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Double Dissociation of Auditory Attention Span and Visual Attention in Long-Term Survivors of Childhood Cerebellar Tumor: A Deterministic Tractography Study of the Cerebellar-Frontal and the Superior Longitudinal Fasciculus Pathways

Alyssa S. Ailion[1], Tricia Z. King[1,*], Simone R. Roberts[1,2,3], Brian Tang[1], Jessica A. Turner[1], Christopher M. Conway[1] and Bruce Crosson[1,2,3,4]

[1]Department of Psychology and the Neuroscience Institute, Georgia State University, Atlanta, GA 30302-5010, USA
[2]Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA
[3]Atlanta VA Center of Excellence for Visual and Neurocognitive Rehabilitation, Atlanta, GA, USA
[4]Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA, USA

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Abstract

Objective: Right cerebellar-left frontal (RC-LF) white matter integrity (WMI) has been associated with working memory. However, prior studies have employed measures of working memory that include processing speed and attention. We examined the relationships between the RC-LF WMI and processing speed, attention, and working memory to clarify the relationship of RC-LF WMI with a specific cognitive function. Right superior longitudinal fasciculus II (SLF II) WMI and visual attention were included as a negative control tract and task to demonstrate a double dissociation. **Methods:** Adult survivors of childhood brain tumors [$n = 29$, age: $M = 22$ years ($SD = 5$), 45% female] and demographically matched controls were recruited ($n = 29$). Tests of auditory attention span, working memory, and visual attention served as cognitive measures. Participants completed a 3-T MRI diffusion-weighted imaging scan. Fractional anisotropy (FA) and radial diffusivity (RD) served as WMI measures. Partial correlations between WMI and cognitive scores included controlling for type of treatment. **Results:** A correlational double dissociation was found. RC-LF WMI was associated with auditory attention (FA: $r = .42$, $p = .03$; RD: $r = -.50$, $p = .01$) and was not associated with visual attention (FA: $r = -.11$, $p = .59$; RD: $r = -.11$, $p = .57$). SLF II FA WMI was associated with visual attention (FA: $r = .44$, $p = .02$; RD: $r = -.17$, $p = .40$) and was not associated with auditory attention (FA: $r = .24$, $p = .22$; RD: $r = -.10$, $p = .62$). **Conclusions:** The results show that RC-LF WMI is associated with auditory attention span rather than working memory *per se* and provides evidence for a specificity based on the correlational double dissociation.

Keywords: Structural MRI, Diffusion tractography, Cerebellum, Neurocognitive outcomes, Cognition, White matter pathway, Working memory, Digit span

INTRODUCTION

Cerebellar brain tumors are the most common tumor location in children (Ostrom et al., 2015) and correspond with disruption in core cognitive processes of processing speed, attention, and working memory (King et al., 2017; Palmer et al., 2008; Wolfe et al., 2012). Prior studies have found lower white matter integrity (WMI) in the bilateral multisynaptic cerebellar-frontal pathway following cerebellar tumor treatment, which has been proposed as the mechanism for weaknesses in verbal working memory (Law et al., 2011, 2015b; Rueckriegel et al., 2015). However, working memory is a complex mental process with multifactorial contributions from other cognitive skills (i.e., processing speed, attention). Thus, based on theoretical models, early white matter injuries in cerebellar tumor survivors may be related to slowed processing speed and poor attention that underlie working memory, which then has a cascading impact on broader aspects of learning and cognition (Palmer, 2008; Miller, 2013). Given the importance of understanding deficits in processing speed and attention in theoretical models, as well

*Correspondence and reprint requests to: Tricia Z. King, Department of Psychology, Georgia State University, P.O. Box 5010, Atlanta, GA 30302-5010, USA. E-mail: tzking@gsu.edu

as the early vulnerability to white matter injury, additional research on the contribution of processing speed and attention is necessary to understand the aforementioned working memory findings. However, to date, only one diffusion-weighted neuroimaging study on the cerebellar pathways in brain tumor populations has included measures of attention and processing speed (Rueckriegel et al., 2015). We have investigated the segments of the cerebellar-frontal pathway in a prior paper, which provides correlational evidence that type of brain tumor treatment has a differential effect on each structural segment of this pathway (Ailion et al., 2019). The purpose of the current study is to expand on this literature and investigate the neurocognitive contribution of this white matter pathway. Specifically, we invesigated whether WMI of the cerebellar-frontal pathway was specific to working memory or if it also specifically disrupts the underlying skills of processing speed or attention span, which in turn may disrupt many other cognitive skills, including working memory. We defined the key cognitive constructs as follows. Processing speed is the speed of thinking (Bunce and Macready, 2005). Attention is the ability to immediately hold information in mind. Working memory is keeping information accessible to your immediate attention for the purposes of manipulating it (Baddeley, 1996).

The complexity of treatment factors was important to consider for the current study on childhood tumor survivors. Surgery, younger age at diagnosis, radiation dosage, and longer time since treatment have been related to lower global white matter volume and integrity (e.g., Aukema et al., 2009; Khong et al., 2003; King, Wang, and Mao, 2015b; Law et al., 2011; Merchant et al., 2008; Palmer et al., 2012; Reddick et al. 2005). Longitudinal studies of global brain volume have suggested both a progressive loss of white matter and a failure to develop normal white matter volume gains (for review, see Ailion et al., 2017; Mulhern et al., 2001; Palmer et al., 2002; Reddick et al., 2000; Riggs et al., 2014). These changes may be related to an underlying disruption in the vascular system or be due to cellular pathology (Reinhold et al., 1990; Shan et al., 2006) that would likely impact global WMI. Thus, white matter is vulnerable to brain tumor treatment, which may be compounded over time, and more research is needed to understand these changes in long-term survivors of childhood brain tumors and how they correspond to neuropsychological functions.

Furthermore, the literature suggesting global white matter volume loss in brain tumor populations highlights the need to determine the specificity of the relationship between the cerebellar-frontal WMI and working memory. Lower WMI in the cerebellar-frontal pathway or poorer working memory could simply be indicative of lower WMI across all white matter pathways. Therefore, lower global white matter volume presents as a potential confound to lower WMI within specific pathways. The current study adds to the prior literature by testing a theoretically and empirically informed double dissociation with a comparison white matter pathway and a comparison cognitive task as well as global white matter volume to test the specificity of the brain–behavior relationship. Double dissociations are conducted by investigating the specificity of two brain–behavior relationships to determine whether the brain regions correspond with the hypothesized behaviors independent of one another (e.g., integrity of brain region A correlates with Behavior A; integrity of brain region B correlates with Behavior B and integrity of brain region A does not correlate with Behavior B, integrity of brain region B does not correlate with Behavior A). Prior studies have described the statistical approach and importance in other clinical populations (i.e., Bechara et al., 1995; Friederici et al., 1998; Nomura et al., 2010).

The right superior longitudinal fasciculus (SLF) was selected as a comparison pathway because it is a long-range pathway that has been correlated with a cognitive skill distinct from working memory and is responsible for visually mediated information. This pathway has been associated with the dorsal stream, also known as the "where" pathway (Hoeft et al., 2007; Thiebaut de Schotten et al., 2011). The current study focused on the SLF II, which connects the angular gyrus in the parietal lobe to the dorsolateral prefrontal area (Doricchi et al., 2008; Hoeft et al., 2007; Kamali et al., 2014; Makris et al., 2005). Within this pathway, the parietal region (posterior inferior) has been involved in spatial attention on the basis of human and animal studies (Bisley and Goldberg, 2003; Mesulam, 1981), and the SLF II links visual information to the prefrontal cortex (Makris et al., 2005). One theory regarding the function of this reciprocal pathway has been that the right prefrontal cortex regulates visual attention (Makris et al., 2005). Prior literature suggests that right SLF II WMI should be correlated with visual cancellation task performance (Doricchi and Tomaiuolo, 2003; Makris et al., 2005; Thiebaut de Schotten et al., 2011; Urbanski et al., 2008). Based on this evidence, the right SLF II was hypothesized to be related to visual attention. Furthermore, the right SLF II has not been correlated with measures of verbal working memory (Karlsgodt et al., 2008), and no literature has suggested that the cerebellar-frontal pathway should be related to a measure of visual attention. Therefore, based on all available evidence, the cerebellar-frontal relationship to working memory should demonstrate a double dissociation from the relationship between SLF II and visual attention.

Prior studies investigating the cerebellar-frontal pathway in brain tumor survivors did not include a control tract and corresponding control task to provide evidence that this relationship is in fact specific to the cerebellar-frontal pathway and working memory (Law et al., 2011 & 2015a, 2015b; Rueckriegel et al., 2015), as opposed to a proxy for more diffuse neuroanatomical changes. This proposed double dissociation would suggest that lower WMI was both pathway and task-specific and would provide evidence against the argument that diffuse WMI reductions were correlated with gross reductions in neurocognitive performance.

The current study was informed by models of working memory deficits (see King et al., 2017; Miller, 2013; Palmer, 2008) and therefore included careful selection of the measurement of theoretically underlying skills of

processing speed, attention, and working memory. All of the prior literature on the cerebellar-frontal pathway has been in brain tumor survivors who were about 5 years post-diagnosis and treatment (e.g., Law et al., 2011, 2015b). The current study investigated a longer follow-up period ($M = 13$ years post-diagnosis) to advance the literature on long-term survivor outcomes following cerebellar tumor treatment, particularly given the long-term impact of cranial radiation treatment (RT). Overall, the current study is an important next step to address the limitations of the existing literature.

First, we interrogated the relationship between WMI in the right cerebellar-left frontal (RC-LF) pathways and specific cognitive constructs. Then, we investigated a correlational double dissociation between integrity of the RC-LF and the right SLF II pathways with both working memory and visual attention performance. We hypothesized that lower WMI in the cerebellar-frontal pathways would be associated with lower working memory, but not visual attention performance. We also hypothesized that lower WMI in the right SLF II would be associated with lower visual attention performance, but not lower working memory performance.

METHODS

Data were obtained from a larger study on the long-term outcomes following pediatric brain tumor diagnosis and treatment (PI: T.Z. King #RSGPB-CPPB-114044). Detailed methods and study procedures are described by King et al. (2015b) and Ailion et al., (2016 & 2019). In brief, survivors either were part of a long-term follow-up of a prior longitudinal study of childhood brain tumors, recruited from a database of brain tumor survivors obtained from Children's Healthcare of Atlanta, or responded to an annual newsletter circulated by the Brain Tumor Foundation of Georgia. Patients were recruited both based on retrospective records from the longitudinal study and prospectively based on the presence of a brain tumor, independent of referral for cognitive concerns. All participants passed a vision screen and hearing screen with a standard audiometer. Control participants were recruited from the Georgia State University community through the psychology participant pool, fliers posted around the community, and the Georgia State University/Georgia Institute of Technology Joint Center for Advanced Brain Imaging. The Georgia State University (IRB# H03177) and Georgia Institute of Technology (IRB# H14088) Institutional Review Boards reviewed and approved all studies.

Participants

A total of 44 participants with tumors in the posterior fossa completed the study. Participants were excluded based on the following criteria: global functional impairment ($n = 2$), pervasive developmental disorder ($n = 1$), English as a second language ($n = 1$), less than 5 years from diagnosis ($n = 1$), or younger than 16 years old at exam ($n = 6$). Younger patients were excluded to account for heterogeneity related to brain development and to maintain the same neuropsychological assessment measures across participants at different ages. An additional three participants ($n = 3$) had poor quality imaging data due to motion, and one participant had significant hydrocephalus that resulted in abnormal brain structure ($n = 1$; very enlarged ventricles). Survivors were matched with controls on demographic factors that included age, sex, level of education, and handedness. The total sample included 29 survivors and 29 controls with neuroimaging data for processing. Healthy controls reported ethnicity in the sample was 62% Caucasian, 31% African-American, 3% Hispanic, and 3% Asian.

Survivor Demographics

The survivor participants were on average 8.55 years old ($SD = 4.88$; range 0–18) at diagnosis, and their average age at exam was 21.34 years ($SD = 5.35$; range 16–35). The average Full-Scale IQ (Wechsler Abbreviated Scale of Intelligence 2nd edition; WASI-II; Wechsler, 1999) was 99.07 ($SD = 13.32$). Prior literature on brain tumor survivors has reported a lower Full Scale Intelligence Quotient (FSIQ); our sample average for FSIQ is higher than the literature suggests because the chosen measure of intelligence (WASI-II) reduces the impact of attention and processing speed. Thirteen individuals were diagnosed with astrocytoma, 12 with medulloblastoma, and the remaining 4 individuals were diagnosed with an ependymoma, a glioma, a primitive neuroectodermal – not otherwise specified, and a choroid plexus tumor. Furthermore, 7% of the sample underwent biopsy alone, 24% had a subtotal resection, and 69% had a gross total resection. Ethnicity in the sample was 72% Caucasian, 14% African-American, 7% Hispanic, and 7% Asian. With regard to treatment history, 83% of the sample had hydrocephalus, 52% had RT, 48% had chemotherapy (only one participant had chemotherapy without RT), 55% had a hormone deficiency, and 3% had a seizure disorder (at the time of tumor discovery). Of the survivors who had hydrocephalus, 33% of them had a ventriculoperitoneal shunt placed. None of the survivors had posterior fossa syndrome. Of those who had RT ($n = 15$), 80% had whole brain RT and an additional focal boost to the posterior fossa, the remaining 20% of participants ($n = 3$) received only focal RT. RT dosage ranged from 5040 to 6300. Treatment protocol numbers included: 9961 Arm A ($n = 2$), Children's Cancer Group (CCG) 9961 Arm A ($n = 3$), CCG 9961 Reg B ($n = 1$), CCG 9892 ($n = 1$), CCG 88703-NOS ($n = 1$), Pediatric Oncology Group (POG) 8633 ($n = 1$), POG 8695 ($n = 1$), POG 8930 ($n = 1$), and study number for a clinical trial 0331 ($n = 1$), and three participants did not have protocol numbers listed.

Based on prior literature, potential confounds or covariates included longer time since treatment, younger age at diagnosis, and RT (Aukema et al., 2009; Khong et al., 2003; Law et al., 2015a; Merchant et al., 2008; Mulhern et al., 2001; Palmer et al., 2012; Reddick et al. 2005). Correlations

revealed a number of associations between treatment factors and neurocognitive measures. Therefore, the Neurological Predictor Scale (NPS; King and Na, 2016; Micklewright et al., 2008; Taiwo, Na, and King, 2017) was used as a cumulative measure of treatment (i.e., RT) complications, such as hydrocephalus, hormone deficiency, and seizures. The construct validity for cumulative treatment burden has been established in several prior studies that have documented the association between NPS and WMI (King et al., 2015b), subcortical volume (Jayakar et al., 2015), and cerebellar atrophy (Ailion et al., 2016).The average NPS score for the sample was 6 [$SD = 2.54$; range 2 (low treatment burden)−9 (high treatment burden)]. Tumor grade was defined as low- or high-grade tumor based on World Health Organization (WHO) guidelines. Sample size limited the number of treatment factors that could be included as covariates; therefore, NPS was investigated as a cumulative measure of disease severity.

Neuropsychological Measures

Processing speed was measured using the Oral version of the Symbol Digit Modality Test (Smith, 1982). The Digit Span Forward subtest raw number of digits recalled from the Wechsler Memory Scale (WMS-III) was used as a measure of basic auditory attention span (Wechsler, 1997).

Digit Span Forward was used as a measure of auditory attention. Prior researchers have found that the Digit Span Forward average number of digits accurately repeated in a healthy population was 7 with a standard deviation of 2 (Miller, 1956; Shiffrin and Nosofsky, 1994). Digit Span Forward raw scores were used in all analyses. The test–retest reliability for the digits forward measure was .83 (Wechsler, 1997). The Digit Span Backward raw number of digits recalled from the WMS and the Auditory Consonant Trigrams (ACT) 36-s trial were used to measure working memory (Brown, 1958; Peterson and Peterson, 1959). During test development, Digit Span Forward and Backward were combined into an index score based on their high correlation in the healthy normative sample. However, in clinical populations, these subtests are distinct constructs (Black and Strub, 1978; Kiefer et al., 2002). As such, combined index scores result in a poor specificity of neurocognitive processes (Dennis et al. 2009) and biased psychometric distributions (Lezak et al., 2012). Therefore, the combined score in neurological populations may obscure the measurement of important and distinct functions (Lezak et al., 2012; Weinberg et al., 1972). Therefore, Digit Span raw forward and backward were analyzed separately. Raw scores were used because separate *z*-scores were not available.

The ACT required the examiner to say three consonant letters and then instruct the participant to count backward from an established starting number (Brown, 1958; Peterson and Peterson, 1959). After a period of distraction by actively counting backward for each trial (9, 18, or 36 s), participants had to accurately recall the consonant letters. The raw score for each trial was converted into a *z*-score based on population norms. *Z*-scores of the 36-s trial were used to measure working memory. Test–retest reliability was .71 (Stuss, Stethem, and Pelchat, 1988; Spreen and Strauss, 1998).

The Visual Scanning subtest of the Trail Making Test from the Delis–Kaplan Executive Functioning Systems (DKEFS) was used to provide a measure of visual attention (Delis, Kaplan, and Kramer, 2001). The Visual Scanning subtest of the Trail Making Test produced two scores, the time to identify targets and the number of errors. The DKEFS manual provided norms based on a standardization sample (Delis, Kaplan, and Kramer, 2001) to obtain standard scores. The test–retest reliability was .56 for the Visual Scanning subtest (seconds to complete; all ages; Delis, Kaplan, and Kramer, 2001). The number of errors was used to obtain a measure with a minimal time component. Based on the evidence that the pathway between parietal and frontal lobes regulates visual attention (Bisley and Goldberg, 2003; Makris et al., 2005; Mesulam, 1981), this measure was hypothesized to be associated with SLF II WMI. Furthermore, prior research found that letter cancellation was associated with the right SLF II (Doricchi and Tomaiuolo, 2003; Urbanski et al., 2008).

Diffusion-Weighted Imaging

Diffusion-weighted imaging (DWI) was used to measure the rate and directionality of water diffusion, to infer microstructural features of neural axons, and estimate the locations of neural axons *in vivo* (Cascio, Gerig, and Piven, 2007). Radial diffusivity (RD) has been described as an effective measure of myelination, particularly in frontal regions (Bartzokis et al., 2012). In the current study, fractional anisotropy (FA) was selected as the primary scalar metric so that the results of the study could be compared with prior literature, and RD was selected due to the importance of capturing frontal lobe myelin degeneration. Higher FA and lower RD were considered proxies for greater WMI (Viallon et al., 2015).

Image Acquisition

All participants completed an awake MRI scan using the same 3-T Siemens Trio system and a standard 12-channel head coil, which included a sagittally acquired, T1-weighted MPRAGE image (FOV = 256 mm, voxel size = 1×1×1 mm, TR/TE = 2250 ms/3.98 ms, flip angle = 9°), a diffusion-weighted, spin-echo echo planar imaging sequence with 30 gradient directions acquired along the anterior-to-posterior phase encoding direction (FOV = 204 mm, voxel size = 2×2×2 mm, TR/TE = 7700 ms/90 ms, flip angle = 90°, b = 1000 s/mm^2, GRAPPA parallel imaging acceleration factor = 2, number of slices = 60), and one unweighted diffusion volume ($b = 0$ s/mm^2 The same method and preprocessing pipeline were used as described in a prior DWI study with

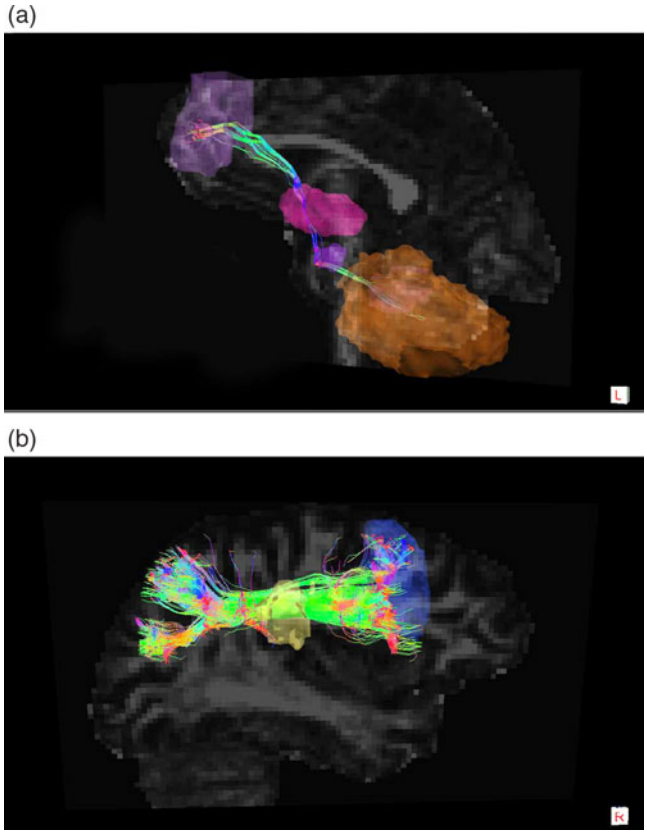

Fig. 1. Tractography pathways: (a) right cerebellar-left frontal pathway, (b) superior longitudinal fasciculus pathway.

this sample (Ailion et al., 2019). Global gray and white matter values reported in the tables are based on Voxel-Based Morphometry, with detailed procedures described in Ailion et al. (2019). For additional information on how regions of interest were defined, please see the Appendix.

Deterministic Tractography: Processing

Deterministic tractography processing is described in detail in Ailion et al. (2019) PanTrack was used for network tractography to generate all of the direct connections between the right cerebellum and the left middle frontal gyrus (MFG) as well as the connections between the right MFG and the right parietal lobe. PanTrack output was then viewed in TrackVis. Each pathway was qualitatively confirmed for every participant, prior to manual filtering and applying streamline exclusions. The cerebellar-frontal pathway was defined as streamlines that began in the right cerebellum and continued to the left red nucleus (RN), left thalamus, and terminated in the left MFG (see Figure 1). Streamlines that crossed through the corpus callosum were excluded. The right SLF II was defined using the boundaries described by Thiebaut de Schotten et al. (2011). TrackTools was used to create a voxel-based mask ($1\times1\times1mm^3$) of the cerebellar-frontal and SLF II pathways. FA and RD values were extracted for each pathway mask using FSLmeants.

Statistical Plan and Tests of Assumptions

SPSS Statistics version 20 was used for analyses. Pearson's correlations were used to test the double dissociation between the measures of WMI of the pathways of interest and cognitive performance within the survivor and control groups. Partial correlations were used to account for treatment factors and other covariates when appropriate (i.e., age at diagnosis). A total of 64 analyses were computed. The Benjamini–Hochberg statistical correction for family-wise error was used with the recommended 5% false positive rate to correct for multiple comparisons, and all reported analyses survived statistical correction (Benjamini and Hochberg, 1995; Bennett et al., 2009).

Outliers were defined using the outlier labeling rule (Hoaglin and Iglewicz, 1987). Outlier analysis was conducted, and extreme scores for survivors and controls were changed to the next score (Osborne and Overbay, 2004). There was no difference in outliers between groups. Assumptions for analyses were tested for each dependent variable (e.g., normality, homogeneity of variance). Variables that did not follow a normal distribution were not able to be successfully transformed to a normal distribution. Therefore, nonparametric statistical tests (Kendall's tau-b) were reported for the variables that violated the assumption of normality.

RESULTS

Survivor and Control Groups

Survivors and controls were demographically matched (see Table 1). Survivors exhibited significantly lower global gray matter volume and global white matter volume when compared to controls based on an independent samples t-test. High- and low-grade tumor groups had similar demographics (see Table 2). Subgroup comparisons identified that survivors with high-grade tumors had lower global volume (white and gray matter) and lower WMI when compared to those with low-grade tumors and controls based on Cohen's d effect size comparisons. For the SLF II, larger group differences (i.e., high grade *vs*. control) were able to be identified using RD, whereas FA was more useful at detecting more subtle group differences (i.e., high grade *vs*. low grade).

Confound Analyses

Age at diagnosis was positively correlated with cerebellar-frontal FA and global white matter volume ($r = 0.44$, $p < .05$; $r = .46$, $p < .05$, respectively) and therefore was included as a covariate. Tables of analyses include comparison correlations with and without treatment severity as a covariate (see Tables 3–5).

Relationship between the Cerebellar-Frontal Pathway and Cognitive Skills

First, we investigated the correlations between the cerebellar-frontal pathway and processing speed [Oral Symbol Digit

Table 1. Survivor and control demographic and descriptive comparisons

	Survivors $n = 29$ M (SD)	Controls $n = 29$ M (SD)	Group differences	Cohen's d
Gender	45% Female	48% Female		
Age at exam (years)	21.34 (5.35)	22.43 (5.20)	$t = .79$, $p = .56$	−.02
Years of education	13.28 (2.79)	14.34 (2.79)	$t = -1.77$, $p = .08$	−.38
Age at diagnosis (years)	8.55 (4.88)			
Radiation	$n = 15$ 52%			
Chemotherapy	$n = 14$ 48%			
High-grade tumor	$n = 14$ 48%			
Hydrocephalus	$n = 24$ 83%			
Seizure medication	$n = 1$ 3%			
Hormone deficiency	$n = 16$ 55%			
Global gray and white matter volume**	0.77 (.05)	0.81 (.02)	$t = 4.04$, $p < .01$	−1.05
Global white matter volume*	0.31 (.02)	0.32 (.02)	$t = 2.46$, $p = .02$	−.50
Cerebellar-frontal FA	0.32 (.06)	0.32 (.05)	$t = -0.04$, $p = .97$	.00
Cerebellar-frontal RD**	0.0013 (.0003)	0.0011 (.0001)	$t = -2.64$, $p < .01$	.89
SLF II FA	0.28 (.05)	0.26 (.05)	$t = -1.51$, $p = .14$	.40
SLF II RD**	0.0008 (.0001)	0.0007 (.0001)	$t = 3.81$, $p < .01$	1.00

Note. ** indicates $p < .01$ and * indicates $p < .05$; all volume measures are whole brain gray matter and white matter or white matter alone divided by intracranial vault; FA = fractional anisotropy; RD = radial diffusivity; SLF II = superior longitudinal fasciculus.

Modality test (OSDMT)], auditory attention span (Digits Forward), and working memory (ACT 36 Second and Digits Backward). In the survivor group, auditory attention span was correlated with cerebellar-frontal WMI, and this relationship remained significant after using partial correlations to account for treatment factors (see Table 3). Importantly, the Digit Span Backward and working memory did not correlate with any of cerebellar-frontal WMI, which suggests a unique contribution of auditory attention span (FA $r = .03$, $p > .05$; RD $r = .05$, $p > .05$). We also included the combined Digit Span score in Table 3, and the results were consistent with and replicated prior results (i.e., Law et al., 2015b; FA $r = .39$, $p < .05$; RD $r = .31$, $p < .05$). However, prior studies described the combined score finding as being representative of working memory.

Double Dissociation

The goal of the current study was to establish the specificity for the relationship between cerebellar-frontal WMI and working memory via a double dissociation with the right SLF II pathway and visual attention. However, auditory attention span, rather than working memory, was associated with the cerebellar-frontal WMI. Therefore, auditory attention span, rather than working memory, was selected for the double dissociation.

The first condition to establish this double dissociation was that measures of WMI in the cerebellar-frontal pathway in survivors correlated with auditory attention span and was met for both FA and RD. The second condition was that auditory attention span was not correlated with WMI of the control tract (right SLF II). As shown in Table 4, these correlations were nonsignificant with or without controlling for NPS. The third and fourth conditions were that visual attention be correlated with WMI measures for right SLF II and not with integrity measures for the cerebellar-frontal pathway. As can be seen in Table 4, FA for SLF II correlated with visual attention in the survivor group with and without controlling for NPS; however, these correlations were not significant for RD. The general pattern for the SLF II and visual attention is consistent with what we would expect, such that white matter injury is more associated with speed than accuracy. Neither cerebellar-frontal WMI measure showed a significant association with visual attention. Hence, the conditions of the double dissociation were met for FA measures but could not be met for RD measures due to a lack of significant correlation between RD of right SLF II and visual attention. Therefore, the combined results support the hypothesis of a double dissociation with brain–behavior specificity for each pathway using FA measures in the survivor group. In the control sample, the double dissociation was not present (see Table 4). It is plausible that the differences in WMI and neuropsychological measures are less meaningful in healthy individuals because there is no disease process to explain the statistical variance in either variable and the variables may all be within normal limits. Further analysis of variance between samples supports this theory, and there is significantly more variablity in cognitive outcomes to be explained in our brain tumor poulation (Levene's test of equal variance Digit Span Forward = $F(1,56) = 0.38$, $p = 0.54$; DKEFS Visual Scanning $F(1,56) = 0.07$, $p = 0.80$). Our current correlational double dissociation was robust

Table 2. Subgroup descriptive statistics and effect sizes

	Subgroup descriptive statistics						Subgroup differences Cohen's d		
	Low grade $n = 15$ *M* (*SD*)		High grade $n = 14$ *M* (*SD*)		Controls $n = 29$ *M* (*SD*)		Low grade *versus* high grade	Low grade versus controls	High grade *versus* controls
Gender	40% Female		50% Female		48% Female				
Age at exam (years)	21.27 (5.18)		21.43 (5.72)		22.43 (5.20)				
Years of education	13.53 (2.72)		13.00 (2.94)		14.34 (2.79)				
Age at diagnosis (years)	10.00 (4.63)		7.00 (4.82)						
	Range 1–18		Range 1–17						
Radiation	$n = 2$	13%	$n = 13$	93%					
Chemotherapy	$n = 0$	0%	$n = 14$	100%					
Hydrocephalus	$n = 12$	80%	$n = 12$	86%					
Seizure medication	$n = 1$	7%	$n = 0$	0%					
Hormone deficiency	$n = 12$	80%	$n = 13$	93%					
Global gray matter + white matter	.79 (.06)		.75 (.03)		.81 (.02)		.83**	−.52*	−2.54**
Global white matter volume^{+}	.32 (.02)		.30 (.03)		.32 (.02)		.79*	.00	−.85**
Cerebellar-frontal FA	.32 (.04)		.31 (.07)		.32 (.05)		.18	.00	−.18
Cerebellar-frontal RD^{+}	.0012 (.0002)		.0013 (.0003)		.0011 (.0001)		−.40	.71*	1.06**
SLF II FA^{+}	.30 (.05)		.25 (.04)		.26 (.05)		1.10**	.80**	−.21
SLF II RD^{+}	.0007 (.0001)		.0008 (.0001)		.0007 (.0001)		−1.00**	.00	1.00**
Percent impairment on cognitive measures. Impairment is defined as 1.5 *SD* below the mean									
Oral Symbol Digit Modality Test	−.50 (1.38)		−1.58 (1.14)		.03 (1.07)		$c^2 = 6.15$	$c^2 = .21$	$c^2 = 16.45$
	$n = 2.13\%$		$n = 8.57\%$		$n = 0.0\%$		Fp = .02	Fp = .26	Fp < .01
Digit Span Forward	7.00 (1.20)		5.64 (1.22)		7.14 (1.22)		$c^2 = 3.58$	–	$c^2 = 6.68$
	$n = 0.0\%$		$n = 3.21\%$		$n = 0.0\%$		Fp = .10		Fp = .03
Digit Span Backward	4.93 (1.39)		4.00 (.78)		5.07 (1.33)		$c^2 = 1.03$	$c^2 = .44$	$c^2 = 4.08$
	$n = 2.13\%$		$n = 4.29\%$		$n = 2.7\%$		Fisher's $p = .39$	Fp = .59	Fp = .07
Working Memory	.01 (1.17)		−.98 (1.09)		.47 (.92)		$c^2 = 3.72$	–	$c^2 = 11.72$
	$n = 0.0\%$		$n = 5.36\%$		$n = 0.0\%$		Fp = .08		Fp < .01
Visual Scanning	1.07 (1.22)		.64 (1.15)		.79 (1.16)		–	$c^2 = .53$	$c^2 = .49$
	$n = 0.0\%$		$n = 0.0\%$		$n = 1.3\%$			Fp = 1.00	Fp = .67

Note. All volume measures are gray matter and white matter or white matter alone divided by intracranial vault; $^{+}$ indicates significant difference; Cohen's d: small = .2–.3, medium = .5*, large ≥ .8**; Working Memory = Auditory Consonant Trigrams 36 Second Trial; Visual Scanning = Delis–Kaplan Executive Function System, Trail Making Test, Visual Scanning; c^2 = chi-square; Fisher's *p* (Fp) is Fisher's Exact Test; FA= fractional anisotropy; RD= radial diffusivity; SLF II = superior longitudinal fasciculus.

Table 3. Summary of correlation results for single dissociation

	Processing speed OSDMT (*z*-score)	Working memory ACT 36 Second (*z*-score)	Auditory Attention Span Digit Span Forward (raw)	Digit Span Backward (raw)	Combined Digit Span Forward and Backward (*z*-score)
Survivors only ($n = 29$)					
Right cerebellar-left frontal FA	$r = .14$	$r = .09$	$\tau b = .40^{**}$	$\tau b < .00$	$\tau b = .36$
Right cerebellar-left frontal RD	$r = -.16$	$r = .11$	$\tau b = -.34^{*}$	$\tau b = .01$	$\tau b = -.32$
Survivors only ($n = 29$) partial correlations (controlling for NPS)					
Right cerebellar-left frontal FA	$r = .02$	$r = .11$	$r = .42^{*}$	$r = .03$	$r = .39$
Right cerebellar-left frontal RD	$r = -.16$	$r = .08$	$r = -.50^{*}$	$r = .05$	$r = -.31$
Survivors only ($n = 29$) partial correlations (controlling for NPS and age at diagnosis)					
Right cerebellar-left frontal FA	$r = -.11$	$r = -.07$	$r = .39^{*}$	$r = .07$	$r = .36$
Right cerebellar-left frontal RD	$r = .10$	$r = .36$	$r = -.37^{*}$	$r = .04$	$r = -.29$
Controls only ($n = 29$)					
Right cerebellar-left frontal FA	$r = -.35$	$r = .16$	$\tau b = -.03$	$\tau b = .08$	$\tau b = -.02$
Right cerebellar-left frontal RD	$r = .33$	$r = .08$	$\tau b = .06$	$\tau b = .06$	$\tau b = .11$

Note. *indicates $p < .05$ and **indicates $p < .01$; NPS = Neurological Predictor Scale; processing speed measured by the Oral Symbol Digit Modality Test (OSDMT); working memory measured by the Auditory Consonant Trigrams 36 Second Trial; Auditory Attention measured by the Digit Span Forward subtest; FA = fractional anisotropy; RD = radial diffusivity; τb = Kendall's tau-b.

Table 4. Summary of correlation results for double dissociation

	Auditory attention Span (raw)	Visual attention	Visual attention # of errors
Survivors only ($n = 29$)			
Right cerebellar-left frontal FA	$\tau b = .40^{**}$	$\tau b = -.03$	$\tau b = -.18$
Right cerebellar-left frontal RD	$\tau b = -.34^{*}$	$\tau b = -.04$	$\tau b = .04$
Right SLF II FA	$\tau b = .19$	$\tau b = .31^{*}$	$\tau b = .07$
Right SLF II RD	$\tau b = -.09$	$\tau b = -.22$	$\tau b = .03$
Survivors only ($n = 29$) partial correlations (controlling for NPS)			
Right cerebellar-left frontal FA	$r = .42^{*}$	$r = -.11$	$r = -.20$
Right cerebellar-left frontal RD	$r = -.50^{*}$	$r = -.11$	$r = -.02$
Right SLF II FA	$r = .24$	$r = .44^{*}$	$r = .09$
Right SLF II RD	$r = -.10$	$r = -.17$	$r = .24$
Controls only ($n = 29$)			
Right cerebellar-left frontal FA	$\tau b = -.03$	$\tau b = -.15$	$\tau b = .07$
Right cerebellar-left frontal RD	$\tau b = .06$	$\tau b = .19$	$\tau b = .09$
Right SLF II FA	$\tau b = .14$	$\tau b = -.03$	$\tau b = .08$
Right SLF II RD	$\tau b = .21$	$\tau b = .27$	$\tau b = -.21$

Note. *indicates $p < .05$ and **indicates $p < .01$; NPS = Neurological Predictor Scale; FA = fractional anisotropy; RD = radial diffusivity; Visual Attention = Delis–Kaplan Executive Function Scale, Trail Making Test, Visual Scanning Trial *z*-score; SLF II = superior longitudinal fasciculus; τb = Kendall's tau-b.

with the survivor group with or without controlling for treatment severity and highlights the importance of examining these relationships with other neurological populations (see Figure 2).

Analyses were also computed with global white matter volume relative to intracranial vault, to determine that the results were not due to overall reductions in global white matter volume (see Table 5). In the survivor group analyses,

Table 5. Double Dissociation: correlations between global white matter volume and neurocognitive measures

	Auditory attention Span (raw)	Visual attention	Visual attention # of errors
Survivors only ($n = 29$)			
Global white matter volume/ICV	$\tau b = .36$*	$\tau b = -.19$	$\tau b = -.01$
Survivors only ($n = 29$) partial correlations (controlling for NPS)			
Global white matter volume/ICV	$r = .55$**	$r = -.20$	$r = -.05$
Controls only ($n = 29$)			
Global white matter volume/ICV	$\tau b = .12$	$\tau b < .01$	$\tau b = -.12$

Note. *indicates $p < .05$ and **indicates $p < .01$; ICV = intracranial vault; NPS = Neurological Predictor Scale; visual attention = Delis–Kaplan Executive Function Scale, Trail Making Test, Visual Scanning Trial z-score; τb = Kendall's tau-b.

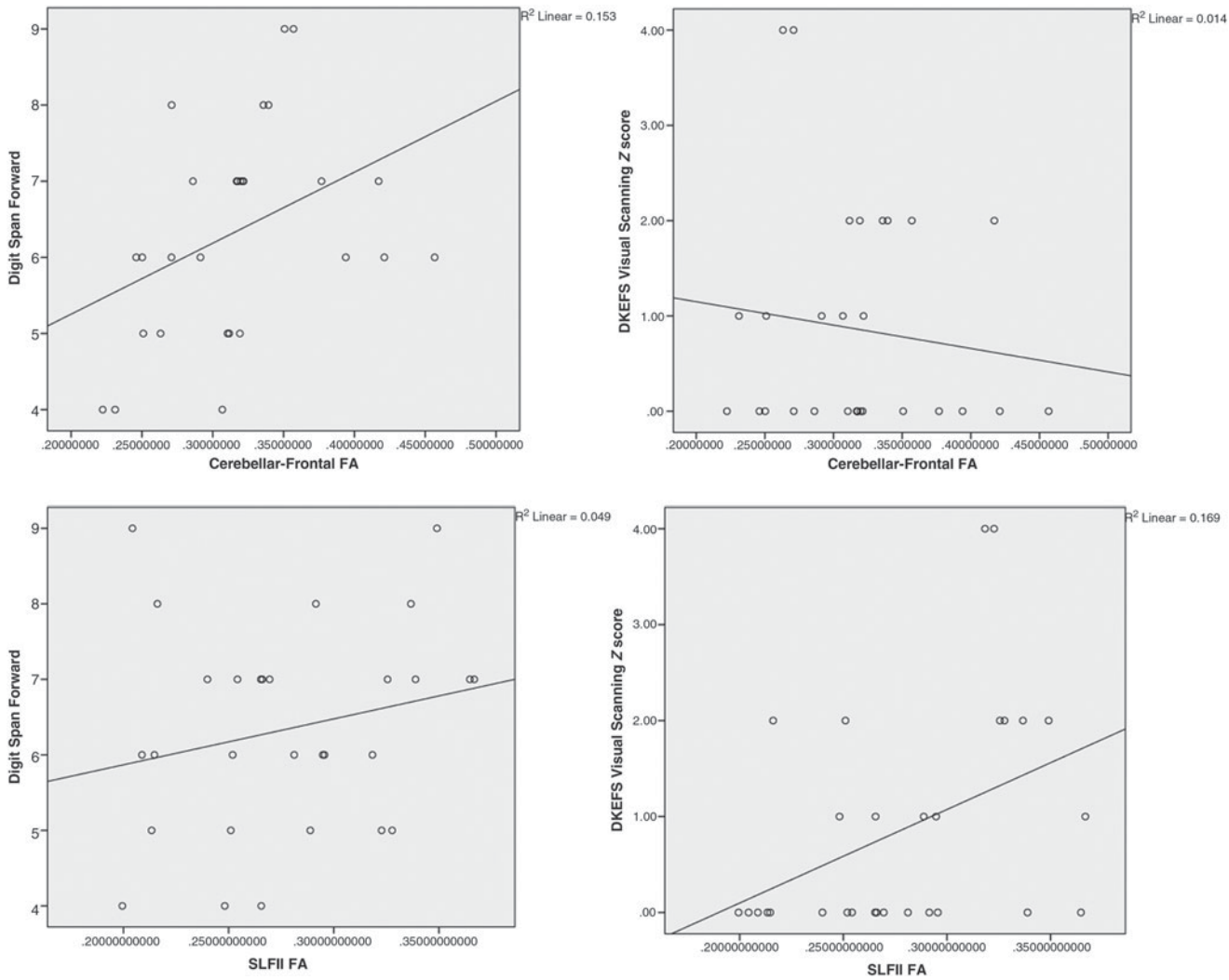

Fig. 2. Scatterplots of double dissociation in survivor group.

global white matter volume was correlated with auditory attention span ($\tau b = .36$, $p < .05$), and this relationship remained significant when controlling for treatment factors. This finding is further explained in the Discussion section. Across the groups, the results did not reach statistical significance for the right SLF II (see Table 4). In the control group, these relationships between neurocognitive measures and global white matter volume did not reach statistical significance.

DISCUSSION

The white matter pathway connecting the cerebellum and the frontal lobe is commonly studied in the childhood brain tumor population (Ailion et al., 2017 & 2019). The current study advances the existing literature on this pathway by providing theory-driven evidence about the specific neurocognitive performance that is associated with cerebellar-frontal WMI and provides evidence for a correlational double dissociation that provides specific differential associations for key brain–behavior relationships. First, the results identified a significant correlational association between auditory attention span and cerebellar-frontal WMI, which further refines the literature suggesting the cerebellar-frontal pathway relates to auditory attention span. Our results are consistent with Law et al. (2011)'s findings that cerebellar-frontal connections are associated with aspects of executive functioning and that damage to cerebellar-frontal connections mediates reductions in executive functioning in brain tumor survivors. However, methodological limitations likely obscured this finding in prior studies. Specifically, previous studies used Digit Span Forward and Backward as a combined score (Law et al., 2011 & 2015b). Of note, in the current sample, the results did not only replicate the relationship between Digit Span total score and the cerebellar-frontal pathway but also highlight the importance of auditory attention span specifically and showed no relationship with Digit Span Backward – the measure that is considered working memory (see Table 3). During test development, Digit Span Forward and Backward were highly correlated in the healthy normative sample and therefore combined in an index score. However, in clinical populations, these subtests are distinct constructs (Black and Strub, 1978; Kiefer et al., 2002). As such, combined index scores result in a poor specificity of neurocognitive processes (Dennis et al. 2009) and biased psychometric distributions (Lezak et al., 2012). Therefore, the combined score in neurological populations has been described as inappropriate because it obscures the measurement of important and distinct functions (Lezak et al., 2012; Weinberg et al., 1972). This finding has several implications for neuropsychological test selection and recommendations. For children with cerebellar-frontal pathway vulnerabilities, it will be critical to assess auditory attention span and interpret the Digit Span composite scale using a process approach to ensure children's weaknesses are identified. Furthermore, these children likely have greater challenges with holding auditory information in mind and would benefit from intervention strategies design to support short auditory attention span (i.e., writing down instructions, repetition, audio-recording, and technology to support these processes).

The relationship between the cerebellar-frontal pathway and auditory attention span is consistent with the theory that the cerebellum's role in working memory is error-driven adjustment of information from the phonological store and the articulatory control system (Desmond et al., 1997). The cerebellar-frontal network has been implicated in the phonological loop, articulatory rehearsal, and mental subvocalization, all of which are required for auditory attention span for verbal information (Baddeley, 1996; Ben-Yehudah et al., 2007; Desmond et al., 1997). The Digit Span Forward task relies on the phonological store and mental subvocalization systems (Baddeley, 1996; Gerton et al., 2004). Whereas, Digit Span Backward adds the component of manipulation, which is consistent with Baddeley's (1996) notion of the Central Executive (Gerton et al., 2004). Correspondingly, the cerebellar-frontal network is activated during encoding and maintenance of verbal information during a Sternberg verbal working memory task (Chen and Desmond, 2005). Similarly, King et al. (2015a) found that frontal and parietal functional activation distinguished between working memory and attention tasks. Therefore, the current study findings of the specificity in the relationship between cerebellar-frontal WMI and auditory attention span are consistent with Desmond et al.'s (1997) theoretical model and prior network activation studies (Chen and Desmond, 2005; King et al., 2015a). As such, complementary neuroimaging methods help us to build a more sophisticated understanding of brain–behavior relationships.

Both cerebellar-frontal WMI and global white matter volume were related to auditory attention span. Global brain volume metrics average all reductions in white matter volume, which may not be equally distributed throughout the brain. In cerebellar brain tumor survivors, lesions and atrophy in posterior fossa regions contribute to a reduction in global volume. Correspondingly, survivor cerebellar-frontal FA demonstrated a moderate correlation with global white matter volume, whereas SLF II FA was not correlated with global white matter volume. Therefore, white matter volume reductions that were captured in the global white matter volume metric may be concentrated in the posterior fossa and subcortical regions, and our concurrent research supports this theory (see Ailion et al., 2019). Given the high correlation between cerebellar-frontal WMI and global white matter volume, the association between global white matter volume and Digit Span Forward does not alone suggest that these results are due to diffuse white matter damage.

The double dissociation confirmed the specificity of the relationship between cerebellar-frontal WMI and auditory attention span in the survivor group. The data support a correlational double dissociation between cerebellar-frontal FA (correlated with auditory attention span) and SLF II FA (correlated with visual attention). Cerebellar-frontal WMI was not correlated with visual attention performance, and SLF II WMI was not associated with auditory attention span. If global white matter volume reductions explain auditory attention span, as the correlation between whole-brain white matter and Digit Span Forward suggests, then the right SLF II also should be correlated with auditory attention span. In sum, the results from the double dissociation provide a compelling argument for the brain–behavior specificity of visual and auditory attention span with two distinct brain networks and against diffuse brain disruptions.

Limitations

The brain regions of interest are part of dynamically interrelated networks; therefore, the results may have been influenced by larger network-related abnormalities associated with tumor development and treatment. The current study addressed global network influences by including a double dissociation with a comparison brain–behavior relationship and investigating global brain volume. In addition to a double dissociation and global volume measures, the current study included a healthy comparison group. While no causal conclusions can be drawn, the synthesis of findings from a double dissociation, comparison global metrics, and a healthy comparison group collectively provided support for brain–behavior specificity. Furthermore, an inherent limitation of neuropsychological measures of processing speed is almost all measures have a component of Visual Scanning and motor skills. We addressed the limitation of motor skills by using the OSDMT; however, additionally, an important future direction is the development of processing speed measures with fewer visual demands.

Additionally, brain tumor populations are difficult to study due to differences in the speed of tumor growth, the age of tumor identification, pathology, and location of the tumor within the posterior fossa. Therefore, heterogeneity among tumor and treatment factors could have contributed to the results and impacts the ability to draw definitive conclusions. The current study statistically accounted for the influence of treatment factors to ensure that tumor and treatment factors do not better explain the results. The current study had many participants, given the context that this is a patient population of long-term survivors of childhood brain tumors on average 13 years post-diagnosis. While it would be desirable to replicate findings with a larger and more homogenous sample, it is challenging to follow brain tumor survivors this long post-diagnosis due to difficulties tracking patients over time and across their transition into adulthood. Due to the rare nature of studying this population, we did not account for possible sampling bias, although this should be considered for future prospective studies.

Some results were inconsistent across measures of FA and RD, which is not atypical because RD is considered a more specific metric. Larger group differences (i.e., high grade, low grade) were present using RD when compared to FA across white matter pathways. Prior literature suggests that RD is sensitive to demyelination (Song et al., 2005; Bartzokis et al., 2012), so it is possible that these findings reflect a demyelinating process. In the survivor group double dissociation, SLF II FA but not SLF II RD was associated with visual attention. The RD metric was selected for the current study because of its sensitivity to myelin content in late-myelinating regions; however, RD has demonstrated less sensitivity in earlier-myelinating regions in the posterior brain (Bartzokis et al., 2012). Therefore, the discrepancy between SLF II FA and RD is consistent with the literature that suggests that RD would not be sensitive to white matter changes in early-myelinating posterior brain regions. For cortical and more posterior pathways like the SLF II, FA was more useful at detecting more subtle group differences (i.e., high grade *vs.* low grade). For further discussion, please see Ailion et al. (2019). Additionally, it would be ideal to collect data using a multi-shell DWI acquisition method for future studies, as a multi-shell acquisition can generate a diffusion model that is sensitive to a wider range of cellular profiles.

Strengths

This study was the first known to date to identify a double dissociation of specific white matter tracts and cognitive performance relationships in a childhood brain tumor population of survivors from childhood brain tumors. Neurocognitive impairments in brain tumor populations have been attributed to both focal and diffuse disruptions in brain volume and WMI (Ailion et al., 2017); therefore, prior literature obscures whether brain tumor survivors exhibit neurocognitive difficulties as a result of diffuse or focal brain damage. However, brain–behavior double dissociations provide evidence for specificity, particularly in the context of brain disease. One study on brain tumors that included a control region found that the putamen was more robustly impacted than the hippocampus, and hippocampal volume was related to attention but not verbal memory (Jayakar et al., 2015). These results highlight the importance of comparison brain regions and control tasks in order to understand related cognitive constructs. The current study investigated the cerebellar-frontal white matter pathway and corresponding neurocognitive measures with a control brain–behavior relationship to account for diffuse neurological injury and found evidence for a brain–behavior correlational double dissociation. Therefore, neurocognitive performance can be localized to specific and theoretically supported white matter pathways and the idea that neurocognitive difficulties are due to diffuse neurological injury in this population may be overly simplistic.

Results of the current study increase the specificity of the prior literature that has suggested that the cerebellar-frontal pathway is associated with verbal working memory (i.e., Digit Span total, Law et al., 2011, 2015b; Rueckriegel et al., 2015). The convergence of a number of guiding theoretical models and frameworks provided a rationale to increase the specificity of neurocognitive measurement of these constructs. A theoretical approach allows the results to have conceptually meaningful significance. The results of the current study provide empirical support for the theory that the cerebellum and its frontal white matter connections are implicated in the phonological loop and more specifically correlated with auditory attention span. Furthermore, these results increase the specificity of the current knowledge and highlight that specific white matter pathways correlate with different attentional skills (i.e., auditory attention span *vs.* Visual Scanning). Future research that examines additional cognitive constructs including but not limited to sustained attention and cognitive control may further fine-tune

our understanding of these core cognitive processes in neurological disease. Complementary neuroimaging innovations will assist in advancing our understanding of brain systems and cognition. The cerebellar-frontal pathway will be an important pathway to continue to understand in childhood cerebellar brain tumor survivors.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

SUPPLEMENTARY MATERIAL

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