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Corpus Callosum and Word Reading in Adult Survivors of Childhood Posterior Fossa Tumors

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CORPUS CALLOSUM AND WORD READING IN ADULT SURVIVORS OF

CHILDHOOD POSTERIOR FOSSA TUMORS

by

KRISTEN M. SMITH

Under the Direction of Tricia Z. King PhD

ABSTRACT

Adult survivors of childhood posterior fossa tumors can experience reading difficulties related to white matter integrity. Previously, reading was shown to be related to cortical white matter tracts, however information transfer across the corpus callosum (CC) may also play a role in reading. The current study used both macro- and microstructural measures of the WM structure of the corpus callosum. The current study examined how white matter volume and fractional anisotropy (FA) in five divisions of the CC was related to degree of neurological risk and reading skill, and tested two mediation models predicting reading. Participants included 20 adult survivors of

childhood posterior fossa tumor and 23 healthy controls. Volume and FA were measured in five divisions of the mid-sagittal corpus callosum. Total intracranial vault was used as a covariate in volume analyses. FA was reduced in CC1 and volume was reduced in each subregion in survivors. Volume but not FA was related to degree of neurological risk. Results identified that reduced volume in CC1 and CC5, and FA in CC5 appear to be specifically related to reading skill in line with the cortical reading regions that connect in these subregions of the CC. Mediation models indicate that processing speed is the mechanism by which volume is related to reading skill. These findings have implications for addressing processing speed in reading interventions in survivors and provide insight into the interhemispheric connections in the reading network.

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May 2017

DEDICATION

This dissertation is dedicated to my family, friends, colleagues, and mentors who offered their unconditional support during this project.

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1   INTRODUCTION

Reading is a complex, learned skill that requires effective integration of orthographic, phonological, and semantic information across cerebral hemispheres. Most reading research focuses on the cortical functional network for word decoding (see Figure 1A), consisting of an anterior region (inferior frontal gyrus) and two posterior regions (parietotemporal and occipitotemporal) (Pugh et al., 2001; Shaywitz et al., 2002). Indeed, previous work in our lab has found cortical white matter pathways connecting posterior regions (parietotemporal and occipitotemporal) areas to be specifically important for reading in survivors (see Figure 1B; Smith, King, Jayakar, & Morris 2014b). It is important to note however, that there is a more complex network of interacting regions involved in reading and this network includes effective interhemispheric communication between the right and left hemispheres (cortical homologues) through the corpus callosum (CC) (Lebel et al., 2013). As such, examining the broad neural network is important to fully understanding reading in the brain. Thus, one goal of this study was to expand the investigation of the neural basis of reading in brain tumor survivors from left hemisphere cortical regions to the corpus callosum white matter. The structure of the CC has been linked to reading in typically developing populations as well as reading disabilities (e.g., Lebel et al., 2013). It is unclear whether that link holds true for brain tumor survivors whose early brain insult may have changed how the brain supports reading skills.
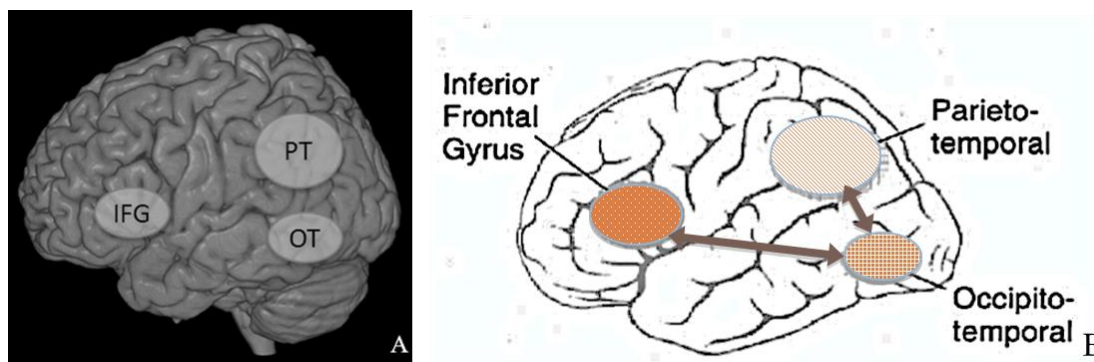
Figure 1. A: Three primary cortical regions of the reading system: IFG=inferior frontal gyrus; PT=parietotemporal region; OT=occipitotemporal region.B: White matter tracts connecting reading system that correlated with reading in survivors in Smith et al., (2014b)

Children with a history of posterior fossa brain tumor can experience reading

difficulties that persist into adulthood (Beebe et al., 2005; Kieffer-Renaux et al., 2000;

Reddick et al., 2003; Reeves et al., 2006; Smith, King, Ailion, Morris, & Krawiecki

2014a). The posterior fossa region of the brain is the most common location for brain

tumors in childhood (Yeates, Ris, Taylor, & Pennington 2010). The posterior fossa is

located at the base of the brain and includes the cerebellum, brainstem, and fourth

ventricle. Treatments for children with posterior fossa tumors range from neurosurgery

only, to neurosurgery plus radio- and chemotherapy depending on the type of tumor

(Yeates et al., 2010).

Brain tumor treatment and complications are known to affect white matter and

gray matter macrostructure and function (Mulhern, Merchant, Gajjar, Reddick, & Kun

2004; Zhang et al., 2008). Additionally, integrity of white matter (i.e., microstructure) can

be impacted by treatment and complications including the CC (King, Wang, & Mao

2015; Reddick et al., 2006; Wang et al., 2009). White matter is critical to carrying neural

signals between brain regions and reductions in its structure could impact reading

development and skill level. The impact on white matter may also affect core cognitive

skills such as processing speed that are commonly disrupted in survivors. These core cognitive skills are hypothesized to impact broad outcomes such as reading (Palmer 2008; Smith et al., 2014b).

Previous work by our research team tested a neurocognitive model in long-term survivors (at least 5 years from diagnosis) and found that white matter integrity of cortical reading tracts were related to word reading skill (Smith et al., 2014b). In addition, processing speed mediated the association between white matter integrity and reading skill. The mediation of processing speed was moderated by group and was unique to survivors and not significant in controls. In other words, the role of processing speed varied based on group. Extending this neurodevelopmental model to the CC could help develop a more nuanced understanding of the development of the reading network with regard to interhemispheric communication after a childhood brain tumor. The purpose of this dissertation was to further examine the neural basis of reading in childhood brain tumor survivors and build a theory-based neurocognitive model to predict reading outcome from brain structure (i.e., CC white matter), cognitive skill (i.e., processing speed), and degree of neurological risk. Subsequent sections review areas important to the study of reading in brain tumor survivors including: CC white matter structure, processing speed, and neurological risk.

1.1 Corpus Callosum

The corpus callosum (CC) is a dense band of medial white matter tracts that connect the right and left hemispheres of the cortex. It is the largest bundle of axons (white matter) in the brain with over 200 million axons and it is the primary mode of interhemispheric communication (Aboitiz, Scheibel, Fisher, & Zaidel 1992). Fibers in the

CC run in the right to left direction and synapse in multiple cortical areas. Fibers extend

to the frontal, parietal, temporal, and occipital lobes. The CC is often subdivided in the

anterior-posterior direction in research as an attempt to separate the fibers of the CC

that extend to different regions of the cortex. The CC is typically divided subdivisions

viewed from the mid-sagittal magnetic resonance imaging (MRI) scans (see Figure 2).

Most studies examine the most anterior division, termed the genu, and the most

posterior division, termed the splenium. In terms of the middle of the CC, some work

describes it as one region, termed the body, and some further subdivide the body into

two to four subregions. The exact demarcation of each subregion can vary by study and

method.

Figure 2. Mid-sagittal view of the corpus callosum. The genu is the anterior most region, the splenium is the posterior most region, and the body is between the two. The CC is the largest white matter tract in the brain with fibers connecting the right and left cerebral hemispheres.

Some studies reporting on the CC may use macrostructure (e.g., volume) from a

structural MRI scan. Macrostructure measurements are taken from structural scans that

segregate white matter voxels from gray matter and cerebrospinal fluid (CSF). Other studies measure microstructure, which requires a specialized DTI scan sequence and allows a measure of white matter integrity. Fractional anisotropy (FA) is the most common microstructure measure and is the measure of the directionality of white matter pathways such that high directionality suggests a stronger white matter tract. The current study used both macro- and microstructural measures of the corpus callosum.

The CC undergoes maturation and myelination throughout childhood and adulthood. White matter maturation is most dramatic in infancy, but continues in childhood and into adulthood. The growth trajectories in the corpus callosum of volume and FA appear to both peak in the 3rd decade (Westlye et al., 2010). Thus, brain insult during this developmental period could impact structural development of the CC. Myelination of the CC occurs in the posterior to anterior direction, paralleling cerebral myelination (Thompson, Narr, Blanton, & Toga 2003). The childhood and adult developmental changes in the corpus callosum are likely due to myelination, increases in axonal size, and synaptic pruning (Carlson, Earls, & Todd 1988; Huttenlocher 1990). These changes likely reflect the refinement of hemispheric specializations (Thompson et al., 2003).

1.2   Neurological Risk Factors

There are several ways in which white matter can be impacted in a childhood brain tumor survivor. Brain tumor presence and neurosurgery in the cerebellum may impact brain regions beyond the cerebellum through diaschisis based on neural connections. Thus not only may the structural integrity of the cerebellum be impacted, but also the structure of areas connected to the cerebellum such as the frontal lobes.

The cerebellum and frontal lobes are connected via the thalamus. Treatments for certain posterior fossa brain tumors include radiation therapy and chemotherapy and are critical for survival but are neurotoxic, particularly to white matter in the brain. Radiation therapy in both low and high doses disrupts white matter development and causes axonal damage (Padovani, Andre, Constine, & Muracciole 2012). Chemotherapy also has been linked to reductions in white matter (Anderson & Kunin-Batson 2009; Deprez et al., 2012). In the corpus callosum, specific decreases in white matter microstructure have been detected after treatment with radiation and chemotherapy (Leung et al., 2004; Padovani et al., 2012). In addition to treatment factors, neurological complications common to posterior fossa tumors such as hydrocephalus also can damage the brain's white matter. Hydrocephalus is a common complication in childhood posterior fossa tumors in which excess cerebrospinal fluid (CSF) builds up in the brain due to a disruption of the flow and the formation or reabsorption of CSF. This often leads to increased pressure in the cranium. This pressure on brain tissue can cause damage to white matter pathways (Fletcher et al., 1992). The corpus callosum has been shown to be an area of vulnerability to hydrocephalus (Yuan et al., 2009; Yuan et al., 2012; Yuan et al., 2013). Other common factors in childhood brain tumors also have an impact on the brain, including seizure medication and hormone deficiency (Ris & Noll 1994).

In addition to these individual risk factors, the combination of these factors have an additive effect (Micklewright, King, Morris, & Krawiecki 2008) and were recently found to be strongly related to the microstructural white matter integrity of the brain (King et al., 2015). Using TBSS to measure WM fractional anisotropy across the whole

brain, King et al., (2015) found that a mixed group of brain tumor types and treatments had reduced integrity compared to healthy controls in clusters that overlap with the CC, but appear to be lateral regions of the CC. When participants were divided into treatment subgroups, the anterior CC (genu) appeared to be more prominently reduced in both survivors with surgery only and survivors additionally treated with radio- and chemotherapy. However this effect was more pronounced in the group with more treatment (radio- and chemotherapy). Given that multiple factors appear to affect the CC, it is important to test for the effect of cumulative neurological risk factors on white matter structure of CC subregions. A scale has been specifically developed to measure cumulative neurological risk in childhood brain tumors (The Neurological Predictor Scale [NPS]; Micklewright et al., 2008). NPS score is associated with long term cognitive and adaptive outcomes in adult survivors of childhood brain tumors (King & Na 2015). In addition to examining CC structure and reading, this dissertation sought to examine the impact of neurological risk on white matter structure using the NPS.

1.3   Corpus Callosum and Childhood Brain Tumor

In short term survivors (under 5 years from diagnosis), CC volume has been shown to be reduced (Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin 2006; Palmer et al., 2002; Zhang et al., 2008). Subregion white matter of the CC has been directly studied in two prior BT samples (mostly short-term). A longitudinal study over four years in children (age 3-17 years) at least one year from treatment for medulloblastoma (i.e., RT and chemotherapy [RTC]) found decreased volume of white matter across all seven CC subregions measured (Witelson 1989), in contrast to the expected increase observed in healthy white matter volume childhood (Palmer et al., 2002). Volume

reductions among CC subregions were observed throughout the CC but were most evident in the splenium (defined as 1/5th of CC; see Figure 2). This study, however, did not employ a control group. Another study used diffusion tensor imaging (DTI) to compare a mixed group (2-13 years since treatment) of medulloblastoma survivors (RTC) and a non-CNS cancer group, acute lymphocytic leukemia (ALL; treated with chemotherapy) with controls (Aukema et al., 2009). The mixed survivor group had reduced white matter integrity (DTI FA) in the genu of the CC compared to controls (not the body or splenium). The authors also compared patient subgroups that should be interpreted with caution due to very small sample (i.e., n=6 medulloblastoma). Subgroup analysis indicated that medulloblastoma survivors had reduced white matter integrity in the splenium and body of the CC compared to ALL. Patient subgroups were not compared to controls. The different results found when patients with different degrees of neurological risk were combined and separated suggests an effect of neurological risk, and potentially different results when risk is not taken into account. The mixed results of prior studies highlight the importance of accounting for degree of neurological risk. Both direct studies of the CC subregions in mostly short term survivors demonstrate the need to examine the long-term effects of brain tumor history on CC macro- (volume) and microstructure (FA). Survivors are infrequently studied after 5 years post diagnosis despite the fact that many continue to experience cognitive and functional difficulties. This study seeks to address this gap in the literature and add to the new literature on long-term effects of childhood brain tumor and its treatment sequelae.

In whole-brain research in survivors, white matter was investigated on a voxel-wise basis over the whole brain. A consistent finding of these studies is reduced

fractional anisotropy and volume in the corpus callosum, among other brain regions, in survivors (King et al., 2015; Leung et al., 2004; Palmer et al., 2012; Rueckriegel et al., 2010; Zhang et al., 2008). Three of these 5 studies report various specific locations of the CC reduction, likely based on anatomical atlas' defining the genu, body, and splenium of the CC, though specific atlases were not reported. In one study splenium and genu were reduced in survivors (Zhang et al., 2008), the body in another (Rueckriegel et al., 2010), and genu, body, and splenium in the third study (Leung et al., 2004). Different CC locations in these three studies could be related to several factors. First, to the different methods employed (macrostructure voxel based morphometry, microstructure voxel based morphometry, microstructure tract-based spatial statistics). Second, mixed results could be related to the inherent correction procedures in whole brain analyses that may make smaller effects harder to detect, and third to differences in control groups (one of which was a clinical control group [e.g., headaches] that may have subtle microstructural differences). Mixed findings from whole CC differences in survivors to partial regions in whole brain analyses, demonstrate a need for a direct, functionally based ROI approach to help to clarify the impact on CC subregion white matter in survivors.

Most work mentioned above was comprised of a uniform sample of survivors treated with both radiation therapy and chemotherapy. Thus it is unclear whether the difference in white matter integrity is due to certain treatments, complication factors, or an additive effect of multiple neurological risk factors. Little work has addressed whether the degree of neurological risk predicts CC structure in a broader spectrum of risk in survivors. In other words, samples with varying levels of treatment may in turn have

varying degrees of impact on subregions CC. In the first study of long-term survivors

using DTI, our lab found not only that the CC white matter was reduced in long-term

survivors, but that a measure of cumulative neurological risk (NPS) was strongly

correlated with white matter integrity in the CC in a group comprised of both survivors

treated with radiation therapy and chemotherapy, and those with surgery only (King et

al., 2015). This proposal seeks to extend this work to measure the CC subregions

directly to address how broad the impact of neurological risk across subregions of the

CC. Furthermore, examining the relationship of structural changes to behavior,

specifically reading skill, can lead to better understanding of neurological risk on CC

subregions and reading relationships.

1.4   Corpus Callosum and Reading Skill

When mapping reading onto the CC one could hypothesize that the regions of

the CC that specifically connect the left and right sided cortical hubs in the reading

system would have the strongest relationship to reading. Regions of the CC that

specifically connect the cortical reading system include CC subregions with fibers

connecting right and left inferior frontal, temporal, posterior parietal, and occipital areas

(see Figure 1A). These connective regions are the most anterior and most posterior

portions of the CC (the genu and the splenium) (de Lacoste, Kirkpatrick, & Ross 1985).

According to Hofer and Frahm (2006) report of tractography of the corpus callosum, the

genu connects to the prefrontal regions of the cortex and includes the anterior 1/6th of

the CC (see Figure 3). The splenium connects posterior parietal, temporal and occipital

regions of the brain and covers the posterior 1/4th of the CC (see Figure 3).

Reading skill has a rich history of being associated with interhemispheric transfer of information in the CC (Damasio & Damasio 1983; Dejerine 1892; Funnell, Corballis, & Gazzaniga 2000; Geschwind 1972). Pure alexia, the loss of the ability to read, while preserving writing ability, was first described by Joseph Jules Dejerine in 1892 (Dejerine 1892). Post mortem analyses show that the splenium of the CC is commonly damaged jointly with the occipital lobe in pure alexia (Binder & Mohr 1992; Damasio & Damasio 1983; Dejerine 1892; Geschwind 1972). In a patient who underwent a corpus callosotomy (surgery to split the CC right and left hemispheres) rostral and splenial aspects of the CC were later found to be partially spared. The spared splenium was hypothesized to be associated with this patient's successful transfer of word information, while other visual information was unsuccessfully transferred across hemispheres (Funnell et al., 2000). This research identifying a link between interhemispheric transfer in the CC and reading ability in callosotomy and lesion patients spurred CC research in typical and atypical reading development, which also has supported the structure of the splenium in reading (e.g., Lebel et al., 2013).
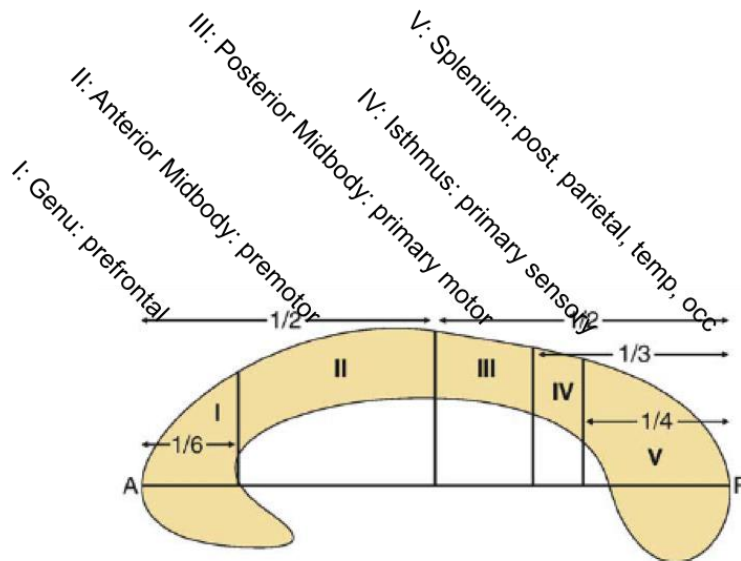
Figure 3. Hofer and Frahm (2006) tractography based functional subdivisions of the corpus callosum. Labels include general name of subregion and cortical regions identified connecting through this subregion of the CC.

The splenium appears to have the most consistent relation to reading, supporting parietal, temporal, and occipital reading connections (Dougherty et al., 2007; Hofer & Frahm 2006; Odegard, Farris, Ring, McColl, & Black 2009). The anterior CC, connecting prefrontal regions (i.e., genu) also may relate to reading as well, but results are mixed (Elnakib, El-Baz, Casanova, Gimel'farb, & Switala 2010; Hynd et al., 1995; Lebel et al., 2013). Previous work has found the splenium to be different in individuals with reading disorders compared to typical readers in children (Hasan et al., 2012b) adults (Duara et al., 1991; Frye et al., 2008; Rumsey et al., 1996) and mixed-age samples (Kilian et al., 2008). Posterior CC differences were the primary finding in most of these studies with many specific to the splenium (Duara et al., 1991; Kilian et al., 2008; Rumsey et al., 1996) (but see Elnakib et al., 2010; Hasan et al., 2012a). Furthermore, splenium was observed to correlate with word and pseudoword reading in children (Dougherty et al., 2007; Odegard et al., 2009) (but see Hasan et al., 2012a)

and adults (Frye et al., 2008; Lebel et al., 2013). The correlation between reading and white matter appears to be similar for both individuals with reading disorders and typically developing individuals (Frye et al., 2008). A subset of studies also found anterior CC to be related to reading (Elnakib et al., 2010; Hynd et al., 1995; Lebel et al., 2013). The relationship between reading and CC white matter structure also has held in a sample with traumatic brain injury. For example, in childhood traumatic brain injury, reading performance was positively associated with white matter FA in the splenium (Ewing-Cobbs et al., 2008). This relationship also might be expected after insults associated with brain tumors.

Studies have yet to directly examine reading skill with theoretical aims related to CC structure in childhood brain tumors. In one exploratory whole brain analysis, relating white matter to pseudoword reading, the CC was not a significant structure related to pseudoword reading in short term brain tumor survivors (Palmer et al., 2010). This study's lack of CC findings could be related to correction procedures in voxel-based analyses, which can be vulnerable to type II errors, potentially precluding researchers from detecting a subtle relationship in the CC. In addition, the study utilized pseudoword reading, which could have slightly different structural relationships than real word reading. Also, this study did not utilize a control group. Given that few researchers have specifically studied the structural basis of reading in survivors of childhood brain tumors, multiple methods are important to begin this area of research. These methods include exploratory whole brain methods that search for a potential effect in each voxel of the brain but also specific theory-based regional analyses based on the extensive white matter and reading literature such as the current proposal. Previous work in our lab

found word reading in adult survivors of childhood brain tumors to be related to two cortical white matter tracts hypothesized to connect reading related regions (inferior frontal occipital fasciculus and parietotemporal-occipitotemporal connection; (Smith et al., 2014b). Therefore we predicted that the subregions of CC that connect these regions (genu and splenium) would be correlated with reading skill.

1.5 Role of Core Cognitive Skill: Processing Speed

Understanding why survivors tend to struggle with learning and advancing reading is important for guiding intervention. The development of core cognitive abilities can impact reading acquisition and maintenance and therefore be important to examine. Broad outcomes such as reading in childhood brain tumor survivors are hypothesized to relate to core cognitive skills such as processing speed (Palmer 2008). Palmer (2008) proposed a conceptual model in which disease and treatment risk factors are associated with academic achievement through core cognitive functions. Difficulties with core cognitive skills (i.e., processing speed, attention, working memory) are hypothesized to lead to problems with reading. Yet the achievement and cognition aspect of the model has not been adequately studied. 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). Information processing speed refers to the efficiency of processing simple cognitive or perceptual information (Palmer 2008). When this conceptual model was tested by our research team with processing speed, working memory, and attention span predicting intellectual and academic outcomes, processing speed was most strongly associated with academic outcomes (King, Ailion, & Hufstetler in preparation).

In a previous study in our lab, word reading was regressed on both processing speed (Oral Symbol-Digit Modalities) and working memory (Auditory Consonant Trigrams) in long term survivors. Processing speed contributed unique variance to reading skill while working memory did not contribute significant unique variance (1% of the variance in word reading predicted by working memory) (Smith, King, Morris, & Krawiecki 2011). Using the same regression method, another task requiring working memory and attention (digit span- backward span) contributed 0.4% unique variance in word reading after processing speed was accounted for (Unpublished Data). Further, Digit Span normative score for forwards and backwards combined explained just 2% of the variance in word reading above processing speed. Processing speed contributed unique variance in each case. Thus, previous work in our lab with long terms survivors of childhood brain tumors suggests that processing speed is a stronger predictor of word reading compared with attention and working memory tasks.

In brain tumor survivors treated with radiation, processing speed has been shown to be slow even when attention and working memory deficits were not found (Briere, Scott, McNall-Knapp, & Adams 2008; Mabbott, Penkman, Witol, Strother, & Bouffet 2008). Difficulties in processing speed are observed in both individuals who received treatment with surgery only and those treated with radiation therapy (Kieffer-Renaux et al., 2000; Mabbott et al., 2008; Ronning, Sundet, Due-Tonnessen, Lundar, & Helseth 2005). Although findings with survivors who were treated with surgery only are more variable. Processing speed has been found to be further impaired when surgery was accompanied by treatment with radiation or shunt placed for hydrocephalus (Mabbott et al., 2008; Ronning et al., 2005). 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 (Briere et al., 2008; Mabbott et al., 2008). Reduced processing speed is hypothesized to be preceded by changes in white matter structure (Palmer 2008).

Greater white matter integrity and organization increases the efficiency and speed of neural conduction. Thus it follows that cognitive processing speed should be directly related to the integrity of white matter pathways in the brain. Indeed, previous studies have shown relationships between processing speed and white matter integrity measures in healthy brains as well as brains with white matter abnormalities (Penke et al., 2010; Turken et al., 2008). White matter abnormalities in the periventricular region (including CC) in particular are associated with poorer processing speed (Van den Heuvel et al., 2006).

With regard to 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.

In survivors of childhood brain tumor, processing speed performance was a significant factor influencing the relationship between cortical white matter microstructure and reading uniquely in survivors (Smith et al., 2014b). The tract with the largest effect in the model was connecting the posterior reading regions: parietotemporal to occipitotemporal. These posterior areas communicate across hemispheres via the splenium (Hofer & Frahm 2006). Thus, the splenium also may be relevant for reading in brain tumor survivors. Indeed, the corpus callosum microstructure was broadly associated with processing speed in brain tumor survivors (Palmer et al., 2012). Structure of the splenium also has been associated with processing speed in childhood neurological populations (traumatic brain injury, brain tumor, epilepsy) as well as within typically developing adolescents and young adults (Fryer et al., 2008; Hermann, Hansen, Seidenberg, Magnotta, & O'Leary 2003; Madden et al., 2004; Palmer et al., 2012; Wu et al., 2010). Expanding this model of how white matter and processing speed predict word reading by testing another hypothesized component of the reading system, the CC, can strengthen our understanding of brain behavior systems and relationships.

Table 1. Comparing common names for CC subregions used in the literature and used by Hofer and Frahm (2006)

CC1	CC2	CC3	CC4	CC5
Genu	Anterior midbody	Posterior midbody	Isthmus	Splenium
Genu	Body	Body	Body	Splenium
Anterior 1/6th	1/3rd	1/6th	1/12th	Posterior 1/4th

Note. The current study refers to our results using the top row naming to describe CC subregions but also uses other names when referring to the literature. The bottom row refers to the size of the CC in each subregion used in the current study.

1.6 Aims and Hypotheses

1.6.1 Aim 1

Investigated the white matter structure of 5 CC subregions in survivors compared to healthy controls using volume and fractional anisotropy (FA).

1.6.2 Hypothesis 1

It was hypothesized that survivors would have reduced structure (volume and FA) compared to healthy controls. The CC subregions were expected to be globally affected in survivors given previous work in short-term survivors.

1.6.3 Aim 2

Examined how cumulative neurological risk (using NPS scores; Micklewright et al., 2008) was related to white matter structure (volume and FA) in each CC subregion. Only survivors were analyzed in this aim given that the NPS is not appropriate for controls without neurological risk.

1.6.4 Hypothesis 2

It was hypothesized that degree of neurological risk would be negatively correlated with white matter structure (volume and FA) in the CC subregions.
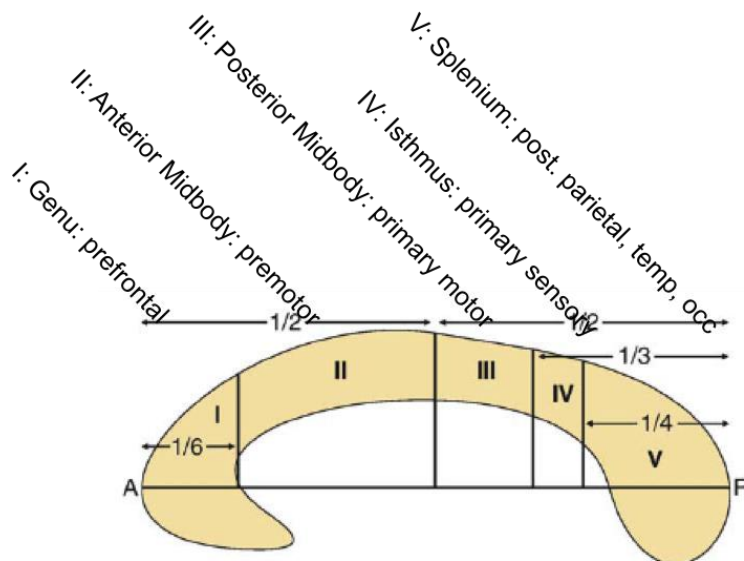
Figure 3. Hofer and Frahm (2006) tractography based functional subdivisions of the corpus callosum. Labels include general name of subregion and cortical regions identified connecting through this subregion of the CC.

1.6.5 Aim 3

Investigated the relationship of word reading with the genu and the splenium subregions of the corpus callosum (i.e., CC1 & CC5). To test the specificity of reading to these specific subregions, a control subregion was tested, the posterior midbody region (CC3). This region was not hypothesized to connect to specific reading related cortical regions. To test the specificity of reading, a control task, motor speed was tested in relation to white matter, and was not expected to associate with white matter in the genu and splenium.

1.6.6 Hypothesis 3

It was hypothesized that word reading would be positively associated with splenium and genu white matter structure (volume and FA) given that these regions connect anterior and posterior reading regions of the brain and have been related to

reading in non-BT samples (see Table 2). The region with the highest correlation with reading was used in aim 4.

Table 2. Hypothesized correlations of word reading with the genu, splenium, and control region of the CC.

WM structure	CC1 +	CC2	CC3 [control] NS	CC4	CC5 +

Note. +=positive correlation, NS=not significant. CC subregions are labeled based on Hofer and Frahm (2006) subdivisions.

1.6.7 Aim 4

Investigated comprehensive models of reading outcomes comprised of: neurological risk, white matter structure and processing speed; complimenting and extending the Smith et al. (2014b) model. CC white matter was tested as the mediator between NPS and reading skill in model 1.

As a core cognitive skill, processing speed was expected to mediate the relationship between white matter structure and word reading skill in model 2. Thus, white matter structure was proposed to influence reading skill through the indirect effect of processing speed. Given that NPS was expected to be responsible for the variance in CC structure in the previous model, it was removed from the second model leaving CC structure as the independent variable to represent the variance in NPS.

1.6.8 Hypothesis 4

It was hypothesized that CC structure would significantly mediate the relationship between neurological risk and reading such that CC structure explains reading outcomes by risk. For model 2, it was hypothesized that processing speed would significantly mediate the relationship between white matter structure and word reading.

2   METHOD

2.1   Participants

Participants involved in this archival study were recruited as part of a larger study of long-term neuropsychological outcome of survivors of childhood brain tumors (American Cancer Society, Principal Investigator: T.Z. King, #RSGPB-CPPB-114044 and current pilot study with Emory). Brain tumor survivors were recruited from a Brain Tumor Foundation of Georgia newsletter and opt-in letters mailed to survivors identified by: 1) a previous longitudinal study, in which they participated as children and 2) a local children's hospital. 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.

The current study focused on survivors with posterior fossa tumors. Within this group, survivors were included if they were 17 years of age and older at exam, at least 5 years from diagnosis, a native English speaker, demonstrated adequate vision for reading, and if their MRI scan was free of metal artifact or distortion impacting the corpus callosum. Survivors were excluded if they were diagnosed with developmental disabilities (e.g., pervasive developmental disability) or neurofibromatosis or if they demonstrated global impairment determined by both a full scale IQ score of less than 70 and an SIB-R Broad Independent Living score of less than 70 (n=1). Twenty survivors of childhood brain tumor and 23 controls met inclusion criteria (including scan motion criteria described later) and were used in study analyses. One survivor did not complete the reading measure due to the participants familiarity with the measure, so a total of 19 survivors were used in analyses involving reading scores. See Table 3 for survivor characteristics.

Table 3. Survivor sample tumor and treatment characteristics

	Survivors (N=20)
Age at diagnosis (range)	9.70 (1-18)
Years since diagnosis (range)	14.36 (5-31)
Tumor location PF	100%
Type of tumor	
Astrocytic	50%
Embryonal	45%
Choroid plexus	5%
Hydrocephalus	70%
Radiation	55%
Focal only	10%
CSI with boost	45%
Chemotherapy	45%
Neurosurgery	100%
Seizures	5%
Hormone deficiency	60%

Note. Ages in years; F=female; C=caucasian,
PF=posterior fossa.

Healthy comparison participants were carefully matched with survivors on

demographic factors including: age, sex, race, and socioeconomic status. Comparisons

were selected from among approximately 60 controls to optimize matching. The healthy

control group was recruited from two local university's psychology department research

subject pool, friends of survivors, and community sample fliers. The psychology

department research pool tended to be comprised of students from diverse educational

backgrounds, and with a range of ethnic and socioeconomic backgrounds including first

generation college students. Inclusion criteria for control participants included English

as their native language and structured clinical interviews (SCID) (First, Spitzer, Gibbon,

& Williams 2002) indicating free of current psychopathology or substance use. This

study was approved by the Georgia State University Institutional Review Board (IRB:

H03177 & H08323) and the Georgia State University/Georgia Institute of Technology Joint Center for Advanced Brain Imaging (IRB: H09157). All adult participants (18 years and older) signed informed consent and for participants under 18, assent and consent was provided by the participant and the parent, respectively.

2.2 Measures

2.1.1 Word Reading Skill

Reading achievement was examined with the Letter-Word Identification (LWID) subtest of the Woodcock Johnson Tests of Achievement III (Woodcock, McGrew, & Mather 2001b). LWID is a measure of real word decoding. For this task, participants were presented with written words to read orally and the score was based on correct pronunciation (Woodcock, McGrew, & Mather 2001a). This measure has been utilized to quantify reading ability in survivors of childhood brain tumors, and children with dyslexia, and has been linked to white matter structure (including in the CC) over a range of ability levels (Frye et al., 2010). 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 (Woodcock et al., 2001a). 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., 2001a) were used as the primary dependent variable for aims 3 and 4.

2.1.2 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 Oral Version is a perceptual task that unlike many tests of processing speed does not involve a motor component. Instead it is based on a verbal response, allowing a more pure measure of information 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 (Smith 1982). The participant was given a 90 second time limit to complete as many items as they can. The score was 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 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 (Smith 1982) were used as the mediating variable in aim 4. The written version of the SDMT was used in exploratory analyses as a motor processing speed task.

2.1.3 Degree of Neurological Risk

Neurological Predictor Scale (NPS) scores were calculated to measure cumulative neurological impact. Brain tumors are a unique neurological population in

that they can be accompanied by varying degrees of neurological complications. These include brain tumor related complications (e.g., hydrocephalus) and life-saving yet neurotoxic treatments (e.g., radiation and chemotherapy). While outcome studies may include some of these factors, most studies do not test for the effect of multiple factors on outcome (Ris & Noll 1994). Yet adding each individual factor to analyses would require a much larger sample size. The problem of the desire to quantify all risk factors provided the impetus to create one scale to account for these cumulative effects of neurotoxic insults (Micklewright et al., 2008)**.** The NPS provided one total score accounting for neurosurgery, focal and diffuse radiation therapy, chemotherapy, hydrocephalus, seizure medications, and hormone deficiency. Four major domains comprise the items in the NPS based on a review of the relationship between treatment factors and neurological complications (Micklewright et al., 2008; Ris & Noll 1994). The domains include: tumor-related conditions, operative events, radiation treatment, and chemotherapy. Components of the NPS include whether one has had a surgical biopsy only, a single neurosurgery or multiple surgeries to remove the tumor; whether the participant was diagnosed with a hormone deficiency; whether they were prescribed seizure medication; whether the participant received focal radiation, whole brain or craniospinal radiation, or whole brain and focal radiation therapy; and whether the participant received chemotherapy. Higher point values were added to the total for multiple events (i.e., whole brain and focal radiation therapy; and prescribed seizure medication and diagnosed with a hydrocephalus). The initial study demonstrated that the NPS score accounted for additional variance beyond individual risk factors in predicting intelligence and adaptive measures in childhood brain tumor patients

(Micklewright et al., 2008). It was recently replicated in long-term survivors of childhood brain tumors (King & Na 2015). In addition, a recent study found that the NPS was predictive of cognitive measures of working memory and processing speed (McCurdy, Rane, Daly, & Jacobson 2016). Scores can range from 0 to 11.

2.1.4 Motor Speed

Finger tapping motor speed was used as a control variable, in place of word reading skill, and was not expected to be highly associated with white matter in the splenium or genu, or processing speed. Although there is a rich history of motor skills such as motor articulation and sequencing being related to language and communication, (Hadar, Wenkert-Olenik, Krauss, & Soroker 1998; Hickok 2012; Rizzolatti & Arbib 1998), finger tapping speed was chosen as a more basic motor ability not requiring sequencing or articulation. In a previous sample of survivors in this lab, motor speed was unrelated to word reading skill and explained less than 1% of the variance in reading (Smith et al., 2014b). Furthermore, while processing speed and motor speed are both measures of cognitive speed, they were unrelated statistically (4% variance in processing speed explained by motor speed) (Smith et al., 2014b). Given previous data described above, it is less likely that motor speed and processing speed are measuring the same construct.

With regard to anatomical localization of finger tapping speed in the brain, previous work has noted activation in the primary motor cortex, cerebellum, and pre supplementary motor area during the finger tapping task to be used in the current study (Johnson et al., 2000; Lutz, Koeneke, Wüstenberg, & Jäncke 2004). If finger tapping speed was strongly associated with language-related motor areas in the brain, we

would expect activation in the motor programming area Brodmann Area (BA) 44 (Fridriksson et al., 2008; Skipper, Nusbaum, & Small 2005). Activation in BA 44, however, has not been reported (Johnson et al., 2000; Lutz et al., 2004). This suggests that the finger tapping task is less likely to be related to language and reading. This localization would suggest that finger tapping speed would be related to frontal motor areas of the CC including primary and pre-motor areas. These divisions of the CC are hypothesized to be in the body of the CC, close to the genu, but hypothesized to be separate (Hofer & Frahm 2006). This suggests that the finger tapping task is less likely to be related to the genu and splenium areas of the CC.

The finger tapping task is a widely used task from the Halstead-Reitan battery (Lezak 2004). Participants use their index finger to tap a tapping key as quickly as they can for 10 second trials. The first 5 trials within 5 taps of each other were averaged. Each hand was tested separately. The average taps for each hand was compared to normative values. The current study utilized the dominant hand z-score (Heaton, Grant, & Matthews 1991).

2.1.5 Adaptive Function

The Scales of Independent Behavior- Revised (SIB-R; Bruininks 1996) is a measure of adaptive function that spans children to older adults. It was conducted as an interview with an informant who was aware of the participants' daily living skills. The broad independent living standard score was used to help determine global impairment for potential exclusion.

2.1.6 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) wasused in this study as a measure of intellectual outcome for descriptive purposes. The FSIQ also was used to help determine global impairment for potential exclusion. 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 also was 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 be 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). 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).

2.1.7 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 to compare the SES between the groups using the Fisher Exact Test.

2.1.8 Psychiatric Screening

The Structured Clinical Interview of the DSM-IV Axis I Disorders (SCID) Research Version (First et al., 2002) was used to screen for diagnosable psychiatric disorders including mood disorders, anxiety and phobic disorders, substance use, and schizophrenia, that are part of the study's exclusion criteria.

2.1.9 Image Acquisition

A Siemens Trio 3T scanner with a standard RF 12 channel head coil was used to obtain DTI and anatomical T1-weighted data. A 30 direction single shot spin echo diffusion-weighted sequence with 60 contiguous axial slices interleaved and 2 non-diffusion weighted images was acquired with 2 x 2 x 2 mm resolution and coverage of the whole head (b value=1000s/mm^2, TE/TR= 90ms/7700ms, FOV=204mm, GRAPPA=2). 3D T1-weighted image was acquired using a magnetization prepared rapid gradient-echo (MPRAGE) sequence (176 contiguous sagittal slices, TR=2250 ms,

TE=3.98 ms, flip angle=9 degrees, voxel=1 x 1 x 1 mm). Functional MRI data and

corresponding field map obtained in the same scan were used to optimize the

coregistration of the DTI and T1 images. The fMRI and field map were used to

approximate the geometric distortion caused by magnetic field inhomogeneties in the

DTI data. The fMRI sequence parameters were as follows: gradient-recalled echo-

planar imaging sequence (EPI) 180 volumes, repetition time (TR) = 2130 ms, echo time

(TE) = 30 ms, flip angle = 90 degrees, 40 contiguous slices, slice gap = 0 mm, nominal

resolution = 3 x 3 x 3 mm. Field map parameters include: TR = 488 ms, TE = 4.92/7.38

ms, flip angle = 60 degrees, voxel size = 3 x 3 x 3 mm.

2.1.10 White Matter Microstructure and Macrostructure

White matter microstructure was measured using diffusion tensor imaging (DTI).

DTI is a noninvasive, in vivo tool used to indirectly measure the quality of white matter

structure based on the diffusion of water within tissue. Among bundles of myelinated

axons, water diffuses along the direction of the axon in an anisotropic (directional)

manner (Cascio, Gerig, & Piven 2007). This diffusion of water is quantified in this study

using fractional anisotropy (FA). FA is an indirect normalized measure of directional

diffusion. High anisotropy or FA value suggests fast water diffusivity parallel to the

fibers, and slow diffusivity perpendicular to the fibers (Assaf & Pasternak 2008). The FA

index ranges between 0 and 1, with a value of 1 suggesting maximal directional

diffusion, and a value of 0 suggesting isotropic diffusion (see Figure 4). DTI is sensitive

to changes in WM due to injury, damage or development (Assaf & Pasternak 2008). As

an indirect and nonspecific measure, FA can be influenced by other cellular properties

such as inflammation, axon density, axon diameter, and crossing fibers (Tournier, Mori,

& Leemans 2011; Wheeler-Kingshott & Cercignani 2009). Therefore, changes in these

cellular properties *instead of* white matter integrity also could lead to changes in FA and

differences should be interpreted with caution. A well-known weakness of fractional

anisotropy is the potentially inaccurate classification of directional integrity in voxels that

contain crossing fibers (Oouchi et al., 2007). FA can be lower in areas with crossing

fibers which would be more reflective of the crossing pattern rather than the integrity of

the white matter. The structure used in this study, the CC, however, is a densely packed

fiber system of tracts containing straight fibers travelling in the left to right direction in

which error from crossing fibers is less relevant (Oouchi et al., 2007; Wahl et al., 2007).

The current study defined white matter microstructure as the average FA value.
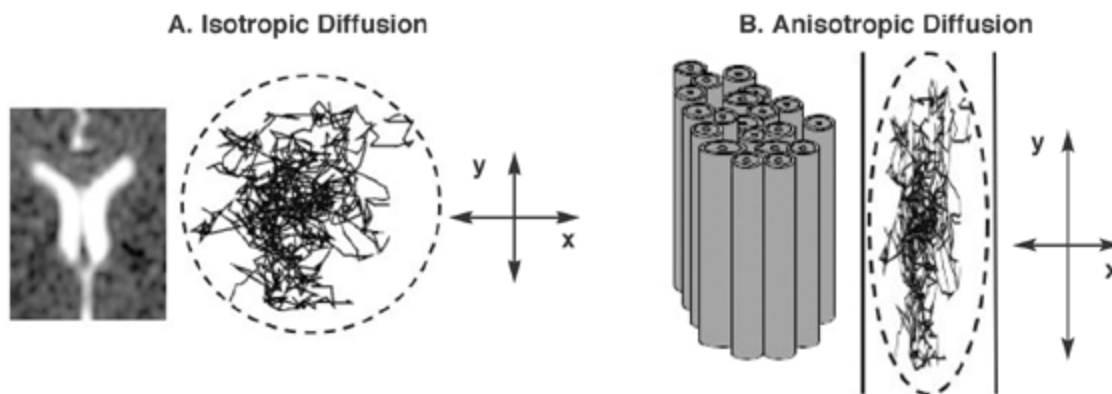
Figure 4. Isotropic and anisotropic diffusion. (A) Water molecules in the brain are constantly moving (i.e., in Brownian motion). When motion is unconstrained, as in the large fluid–filled spaces deep in the brain (i.e., the ventricles, as illustrated in the MR image on the left), diffusion is isotropic, which means that motion occurs equally and randomly in all directions. (B) When motion is constrained, as in white–matter tracts (illustrated on the right), diffusion is anisotropic, meaning that motion is oriented more in one direction than another (e.g., along the *y* axis rather than along the *x* axis). Figure copied from Rosenbloom, Sullivan, and Pfefferbaum (2003).

White matter macrostructure was obtained from the same scanning session.

Macrostructure was computed and defined as the volume in mm^3. Volume is a measure

of the size of the white matter region, while DTI provided a measure of the underlying white matter integrity within the region. Measuring both macro- and microstructure in the CC may lead to a richer picture of this white matter pathway (Cardenas et al., 2014).

2.1.11 Callosal Division Plan

The CC is commonly identified on the mid-sagittal slice (see Figure 2) and is divided into anterior and posterior segments using various described division schemes (Hofer & Frahm 2006; Witelson 1989) based on hypothesized functional connections. It is important to divide CC based on functional domains as much as possible for more precise interpretations of the functional importance of each region. However, there are no anatomical landmarks in the CC to guide functional division. Many previous studies divide CC using the Witelson scheme (Witelson 1989) dividing the CC into 5 subregions (2 anterior, 3 posterior), but this work was based on experimental research in nonhuman primates. Recent work has updated the Witelson (1989) scheme using human DTI tractography through the CC (Hofer & Frahm 2006) to define more functionally precise subregions in humans. Among division schemes, there is disagreement about the size of the genu (see Chao et al., 2009; Hofer & Frahm 2006; Lebel, Caverhill-Godkewitsch, & Beaulieu 2010; Zarei et al., 2006) with some CC DTI studies tracking prefrontal connections extending into the anterior midbody region (Chao et al., 2009; Zarei et al., 2006). This disagreement may be related to the size and coverage of frontal seed regions of interest when tracking through the CC. However, no scheme of approximated mid-sagittal subdivisions of the corpus callosum will be perfect given individual variability and partially overlapping of tracts with current technology. The Hofer and Frahm (2006) divisions appear to include the highest probability of

prefrontal connections within the genu as well as best divide the splenium to have the greatest chance of tracking important posterior cortical components in each individual, which was a focus of this study (see Figure 3).

The Hofer and Frahm (2006) scheme maintains the 5 subregions of the Witelson (1989) scheme (2 anterior, 3 posterior) but at different sizes based on DTI tractography of cortical connections (see Figure 5). Compared to the Witelson (1989) scheme, Hofer found that the most anterior region (connecting prefrontal) was smaller, the splenium (connecting parietal, temporal, occipital) was larger, and the anterior midbody (connecting premotor and supplementary motor) was larger. Utilizing the updated Hofer and Frahm (2006) schematic may produce more precise functional divisions of the CC and thus allow for more reliable structure-function associations to be tested. This method has been implemented in multiple studies of the CC (Andrews et al., 2010; Schoene-Bake et al., 2009; Wahl et al., 2007).
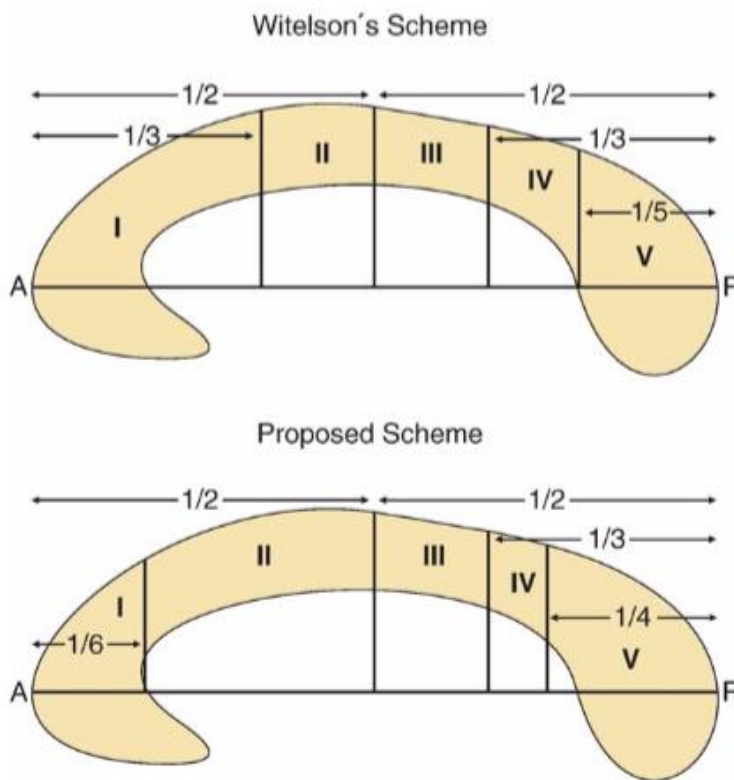
Figure 5. Side by side comparison of Witelson's (1989) scheme and Hofer and Frahm's (2006) "proposed" scheme. Hofer and Frahm's (2006) scheme based on DTI tractography through the corpus callosum. Figure coped from Hofer and Frahm (2006).

2.1.12 Imaging Data Processing

Motion. Both DTI and T1 MPRAGE images were manually checked for motion artifact. Participants with greater than 10 DTI volumes with artifact were excluded from further analyses (n=3; 3 survivors, 0 controls); participants with 1-10 volumes containing artifact, volumes were removed from the dataset (n=5; 3 survivors, 2 controls). After excluding for extensive motion during DTI, none of the remaining participants had significant motion artifact in their MPRAGE image. The final sample included 19 survivors and 23 controls.

Image processing. FMRIB's Software Library (FSL) 5.0 and Freesurfer were primarily used for image processing and co-registration (Smith et al., 2004; Tabachnick & Fidell 2001; Woolrich et al., 2009). Diffusion image processing was completed in FDT (FMRIB's Diffusion Toolbox) part of FSL 5.0. Eddy current correction was performed to correct for induced distortions on the images from eddy currents in the gradient coils. Skull stripping was also performed. DTFIT fit a diffusion tensor model at each voxel and produced an individual brain map of fractional anisotropy (FA) values. The T1 MPRAGE images were skull stripped and processed using the standard Freesurfer cortical reconstruction "recon-all" pipeline.

A functional dataset from the same scan session and the corresponding field map was used to estimate the phase shift of an EPI scan and apply it to the diffusion weighted scan. This extra step corrected for EPI distortions and improved the registration of the MPRAGE and DTI images. Without this step, T1 and DTI images were mis-aligned in areas that are vulnerable to inhomogeneties in the magnetic field such as inferior frontal and temporal regions that would impact the anterior CC in particular. The alignment of DTI and T1 images was manually checked at each step of the process.

With regard to processing the field map, the anatomical and phase data were extracted and then prepared using the FSL function, "fsl_prepare_fieldmap." The fMRI data was checked for outliers, despiked, and time shifted so that all slice timing was the same. The dataset was aligned to the base volume and a mean volume was obtained. FSL's "epi_reg" registered the fMRI time series/field map to the T1 dataset with simultaneous registration and EPI distortion correction.

The DTI and fMRI data were coregistered using the linear FLIRT function in FSL with 6 degrees of freedom. The linear coregistration and the voxel based warp field generated from the "epi_reg" was applied to the DTI data and the FA map. At this point, the FA data were corrected for EPI distortion. The FA data and the MPRAGE were co-registered using boundary based registration (BBR) with automatic registration and manual registration adjustment. A co-registered FA image and MPRAGE image were produced. The FA/MPRAGE coregistration was manually checked and alignment was good for CC boundaries. FMRIB's Automated Segmentation Tool (FAST) was then run on the co-registered MPRAGE image to obtain the WM segmentation image to use for manual corpus callosum tracing (Zhang, Brady, & Smith 2001).

CC mask. Participants' coregistered T1 and DTI images in native space were aligned to the anterior commissure (AC) and posterior commissure (PC). Images were *not* normalized to a template brain in order to keep the size and shape of the CC intact. The mid-sagittal CC was manually outlined using the T1 white matter segmentation image that was co-registered to the FA map. The mid-sagittal slice of the CC was chosen based on the presence of the interthalamic mass. For those in which the interthalamic mass was not identifiable or not present, the mid-sagittal slice was chosen by the smallest presence of the thalamus in the sagittal view which was also the slice that appeared to equally divide both anterior and posterior commisures (left to right) in the axial view. The CC was traced on this slice and traced on one slice to the right and left of the mid-sagittal slice for a total of 3 slices. Voxels were included in the corpus callosum tracing if they had a white matter volume probability of 50% or greater based on segmentation of the T1 image. A second rater manually outlined the CC of all

participants to determine inter-rater reliability. Inter-rater reliability was assessed with the intra-class correlation as in previous studies (Bartko 1966) and was found to be excellent (ICC (2,1)=.99). Individual CC masks were overlaid on DTI space to check co-registration. Even with the optimization of co-registration procedures, the CC mask to the DTI space remained slightly misaligned. To correct for this slight misalignment, the CC mask was eroded by one voxel in the anterior to posterior direction, and one voxel in the superior to inferior direction. The resulting masks showed good alignment with the CC in DTI space.

The manually drawn CC mask for each participant was divided into subdivisions based on the length of the total CC using the size approximations from Hofer and Frahm (2006), creating separate masks for each of 5 CC divisions for each participant (see Figure 5). This segmentation was done using an automated script in Insight Toolkit Snake Automatic Partitioning 3.2 (ITK-SNAP; Yushkevich et al., 2006). Each division mask was overlaid on the participants' co-registered FA image and the average FA value within the CC subregion mask was extracted. Volume was calculated as the size in mm^3 of each subregion. The average FA and the volume were used for microstructure and macrostructure analyses, respectively.
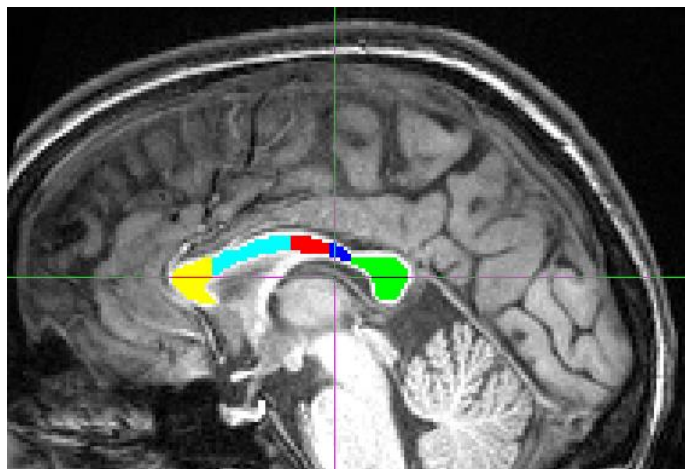
Figure 6.Example of one participant's five CC subregions overlaid on their T1 MPRAGE image. Each subregion is represented by a different color.

2.1.13 Total Intracranial Vault

When comparing volume for a specific brain region (i.e., CC macrostructure) across individuals, it is important to account for the effects of variability in head size (O'Brien et al., 2006). This is because the size of brain structures vary based on head size. For example, smaller regional volumes (i.e., the CC) may be related to a smaller brain and body size rather than the function of the specific region. Thus, in order to use variation in brain region size to explain function, the effect of total brain size should be removed. Common methods of total brain size include: brain tissue (gray matter [GM] + white matter [WM]) and total intracranial vault (TICV) including GM, WM, CSF within the cranial vault space.

Choosing the appropriate brain size measure depends on the population being studied. In typical brains, total brain tissue may be an adequate measure of head size. However, factors such as neurological disease and aging can impact the volume of brain tissue (white matter & gray matter). Thus total brain tissue volume in neurological or aging populations with tissue atrophy, would represent a post-disease state of tissue, rather than head size. Measuring post-disease tissue volume may be confounded with the research question of disease-related regional volume and thus remove variance from the measure of interest. Instead, pre-disease or "maximal" brain sizes are appropriate measures for head size control measures in populations with neurological disease. In the context of childhood brain tumors, tissue volume is likely to be reduced due to tumor removal, hydrocephalus-related enlarged ventricles, and neurotoxic

treatments. Therefore a measure of total brain tissue (GM + WM) would be impacted by disease and treatment factors. Thus, a measure of maximal brain size, total intracranial vault volume (TIV) (GM + WM + CSF) would be most representative of head size unrelated to disease factors (Ailion et al., 2016). TIV is thought to be more appropriate within the context of brain atrophy (O'Brien et al., 2006; Whitwell, Crum, Watt, & Fox 2001). In the current study, testing the effects of group on CC volume, or CC volume on reading skill using TIV as a covariate would be less likely to remove variance related to CC structural variance due to disease factors. TIV was covaried for in all statistical analyses involving volume using the widely used covariance method (O'Brien et al., 2006; Whitwell et al., 2001). TIV was measured using an automated atlas-based measure that has shown to be proportional to manual measures of total intracranial vault (Buckner et al., 2004). This measure is supported in dementia populations with brain atrophy (Buckner et al., 2004).

Even after accounting for TIV, one potential confound remains to be accounted for was the potential difference in cranial vault size due to the effect of a craniotomy during development in the brain tumor survivors. To attempt to test for cranial vault size differences, age at diagnosis was used as a developmental marker of cranium maturation. Age at diagnosis was not significantly correlated with vault size (TIV) (r=-.28, p=.24) suggesting that cranial vault size was not substantially impacted by craniotomy during development.

2.2   Procedure

Typically cognitive measures and the MRI scan (including DTI) occurred over two visits, but occasionally, one visit, depending on the participants' preference. The DTI

scan was part of a longer MRI scanning session that included a total of one hour in the

scanner. Demographic variables were collected via self-report. Medical variables for

survivors were verified through a medical records review.

MRI does not pose any known risks to participants and is used extensively in

clinical and research settings. 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 were compensated for their participation in this

research study.

2.3 Analyses

2.3.1 Potential Confound Analyses

Extraneous variables other than the current study's hypothesized independent

variables may influence the current study's outcome variables of CC white matter

structure (Aim 1 & 2) and word reading (Aims 3 & 4). These variables can act as a "third

variable" potentially obscuring the true relationship between independent and

dependent variables such as CC white matter structure and word reading (Aim 3). A

confound was defined as a variable that is significantly related to the independent

variable as well as correlated with the dependent variable. In each aim, demographic

variables of age, sex, ethnicity, and SES were evaluated as potential confounds. In aim

one, a confound was a variable that is different between groups and correlated with

white matter structure. For aim 2, a confound was a variable that is significantly

correlated with NPS as well as with white matter structure. For aims three and four a

confound was a variable significantly related to white matter structure and to word

reading. If a variable meets this criteria, it was considered a potential confound and was controlled for in the respective analyses as a covariate.

Extraneous variables (sometimes also called covariates) are defined as undesirable variables that impact outcome yet do not relate to the independent variable. Variables predicting significant and unique variance in the dependent variable were added to the analysis as covariate(s). Potential covariates for each analysis are discussed in the analyses section for each aim.

Specific to analyses of white matter volume, total intracranial volume (TIV) served as a covariate to control for effects of head size on the size of the corpus callosum. Total intracranial volume was added as a covariate in analyses given the conceptual relationship and strong research support (O'Brien et al., 2006; Whitwell et al., 2001).

All variables were checked for outliers. Data was checked that it meets assumptions for each analysis; i.e., correlation (normal distribution), ANOVA (normal distribution, independent observations, similar group variances), and regression (non-zero variances, multicollinearity, homoscedasticity, independence of errors, normality distributed errors, independence, linearity). If violations occur, it was addressed by making appropriate adjustments for the sample and analysis based on statistical recommendations of Field (2009).

2.3.2 Aim 1: Analyses of Variance

To address the first aim of this study, to test the difference in white matter structure across groups, one-way analyses of variance (ANOVA) was conducted with an independent variable of Group with 2 levels- survivor and control. The dependent

variable was white matter microstructure (average fractional anisotropy (FA) values or volumes) for each of the five subregions of the corpus callosum. Five separate ANOVAs were tested for each of the five CC subregion volumes, and repeated for subregion FA. Given that a priori hypotheses are made for each contrast, correction for multiple comparisons was not implemented. Effect sizes were computed using Eta squared.

Separate ANOVAs were chosen to investigate the dependent variables of white matter structure in each subregion rather than a single multivariate analysis of variance (MANOVA) testing the subregions together. A MANOVA can be more powerful than multiple ANOVAs if used appropriately, by reducing error. However, degrees of freedom are lost with each additional dependent variable. If dependent variables are highly correlated (multicollinearity), which was expected with the structure of the CC subregions, MANOVA is no longer advantageous to use because the power to detect effects on individual dependent variables is reduced (Field 2009).

In this analysis, involving both survivors and controls, potential confound variables of age, gender, ethnicity, and SES were not significantly different between groups. In addition, these variables were not strongly correlated with structure of CC. Given that demographic variables were not significantly different between groups (Survivor & Controls) and they were not associated with CC subregion white matter structure, these variables were not added as covariates.

2.3.3 Aim 2: Correlation

To address the second aim of the study, to examine the relationship between white matter structure and reading skill, bivariate correlations were conducted for the

genu and splenium subregions, for all participants together. R-values and R^2 values were used as measures of effect size.

In this analysis combining both survivors and controls, potential confound variables of age, sex, ethnicity, and SES were tested. Demographic variables were not significantly related to CC subregion structure nor were they associated with word reading and thus these variables were not included as covariates.

2.3.4   Aim 3: Correlation

To address the third aim of the study, to examine the relationship between white matter structure and neurological risk, bivariate correlations were conducted for each CC subregion structure (volume and FA) for survivors only. R-values and R^2 values were used as measures of effect size.

Demographic variables were not significantly related to CC subregion structure nor were they associated with NPS and thus these variables were not included as covariates.

2.3.5   Aim 4 Regression

To address the third aim of the study, to construct a larger model of reading outcomes including investigating the role of processing speed, neurological risk, as well as CC structure, two hierarchical multiple regression analyses were conducted with bootstrapping to test for the significance of the indirect effect. The first model tested the relationship between neurological risk (NPS; IV) and word reading (LWID; DV) though CC structure (MV: mediating variable). The CC subregion with the strongest correlation with reading in aim 3 was used in analyses. The second regression model tested the relationship of CC structure (IV) to word reading (DV) though processing speed

(OSDMT; MV). Guidelines developed by Preacher, Rucker, and Hayes (2007) were followed to test the mediation models.

The Dr. Andrew Hayes' SPSS "indirect" macro was used to estimate the total, direct, and single-step indirect effects of white matter structure on word reading through processing speed. (http://www.afhayes.com/spss-sas-and-mplus-macros-and-code.html) (Hayes 2013). The model first calculates significance based on the Sobel test for the indirect effects and provides p-values for significance levels. Estimates of all paths are calculated using ordinary least squares regression. Then the model provides a 95% bootstrap confidence interval (bias-corrected accelerated) for the indirect effect (Preacher & Hayes 2008). The number of bootstrap samples was set at 10,000. 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 indirect effect (Preacher et al., 2007). Normal theory tests generated in the SPSS macro were verified by bootstrapping (Preacher et al., 2007). Bootstrap confidence intervals (bias corrected and accelerated) informed the statistical significance of the conditional indirect effect. A confidence interval that does not include zero was considered a statistically significant indirect effect. The effect size for the mediation was measured using R^2 values.

2.3.6 Specificity Analyses

To increase confidence that the CC structure was related to reading areas and not an effect of global CC white matter, a control subregion was tested. The posterior

midbody region (CC3) is thought to connect primary motor cortices and not

hypothesized to connect to specific reading related regions, and was expected to have

a low effect size when correlated with word reading.

Furthermore, to increase confidence that structure was related to word reading

specifically rather than cognitive ability in general, motor speed was tested as a control

task. Motor speed is thought to have a weaker relationship with the splenium (lower

effect size than reading), as pre-motor and primary motor regions of the brain are

hypothesized to connect in more anterior areas of the CC (e.g., CC2 & CC3). To test

the specificity of word reading in the larger model, motor speed was again tested as a

control task in the moderated mediation model.

3   RESULTS

Table 4. Demographics and descriptive statistics of the Survivor group and the Control group

	Survivor (n=20)		Control (n=23)		Group differences		Correlations with LWID	
	Percent				χ2	p (2-tailed)	ρ	p (2-tailed)
Gender (Female)	55.00		56.52		0.01	0.92	-0.18	0.26
Ethnicity (Caucasian)	85.00		71.43			0.45	-0.16	0.32
SES (high)	64.71		72.73		0.29	0.59	-0.14	0.41
	Mean (SD)				t	p (2-tailed)	r	p (2-tailed)
Age (years)	23.50	(6.06)	23.14	(5.57)	0.20	0.84	0.04	0.78
Age range	17-35		18-41					
WJ- Letter-word identification (LWID)	-0.15	(0.59)	0.18	(0.48)	-1.97	0.06		
Oral- Symbol-Digit Modalities Test (OSDMT)	-1.31	(1.27)	0.21	(1.08)	-4.25	<.001		
Finger Tapping Test	-0.95	(1.90)	0.26	(1.17)	-2.50	0.02		
WASI- Performance IQ (PIQ)	-0.03	(0.92)	0.66	(0.69)	-2.77	0.01		
WASI- Verbal IQ (VIQ)	-0.03	(0.88)	0.59	(0.78)	-2.41	0.02		

Note. Pearson correlation coefficient was used for age. Nonparametric correlations (Spearman's rho) was used for categorical variables of: sex, ethnicity, and socioeconomic status. Pearson Chi-Square test was used for gender and SES while the Fisher Exact test was used for Ethnicity. LWID=WJ Letter-word identification; SES=socioeconomic status. All scores for neuropsychological measures are presented as z-scores.

3.1   Potential Confound Analyses

Results of the potential confound analyses (see Table 4) indicated that no variable tested *both* correlated with the outcome variable and was significantly different between groups. Given that the specifications for a confound were not met for any of the tested variables, no covariates were added to the planned analyses. The exception was the addition of total intracranial vault (TIV) in all analyses involving volume. TIV was added to each volume analysis to control for relative head size.

The survivor group scored significantly lower on processing speed, motor speed, performance IQ and verbal IQ. Word reading was a marginal trend at p = .06. Clinical impairment was described as a z score equal to or less than 1.50. 10.5% of survivors were impaired on word reading, 35% on processing speed, 10.5% on VIQ, 10.5% on PIQ, and 30% on motor speed. Scores for controls did not reach clinical impairment levels except for 9% on motor speed.

TIV was not significantly different between groups (t=.03, p=.98) suggesting that TIV was measuring maximal intracranial vault size rather than disease state. Therefore, TIV was utilized confidently as a covariate in all analyses with CC volume.

All variables were checked for normality, outliers, multicollinearity, and nonlinear relationships. Two participants had scores on the word reading task that were statistically significant outliers. These scores indicated low reading and were determined to be valid scores. Thus, these scores were kept in analyses and modified to be the same as the next lowest reading score (Tabachnick & Fidell 2001). With this change no scores were statistically significant outliers.

3.2 Aim 1: Is CC structure reduced in survivors compared to controls?

3.2.1 Macrostructure (volume)

All CC divisions were significantly lower in volume in the survivor group

compared to the control group except CC3 which was a trend at p=.05 (See Table 5).

To examine clinical significance of this difference, the number of survivors whose

volumes fell below the general range of controls in scatterplots was estimated and

ranged from 0% to 50% (CC1: 0%, CC2: 20%, CC3: 35%, CC4: 20%, CC5: 50%). This

suggests that, at most, only half of the survivors in the sample had volumes outside of a

typical range as suggested using the control sample. Given reduced volume, we were

interested in how volumes correlated with development and so we correlated volume

with age at diagnosis. Volume showed moderate to large correlations with age at

diagnosis such that younger age at diagnosis was associated with lower volumes (CC1:

r=.51; CC2: r=.58; CC3: r=.46; CC4: r=.45; CC5: r=.35).

Table 5. Estimated marginal mean volumes for survivors and controls for each CC division and group differences

| | Mean (SD) | | | | Group differences | |
Volume	Survivor (n=20)		Control (n=23)		F	p (2-tailed)	Partial Eta Sq
CC1	310.58	(10.98)	319.36	(10.24)	9.26	<.001	.32
CC2	265.14	(15.97)	315.92	(12.90)	6.50	.004	.25
CC3	106.61	(7.48)	128.12	(6.97)	3.24	.05	.14
CC4	42.37	(4.31)	56.37	(4.02)	4.67	.02	.19
CC5	385.47	(18.16)	445.20	(18.16)	6.47	<.001	.24

Note. Total intracranial volume was used as a covariate.

3.2.2 Microstructure (DTI)

The divisional pattern of FA values in the CC for each group are consistent with

previously published values in that CC1 and CC5 have higher FA than middle CC

regions (Hofer & Frahm 2006; see Table 6). This provided a level of confidence in the overall FA values. CC1, the most anterior had significantly lower FA in survivors; other divisions, however, were not significantly different. FA correlations with age at diagnosis showed small to large effect sizes such that younger age at diagnosis was associated with lower FA (CC1: r=.25; CC2: r=.36; CC3: r=.42; CC4: r=.55; CC5: r=.24).

Table 6. Average DTI Fractional Anisotropy (FA) values for survivors and controls for each CC division and group differences

| | Mean (SD) | | Group differences | | |
	Survivor (n=20)	Control (n=23)	F	p (2-tailed)	Partial Eta Sq
FA_CC1	.73 (.04)	.76 (.04)	6.31	.02	.13
FA_CC2	.65 (.05)	.66 (.04)	1.16	.29	.03
FA_CC3	.68 (.05)	.67 (.05)	.38	.54	.01
FA_CC4	.61 (.08)	.62 (.07)	.17	.68	.00
FA_CC5	.78 (.03)	.78 (.04)	.09	.76	.00

3.3   Aim 2: How does level of neurological risk relate to CC structure?

3.3.1 Macrostructure (volume)

In terms of volume, NPS was related to volumes CC2, 3, 4, and 5 in survivors suggesting that higher treatment risk was related to lower volume in those regions of the CC (CC1 was a trend at p=.07; See Table 7).

Table 7. Partial correlations of neurological risk (NPS) with volumes in each CC division, covarying for TIV

| | NPS | |
Volume	r	p
CC1	-.42	.07
CC2	-.72	<.001
CC3	-.63	.004
CC4	-.72	.001
CC5	-.52	.02

3.3.2 Microstructure (DTI)

NPS was not correlated with CC region FA (See Table 8).

Table 8. Pearson correlations of neurological risk (NPS) with FA values in each CC division

FA	NPS r	p
CC1	.20	.40
CC2	.06	.79
CC3	.17	.48
CC4	-.15	.53
CC5	.20	.39

3.4   Aim 3: Is reading skill related to frontal and posterior areas of the CC? And is it specific?

3.4.1 Macrostructure (volume)

With regard to volume, CC regions 1-5 were all significantly positively correlated with reading (see Table 9).

Table 9. Partial correlations of word reading with volume in each CC division, covarying for TIV

Volume	Reading r	p
CC1	.32	.04
CC2	.48	.001
CC3	.38	.01
CC4	.38	.01
CC5	.39	.01

3.4.2 Microstructure (DTI)

FA in CC5 was significantly negatively related to reading; CC1 was not significantly related to reading (see Table 10).

Table 10. Correlations of word reading with FA in each CC division

	Reading	
FA	r	p
CC1	-.06	.69
CC2	-.01	.95
CC3	-.08	.60
CC4	-.04	.79
CC5	-.33	.04

3.4.3 *Specificity of structure/function relationship*

To test for the specificity of reading skill in relation to CC regions, motor skill was correlated with each CC region. Motor skill was not expected to be related highly to prefrontal connections (CC1) or posterior parietal, temporal, and occipital connections (CC5). In terms of CC volume, CC 2, 3, and 4 (body of the CC) was significantly correlated with motor skill, consistent with the crossing of motor tracts hypothesized to be in areas 2 and 3 (and not areas 1 and 5; see Table 11).

Table 11. Partial correlations of motor speed with volume in each CC division, covarying for TIV

	Motor	
Volume	r	p
CC1	.20	.22
CC2	.47	.002
CC3	.34	.03
CC4	.32	.04
CC5	.25	.12

In FA analyses, motor skill was not significantly correlated with any CC division including CC5 providing preliminary evidence for the specificity of CC5 FA and reading skill in the current sample (see Table 12).

Table 12. Correlations of motor speed with FA in each CC division

FA	Motor	
	r	p
CC1	.22	.15
CC2	.07	.66
CC3	-.09	.55
CC4	.06	.72
CC5	-.03	.86

3.5 Aim 4:

CC2 volume had the most robust correlation with reading (r = .48) and was therefore utilized in the two models in this aim. NPS had a significant effect on word reading (Path c: B=-.15, SE=.04, p=0.005) such that higher NPS related to lower word reading. Volume of CC2 was significant when regressed on NPS (path a: B=-.002, SE=.003, p<.0001), such that higher NPS related to lower volume. The effect of volume on word reading was not statistically significant (path b: B=42.82, SE=.045, p=0.005). The statistical significance of the entire model of the indirect effect of NPS on word reading through CC2 volume, was tested with bootstrapping with 10,000 samples and was not significant (B=-.07, SE=.06, CI: -.19, .04). While the mediation model was not statistically significant, the standardized coefficients of volume on reading while controlling for NPS suggest medium effect sizes (b path; β=.37). This suggests that the current model was likely lacking in power. See Figure 7 for mediation model statistics.

Path a	β
CC2 Volume	-.47*

White Matter Structure

Path b	β
CC2 Volume	.37

Neurological Predictors (NPS)

Word reading (LWID)

Path	c	c'	Indirect Effect
	β	β	CI
CC2 Volume	-.62*	-.33	-.19, .04
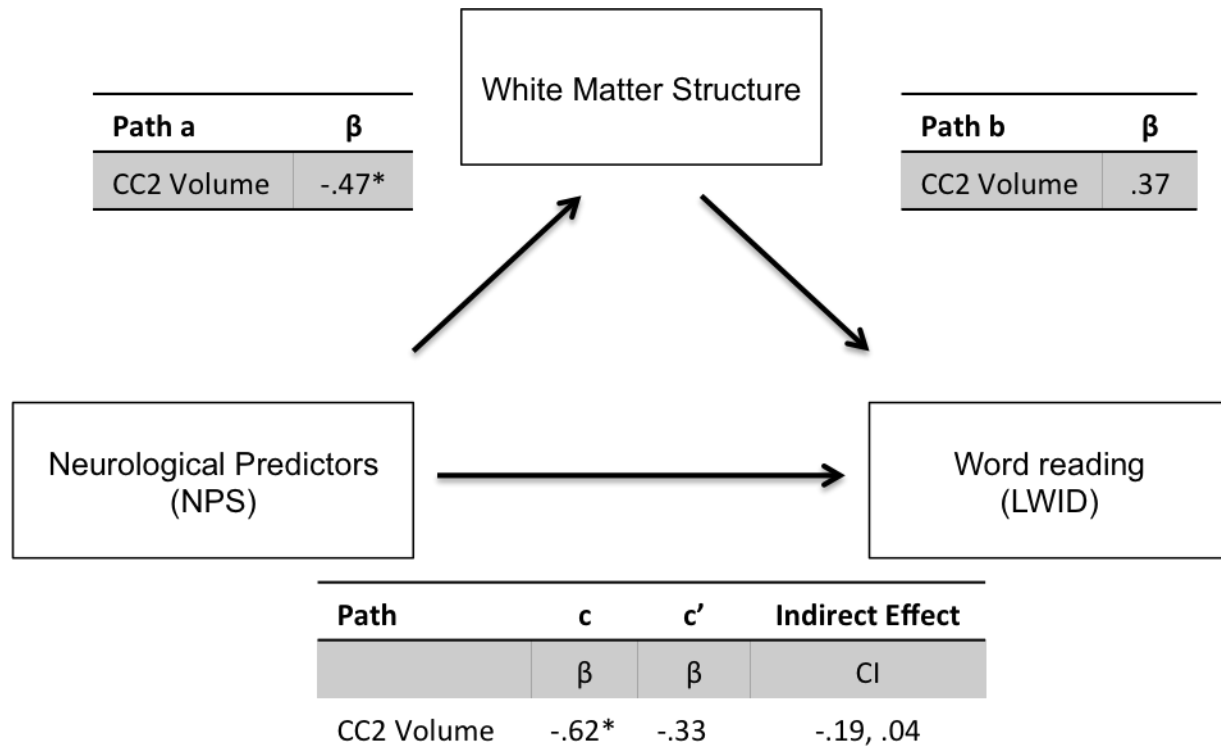
Figure 7. Beta values and significance for each path of mediation model of neurological risk predicting word reading through white matter structure..*p < .05

For the second model, Volume of CC2 had a significant effect on word reading (Path c: B=73.01, SE=22.05, p=0.004) such that lower volume related to lower word reading (See Figure 8). Processing speed was significant when regressed on volume (path a: B=117.39, SE=55.57, p=0.05), such that lower volume related to lower processing speed. The effect of processing speed on word reading was also statistically significant (path b: B=0.24, SE=0.08, p=0.007) such that better processing speed was related to higher word reading. The statistical significance of the entire model of the indirect effect of volume of CC2 on word reading through processing speed, was tested with bootstrapping with 10,000 samples and was significant (B=28.36, SE=16.22, CI: 2.16, 63.87) such that volume was related to lower word

reading through lower processing speed. This mediation model, accounts for 57%

(adjusted R^2) of the variance in word reading.

Path a	β
CC2 Volume	.42*

Path b	β
CC2 Volume	.53*

Path	c	c′	Indirect Effect
	β	β	CI
CC2 Volume	.63*	.38*	2.16, 63.87*
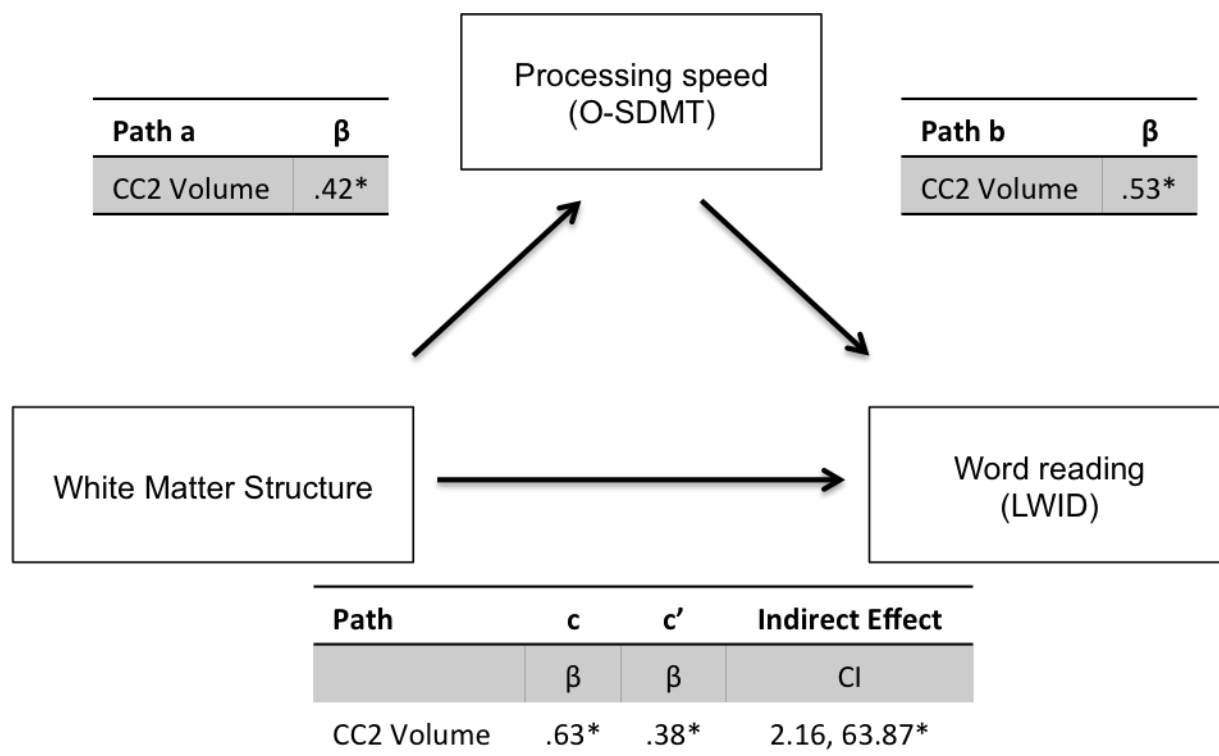
Figure 8. Beta values and significance for each path of mediation model of white matter structure predicting word reading through processing speed..*p < .05 or a confidence interval that does not pass through zero

4 DISCUSSION

The current study presents the results of an investigation into reading and the influence of the structure of the corpus callosum and oral processing speed in long term survivors of childhood brain tumors. We have shown that interhemispheric connections through the corpus callosum are associated with word reading skill and degree of neurological risk. We tested hypotheses with both DTI and volume measures and examined the specificity of reading with a motor control task. The current study provides a model for how the volume of interhemispheric connections in the CC are related to word reading in long-term survivors of childhood brain tumors.

4.1 Aim 1: Survivors show reduced volume across the CC

CC volumes were reduced in survivors compared to controls in line with the findings of Palmer (2010) in short-term medulloblastoma survivors (1-4 years since diagnosis), which also examined a priori CC divisions. Taken together this suggests that in a longer time period from diagnosis (this sample on average 14 years since, range of 5-31 years), CC volume remains diffusely impacted. Additionally, volume correlations with age at diagnosis suggest that structural outcomes are developmentally linked in survivors. Based on number of survivors with volumes lower than the control range of values, CC5 appears to be most consistently reduced in survivors (50%). With regard to resiliency, this suggests that, at most, only half of the survivors in the sample had volumes outside of our control sample range.

Microstructure as measured by fractional anisotropy (FA) was significantly reduced in CC1; other subregions, however, showed minimal effect sizes. The reduced FA in CC1 in survivors suggests that this most anterior area of the corpus callosum is

most vulnerable in the long term from diagnosis. This result is consistent with the posterior to anterior myelination pattern of the CC that suggests that the anterior division, myelinating later, would be most vulnerable to developmental brain insult (Thompson et al., 2003). In survivors, FA in the CC showed small to large correlations with age at diagnosis lending support for developmental disruption of FA (CC1: r=.25; CC2: r=.36; CC3: r=.42; CC4: r=.55; CC5: r=.24). However, correlation of CC1 FA with age at diagnosis was small suggesting that factors other than age are important in the reduced CC1 FA in survivors. Other possible explanations lie in the connections of CC1 to the prefrontal lobes. The reduced FA in the CC1 also may be an indirect effect of damage to the cerebellum through diaschisis. CC1 connects the right and left prefrontal lobes. These prefrontal regions are connected to the cerebellum via the thalamus (Middleton & Strick 2000).

For both methods (FA and volume) taken together, DTI yielded a finding in CC1 but the volume method yielded robust findings across the CC. This is a peculiar pattern of results that requires explanation. While it is not often discussed directly, FA and volume results many times do not line up suggesting they are measuring different underlying cellular architecture (Cardenas et al., 2014; Chan et al., 2010; Cherubini et al., 2010; Clerx, Visser, Verhey, & Aalten 2012). Knowledge of the specific structural substrates that contribute to the measurement of FA and volume is important. With regard to the underlying cellular architecture, changes in the volume of white matter has been shown to indicate changes in myelin and glial processes in animal studies (Nuñez, Nelson, Pych, Kim, & Juraska 2000; Yates & Juraska 2007). Changes in FA values has been shown to reflect changes in fiber density, myelin, and glial cells (e.g.,

oligodendrocytes & astrocytes; Blumenfeld-Katzir, Pasternak, Dagan, & Assaf 2011; Choe, Stepniewska, Colvin, Ding, & Anderson 2012; Sampaio-Baptista et al., 2013). FA may be a better indicator of fiber density than volume, whereas volume may be a better indicator of the number of fibers rather than density (Aboitiz et al., 1992; Choe et al., 2012). With that in mind, while the size of the CC was smaller across the whole CC, perhaps reflecting a fewer number of fibers, only CC1 had reduced integrity perhaps reflecting reduced density of fibers. This may represent two types of white matter disruption.

The above interpretations of the substrates of FA and volume should not be uncritically accepted given that they stem from studies of non-human brains. There are limitations in postulating on the histology of neuroimaging measures of white matter at the voxel level (Walhovd, Johansen-Berg, & Karadottir 2014) due to difficulties translating cellular research in animals to voxel level research in humans. Thus, this interpretation is preliminary. The results of the current study provide impetus to study volume and DTI together to understand more about the sensitivity of each measure to different cellular changes.

4.2   Aim 2: Reduced volume is associated with higher neurological risk

Lower volumes of CC2-5 were related to higher neurological risk. This result was expected given that treatment and complications associated with posterior fossa tumors are known to impact white matter structure. Specific decreases of white matter microstructure have been detected in the corpus callosum after treatment with radiation and chemotherapy (Leung et al., 2004; Padovani et al., 2012). In addition, corpus

callosum has been shown to be an area of vulnerability to hydrocephalus, a common complication (Yuan et al., 2009; Yuan et al., 2012; Yuan et al., 2013).

4.3 Aim 3: Word reading is related volume across CC

Volume in all subregions of the CC was correlated with reading such that increased volume was associated with better reading. For the two previous studies that also correlated reading with volumes in a priori CC divisions, one found reading positively correlated with genu and splenium divisions in children (CC1 & CC5) (N=24; CC divided into 5ths; Hynd et al., 1995). The second study found that the isthmus (~CC4/5) positively correlated with phonemic decoding in adults (N=17; Witelson regions; Welcome & Joanisse 2014). Our findings in all subregions of the CC with adults (N=42) may be due to larger sample size or a stronger effect with the inclusion of a population with brain insult. Volume of CC2 was most robustly related to word reading This might suggest that Broca's language areas extend to the CC2 subregion.

In our sample, controls and survivors combined, better reading was associated with lower FA in CC5 connecting right and left parietal, temporal, and occipital reading areas. In samples of typical readers and those with reading disabilities, relationships with FA vary with regard to the direction of the relationship. Our negative correlation was consistent with other studies examining a priori CC divisions. Reading was negatively correlated with FA in the posterior midbody (~ CC3) in children (Hasan et al., 2012a) and the splenium (CC5) in adults (only splenium studied; Frye et al., 2008).

4.3.1 Specificity

When correlating brain structure to a putative skill, a significant result does not necessarily provide domain-specific evidence relevant *only* to that specific skill.

Therefore, to test whether reading was more likely to represent the specific skill rather than reflecting general cognitive level, motor speed was correlated with CC subregions. Motor speed, however, is generally not considered a domain-general skill. But in survivors it is difficult to statistically differentiate domain-general skills (such as IQ) from domain-specific skills given that childhood brain tumors is a neurodevelopmental condition. As such, the maturation of domain-general skills are impacted by the effect on domain-specific skills (Dennis et al., 2009).

The overlap of reading and motor relationships in the body of the CC, suggests that reading is not only related to hypothesized regions CC1 and CC5, but also related to CC divisions that connect motor and sensory areas of the brain. This could be evidence that reading skill in the brain overlaps with the speech processing systems, in particular, the dorsal stream (Hickok & Poeppel 2007). Hickok and Poeppel have posited a dual stream processing system responsible for speech perception. The ventral stream is involved in auditory recognition. The dorsal stream functions as auditory-motor integration. Structurally, the dorsal stream includes posterior frontal, posterior dorsal of temporal lobe, and the parietal operculum. The pathways from these regions would cross the corpus callosum in areas 2, 3, and 4, which project to motor and sensory cortices. Research has found that both reading and speech processing have overlapping neural networks (Bemis & Pylkkanen 2013). The current findings of reading correlating with the body of the CC (i.e., CC 2-4) in addition to the hypothesized CC1 and CC5 may provide additional support for this overlap.

4.4   Aim 4: Comprehensive model of reading in brain tumor survivors

Effect sizes suggest that with a larger sample of survivors, neurological risk would be related to reading skill through white matter volume in CC2. The model of white matter and processing speed on word reading was statistically significant such that volume of CC2 and processing speed together accounted for 56% of the variance in word reading. The significant mediation model suggests that volume is related to word reading through the indirect effect of processing speed. This specific relationship between white matter structure, processing speed, and reading in brain tumor survivors is consistent with previous research (King et al., in preparation; Palmer 2008; Smith et al., 2014b). This current study extends this neurodevelopmental model to the corpus callosum subregion volume with adult survivors of childhood posterior fossa tumor. The model indicates that core cognitive skills (e.g., processing speed) are an integral component of the structure-function relationship. With regard to intervention, these results suggest that 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).

Prior work supports processing speed as the mediator in this theoretical model, but there are multiple components involved in the processing speed task. The current processing speed task employed could be an index for another skill such as intention, perceptual processing, attention, and articulatory motor processes. It is unclear which

component or combination of components is the important mediating variable in this relationship.

Given that CC2 also was correlated with motor speed, post-hoc analyses tested motor tasks as the mediator between CC2 and reading (in place of processing speed). Both the written form of the processing speed task, and the motor speed task were not significantly related to word reading. These results suggest that the relationship between the oral processing speed task used and word reading is not accounted for by motor-related speed. Also, even though CC2 connects motor cortices, this connection also likely includes language areas associated with Broca's regions.

4.5 Limitations

While the current study took a direct approach to examining the CC, we were not able to in conjunction, examine other regions of the reading system in a network model without reducing the sample size. It would have been difficult to also test other brain areas because of the commonality of metal artifact (e.g., shunts) or enlarged ventricles that exclude some participants from cortical analyses or analyses involving spatial normalization. However, by analyzing the mid-sagittal corpus callosum, we were able to include potentially more severe cases to the sample increasing the generalizability to a broader range of survivors. Given that the CC boundaries were determined based on the percent white matter in each voxel, the volume results are limited by the potential bias introduced measuring the CC volume based on the white matter segmentation of the T1 image.

The exact functional boundaries of the divisions of the CC vary individually. Using a DTI tractography-based template derived from typically developing adults

provides only an estimate of the boundaries for each individual and does not account for potential variability in tract locations following cerebellar tumor and treatment. However, using DTI-derived functionally based subdivisions in mid-sagittal region provides the greatest confidence in the functional connections of subregions for the current method.

This study was limited in the sample size of survivors in each treatment subgroup and thus treatment subgroups were not analyzed. That said, the long-term nature of the current sample is unique as this patient group is often not receiving regular hospital follow up this length of time from their diagnosis (Mean=14, Range=5-31 years post), and thus, more difficult to recruit. The difference in CC structure between the treatment subgroups showed a negligible to small effect sizes for FA. Volume, however, showed moderate to high effect sizes suggesting the high risk treatment group had reduced CC volume. Future research may analyze treatment groups separately with a larger sample.

4.6 Strengths and contributions

This study attempted to link neurological risk, in-vivo brain structure, and processing speed to predict word reading outcome in posterior fossa tumor survivors. Empirically building upon theory-based models is important for a more comprehensive understanding of the relationships among the multiple variables that affect reading outcomes in survivors.

Another strength of this study is the use of a single measure of neurological risk (NPS) that accounts for multiple risk factors to address the cumulative nature of neurological complications common to this population. The extended long-term nature of this sample is another aspect that makes the study unique. It is critical to understand outcomes in long-term survivorship to develop recommendations for remediation.

The direct analysis of CC subdivisions is a strength of this study as it allows comparison of effect sizes across subregions and allows for small effect size brain-behavior relationships to be observed (compared with exploratory whole brain analyses). Also, testing for specificity of hypothesized relationships is infrequently reported with regard to reading and white matter in survivors, but is essential to expanding empirical and conceptual knowledge of brain-behavior relationships.

Future research is needed to determine how the relationships between white matter, processing speed, and reading develop over time (from diagnosis to long-term outcomes) as well as how other structures along the fronto-thalamo-cerebellar pathway are affected in brain tumor survivors. More broadly, investigating both volume and DTI measures concurrently in the study of typical and neurological populations would increase the understanding of these complimentary methods. Future research with a larger sample should also test hypotheses with different treatment groups.

4.7 Conclusions

The current study provides a model for how the structure of interhemispheric connections in the CC are related to word reading in long-term survivors of childhood brain tumors. CC volume was a robust predictor of reading and this relationship was shown to be mediated by processing speed. This model supports processing speed as a core cognitive skill operating as the link between white matter volume and reading skill.

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