n=1), unable to complete study measures due to visual impairment (n=1) and inclusion comprised of: scan date on or before March 31, 2012. Survivors were clear of current psychopathology except one participant who met diagnostic criteria for Dysthymia. Nineteen survivor participants met this study’s criteria.

The healthy comparison group was recruited from the Georgia State University psychology department subject pool. Nineteen healthy comparison participants were chosen from a group of over 75 participants to demographically match the survivor group by: age, sex, ethnicity, socioeconomic status, and level of education.

Inclusion criteria for comparison participants included: English as their native language and at least 18 years of age at the time of the study visit. Undergraduate participants were excluded if they reported past or present neurological insult. Participants were carefully screened for diagnostic criteria of: current Major Depressive Disorder, illicit substance abuse or dependence, or presence of a psychotic disorder based on a structured DSM-IV based clinical interview. Self reported demographic information included: age, sex, ethnicity, years of education, socioeconomic status. For survivors, additional medical variables were gathered including: age at diagnosis, time since diagnosis and treatment type (radiation therapy, chemotherapy, and surgery), radiation dose, treatment with a shunt for hydrocephalus, and treatment with seizure medications.

Data from one survivor were excluded due to extreme scores on the neuropsychological measures, and deemed a multivariate outlier. Three participant's data (2 comparison, 1 survivor) did not produce a tract output for the PT-OT connection. Another three participant's data (2 comparison, 1 survivor) produced the incorrect tract from the ROIs intended to produce the IFOF. For one participant, the superior ROI for the CST was not able to be drawn due to tumor location in that area. These data could not be corrected and therefore were excluded from analyses. These participant's other tract data was appropriate and was used in analyses. With these specific tracts excluded, the sample size for each comparison was different. However, the sample size was never lower than 17 (comparison group) compared with 16 (survivor group).

For the final sample of 37 participants, the mean age at the time of study participation was 24.19 years (SD=4.51); ages ranged from 19.42 to 40.67 years (see Table 2 in Results). Participants had completed an average of 14.16 years of education (SD=1.52). The sample was 62% female and 79% had high socioeconomic status. Sixty-two percent of participants were of Caucasian ethnicity, 48% Other ethnicity included: African American, Asian, Hispanic, and Mixed.

Table 1 provides a summary of the relevant disease and treatment related variables in the survivor group. Survivors were an average of 7.22 years old when diagnosed. The average time since diagnosis was 17 years and ranged from five to 23 years. Half the group received radiation and chemotherapy and cerebellar tumors also accounted for 50% of participants. The group is heterogonous for tumor type and pathology.

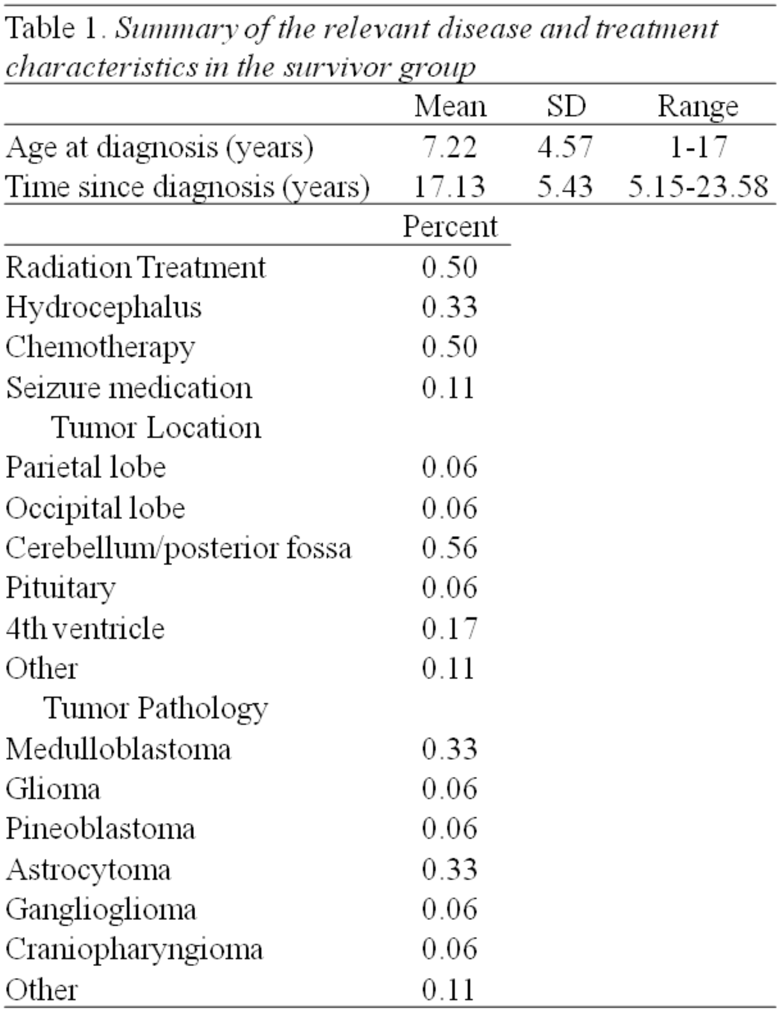


Table 1. *Summary of the relevant disease and treatment characteristics in the survivor group*

	Mean	SD	Range
Age at diagnosis (years)	7.22	4.57	1-17
Time since diagnosis (years)	17.13	5.43	5.15-23.58
	Percent		
Radiation Treatment	0.50		
Hydrocephalus	0.33		
Chemotherapy	0.50		
Seizure medication	0.11		
Tumor Location			
Parietal lobe	0.06		
Occipital lobe	0.06		
Cerebellum/posterior fossa	0.56		
Pituitary	0.06		
4th ventricle	0.17		
Other	0.11		
Tumor Pathology			
Medulloblastoma	0.33		
Glioma	0.06		
Pineoblastoma	0.06		
Astrocytoma	0.33		
Ganglioglioma	0.06		
Craniopharyngioma	0.06		
Other	0.11		

2.2 MEASURES

2.2.1 Reading Achievement. Reading achievement was examined with the Letter-Word Identification subtest of the Woodcock Johnson Tests of Achievement III (Woodcock, McGrew, & Mather, 2001b). Letter-Word Identification (LWID) is a measure of real word decoding. This measure has been utilized to quantify reading ability in survivors of childhood brain tumors. LWID also is frequently used as a measure of reading decoding skill in functional and structural studies of skilled and poor reading. Moreover, previous studies have linked real word decoding to white matter integrity in adults and children over a range of reading ability levels.

For this task, participants are presented with written words to read orally. Score is based on correct pronunciation. Items increase in difficulty and items appear less and less frequently in written English (Woodcock, McGrew, & Mather, 2001a). The Woodcock Johnson Tests of Achievement III was normed on a sample of 8,818 persons aged 2-80 years of age, demographically proportional to the U.S. population in accordance with the 2000 census projections (McGrew & Woodcock, 2001). LWID has a split-half reliability coefficient of .91 in the 5-19 age range and .94 in adults. Test-Retest reliability in adults 19-44 years of age for LWID ranges from, r = 0.90 at less than a year interval to 0.87 at 3-10 years interval. LWID evidenced convergent and discriminant validity as it correlated highly with similar constructs such as Verbal Comprehension and correlates at a lower level with relatively unrelated constructs such as Visual Matching. LWID z-scores computed from normative data (Woodcock et al., 2001b) were used as primary dependent variable.

2.2.2 Information Processing Speed. The Symbol Digit Modalities Test (SDMT) Oral Version was used in this study as the measure for information processing speed. The SDMT is a perceptual task that unlike most other tests of processing speed, does not involve a motor component, but instead, a verbal response, allowing a more pure measure of processing speed as opposed to motor speed. The SDMT involves converting simple meaningless geometric designs intro oral number responses according to a key that matches each symbol to a number (A. Smith, 1982). The participant is given a 90 second time limit to complete as many items as they can. The score is based on the number of items correctly completed within the time limit. The test-retest reliability is stable at 0.76. The SDMT was originally designed to screen for cerebral dysfunction and appears to be highly sensitive to diverse etiologies of cerebral dysfunction. A task that is similar to the SDMT is a primary measure of processing speed in the commonly used Wechsler Intelligence tests (Coding subtest). The SDMT has been used extensively as a measure of processing speed in a range of populations including various types of brain disorders (Christodoulou et al., 2003; Hohol et al., 1997; Huijbregts et al., 2004; Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Landro, Celius, & Sletvold, 2004; Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007; Perrine et al., 1995; Sheridan et al., 2006). In a study of participants with multiple sclerosis, this measure was strongly associated with structural components in the brain (Christodoulou et al., 2003). It is frequently used in research with different brain injury populations and has shown good test-retest reliability among these groups (Benedict et al., 2008). Oral SDMT z-scores computed from normative data (A. Smith, 1982) were used as the mediator variable in regression analyses.

2.2.3 Math Calculation Skill. Math calculation skill was examined as a control task dependent variable to be compared with reading. To measure this skill, the Calculation subtest of the Woodcock Johnson Tests of Achievement III (Woodcock et al., 2001b). Calculation is a measure of ability to perform mathematical computations. Items increase in complexity and include: addition, subtraction, multiplication, division, and combinations of these in addition to geometric, trigonometric, logarithmic, and calculus operations (McGrew & Woodcock, 2001). The Woodcock Johnson Tests of Achievement III was normed on a sample of 8,818 persons aged 2-80 years of age, demographically proportional to the U.S. population according to the 2000 census projections. This subtest has a median split-half reliability of 0.89 in the adult age range. Test-Retest reliability was, r = 0.94 in a one year interval. Calculation evidenced convergent and discriminant validity as it correlated highly with similar constructs such as

Analysis-Synthesis and correlates at a lower level with relatively unrelated constructs such as Picture Recognition. Calculation z-scores computed from normative data (Woodcock et al., 2001b) were used as the dependent variable in the control task analyses.

2.2.4 Skilled Motor Speed. Skilled motor speed was used as a second control task. This construct was measured using the Grooved Pegboard test- dominant hand score (Ruff & Parker, 1993). This task requires the participant to fit key-hold-shaped pegs into holes in a pegboard using only one hand at a time. The participants are encouraged to go as quickly as possible without making mistakes. The raw score is the amount of time in seconds that it takes the participant to put a peg into each hole on the board. The Grooved Pegboard is a common measure of skilled motor speed and is a component of several standard neuropsychological batteries (Ruff & Parker, 1993). It has been shown to be sensitive to detection of change in skilled motor speed due to disease progression, more sensitive than other motor tasks (Bryden & Roy, 2005). In addition, this test is used to examine lateralization of function (Bryden & Roy, 2005). Grooved Pegboard dominant hand z-scores computed from normative data (Ruff & Parker, 1993) were used as the control task dependent variable.

2.2.5 White matter integrity and tracts. Diffusion Tensor Imaging (DTI) is part of a MRI scan that measures the diffusion of water molecules is measured through tissue. The strength of white matter in the brain can be assessed based on the measured diffusivity. Water molecules cannot diffuse through white matter, therefore white matter tracts are indirectly measured through diffusivity. Several types of diffusivity scores can be computed from the data. Fractional Anisotropy (FA) is a measure of white matter integrity derived from diffusion tensor imaging. The score for FA ranges between 0 and 1 with 1 being high white matter integrity and 0 being low integrity. Mean diffusivity (MD) is the average of the three diffusivities or eigenvectors (λ_1,

λ_2, λ_3) in three directions- axial or parallel, radial and perpendicular to axonal fibers (Nagesh et al., 2008).

Probabilistic tractography was used to measure the connections between the reading-related functional regions. Probabilistic tractography is a measure of white matter tract connectivity which repetitively samples voxel-wise principal diffusion direction. This creates a distribution of the most likely dominant pathway between the regions which has taken into account uncertainty in the data (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). Seed regions of interest can be used to compute the likely principal tract between areas in the brain.

FSL Diffusion Toolbox (FDT 2.0) was utilized for diffusion data processing and tractography analyses (S. M. Smith et al., 2004; Woolrich et al., 2009). The BEDPOST tool estimated the diffusion parameters for each voxel and the Probtrackx algorithm repetitively samples from the distributions on voxel-wise principal diffusion directions to compute the streamline/tract (Behrens et al., 2003). The resulting tract output was thresholded at 50% and converted to standard space. The tract was then overlayed on the individuals FA map that had been converted to standard MNI space to compute the average FA value within the tract. For MD, a similar approach was utilized in which the standardized and thresholded tract was overlayed onto the standardized MD map and the average MD value was computed within the tract. All tracts were visually inspected to ensure that the program did indeed identify the expected neuroanatomically consistent tract between the regions of interested, and to verify that the threshold value was appropriate. Tracts were removed from analyses if the output includes the incorrect tract or if the output did not identify a tract between the ROIs.

2.2.6 Regions of Interest. The inferior frontal and parietotemporal reading regions were hypothesized to be structurally connected through the arcuate fasciculus (sometimes considered part of the superior longitudinal fasciculus). Recent work on the structure of this tract has discovered that the arcuate fasciculus actually contains multiple tracts. Three tracts in particular: one connecting superior temporal with inferior frontal, a second connecting inferior frontal with the inferior parietal lobule and a third segment connecting superior temporal to the inferior parietal lobule (Catani & Mesulam, 2008; Wakana et al., 2007). Therefore, the specific tract that was chosen for this study was the segment connecting the IFG and PT reading areas- the second tract described above. This tract segment runs anterior to posterior, connecting inferior frontal areas with parietotemporal reading areas. Published guidelines were used to create the ROIs to enter in the probabilistic tractography analyses to obtain the arcuate fasciculus (Catani & Mesulam, 2008; Wakana et al., 2007). Although a specific segment of the arcuate fasciculus will be measured, for the purposes of this study, this segment will be referred to as the arcuate fasciculus in this document.

The structural connection between the inferior frontal gyrus and the occipitotemporal area was hypothesized to be consisting of the inferior fronto-occipital fasciculus (IFOF) (Vandermosten et al., 2012). The IFOF runs anterior-posterior and connects visual association areas with frontal association areas. Previously validated ROI guidelines were used to create the ROIs to enter in the probabilistic tractography analyses (Vandermosten et al., 2012; Wakana et al., 2007).

The specific tract connecting PT and OT reading areas was unknown and not well defined. Therefore, regions of interest included gray matter areas in the PT and OT. The PT was defined as the Angular gyrus using the JHU Histological Atlas probabilistic map thresholded at 50%. The OT area, otherwise known as the Visual Word Form Area, is described as centering over the occipitotemporal sulcus, but does not have specific gyral boundaries and has primarily been defined functionally. Therefore, the center coordinates of this tract (MNI coordinates x: − 44, y: − 58, z: − 15) were used to create a 5 mm radius sphere with the coordinates at the center (Noble, Wolmetz, Ochs, Farah, & McCandliss, 2006). This sphere was used as the ROI for the OT area as has been implemented in previous research (Noble et al., 2006).The tract connecting these areas likely runs in the superior-inferior direction.

The cortico-spinal tract (CST) was chosen as a control tract given that it is not expected to be related to reading skill. Rather this tract is known to be associated with the relay of sensorimotor information (Binkofski et al., 1996; Schaechter, Perdue, & Wang, 2008). Previously validated ROI guidelines were used to create two ROIs to enter in the probabilistic tractography analyses (Wakana et al., 2007).

2.2.7 Psychiatric Screening. The Structured Clinical Interview of the DSM-IV Axis I Disorders (SCID) Research Version was used to screen for diagnosable psychiatric disorders that are part of the study's exclusion criteria. The SCID is a semi-structured interview for making the major DSM-IV Axis I diagnoses. The SCID assesses psychiatric disorders based on the exact criteria in the DSM-IV. Limited data is available on its validity with other diagnostic interviews, but one study in a sample of participants with neurological disorders, found high concordance with another standardized psychiatric interview, the Mini International Neuropsychiatric Interview (Jones et al., 2005). This measure was used screen comparison participants prior to completing study measures. This was also used to identify diagnostic criteria present in the survivor group.

2.2.8 Intelligence. The Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) is a commonly used abbreviated test of intelligence. It includes 4 core subtests derived from the unabbreviated Wechsler Adult Intelligence Scale III: Vocabulary, Similarities, Matrix

Reasoning, and Block Design. These subtests measure: ability to verbally define words, verbal and perceptual reasoning, and perceptual-motor problem solving. The Full Scale Intelligence Quotient (FSIQ) will be used in this study as a measure of intellectual outcome. The WASI has been used in traumatic brain injury populations, PTSD, and other clinical samples. The FSIQ for the WAIS has demonstrated high internal consistency reliability for adults across age groups between 17 and 89 years (r = .96-.98). Test-retest reliability was also high (r = .92). The FSIQ of the WASI correlates highly with its non abbreviated counterpart, the Wechsler Adult Intelligence Scale III (r = .92). A limitation of the WASI is that the individual index scores tend to less accurate in estimating WAIS-III scores, but this is understandable given that the WASI is not a comprehensive measure of intelligence like the WAIS-III (Axelrod, 2002). Despite this limitation, it remains a good measure of the construct of general intelligence and is advantageous in time limited situations (Ryan et al., 2003). Full Scale, Performance and Verbal Index z-scores were used for descriptive purposes. This measure was not used in confound analyses due to previously described limitations in developmental populations (Dennis et al., 2009).

2.2.9 Socioeconomic Status. The Hollingshead Four Factor Index of Social Status (Hollingshead, 1975) was used to calculate socioeconomic status (SES) of each participant. The scale is based on occupation and years of education completed. The scale also uses marital status to determine how to compute the final score. A ranking is obtained for occupation and education. The final score is translated to a score of 1 through 5. With 1 being the highest SES, and 5 being the lowest SES. For the purposes of this study, we dichotomized SES with scores of 1, 2, and 3 the first group, and scores of 4 and 5 in the second group. This was done so that we could compare the SES between the groups using the Fisher Exact Test.

2.3 PROCEDURE

The neuropsychological tests and psychiatric interview were administered by trained graduate students in psychology and supervised by a licensed clinician. Questions that came up during the testing and scoring of the tests were discussed with the licensed psychologist to determine resolution. Testing was conducted in the Psychology Clinic in the Department of Psychology at Georgia State University. Each participant was administered the tests in the same order. The tests were carefully ordered so as not to over tax any one cognitive domain by balancing types of tasks throughout the battery. Fatigue effects were reduced by taking breaks as needed. Examiners periodically asked participants if they would like to take a break and participants were encouraged to let the examiner know if they would like to take a break at any time. The SCID was administered prior to the test battery. Demographic variables were collected via self report. Medical variables for survivors were collected through databases of a previous longitudinal study, from which these participants were recruited. Participants were asked about any medical changes since their participation in the previous study.

DTI scans occurred during a second study visit that utilized the 3 Tesla MRI scanner at the Georgia State/Georgia Tech Center for Advanced Brain Imaging. Trained MRI technicians operated the MRI scanner. The DTI scan was part of a longer MRI scanning session that included a total of one hour in the scanner. MRI does not pose any known risks to participants and is used extensively in clinical and research settings. Even so, participants who were pregnant or may have been pregnant were not scanned. To protect participants from the loud noise that the scanner makes when running, ear plugs and headphones were given to participants to wear during the entire scan. Participants who were survivors of brain tumors received $50 compensation for their time and travel for the first visit, and another $50 if they participated in the MRI visit. Comparison participants received research credit for the participation in first visit and $50 for participation in the MRI visit. A clinical research report was written for the survivors in the study based on the findings of the neuropsychological testing and presented to the participants at a feedback session.

2.4 ANALYSIS

2.4.1 Potential Confound Analyses. To test for confounding variables in the relationship between white matter structure and reading, potential confounding variables were compared across the two groups in this study (survivors and comparison participants) and correlated with the dependent variable (reading). If a variable was both significantly different between groups and had a significant correlation with reading, this variable was considered a potential confound and was controlled for in further analyses as a covariate. The following variables were tested as potential confounds: age, sex, ethnicity, socioeconomic status, and level of education completed. For the purposes of this study's potential confound analysis, self-reported ethnicity was dichotomized into two groups: Caucasian and Other (African American, Asian, Hispanic & Mixed). To test between group differences, t-tests were used for continuous variables: age and education, Chi-square was used for dichotomous variables with cell frequency count of greater than 5 (sex), and a Fisher Exact test was performed if the cell count was not greater than 5 (ethnicity & socioeconomic status).

2.4.2 Correlation Analyses. To address the first aim of the study, to explore the relationship between reading skill and white matter integrity associated with the tracts connecting the three primary functional reading brain regions, one-tailed correlations were conducted for the survivor and healthy comparison groups separately. It was expected that the direction of the correlation would follow increased white matter integrity related to increase in word reading skill. The following measures were correlated: fractional anisotropy (FA) and mean diffusivity (MD) in each of the three white matter connections (IFG-OT [inferior fronto-occipital fasciculus], IFG-PT [Arcuate fasciculus], and PT-OT), with WJ-III Letter Word Identification z- scores. A p-value of less than .05 was considered a statistically significant relationship. However, given the small sample size, effect sizes (r values) were also evaluated.

2.4.3 Moderated Mediation Analyses. Guidelines developed by Preacher et al. (2007) were followed to address the second aim of the study: to investigate the role of processing speed as a mediator in the relationship between integrity of the white matter connection (FA) between the anterior reading area and the ventral posterior reading area (IFG-OT [inferior fronto-occipital fasciculus]) and reading skill with group as a moderator of the indirect effect.

The predictor variable was white matter integrity measured by fractional anisotropy in the IFG-OT connection. The proposed mediating variable was information processing speed z-scores as measured by the SDMT Oral Version. The outcome variable was WJ-III Letter Word Identification z- scores. The moderating variable was Group (comparison=0, survivor=1). Model 5 (Preacher et al., 2007) was utilized because Group was predicted to moderate both the a and b paths of the mediation model, thereby moderating the entire indirect effect.

The Dr. Andrew Hayes' SPSS "modmed" macro was used (http://www.afhayes.com/spss-sas-and-mplus-macros-and-code.html). The model first calculates significance based on the Sobel test for the conditional indirect effects and provides p-values for significance levels. P-values of less than .05 will be considered statistically significant. Then the model provides a 95% bootstrap confidence interval (bias-corrected) for each level of the moderator (with a dichotomous moderator). The number of bootstrap samples will be set at 5,000. The bootstrap approach does not make assumptions about the shape of the sampling distribution like normal theory tests (Preacher et al., 2007). Instead, through bootstrapping, the sampling distribution of the conditional main effect is estimated nonparametrically by sampling with replacement and the bootstrap sampling distribution is used to generate confidence intervals for the conditional indirect effect (Preacher et al., 2007). Normal theory tests generated in the SPSS macro should be verified by bootstrapping (Preacher et al., 2007).

Bootstrap confidence intervals for each level of the moderator informed the statistical significance of the conditional indirect effect in each group. A confidence interval that does not include zero will be considered a statistically significant conditional indirect effect. The B value indicates the direction of the relationship, therefore a positive B value means that the survivors (group 1) show a greater mediating relationship than the comparison groups (group 0).

2.4.4 Further Planned Analyses: Control Tract and Task. To increase confidence that any findings in this study are related to reading skill specifically, and not an effect of general achievement, we investigated the relation between white matter integrity (FA) and math calculation and also skilled motor speed, as mediated by processing speed. Similar to the second aim, a moderated mediation analysis was conducted to examine processing speed as a mediator in the relationship between integrity of the IFOF (FA) and the control task, with the grouping variable moderating the indirect effect. The proposed mediating variable was information processing speed as measured by the SDMT Oral Version (z-scores). The outcome variable was WJ-III Calculation z-scores and Grooved Pegboard dominant hand z-scores, respectively. The moderating variable was Group (Survivor=1, Comparison=0). Bootstrapping set at 5,000 samples was conducted at each level of the moderator to verify the results of the Sobel tests. A confidence interval that does not include zero was considered a statistically significant conditional indirect effect.

To be more confident that any findings in this study were related to the specific white matter areas studied, and not an effect of global white matter structure, we investigated the relation between white matter integrity (FA) in the cortico-spinal tract and reading achievement as mediated by processing speed. Similar to the second aim, a moderated mediation analysis was conducted to examine processing speed as a mediator in the relationship between integrity of the corticospinal tract (FA) and word reading, with the grouping variable moderating the indirect effect. The proposed mediating variable was information processing speed as measured by the SDMT Oral Version (z-scores). The outcome variable was WJ-III Letter Word Identification z-scores. Bootstrapping set at 5,000 samples was conducted at each level of the moderator to verify the results of the Sobel tests. A confidence interval that does not include zero was considered a statistically significant conditional indirect effect.

3 RESULTS

3.1 POTENTIAL CONFOUND ANALYSIS

Results of the potential confound analyses (see Table 2) indicated that no variable tested both correlated with the outcome variable and was significantly different between groups. Education was the only variable that was significantly correlated with word reading, however the groups were not significantly different on years of education. Given that the specifications for a confound were not met for any of the tested variables, no covariates were added to the planned analyses.

Table 2. *Descriptive statistics for each group*

		Survivor			Control				
		n	Mean	SD	n	Mean	SD	t (2-tailed)	p
FA	Inferior frontal-occipital fasciculus (IFOF)	17	0.35	0.03	17	0.36	0.02	1.38	0.18
	Arcuate fasciculus (AF)	18	0.33	0.02	19	0.34	0.02	2.13	0.04
	Parietotemporal - Occipitotemporal (PT-OT)	17	0.29	0.03	17	0.31	0.03	1.23	0.23
	Cortico-spinal Tract (CST)	17	0.44	0.04	19	0.45	0.05	0.43	0.67
MD	Inferior frontal-occipital fasciculus (IFOF)	17	0.81	0.06	17	0.79	0.03	-1.76	0.09
	Arcuate fasciculus (AF)	18	0.82	0.05	19	0.77	0.04	-3.41	<0.01
	Parietotemporal - Occipitotemporal (PT-OT)	17	0.79	0.05	17	0.78	0.04	-0.17	0.86
	WJ- Letter-word identification (LWID)	18	-0.37	0.90	19	0.36	0.55	2.98	<0.01
	Oral- Symbol-Digit Modalities Test (OSDMT)	18	-0.69	1.24	19	-0.16	0.84	1.55	0.13
	WJ- Math Calculation (Math; control task)	18	-0.48	0.91	19	-0.09	0.76	1.39	0.17
	Grooved Pegboard (Dominant hand)	18	-1.31	1.02	19	-0.54	0.98	2.35	0.03
	WASI- Performance IQ (PIQ)	18	0.25	0.96	19	0.45	0.75	1.26	0.22
	WASI- Verbal IQ (VIQ)	18	-0.15	1.23	19	0.44	0.76	1.70	0.10
	WASI- Full scale (FSIQ)	18	0.06	1.19	19	0.61	0.72	1.71	0.01

Note. All scores for neuropsychological measures are presented as z-scores

Descriptive statistics (see Table 3) demonstrate that in terms of white matter tract integrity, the groups differ on both the MD and FA of the Arcuate Fasciculus (AF). On the neuropsychological measures, the groups significantly differ on word reading and skilled motor speed. Surprisingly, given previous research on IQ changes in childhood brain tumor survivors, IQ measures did not differentiate the groups (Palmer, 2008). Reading appears to be mostly intact in this group of survivors. Only 18% of survivors (3 participants) exhibited evidence of word reading impairment based on letter word identification scores of 1.5 or more standard deviations (SD) below the mean. Correlations were run excluding these individuals from the group to test whether these low scorers were driving the results. However, the results did not change appreciably therefore these three participants are included in the reported analyses. No individuals in the comparison group had scores at or below 1.5 SD below the mean.

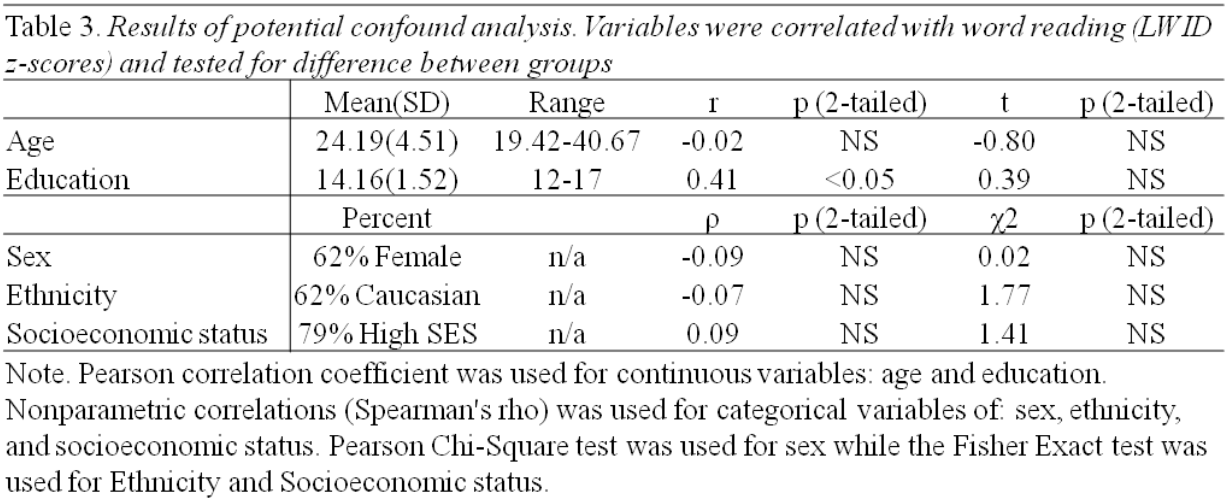


Table 3. *Results of potential confound analysis. Variables were correlated with word reading (LWID z-scores) and tested for difference between groups*

	Mean(SD)	Range	r	p (2-tailed)	t	p (2-tailed)
Age	24.19(4.51)	19.42-40.67	-0.02	NS	-0.80	NS
Education	14.16(1.52)	12-17	0.41	<0.05	0.39	NS
	Percent		ρ	p (2-tailed)	χ2	p (2-tailed)
Sex	62% Female	n/a	-0.09	NS	0.02	NS
Ethnicity	62% Caucasian	n/a	-0.07	NS	1.77	NS
Socioeconomic status	79% High SES	n/a	0.09	NS	1.41	NS

Note. Pearson correlation coefficient was used for continuous variables: age and education. Nonparametric correlations (Spearman's rho) was used for categorical variables of: sex, ethnicity, and socioeconomic status. Pearson Chi-Square test was used for sex while the Fisher Exact test was used for Ethnicity and Socioeconomic status.

3.2 AIM 1

Exploratory Aim 1 examined the relationship between word reading scores and three hypothesized reading-related white matter tracts and the control tract, using both integrity values of fractional anisotropy (FA) and mean diffusivity (MD). See Table 4 for correlations for the individual group and combined group and Figures 3-5 for scatterplots for the reading-related tracts. For FA in the IFOF, the combined group showed a significant correlation with reading (r=.59, p<.001), as well as each group individually (survivor: r=.55, p=.01; comparison: r=.59, p=.006). Thus, greater FA (higher white matter integrity) was associated with better word reading scores. The AF (FA) did not show a significant relationship with reading scores in either whole group or individual groups and the statistical insignificance is consistent with the small effect sizes (r values). The PT-OT connection was significantly correlated with reading for the whole group (r=.56, p=.003) and the survivor group (r=.46, p=.03). This relationship was not statistically significant in the comparison group, but showed a trend toward significance and a medium effect size (r=.40, p=.057) suggesting that this relationship would be statistically significant with a larger sample size. In sum, the white matter integrity (FA) of the tracts extending from the OT area to the IFG and to the PT area (IFOF & PT-OT) show medium to large correlations with word reading.

For tract mean diffusivity, reading was correlated with IFOF in the whole group (r=-.32, p=.03). In addition, mean diffusivity of PT-OT was significantly correlated with reading in the survivor group. Correlations were negative indicating lower MD (higher white matter integrity) was associated with higher reading scores. MD and reading correlations evidenced smaller effect sizes compared to correlations with FA.

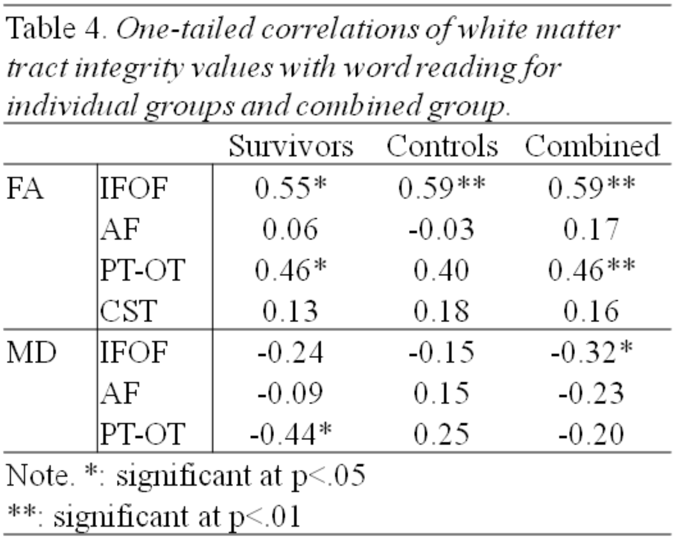


Table 4. *One-tailed correlations of white matter tract integrity values with word reading for individual groups and combined group.*

		Survivors	Controls	Combined
FA	IFOF	0.55*	0.59**	0.59**
	AF	0.06	-0.03	0.17
	PT-OT	0.46*	0.40	0.46**
	CST	0.13	0.18	0.16
MD	IFOF	-0.24	-0.15	-0.32*
	AF	-0.09	0.15	-0.23
	PT-OT	-0.44*	0.25	-0.20

Note. *: significant at p<.05

**: significant at p<.01

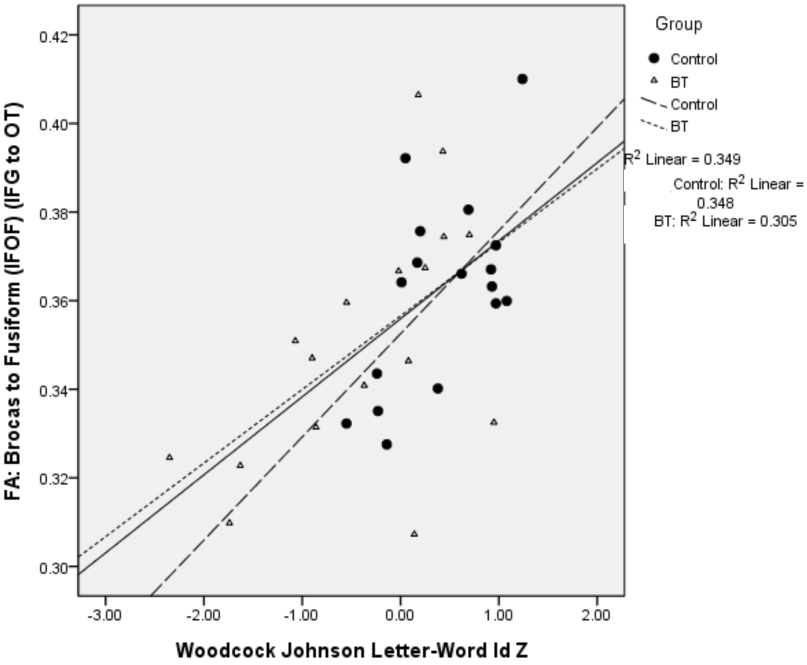


Figure 3. *Inferior fronto-occipital fasciculus (IFOF) tract integrity (FA) and word reading by group. Survivors and comparison groups show a similar positive relationship between IFOF-FA and word reading reflected in R^2 values. The large overlap between the groups highlights seemingly intact reading in survivors.*

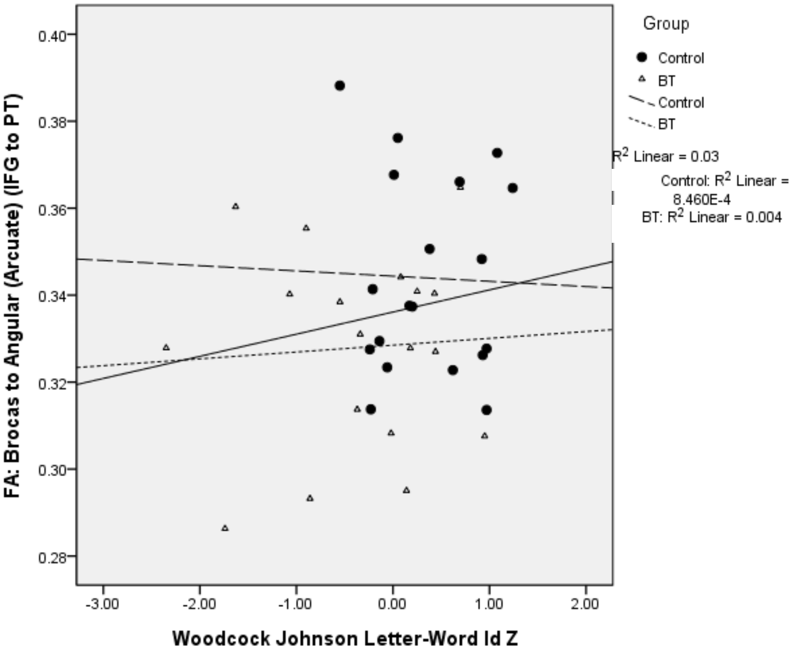


Figure 4. *Arcuate fasciculus (AF) tract integrity (FA) and word reading by group. Both the survivor and the comparison group do not show evidence for a relationship between FA in the Arcuate fasciculus and word reading. There appears to be less overlap between groups consistent with the significant group difference.*

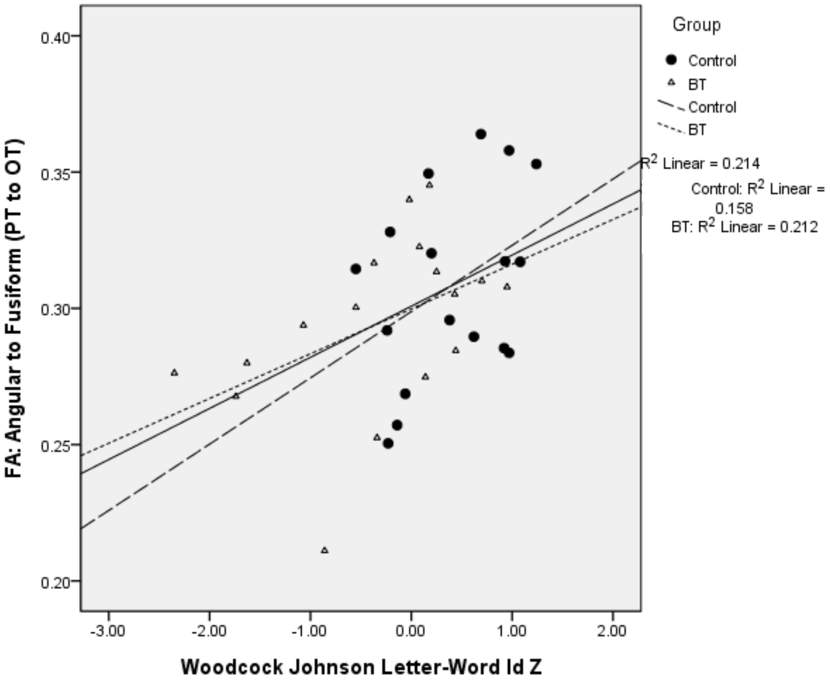


Figure 5. *PT-OT tract integrity (FA) and word reading by group. Survivor and comparison participants show a similar positive relationship between FA in the PT-OT connection and word reading reflected in R^2 values.*

3.3 AIM 2

Aim 2 hypothesized that processing speed would mediate the relationship between FA in the IFOF and word reading, and that the indirect effect would be moderated by group at both a and b paths. See Figure 6 for correlations of a, b, and c paths in each group. In the survivor group, all paths of the model were significantly correlated (IFOF-FA & reading (c): r=.55, p=.01; IFOF-FA & speed (a): r=.66, p=.002; speed & reading (b): r=.75, p<.001), while in the comparison group, only the c path was significantly correlated (r=.59, p<.01).

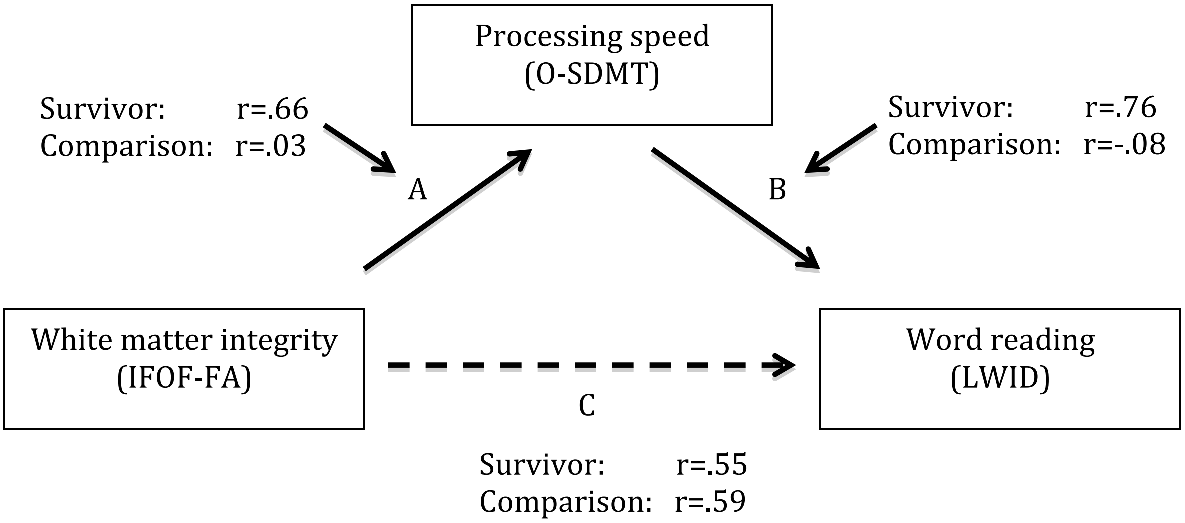


Figure 6. *Hypothesized moderated mediation model including the correlations for pathways a, b, and c for the survivor and comparison group.*

In the moderated mediation analysis, the mediator variable model indicated that the interaction between group and IFOF (FA) on processing speed (path a) was significant (see Table 5; b=28.20, t=2.12, p=.04). The dependent variable model indicated that the interaction of processing speed and group was statistically significant (b=.59, t=2.60, p=.01). Thus, group membership significantly moderated both a and b paths of the model such that the survivor group (Group 1) evidenced the stronger indirect effect given the positive b values for both interactions. The moderation of the conditional indirect effect was verified with bootstrapping with 5,000 samples. The 95% bootstrap bias corrected confidence interval did not contain zero for moderator value of 1 (survivor group), thus confirming the statistical significance of the conditional indirect effect in this group. The result of this moderated mediation is consistent with study predictions for Aim 2.

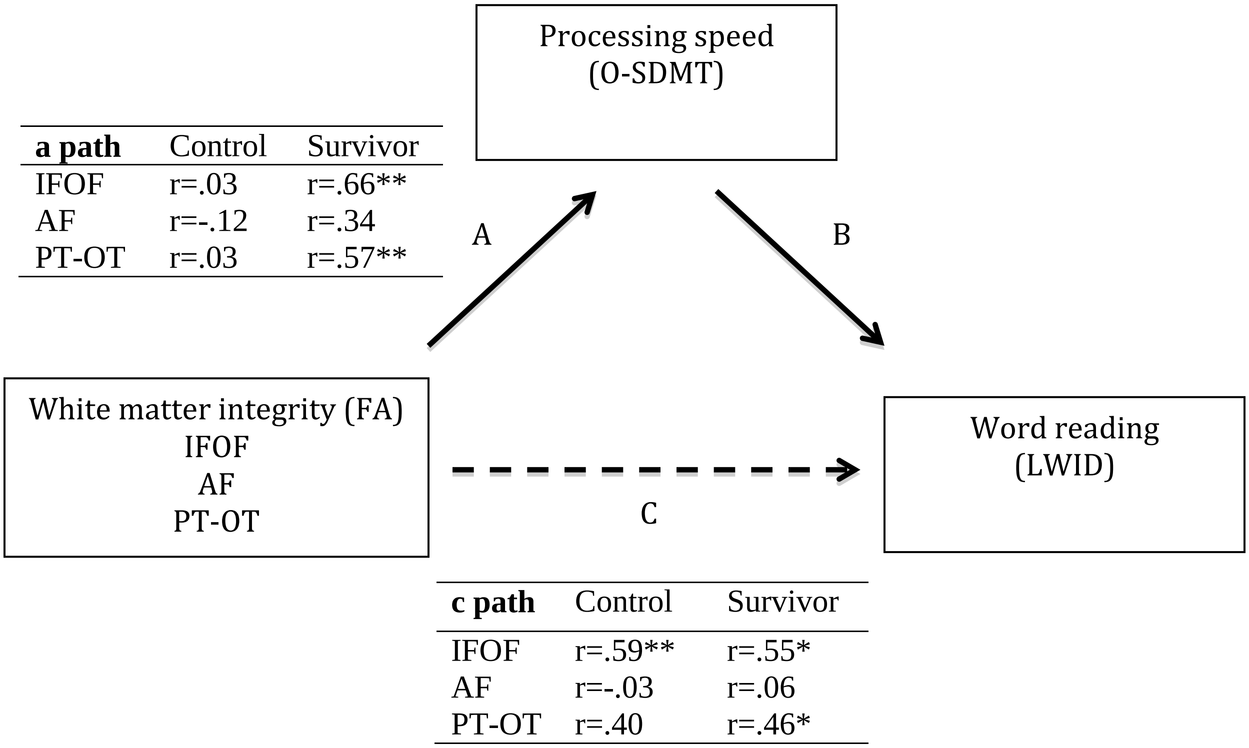
Table 5. *Moderated mediation for the relationship between each white matter tract (FA) and word reading, mediated by processing speed*

	Independent Variables							
	IFOF		Arcuate		PT-OT		CST	
	b (SE)	t	b (SE)	t	b (SE)	t	b (SE)	t
Conditional effects (Mediator Model)								
Constant	-0.67(3.81)	-0.18	0.62(3.74)	0.16	-0.36(2.18)	-0.17	-0.50(2.42)	-0.21
WM integrity (FA) & Proc Speed (a path)	1.28(10.49)	0.12	-2.24(10.84)	-0.21	0.74(7.01)	0.11	0.76(5.37)	0.14
Group	-10.31(4.76)	-2.16*	-7.31(5.19)	-1.41	-6.84(3.09)	-2.21*	-5.35(4.17)	-1.28
FA x Group (Interaction 1)	28.20(13.28)	2.12*	20.56(15.40)	1.33	21.27(10.21)	2.08*	10.70(9.33)	1.15
Conditional effects (Dependent Model)								
Constant	-5.05(2.35)	-2.15*	0.64(2.12)	0.30	-1.64(1.30)	-1.26	-0.64(1.41)	-0.46
FA & Reading (c path)	15.01(6.46)	2.33*	-0.87(6.16)	-0.14	6.56(4.18)	1.57	2.20(3.12)	0.71
Group	3.98(3.35)	1.19	2.24(3.06)	0.73	1.54(2.10)	0.73	1.99(2.54)	0.78
FA x Group (Interaction 1)	-12.09(9.26)	-1.31	-7.77(9.03)	-0.86	-5.99(6.83)	-0.88	-5.21(5.62)	-0.93
Processing Speed & Reading (b path)	-0.07(.17)	-0.40	-0.07(.17)	-0.43	-0.10(0.17)	-0.59	-0.075(0.17)	-0.44
Speed x Group (Interaction 2)	0.59(.23)	2.60*	0.67(.21)	3.27**	0.66(0.22)	2.97**	0.64(0.21)	3.10**
Conditional indirect effect	b (SE)	95% Bca CI	b (SE)	95% Bca CI	b (SE)	95% Bca CI	b (SE)	95% Bca CI
Survivor	15.39(6.21)	**3.84, 38.38**	11.05(7.12)	-2.88, 28.55	12.32(5.28)	**2.88, 28.33**	6.49(4.67)	-2.02, 30.25
Control	-0.09(1.97)	-4,02, 1.86	0.15(1.99)	-1.63, 4.17	-0.08(1.42)	-3.74, 1.54	-0.06(1.00)	-2.28, 0.96

Note. *=p<.05, **=p<.01 , bold= CI significant

3.4 POST-HOC ANALYSES

Although not a part of the initial proposal, I was interested in examining if the moderated mediation model fit with other tracts of the reading system entered as the predictor variable. In order to test these models, the FA values for the AF tract and the PT-OT connection were entered as independent variables in the “modmed” script for SPSS. In comparing different independent variables the conditional effects of the mediator model is important, specifically Interaction 1 between tract integrity and group on processing speed, or the moderation of path a by group. Interaction two will be similar regardless of the independent variable because it is testing the moderation of the b path (although the independent variable is accounted for in this effect). With the Arcuate Fasciculus (AF) entered as the independent variable, the effect of the interaction between group and AF integrity was not significant which was confirmed by bootstrapping. Thus, this moderated mediation model is not supported with AF as the predictor. The correlations for path a and c can be seen in Figure 7. When the PT-OT tract was tested as the predictor variable, the interaction between group and PT-OT integrity was significant. This effect was verified by bootstrapping (5000 samples) that indicated that the conditional indirect effect was significant for the survivor group (CI: 2.88, 28.33). Thus, there is evidence for the moderated mediation model in which group moderates the indirect effect of processing speed on the relationship between PT-OT integrity and word reading.



a path	Control	Survivor
IFOF	r=.03	r=.66**
AF	r=-.12	r=.34
PT-OT	r=.03	r=.57**

c path	Control	Survivor
IFOF	r=.59**	r=.55*
AF	r=-.03	r=.06
PT-OT	r=.40	r=.46*

Figure 7. *Comparison of a and c paths in the mediation model for each tract measured. For the a path, r values are provided. Note. *=p<.05, **=p<.01*

To test the specificity of the model to white matter integrity in the tested tracts of the reading system, the moderated mediation model was tested with a tract outside of the reading system, the corticospinal tract. Correlations with reading indicated no significant association in either group (Survivor: r-.13, p=.31; Comparison: r=.18, p=.23). The interaction between corticospinal tract integrity and group did not significantly predict processing speed (b=.64, SE=.21, p>.05). The bootstrap significance of the conditional main effect confirmed this lack of finding. Therefore consistent with predictions, the corticospinal tract, a tract not primarily associated with reading, did not fit the model.

To test the specificity of the moderated mediation relationship to word reading, rather than academic achievement in general, the model was run with math calculation achievement as the dependent variable and with the FA value of each measured tract as the independent variable (see Tables 6 & 7). With the IFOF tract, although neither interaction reached statistical significance by the Sobel test, the significance of the conditional indirect effect tested with bootstrapping indicated that the conditional indirect effect was present for the survivor group (CI: 1.71, 36.98) and not the comparison group (CI: -1.90, 21.96). There was a similar effect with the PT-OT tract in which bootstrapping indicated significance of the conditional indirect effect in the survivor group (CI: 3.71, 25.43) and not the comparison group (CI: -2.91, 15.61). The model was not significant for the AF tract or the CST. Upon further investigation of math calculation in this survivor sample, this skill was highly correlated with the primary dependent measure of the study to which we were comparing it (word reading; r=.37, p=.01). Further, the tracts in the reading system are purported to reflect the representation and processing of symbols and given that math is also a symbolic language it is possible to suppose that math ability could have a relationship with these tracts. Indeed, recent work on white matter integrity and math skill has found the right hemisphere IFOF to be related to math skill (Rykhlevskaia, Uddin, Kondos, & Menon, 2009). It may be the case that in our survivors, this skill is less lateralized. Therefore, it is likely that math calculation was not a suitable control task for this model for the reasons discussed. Thus, a different control task was chosen and tested in the model.

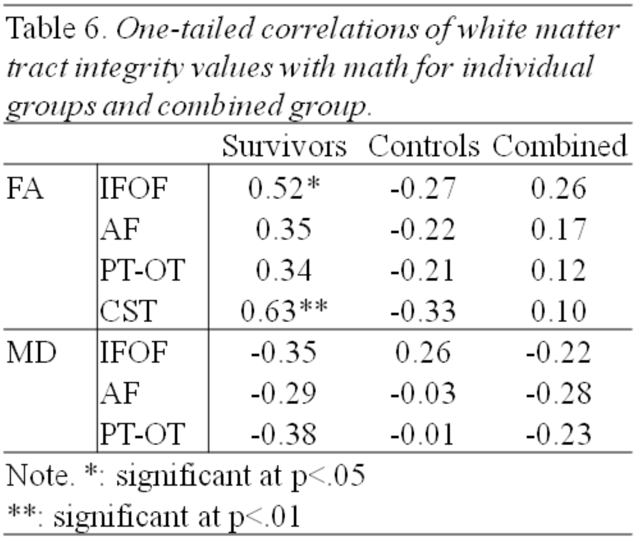


Table 6. *One-tailed correlations of white matter tract integrity values with math for individual groups and combined group.*

		Survivors	Controls	Combined
FA	IFOF	0.52*	-0.27	0.26
	AF	0.35	-0.22	0.17
	PT-OT	0.34	-0.21	0.12
	CST	0.63**	-0.33	0.10
MD	IFOF	-0.35	0.26	-0.22
	AF	-0.29	-0.03	-0.28
	PT-OT	-0.38	-0.01	-0.23

Note. *: significant at p<.05

**: significant at p<.01

Table 7. *Control task: Moderated mediation for the relationship between each white matter tract (FA) and math, mediated by processing speed*

	IFOF		Arcuate		PT-OT		CST	
Conditional effects (Mediator Model)	b (SE)	t	b (SE)	t	b (SE)	t	b (SE)	t
Constant	-2.02(3.84)	-0.53	-0.23(3.78)	-0.06	-0.77(2.18)	-0.36	-0.54(2.41)	-0.23
WM integrity (FA) & Proc Speed (a path)	4.78(10.54)	0.45	<0.01(10.95)	<0.01	1.83(6.99)	0.26	0.71(5.33)	0.13
Group	-8.96(4.75)	-1.88	-6.47(5.21)	-1.24	-6.43(3.08)	-2.09*	-5.30(4.15)	-1.28
FA x Group (Interaction 1)	24.70(13.22)	1.87	18.31(15.44)	1.19	20.18(10.14)	1.98	10.74(9.28)	1.16
Conditional effects (Dependent Model)								
Constant	4.01(3.37)	1.19	2.44(2.75)	0.89	1.68(1.54)	1.09	2.41(1.52)	1.58
FA & Math (c path)	-11.03(9.23)	-1.19	-7.15(7.94)	-0.90	-5.43(4.93)	-1.10	-5.41(3.37)	-1.61
Group	-6.82(4.73)	-1.44	-4.63(3.92)	-1.18	-.95(2.47)	-0.39	-7.99(2.74)	-2.92**
FA x Group (Interaction 1)	18.42(13.02)	1.41	13.25(11.56)	1.15	2.90(8.00)	0.36	17.18(6.06)	2.83**
Processing Speed & Math (b path)	0.30(0.26)	1.16	0.27(0.22)	1.22	0.44(0.22)	2.01	0.29(0.20)	1.46
Speed x Group (Interaction 2)	0.03(0.33)	0.09	0.14(0.27)	0.50	0.09(0.27)	0.31	-0.004(0.24)	-0.08
Conditional indirect effect	b (SE)	95% Bca CI	b (SE)	95% Bca CI	b (SE)	95% Bca CI	b (SE)	95% Bca CI
Survivor	9.81(6.78)	**1.71, 36.98**	7.50(5.56)	-2.61, 24.45	11.53(5.40)	**3.71, 25.43**	3.23(2.87)	-0.94, 16.77
Control	1.45(4.40)	-1.90, 21.96	<0.01(3.87)	-7.42, 6.56	0.80(3.44)	-2.91, 15.61	0.20(1.85)	-2.60, 5.28

Note. *=p<.05, **=p<.01 , bold= CI significant

Skilled motor speed was chosen as the control task and was entered as the dependent variable in the moderated mediation model with separate models for each reading tract and the control tract. For IFOF, the correlation with skilled motor speed indicated a significant positive relationship. In accordance with predictions, the models were not significant with either of the three reading tracts. Thus for a cognitive skill that is not hypothesized to be related to reading skill, the moderated mediation model was not present with tracts in the reading system. For the corticospinal tract, it was hypothesized that there would be a relationship between white matter integrity and skilled motor speed. However moderated mediation was not indicated, and the two variables were not significantly correlated in the survivor group (r=.26, p(1-tailed)=.15).

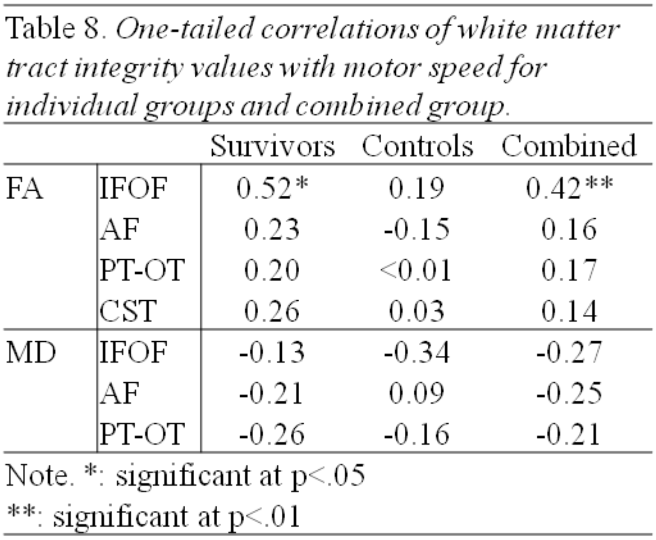


Table 8. *One-tailed correlations of white matter tract integrity values with motor speed for individual groups and combined group.*

		Survivors	Controls	Combined
FA	IFOF	0.52*	0.19	0.42**
	AF	0.23	-0.15	0.16
	PT-OT	0.20	<0.01	0.17
	CST	0.26	0.03	0.14
MD	IFOF	-0.13	-0.34	-0.27
	AF	-0.21	0.09	-0.25
	PT-OT	-0.26	-0.16	-0.21

Note. *: significant at p<.05
**: significant at p<.01

Table 9. *Control task: Moderated mediation for the relationship between each white matter tract (FA) and motor speed, mediated by processing speed*

	IFOF		Arcuate		PT-OT		CST	
Conditional effects (Dependent Model)	b (SE)	t	b (SE)	t	b (SE)	t	b (SE)	t
Constant	-0.67(3.81)	-0.18	0.62(3.74)	0.16	-0.36(2.18)	-0.17	-0.50(2.42)	-0.21
WM integrity (FA) & Proc Speed (a path)	1.28(10.49)	0.12	-2.24(10.84)	-0.21	0.74(7.01)	0.11	0.76(5.37)	0.14
Group	-10.31(4.76)	-2.16*	-7.31(5.19)	-1.41	-6.84(3.09)	-2.21*	-5.35(4.17)	-1.28
FA x Group (Interaction 1)	28.20(13.28)	2.12*	20.56(15.40)	1.33	21.27(10.21)	2.08*	10.70(9.33)	1.15
Conditional effects (Dependent Model)								
Constant	-3.57(4.10)	-0.87	1.49(3.61)	0.41	-0.45(2.37)	-0.19	-0.61(2.38)	-0.26
FA & Motor (c path)	8.48(11.30)	0.75	-5.74(10.49)	-0.55	-0.20(7.65)	-0.03	0.29(5.26)	0.054
Group	-6.58(5.87)	1.12	-5.42(5.21)	-1.04	-2.01(3.84)	-0.52	-3.61(4.28)	-0.84
FA x Group (Interaction 1)	16.35(16.21)	1.01	13.96(15.38)	0.91	4.35(12.48)	0.35	6.47(9.47)	0.68
Processing Speed & Motor (b path)	0.35(0.30)	1.15	0.37(0.28)	1.32	0.35(0.32)	1.12	0.38(0.29)	1.32
Speed x Group (Interaction 2)	-0.54(0.40)	-1.34	-0.26(0.35)	-0.73	-0.25(0.41)	-0.61	-0.26(0.36)	-0.73
Conditional indirect effect	b (SE)	95% Bca CI	b (SE)	95% Bca CI	b (SE)	95% Bca CI	b (SE)	95% Bca CI
Survivor	-5.49(8.06)	-29.91, 11.93	2.07(4.64)	-5.70, 23.79	2.31(5.99)	-12.00, 20.59	1.34(3.12)	-4.78, 17.63
Control	0.45(4.86)	-4.26, 10.34	0.83(5.09)	-11.71, 3.73	0.26(3.34)	-4.09, 5.99	0.28(2.56)	-4.42, 4.90

Note. *=p<.05, **=p<.01 , bold= CI significant

4 DISCUSSION

The results of this study support many of the hypotheses. We used empirically based white matter tracts in the reading circuit and identified a neural mechanism for word reading skill in typically developing adults and long-term survivors of childhood brain tumors. In addition, building upon a neurodevelopmental model, processing speed was found to explain the relationship between white matter integrity and word reading in the survivor group but not in typically developing adults.

4.1 WHITE MATTER INTEGRITY AND WORD READING

We found significant associations between the white matter integrity of the IFOF and PT-OT connection and word reading skill for the combined group of childhood brain tumor survivors and typically developing individuals. This suggests these pathways are important for word reading in adults regardless of prior neurological insult. In the survivor group, both IFOF and PT-OT tracts were significantly associated with reading. In the comparison group, even with a more restricted range of reading skill, the IFOF was associated with reading while the PT-OT tract was not significant but showed a trend toward significance. These findings are in line with previous research that suggests that the relationship between white matter integrity and reading is on the same continuum for both skilled and poor readers irrespective of prior childhood brain tumor (Niogi & McCandliss, 2006).

Firstly, correlational research shows that white matter integrity is related to reading at a range of reading levels (Niogi & McCandliss, 2006) and this association also holds for childhood brain tumor survivors (Palmer et al., 2010). Prior research used exploratory methods such as Tract Based Spatial Statistics and Voxel Based Analysis, to compute clusters that correlate with reading out of whole brain white matter. These studies have found clusters related to reading, primarily in the parietotemporal area mostly corresponding to the superior coronal radiate that were oriented in the superior/inferior direction. In addition, the orientation and location of the significant clusters that were observed did not correspond to extant knowledge about connections between functional reading areas. This has led researchers to question how white matter findings fit into the current functional model of reading. The current study also found a superior/inferior oriented tract (PT-OT) to be related to reading but in a different location from the superior/inferior tract (SCR) found in previous research. Several methodological differences between previous work and the current study may explain the different findings. Previous studies used a whole brain method and included a sample of children with reading disabilities, whereas the current study used empirically driven tracts and an adult sample with childhood neurological insult. Although whole brain analysis methods can be fruitful in discovering unexpected yet meaningful correlations, it is also important to examine relationships using empirically driven and a priori models (Niogi & McCandliss, 2006). The current study adds to previous research by showing that tracts from the OT area are critical for reading in adults.

Vandermosten et al. (2012) used a similar ROI method for the IFOF and AF as the current study, with adults with dyslexia and typically reading adults. They also found IFOF (FA) to be related to an orthography measure. The orthography task involved seeing a word briefly and deciding if it was spelled correctly and it was not correlated with white matter integrity in the arcuate fasciculus, which is also consistent with the current study’s results. In contrast, speech perception and phonological awareness tasks were predictive of arcuate fasciculus integrity. The lack of AF correlation with reading may have been because this tract is less associated to word reading and more related to aspects of speech and phonology processes related to reading.

4.2 IMPORTANCE OF OCCIPITOTEMPORAL PATHWAYS

The arcuate fasciculus connecting IFG and PT regions, did not show a significant relationship with word reading in the present study. This suggests that IFG and PT are not the only players in this system and that the OT area is a critical junction in this system for adults. Previous research suggests that the OT area integrates letters and sounds to effectively analyze visual word forms (Cohen et al., 2002; McCandliss, Cohen, & Dehaene, 2003). This area plays an important role in fluent reading with activation increasing with increasing reading skill in functional studies. Differences arise between poor and skilled readers activation of this region and in general the functional reading system is thought to be less left-lateralized in poor readers (B. A. Shaywitz et al., 2007; S. E. Shaywitz et al., 2003). Further, the functional breakdown in the OT has been suggested as the biomarker for reading disabilities (Pugh et al., 2000). The white matter from the OT connecting with the IFG and PT areas as measured by the IFOF and PT-OT tracts in this study may underlie these findings in functional studies of reading.

Further extending our knowledge of the functional role of the OT are S. E. Shaywitz et al. (2003) hypothesized that both groups of skilled and poor readers are engaging the OT area differently. Poor readers may be utilizing other pathways for word reading such as ones that connect to working memory areas as suggested in (S. E. Shaywitz et al., 2003). Indeed, functional connectivity analyses corroborated this hypothesis and found that typical readers showed functional connectivity between the OT and IFG, whereas poor readers showed functional connectivity between the OT and right prefrontal areas (S. E. Shaywitz et al., 2003). Functional connectivity is a measure of the temporal correlation between separate regions of activation and does not necessarily imply structural connectivity (Fingelkurts, Fingelkurts, & Kahkonen, 2005). This highlights the importance of also studying the structural connections between the areas in the reading system which allows for hypotheses to be drawn regarding how the OT area interacts with the reading system at different levels of reading. This study's results suggest that the IFG-OT (IFOF) and PT-OT connections remain important in adulthood for reading real words. If poor readers have weaker tract integrity as suggested by correlations, Shaywitz's (2003) work might suggest that those readers are more reliant on other tracts or connections from the OT area. Given that the current study, poorer word reading was associated with reduced integrity of IFOF and PT-OT connections, poorer readers may be using other pathways to compensate for inadequate communication from OT in the reading system.

The association of PT-OT tract to word reading is not surprising given that damage to the angular gyrus and its associated connections with the occipitotemporal area results in acquired alexia in which one is unable to read (Damasio & Damasio, 1983). Past research also has found a functional disconnection between the angular gyrus and occipitotemporal regions in adult males with dyslexia (Horwitz, Rumsey, & Donohue, 1998). The connection between these regions is crucial for integrating visual word form with phonological analysis.

4.3 FUNCTIONAL AND STRUCTURAL CONNECTIVITY

The IFOF and PT-OT correlation with reading in the current study is consistent with results of functional connectivity analyses of reading areas. Work with children and adults have found functional connectivity from the OT to PT and IFG in comparison samples, but not in samples with reading disabilities (Horwitz et al., 1998; S. E. Shaywitz et al., 2003). However, the potential correspondence between structural and functional connectivity warrants further research within the same sample.

4.4 OVERALL READING IN THIS SAMPLE

Although our sample included a neurological condition, only 18% (3 participants) of survivors exhibited evidence of word reading impairment (scores of 1.5 or more standard deviations (SD) below the mean). No individuals in the comparison group exhibited word reading impairment. Therefore, in this sample of adult survivors of childhood brain tumors, word reading was intact for the majority of individuals. Letter-Word Identification is not a timed task so it may underrepresent individuals with reading difficulties. However, scores on this measure have been used to divide skilled and poor readers in previous research. Even with relatively few participants in the impaired range, the survivor group exhibited significantly lower mean word reading scores. This is in line with previous survivor research showing greater risk for reading difficulties in survivors (Robinson et al., 2010). In addition, overall correlations of FA and MD and reading in the current study suggest that FA is more highly correlated to reading than MD, consistent with what has been reported in previous research.

4.5 MODERATED MEDIATION MODEL

For the second aim of this study, we tested the mechanism behind the relationship of white matter integrity and word reading as part of a neurodevelopmental model. Specifically, we tested the effect of structural brain changes on reading achievement as mediated by the core cognitive skill of processing speed. Palmer (2008) proposed a neurodevelopmental model in which disease and treatment risk factors along with age at diagnosis are associated with academic achievement and intelligence through core cognitive functions (e.g., processing speed). This has been tested in childhood survivors of CNS and non-CNS tumors (Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006; Reddick et al., 2003) as well as adult survivors (Kohl et al., 2010). The current study built upon this model and added a biological mechanism (white matter) as the predictor of processing speed and word reading. The effect of the mediating variable (processing speed) was proposed to be moderated by group given that the comparison group is not expected to have deficits in processing speed. It was hypothesized that the mediation would be present for the survivor group but not in the comparison group. Therefore, a moderated mediation model was tested.

The significant mediation in the survivor group supports and builds upon the neurodevelopmental model of childhood brain tumors (Palmer, 2008). This current study's model of the relationships between white matter, reading and processing speed is consistent with previous work studying the relationship among these constructs. Poorer reading has been shown to be related to poorer perceptual processing speed in individuals with brain injury and reading disabilities (Barnes et al., 1999; Shanahan et al., 2006). In addition as myelination of axons increases the speed of transmission of neural signals, white matter integrity is hypothesized to be a proxy for speed of neural processing and communication among brain regions and systems. Furthermore, processing speed can be particularly affected in survivors (Palmer, 2008).

For both the AF and the IFOF, group membership (survivor vs comparison) was found to moderate the indirect effect of white matter integrity on word reading through processing speed. The findings supported the hypothesis and indicated that in the survivor group, individual differences in processing speed accounted for the relationship between white matter integrity and word reading. In the comparison group, this relationship was not predicted and indeed, mediation was not present. This analysis provided statistical evidence that the indirect effect of processing speed was dependent on group membership. For the survivors, the unconditional model explained 53% of the variance in word reading for the IFOF tract and 56% of the variance for the PT-OT tract. This model illustrates that *how* white matter integrity and reading are related is a critical difference between the groups. Support for the developmental cascade model is demonstrated by the mediation model that was significantly moderated by group despite similar means between groups in both predictor variables- processing speed and white matter integrity. The developmental cascade hypothesis for brain tumor survivors in which deficits in core cognitive skills such as processing speed in childhood cascades over time to adversely affect the development of broader cognitive outcomes (Fry & Hale, 1996, 2000; Palmer, 2008). This is consistent with empirical evidence that brain tumor survivors experience a slower rate of learning compared to peers. Thus interventions that break the link between processing speed and outcomes would be crucial.

The development of core cognitive skills, particularly processing speed in this study, may be crucial in translating structural connectivity into reading skill for survivors. Reading is a complex learned skill, in which brain areas for language, speech, and vision must be integrated to achieve effective phonological processing and word analysis. Therefore, it makes sense that core cognitive skills may serve as developmental scaffolding as reading is learned and practiced. Stronger core cognitive skills may be a compensation mechanism for overcoming a structurally weak reading system as suggested by previous work in children (S. E. Shaywitz et al., 2003). In the current study, these relationships are shown to extend into adulthood for survivors. Therefore, for childhood brain tumor survivors, the most advantageous interventions may be ones targeted at core cognitive skills such as processing speed. Such interventions may focus on the automaticity and speed of reading to help prevent slow processing speed from cascading into poorer reading outcomes. Currently, reading interventions are being developed and tested that focus on dual aspects of reading difficulties: speed and decoding (Katzir et al., 2006; Wolf, Miller, & Donnelly, 2000).

4.6 MODEL SPECIFICITY

Although math was initially used as a control task, upon further consideration it was determined that this construct was likely a poor control task. In this survivor sample, math skill was highly correlated with word reading. Further, the tracts in the reading system are purported to reflect the representation and processing of symbols and given that math is also a symbolic language it is possible to suppose that math ability could have a relationship with these tracts. Indeed, recent work on white matter integrity and math skill has found the right hemisphere IFOF to be related to math skill (Rykhlevskaia et al., 2009). It may be the case that in our survivors, this skill is less lateralized. These data led us to believe that math skill did not fit the criteria for a control tract.

When skilled motor speed was tested in the model as the dependent variable, the moderated mediation model was not significant for each of the reading-related white matter tracts. This was consistent with predictions and provides further evidence that the model is specific to word reading. Although the model with skilled motor speed was not significant, correlations indicated that in survivors, the IFOF was significantly related to skilled motor speed which calls into question the specificity of the IFOF tract to word reading. Surprisingly, the corticospinal tract was not significantly associated with skilled motor speed. As a major sensorimotor tract in the brain, this tract was expected to be associated with skilled motor speed.

It is possible that in survivors, the integrity of the IFOF may be related to multiple cognitive constructs, therefore, the integrity of this tract may be particularly linked with a broad range of cognitive difficulties. More research on this tract may examine whether this tract could be a marker for cognitive changes in survivors. In contrast, the PT-OT connection appears to be specific to reading and symbol association while not related as strongly to math as the IFOF. In this regard, direct connection between the posterior reading regions appears to be important particular to adults in this study and warrants further research.

4.7 STRENGTHS AND LIMITATIONS

A limitation of this study was that the PT-OT connection was not defined by an a priori anatomical tract, although an empirical research on the functional reading circuit guided the choice of regions of interest. Different ROI methods were utilized for the PT-OT connection compared to the other connections this must be taken into account when comparing results. Sample size of readers in the lower range of skill was limited and affects our ability to generalize these findings to adults with impaired word reading. Using a sample that includes more impaired readers, might enhance comparisons between this study and studies using samples with individuals with dyslexia.

A strength of this study was the use of the empirical literature to drive predictions about specific tracts. The chosen tracts (IFOF and AF) and regions of interest (PT-OT) were based on the extensive literature on the functional reading system and the hypothesized mechanisms of dysfunction that occur in individuals with dyslexia (i.e. poor communication between reading areas). Comparing the tracts within an empirical system can allow researchers to test theoretical relationships and models to investigate potential breakdown in the system as a whole between groups as well as test for indirect effects related to specific tracts to help explain the relationship between reading and underlying white matter. The sample size of 18 was a strong size for a clinical sample in a group that was primarily one to two decades since diagnosis. In fact, to this author’s knowledge, no other study has been published using neuroimaging with childhood brain tumor survivors, the majority of which hare almost two decades from diagnosis. In addition, in order to obtain significance from a moderated mediation analysis in a small sample, a relatively large effect must be present, therefore the significance of the models tested in this sample speak to the strength of the models. This is one of only a few studies to include a model of the relationship between reading and core cognitive skills with survivors, thereby furthering the understanding of core cognitive skills and reading in survivors.

Similar to the trajectory of functional investigations in the literature, structural studies may identify consistent patterns of systemic breakdown correlated with different types of reading tasks to better understand the structural footprint for the development of reading skill. Although a timed reading measure may be more sensitive in the mediation model, processing speed was significantly correlated with the non-timed reading measure in the survivor group, which was a strength in this study. The use of a processing speed measure without a motor component builds on past research on processing speed in survivors in which processing speed was measured with a manual task and was therefore confounded by motor speed (Kieffer-Renaux et al., 2000).

4.8 FUTURE DIRECTIONS

Previous research has identified reduced functional and structural lateralization in poor readers (Niogi & McCandliss, 2006; B. A. Shaywitz et al., 2002). Therefore, it will be important to extend the findings of the current study to determine whether the results reflect reduced lateralization of reading in survivors. In addition, future research could examine the integrity of the corpus callosum, which has been found in past work to be related to level of lateralization in reading (Ben-Shachar et al., 2007).

In addition, future research could further define the function of the IFOF tract in childhood brain tumor survivors as a possible predictor of general cognitive outcome or change in cognition over time. Perhaps certain disease or treatment factors make this tract particularly vulnerable to childhood neurological insult. To learn more about the PT-OT pathway, future research may explore the development of this tract related to reading acquisition.

For brain tumor survivors, prior work suggests risk factors for reading difficulties and white matter damage including disease and treatment factors such as radiation treatment, hydrocephalus, and young age at diagnosis (Ailion, King, Henrich, Morris, & Krawiecki, 2012; Fletcher et al., 1992; Reeves et al., 2006; Steen et al., 2001). Age at diagnosis appears to be more relevant for those survivors who received radiation therapy, but not for those who did not receive radiation treatment (Ailion et al., 2012). More work is needed to determine the effect of disease and treatment factors on outcome for survivors who did not receive radiation therapy. Therefore, it will be important to examine treatment and disease related factors in long-term childhood brain tumor survivors to determine their effect in this model.

4.9 CONCLUSIONS

The current study integrated the reading system literature and the childhood brain tumor literature to build upon a neurodevelopmental model in brain tumor survivors. The results indicate that reading pathways from the occipitotemporal area are important for word reading in adults. In addition, in brain tumor survivors, processing speed accounts for the relationship between white matter integrity and word reading. The research on white matter integrity underlying functional neural circuits is growing as DTI technology and processing approaches rapidly accelerate. Examining the underlying white matter structure is an important and major force in piecing together the development of typical and dysfunctional reading skill.

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