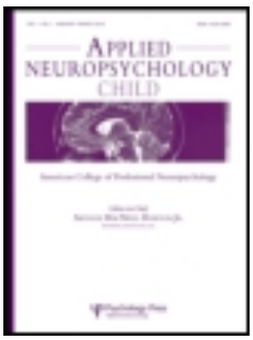

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Applied Neuropsychology: Child

ISSN: 2162-2965 (Print) 2162-2973 (Online) Journal homepage: https://www.tandfonline.com/loi/hapc20

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To cite this article: Holly A. Aleksonis, Ryan Wier, Matthew M. Pearson, Christopher J. Cannistraci, Adam W. Anderson, John F. Kuttesch, Bruce E. Compas & Kristen R. Hoskinson (2019): Associations among diffusion tensor imaging and neurocognitive function in survivors of pediatric brain tumor: A pilot study, Applied Neuropsychology: Child, DOI: 10.1080/21622965.2019.1613993

To link to this article: https://doi.org/10.1080/21622965.2019.1613993

APPLIED NEUROPSYCHOLOGY: CHILD
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Associations among diffusion tensor imaging and neurocognitive function in survivors of pediatric brain tumor: A pilot study

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ABSTRACT

The purpose of this study was to determine associations among neurocognitive outcomes and white matter integrity in the inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UF), and genu of the corpus callosum (gCC) in survivors of pediatric brain tumor and healthy controls (HCs). Eleven survivors (ages 8–16; >2 years post-treatment) and 14 HCs underwent MRI; diffusion tensor imaging tractography (DSI Studio) was used to assess white matter integrity. Participants completed neuropsychological assessment of overall cognitive ability, executive function, processing speed, divided attention, and memory. As previously reported, survivors performed significantly worse than HCs on measures of overall IQ, working memory, processing speed, and executive function ($ps < .01$), but not on measures of long-delay memory. Mean fractional anisotropy was significantly lower in survivors than HC in the right IFOF, left UF, and gCC ($ps < .05$). Correlations with the total sample revealed a number of significant positive associations among white matter tracts and scores on neurocognitive measures. Survivors show deficits on measures of cognitive function and decreased white matter integrity compared to HCs. Results revealed a more general pattern of associations among white matter pathways and neurocognitive outcomes than initially hypothesized. It is possible that survivors with diffuse pathology from treatment effects (i.e., hydrocephalus or posterior fossa syndrome) show more general decreases in cognitive functioning and white matter integrity. Additional research with a larger and more diverse group of survivors is needed to better understand white matter integrity and neurocognitive outcome associations in this population.

KEYWORDS

Central nervous system malignancy; children; executive function; late effects; magnetic resonance imaging; white matter integrity

Introduction

Brain tumors are the second most common cancer diagnosis in children, with over 4,000 new cases reported each year (Ostrom et al., 2018). Fortunately, with advances in medical treatments, the five-year survival rates in children diagnosed with brain tumors is over 70% (CBTRUS, 2018). Improvements in survival rates are in large part due to the advances in treatments and the use of a combination of surgery, chemotherapy, and radiation therapy to improve outcomes. Consequently, increasingly more children are becoming long-term survivors of pediatric brain tumor and, unfortunately, research has shown that these survivors are at increased risk for late effects (Anderson & Kunin-Batson, 2009).

Widely documented late effects in survivors of pediatric brain tumor include deficits in neurocognitive domains (Robinson et al., 2010; Winter et al., 2014). Specific domains of neurocognitive dysfunction found in survivors include overall cognitive ability, executive function, working memory, processing speed, and attention (Wolfe, Madan-Swain, & Kana, 2012). Studies show that even 10 years after diagnosis, survivors show deficits in multiple domains (Briere, Scott, McNall-Knapp, & Adams, 2008; Brinkman et al., 2012).

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/hapc.

Childhood and adolescence are periods of widespread cognitive development, typically including improvements in the key domains of executive function of inhibitory control, working memory, and cognitive flexibility. Paralleling this development are significant changes in white matter integrity and maturation, predominantly in the frontal lobes (Barnea-Goraly et al., 2005; Nagy, Westerberg, & Klingberg, 2004). White matter is highly susceptible to common treatment modalities in survivors of pediatric brain tumor survivors, particularly radiation therapy and intrathecal chemotherapy, rendering adolescence an especially vulnerable period for white matter injury (Makola, Ris, Mahone, Yeates, & Cecil, 2017; Nelson et al., 2014; Rueckriegel et al., 2010). Additionally, white matter is also vulnerable to increased intracranial pressure caused by hydrocephalus, commonly seen in children with posterior fossa tumors, which may also contribute to decreased cognitive outcomes in this population (Hardy, Bonner, Willard, Watral, & Gururangan, 2008; Tan et al., 2018).

One way to assess white matter integrity in the brain is through the use of diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) sequence that is sensitive to microscopic level white matter changes in the brain. This noninvasive method measures the diffusion of water in the brain which can give implications into the integrity of white matter tracts in the brain. Fractional anisotropy (FA) is one parameter used to measure white matter integrity by quantifying the directionality of water diffusion along axons. Greater FA signifies more linear diffusion of water and is a proxy for greater white matter integrity; in contrast, water diffusion that is more lacking in linear direction may indicate comprised white matter.

Research using DTI in pediatric brain tumor survivors and other pediatric populations is somewhat limited, but some studies have shown connections between cognitive domains and specific brain pathways, including the inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UF) and the corpus callosum, specifically the genu (gCC; Ailion, Hortman, & King, 2017). With connections to the frontal and occipital lobes, the IFOF has documented links to neurocognitive domains such as executive function, attention, working memory and processing speed in pediatric cancer survivors and typically developing children (Aukema et al., 2009; Peters et al., 2014). In children with autism spectrum disorder, a study found associations between visuospatial processing and white matter integrity of the right IFOF (McGrath et al., 2013). The UF, with connections between the frontal and temporal lobes, has shown links with performance on declarative memory in typically developing adolescents and survivors of posterior fossa tumors (Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009; Riggs et al., 2014). Additionally, in a group of typically developing children, lower FA values in the UF were associated with lower scores on a verbal memory task (Schaeffer et al., 2014). The corpus callosum has been shown to have associations with processing speed, cognitive flexibility, and inhibition in survivors of pediatric brain tumor (Palmer et al., 2012; Treit, Chen, Rasmussen, & Beaulieu, 2014). In sum, individual DTI studies have shown some links between specific white matter pathways and cognitive domains in varying populations, but breadth of research is still limited in the population of pediatric brain tumor survivors.

Determining how pediatric brain tumor affects the white matter integrity of specific white matter tracts can help explain the types of cognitive deficits that are found in children with pediatric brain tumor and can further help develop interventions to combat these late effects. The purpose of this pilot study was to explore associations between neurocognitive outcomes and white matter integrity in specific white matter tracts in survivors of pediatric brain tumor versus healthy children. This study evaluates the hypothesis that survivors will show deficits on measures of cognitive function and decreases in white matter integrity as measured by mean FA. Additionally, this study explores the associations of integrity in white matter tracts with performance on neuropsychological assessments. Specifically, based on the literature of other populations, we hypothesize that lower mean FA in the IFOF will be associated with lower scores on measures of overall cognitive function, executive function, working memory and processing speed. We hypothesize that lower mean FA in the UF will be associated with lower scores on visual and verbal memory tasks. Finally, we hypothesize that lower mean FA in the gCC will be associated with lower scores on measures of processing speed, cognitive flexibility, and divided attention.

Methods

Participants

Data for these analyses include 11 pediatric brain tumor survivors and 14 healthy controls (HCs). The 11 brain tumor survivors (7 girls) and 14 HCs (8 girls) were a subset of the overall sample in a study of neurocognitive functioning of survivors of pediatric

brain tumor. Twenty-six children who were at least 2 years post-diagnosis of a primary pediatric brain tumor were invited to participate in the study. Survivors were identified through a cancer survivorship clinic, the Department of Pediatric Hematology/Oncology, or the Department of Neurosurgery at a large southern children's hospital and pediatric oncology center. Survivors were invited to participate if they met the following inclusion criteria: (a) 8–16 years old at the time of enrollment, (b) completed treatment for a pediatric brain tumor, (c) in first continuous remission, and (d) English speaking. Exclusion criteria included the following: (a) history of a known pre-existing neurodevelopment disorder, (b) history of very low birth weight (<1500 g), or (c) history of secondary malignancies or relapses. Children with a history of attention deficit/hyperactivity disorder (ADHD) were not excluded. Procedures were approved by the Institutional Review Board. Informed consent and assent were obtained from all participants. Of the 26 contacted, 21 agreed to participate and enrolled in the study. Two children declined due to lack of interest, two families had moved out of the area, and one child agreed to participate but relapsed prior to formal enrollment. Of the 21 who participated in the study, one survivor's data were excluded from present analyses due to missing data, and nine participants' data were excluded due to excessive motion during DTI. This resulted in 11 survivors of pediatric brain tumor that were included in the present analyses. Those included in the present analyses and those excluded did not differ in time since diagnosis, time off treatment, race, parental income level, handedness, or age. There were significantly more males than females excluded from the present analyses ($p = .017$).

Twenty-seven healthy children were contacted to serve as a control group and were matched as closely as possible to the larger sample of survivors by age and gender. Healthy controls (HCs) were also 8–16 years old at the time of enrollment and were English speaking; exclusion criteria included: (a) history of pre-existing neurodevelopment disorder, (b) history of very low birth weight (<1500 g), or (c) history of chronic health condition affecting the central nervous system. In addition to the above exclusion criteria, both survivors and HCs were required to complete screening per imaging center protocol to detect ferromagnetic or implants that are incompatible with MRI. Children with braces were excluded, as metallic orthodontic devices can distort images. Of the 27 HCs contacted, 20 were eligible, agreed to participate, and enrolled in the study. Three children were excluded from initial recruitment because of a pre-existing neurodevelopmental disorder, two declined because of lack of interest, and two had orthodontic devices that precluded undergoing MRI. Of the 20 who participated, two HCs did not return for their scanning appointment and 4 HCs' data were excluded because of excessive motion during DTI. This resulted in 14 HCs that were included in the present analyses. HCs included and excluded in these analyses did not differ on gender, race, parental income level, handedness or age at study entry. Within the total sample, those who were excluded because of excessive motion in the MRI scanner had significantly lower scores on Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2003) Working Memory Index (WMI) ($p = .044$) and approached significance on WISC-IV Full Scale IQ (FSIQ) ($p = .062$).

Survivors and HCs included in these analyses did not differ from one another in age at participation, gender distribution, race, family income, history of ADHD medication by parent report, and history of diagnosis and/or treatment for psychological problems by parent report (Table 1). However, the two groups did differ significantly on level of parental education with HCs' parents having a higher level of formal education ($p = .037$). For brain tumor survivors, mean age at diagnosis was 6.64 years ($SD = 2.82$; range 2.06–11.25) and survivors were 6.38 years post-diagnosis ($SD = 3.12$; range 3.09–10.93) and 6.03 years post-treatment ($SD = 3.13$; range 2.22–10.93) at the time of participation. Tumor pathologies included medullablastoma (2), juvenile pilocytic astrocytoma (6), dysembryoplastic neuroepithelial tumor (2), and germinoma (1). Tumor locations included posterior fossa (8), temporal lobe (1), parietal lobe (1), and hypothalamus (1). All survivors underwent some degree of surgical resection and four received both chemotherapy and cranial radiation. Of those who received cranial radiation, average cumulative dose was 56.65 Gy ($SD = 6.04$; range 54.00–66.60).

Measures

The WISC-IV was administered to participants to measure overall cognitive functioning, including general cognitive ability (FSIQ), working memory (WMI), and processing speed (Processing Speed Index; PSI). The WISC-IV is known for having high validity and test–retest reliability ($\alpha = .97$).

Subtests of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001), a

Table 1. Group comparisons on demographic information.

	BT ($n = 11$) *M* (*SD*)	HC ($n = 14$) *M* (*SD*)	*p*
Age (years)	12.83 (2.51)	13.05 (2.69)	.845
Times since diagnosis (years)	6.38 (3.12)	–	–
Times since last treatment (years)	6.03 (3.13)	–	–
	n (%)	*n* (%)	*p*
Male	4 (36.40)	6 (42.90)	.742
White or Caucasian	10 (90.90)	10 (71.40)	.227
Right-handed	9 (81.8)	11 (78.6)	.840
Parental education			.037
Technical school, high school, or GED completed	3 (27.3)	0 (0)	
At least some college completed	8 (72.7)	14 (100)	
Parental income level			.561
Less than $70,000	5 (45.5)	8 (57.1)	
$70,000 or more	6 (54.5)	6 (42.9)	
Tumor type			
Medulloblastoma	2 (18.2)	–	–
Juvenile pilocytic astrocytoma	6 (54.5)	–	–
Dysembryoplastic neuroepithelial	2 (18.2)	–	–
Germinoma	1 (9.1)	–	–
Treatment received			
Surgery	11 (100)	–	–
Radiation	4 (36.4)	–	–
Chemotherapy	4 (36.4)	–	–

Note. BT = survivors of pediatric brain tumor; HC = healthy control.

comprehensive battery of tests that assess verbal and nonverbal executive function, were also administered. The Verbal Fluency subtest of the D-KEFS, specifically Category Switching, requires the examinee to alternate between naming objects of two different categories as quickly as possible, tapping into cognitive flexibility, verbal fluency, and response inhibition. On the D-KEFS Trail Making subtest, condition 4, Trails Number-Letter Switching, requires the examinee to connect numbers and letters in sequence while alternating back and forth between numbers and letters. This task was used to measure cognitive flexibility and inhibitory control. Similar to the Trail Making subtest, the Color-Word Interference subtest has four conditions with the fourth requiring the examinee to follow a set of rules to either say the name of the color or say the name of the ink the word is printed in. This task is also a measure of cognitive flexibility and inhibition. Most included subtests of the D-KEFS have good test–retest reliability ranging from $\alpha = .65–.80$; the test–retest reliability for Trails Number-Letter Switching is substantially lower, at $\alpha = .20$.

The Children's Memory Scale (CMS; Cohen, 1997) was administered to assess learning and memory. The CMS Stories subtest is a measure of verbal memory with a long-delay score used to measure delayed verbal memory recall. The CMS Dot Locations subtest is a measure of visual memory with a similar long-delay score to measure delayed visual memory recall. It is known to have a high test–retest reliability across age groups of $\alpha = .70–.81$.

Image acquisition

Each participant underwent a magnetic resonance imaging session without sedation on a Philips Achieva 3 Tesla scanner dedicated to research (Philips Healthcare, Best, The Netherlands). During DTI acquisition, transverse multislice spin echo, single shot, echo planar imaging (EPI) sequences were used (10000 ms TR, 60 ms TE, 2.0 mm slices, flip angle 90°), with a reconstructed voxel size of 2.0 x 2.0 x 2.0 mm and a FOV of 256 mm. Diffusion was measured along 32 directions, with a total of 2 diffusion weightings, low b-value = 0 s/mm^2, high b-value = 1000 s/mm^2. Sixty contiguous slices were obtained parallel to the anterior commissure-posterior commissure (AC-PC) plane. High resolution 3D anatomical images were also acquired using an inversion-prepared spoiled gradient recalled echo sequence (IR-3D-TFE), with an inversion time T1 of 400 ms, TR of 15 ms, TE of 3 ms, and a FOV of 256 x 255 x 270 mm with near isotropic resolution.

DTI analysis

All data were first inspected for artifacts or irregularities that may compromise accuracy or reliability. Subsequent DTI analysis was conducted using

deterministic fiber tracking algorithms via the DSI Studio platform (http://dsi-studio.labsolver.org; Yeh, Verstynen, Wang, Fernandez-Miranda, & Tseng, 2013). Fiber tracking parameters included a step size of 0.88 mm, an anisotropy threshold of 0.16, fiber angular threshold of 80 degrees, and minimum fiber length of 20.00 mm. In order to smooth individual fiber trajectories, the propagation directions were averaged with 20% of the previous direction.

For each fiber tract of interest, a multiple region-of-interest (ROI) approach was used to segment white matter pathways, completed by a single rater blind to participant group (KRH). Each tract was rated twice, no less than two weeks apart, and reliability statistics were calculated and exceeded an intra-class correlation coefficient (ICC) of 0.95, suggesting excellent reliability. Average tract FA was obtained for all tracts of interest, using a seed-driven ROI approach, and was done separately for independent bilateral tracts. For the right and left UF, one seed region encompassed the temporal lobe on the posterior-most coronal plane where the sylvian fissure is visualized, and a second seed region encompassed the entire frontal hemisphere anterior to the gCC. For the right and left IFOF, mean FA was calculated using one seed region located posterior to the rostrum of the corpus callosum that encompassed the entire hemisphere and another seed region encompassing the temporal stem in the same hemisphere. A frontal lobe seed region was also used, identical to that previously described. For each of these fiber tracts, a region-of-avoidance (ROA) was also included at the sagittal midline, to eliminate any fibers crossing into the contralateral hemisphere. The gCC was segmented according to the Witelson protocol (Witelson et al., 2008), and seed regions included the genu in the mid-sagittal plane, as well as a coronal ROA located posterior to the rostrum.

Statistical analyses

Before statistical analyses were run, neurocognitive testing was examined within-group to determine if there were any individual outliers that were above or below two standard deviations (SD) from the group mean. In the survivors of pediatric brain tumor group, one FSIQ score and one CMS Dot Locations Long-Delay Score were excluded from analyses as outliers for both being over two SDs below the mean. In the HCs group, one WMI and one PSI were excluded as outliers for being over two SDs above the mean. Also, in the HCs group, one CMS Dot Locations Long-Delay score and one Trails Number-Letter Switching score were excluded from the analyses as outliers for being over two SDs below the mean. Independent samples *t*-tests were used to compare groups' performance on neurocognitive testing and mean FA of white matter tracts. Effect sizes (Cohen's *d*) were also calculated for between group comparisons given limited statistical power with small samples. Additionally, due to the over-performance of the HC group, comparisons were also made between the BT group and normative expectation for neurocognitive testing measures. To assess potential relationships among neurocognitive tests and white matter tracts, partial correlations controlling for parental education were conducted with the total sample.

Results

Group differences

Means, standard deviations, and effect sizes for measures of overall cognitive functioning, executive function, and verbal and visual memory are reported in Table 2. Consistent with analyses run on the full study sample, on the WISC-IV, survivors of pediatric brain tumor tended to score in the low average range, while HCs tended to score in the average to high average range. In this subset of participants, survivors of pediatric brain tumor performed significantly more poorly than HCs on the WISC-IV FSIQ, WMI, and PSI ($ps < .01$). Survivors also performed significantly more poorly on D-KEFS Color Word Inhibition-Switching and Trails Number-Letter Switching ($ps < .01$), also consistent with prior analyses of the overall study sample (Robinson et al., 2014). Performance on D-KEFS Verbal Fluency Category Switching approached significance ($p = .051$) with survivors performing more poorly than HCs. The two groups did not differ on Long-Delay recall memory performance in the CMS Stories and Dot Locations subtest. However, performance on CMS Stories subtest did approach significance ($p = .052$) with survivors performing more poorly than HCs. A similar pattern was observed when survivors were compared to normative expectation, though effect sizes were generally more modest than the HC comparison (see Table 2).

Means, standard deviations, and effect sizes for mean FA of white matter tracts (i.e., the bilateral IFOF, bilateral UF, and gCC) are reported in Table 3 and examples for each tract can be found in Figures 1–3. Lower white matter integrity in survivors of pediatric brain tumor was shown in the right IFOF, left UF and gCC ($ps < .05$) compared to HCs. No

Table 2. Group comparisons on neurocognitive measures.

	BT ($n = 11$) *M* (*SD*)	HC ($n = 14$) *M* (*SD*)	*t*	*p*	Cohen's *d*
WISC-IV					
WMI	91.45 (11.41)	103.54 (6.19)	−3.30	.003	−1.32
PSI	84.00 (11.97)	110.92 (10.72)	−5.81	<.001	−2.37
FSIQ	89.91 (9.47)	115.71 (10.66)	−6.30	<.001	−2.56
D-KEFS					
Verbal Fluency Category Switching	9.36 (3.35)	12.14 (3.35)	−2.06	.051	−0.83
CWI Inhibition/Switching	7.36 (3.80)	11.29 (1.94)	−3.12	.008	−1.30
Trails Number-Letter Switching	7.18 (3.66)	12.15 (1.41)	−4.25	.001	−1.79
Children's Memory Scale					
Dot Locations Long-Delay	10.50 (2.17)	11.58 (1.31)	−1.44	.164	−0.60
Stories Long-Delay	10.82 (2.79)	12.79 (1.48)	−2.12	.052	−0.88
	BT ($n = 11$) *M* (*SD*)	Normative Mean	*t*	*p*	Cohen's *d*
WISC-IV					
WMI	91.45 (11.41)	100.00	−2.48	.032	−0.64
PSI	84.00 (11.97)	100.00	−4.44	.001	−1.18
FSIQ	89.91 (9.47)	100.00	−3.53	.005	−0.84
Verbal Fluency Category Switching	9.36 (3.35)	10.00	−0.63	.543	−0.20
CWI Inhibition/Switching	7.36 (3.80)	10.00	−2.30	.044	−0.77
Trails Number-Letter Switching	7.18 (3.66)	10.00	−2.56	.029	−0.84
Dot Locations Long-Delay	10.50 (2.71)	10.00	0.73	.485	0.17
Stories Long-Delay	10.82 (2.79)	10.00	0.97	.353	0.28

Note. Means and standard deviations are reported in scaled scores except for WISC-IV measures which are standard scores. Scaled scores, $M = 10$, $SD = 3$; Standard scores, $M = 100$, $SD = 15$.

BT = survivors of pediatric brain tumor; HC = healthy controls; WISC-IV = Wechsler Intelligence Scale for Children-Fourth Edition; WMI = Working Memory Index; PSI = Processing Speed Index; FSIQ = Full Scale Intelligence Quotient; D-KEFS = Delis-Kaplan Executive Functional Systems; CWI = Color-Word Integration.

Table 3. Group comparisons on white matter integrity.

	BT ($n = 11$) *M* (*SD*)	HC ($n = 14$) *M* (*SD*)	*t*	*p*	Cohen's *d*
IFOF (R) FA mean	.459 (.026)	.483 (.019)	−2.62	.015	1.05
IFOF (L) FA mean	.471 (.020)	.483 (.022)	−1.46	.159	0.57
UF (R) FA mean	.415 (.019)	.428 (.015)	−1.89	.071	0.76
UF (L) FA mean	.425 (.012)	.442 (.017)	−2.80	.010	1.16
Genu of CC FA mean	.501 (.010)	.515 (.020)	−2.14	.043	0.89

Note. BT = survivor pediatric brain tumor; HC = healthy controls; IFOF = inferior fronto-occipital fasciculus; UF = uncinate fasciculus; CC = corpus callosum; FA = fractional anisotropy; R = right; L = left.

significant group differences were seen in mean FA of the left IFOF or right UF.

Correlations among neurocognitive measures and white matter integrity

Within the total sample, correlations revealed a number of significant associations among white matter tracts and scores on neurocognitive measures (Table 4). Greater mean FA in the right and left IFOF were significantly associated with better performance on WISC-IV PSI and FSIQ, D-KEFS Verbal Fluency and Trails Number-Letter, and CMS Stories Long-Delay. Additionally, greater mean FA in the right IFOF was associated with greater performance on D-KEFS CWI Inhibition/Switching. Greater mean FA in the right and left UF was associated with better performance on WISC-IV FSIQ, D-KEFS Trails Number-Letter, and CMS Stories Long-Delay. Additionally, greater mean FA in the right UF was associated with better performance WISC-IV WMI and greater mean FA in the left UF was associated with better performance on D-KEFS Verbal Fluency. In the gCC, greater mean FA was associated with better performance on the WISC-IV WMI, PSI, and FSIQ, as well as, D-KEFS CWI Inhibition/Switching and Trails Number-Letter. Finally, greater mean FA in the gCC was associated with better performance on the CMS Stories Long-Delay.

Discussion

Survivors of pediatric brain tumor have documented late effects including, deficits in executive functioning, processing speed, memory, and more (Robinson et al., 2010; Wolfe et al., 2012). Treatment for pediatric brain tumor can affect the white matter of a child's brain during a vital time of white matter development and maturation in adolescence (Barnea-Goraly et al., 2005; Nagy et al., 2004). Diminished white matter integrity could possibly contribute to late effects seen in this population of survivors, particularly aspects of neurocognitive function, given the role of white

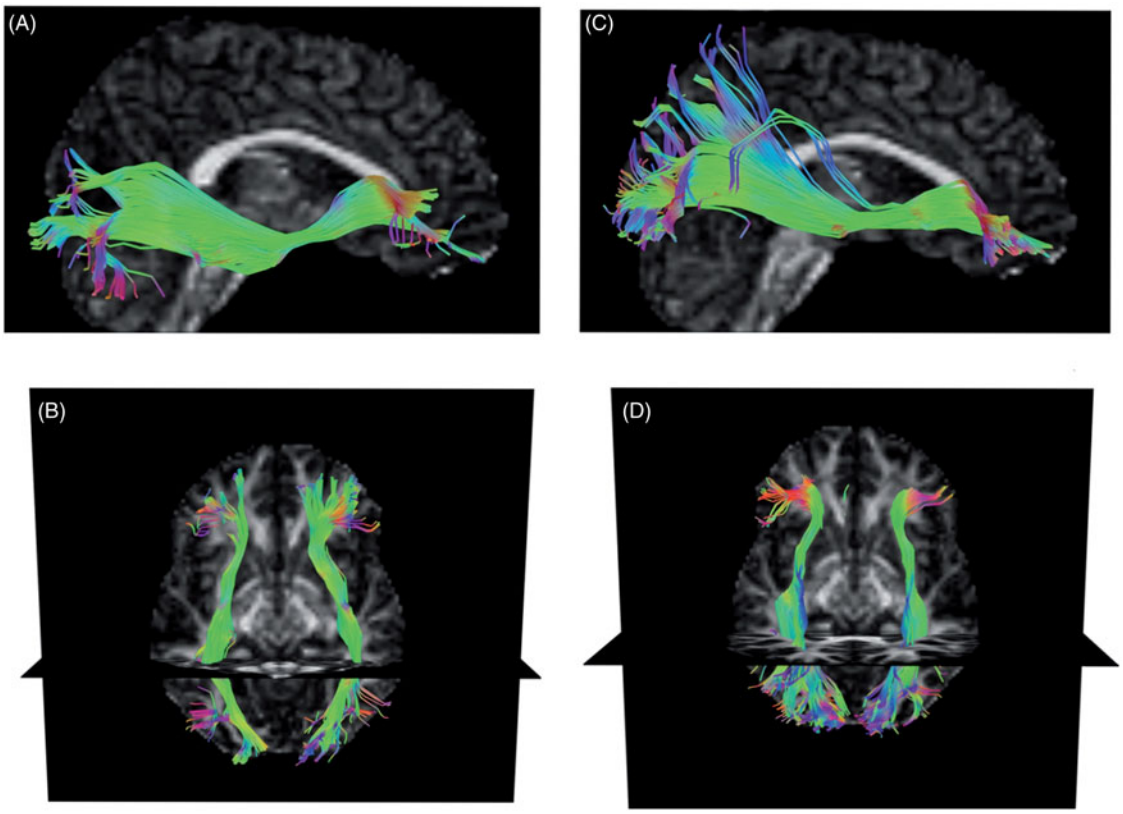

Figure 1. Diffusion tensor imaging example images of the inferior fronto-occipital fasciculus. Images are in radiological convention. A and B: Example of individual brain tractography of prototypical survivor of pediatric brain tumor in this sample. C and D: Example of individual brain tractography of prototypical healthy control in this sample. Images are matched for age and gender. Images are presented in radiological convention.

matter in rapid processing and integration. It is important to identify potential areas in the brain most vulnerable to injury in order to better determine children who are most at risk for long-term neurocognitive sequelae. The goal of this pilot study was to examine links between the integrity of specific white matter tracts and scores on neurocognitive testing.

As hypothesized, survivors of pediatric brain tumor performed more poorly than HCs on measures of cognitive function, specifically tasks involved in cognitive flexibility, working memory, and processing speed. Because HCs scored primarily in the average to high average range, survivors' scores were also compared to normative data to determine whether statistically significant group differences were attributed to an over-performing control group. Results showed that survivors performed significantly worse than normative expectation on Trails Number-Letter Switching and WISC-IV FSIQ, WMI, and PSI. This is consistent with past literature evaluating neurocognitive abilities in survivors of pediatric cancer (Kahalley et al., 2013), with effect sizes generally in the moderate to high range (Robinson et al., 2010). This suggests, albeit within a small and heterogeneous sample, these findings are in line with previous literature that documents the scope of neurocognitive deficits in this population.

No differences in CMS long-delay memory recall were seen in this sample population, which is consistent with Shortman et al. (2014) who also used the CMS as a measure of visual and verbal memory. While other literature has documented deficits on visual and verbal memory tasks (Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013), measurement tools vary, including the California Verbal Learning Test (CVLT), Rey Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Test, and more. It is possible that these other tasks require more complex encoding and retrieval/recall processes and in combination with other neurocognitive domains that survivors of pediatric brain tumor also struggle with (i.e., working memory, processing speed): evidence that more research in this area is necessary to parse out potential areas of weakness in this population.

More importantly, the hypothesis that survivors would show decreased white matter integrity compared to HCs was partially supported. Survivors

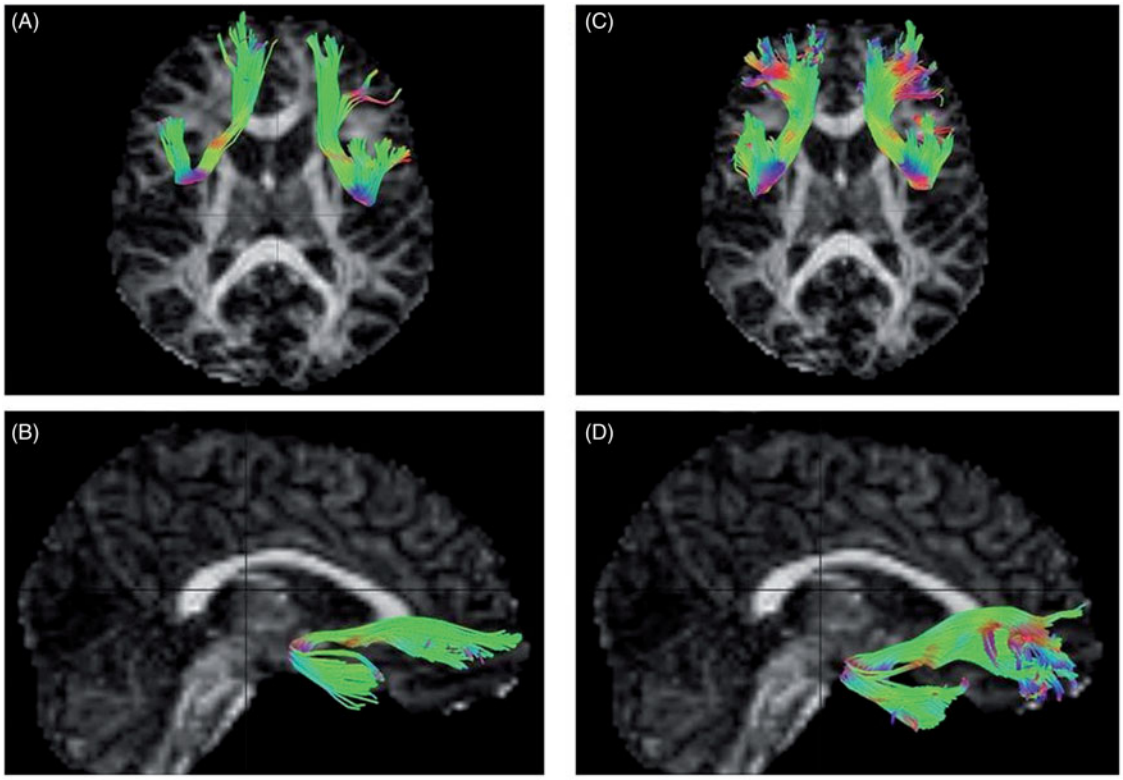

Figure 2. Diffusion tensor imaging example images of the uncinate fasciculus. Images are in radiological convention. A and B: Example of individual brain tractography of prototypical survivor of pediatric brain tumor in this sample. C and D: Example of individual brain tractography of prototypical healthy control in this sample. Images are matched for age and gender.

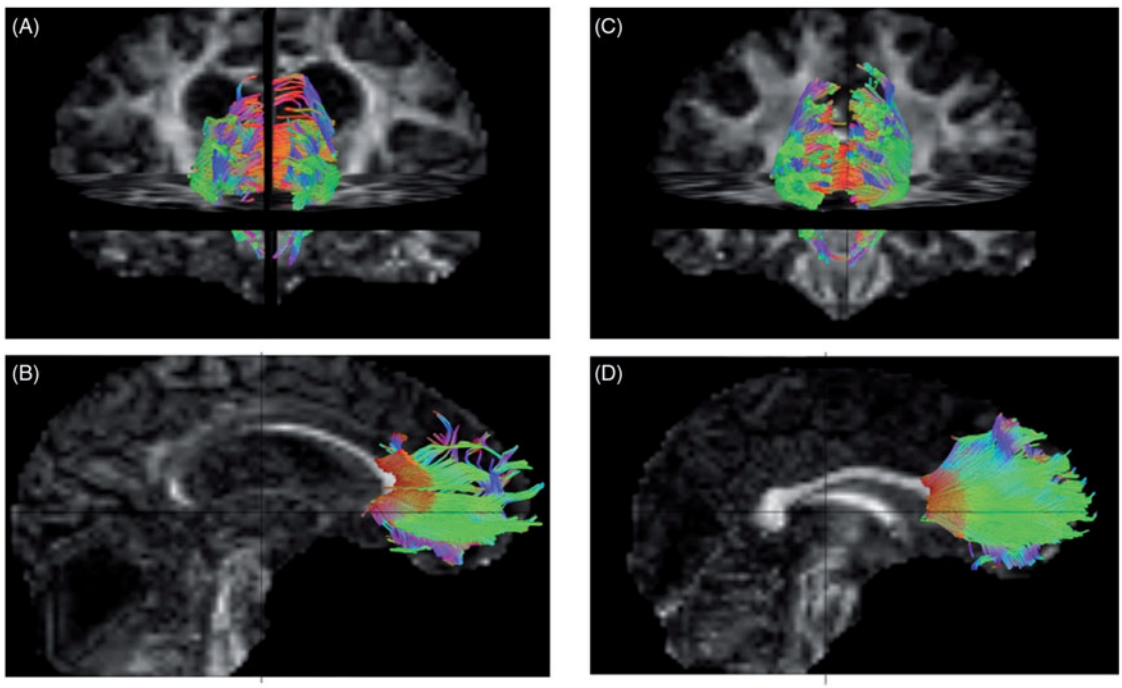

Figure 3. Diffusion tensor imaging example images of the genu of the corpus callosum. Images are in radiological convention. A and B: Example of individual brain tractography of prototypical survivor of pediatric brain tumor in this sample. C and D: Example of individual brain tractography of prototypical healthy control in this sample. Images are matched for age and gender.

Table 4. Correlations of white matter integrity and neurocognitive measures.

	IFOF (R) FA mean	IFOF (L) FA mean	UF (R)FA mean	UF (L)FA mean	Genu of CC FA mean
WISC-IV					
WMI	.311	.366	.462*	.178	.432*
PSI	.552**	.440*	.394	.404	.443*
FSIQ	.624**	.575**	.440*	.470*	.472*
D-KEFS					
Verbal Fluency Category Switching	.646**	.593**	.390	.430*	.314
CWI Inhibition/Switching	.461*	.406	.352	.401	.515*
Trails Number-Letter Switching	.667**	.553**	.496*	.537**	.542**
Children's Memory Scale					
Dot Locations Long-Delay	.199	.130	.166	−.113	−.143
Stories Long-Delay	.572**	.597**	.481*	.488*	.454*

Note. WISC-IV = Wechsler Intelligence Scale for Children-Fourth Edition; WMI = Working Memory Index; PSI = Processing Speed Index; FSIQ = Full Scale Intelligence Quotient; D-KEFS = Delis-Kaplan Executive Functional Systems; CWI = Color-Word Integration; IFOF = inferior fronto-occipital fasciculus; UF = uncinate fasciculus; CC = corpus callosum; FA = fractional anisotropy; R = right; L = left.
*$p < .05$. **$p < .01$.

showed decreased white matter integrity in the right IFOF, left UF, and gCC compared to the sample of controls. Although decreased white matter integrity was not found statistically for the left IFOF or right UF, trends were in the expected direction, with medium to large effects, suggesting a potential issue of statistical power. Most importantly, results revealed multiple relationships among white mater tracts and scores on neurocognitive measures. Measures that reflected executive function, cognitive flexibility, and processing speed were robustly associated with the right and left IFOF and the gCC, which is consistent with past literature on childhood cancer survivors and typically developing children (Aukema et al., 2009; Peters et al., 2014). These prominent white matter pathways integrate brain systems essential to complex problem solving and other higher-order skills that support successful engagement in executive function tasks. Additionally, the right and left UF were also associated with neurocognitive measures that reflect performance on executive function and cognitive flexibility, as well as verbal memory. This novel finding adds to the current literature and provides evidence for a more generalized profile of associations among white matter integrity and neurocognitive domains in this population.

Contrary to our hypothesis that specific white matter tracts would be associated with specific neurocognitive domains, results revealed associations that were much more generalized across domains. A more generalized profile within this sample might show the importance of differentiating between diffuse and focal pathology seen in this population. In particular, the presence of hydrocephalus and posterior fossa syndrome have shown to be associated with decreased general performance in neurocognitive outcomes (Hardy et al., 2008; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). A majority of the survivors in this sample had tumors located in the posterior fossa and could explain the generalized results of these data. In other populations (e.g., pediatric traumatic brain injury), diffuse neuropathology is also common. Literature on pediatric traumatic brain injury shows associations among multiple white matter tracts and measure of cognitive functioning such as processing speed, intelligence, and parent reported executive deficits (Levin et al., 2008; Wozniak et al., 2007). Thus, it is possible that similar to pediatric traumatic brain injury, survivors with more diffuse pathology from treatment effects show more general decreases in cognitive functioning and white matter integrity. However, it is also possible that within this small pilot sample, we simply lacked power to detect meaningful subgroup differences. To directly test this hypothesis, additional imaging with survivors with and without more focal pathology (e.g., encapsulated cortical/supratentorial tumors) and indicators of more generalized disease processes (e.g., hydrocephalus) is an integral next step.

With potential links between white matter integrity and neurocognitive function, it is important to consider the possible effects treatment can have on white matter in the brain. Past literature has shown that surgery, radiation, and chemotherapy treatments after pediatric brain tumor are linked to long-term diffuse white matter disruption (King, Wang, & Mao, 2015; Makola et al., 2017; Nelson et al., 2014). Treatment late effects are important to consider in this population as patients undergo treatment at a particularly important time in development. Treatment at a young age, prior and during adolescence, could potentially derail white matter maturation and have long-term consequences to survivors' development and function. Ideally, we would have liked to examine the role of treatment on neurocognitive outcomes in this study, but unfortunately, small sample sizes inherent in pilot studies prevented us from having adequate power for analyses. Future studies should examine treatment

influence on outcomes and late effects so that when physicians and families make decisions about treatment options they are informed of any possible negative impacts and better anticipate a child's needs in the future.

This is one of a limited number of studies utilizing DTI to investigate possible links between specific white matter pathways and neurocognitive outcomes in a group of pediatric brain tumor survivors with diverse tumor types, an important research area as survivorship increases. A noted strength of this study design is our investigation of specific white matter pathways selected based on past literature in survivors of pediatric brain tumor and other pediatric populations. This allowed for focus on very specific connections in the brain in relation to neurocognitive measures. That said, there are some limitations to note in the study. Particularly, the small sample size of each group decreased our ability to have sufficient power to achieve significance on correlations tests and precluded us from preforming more statistical analyses such as regression models. Additionally, we are aware of the nature of this group of HCs having higher than average scores on neurocognitive measures, and that they may not reflect the overall population of healthy children and adolescents; we attempted to address this by also comparing survivors to normative data, but no such database was available for measures of white matter integrity. The participants included in these analyses were also a subset of participants in the overall study, largely impacted by ability to remain still during the DTI sequence. Though similar demographically, it is possible that participants who successfully completed the MRI session within motion constraints are those who are comparably higher functioning, which may bias both the survivor and HC group. Thus, the effect size of these data analyses may actually have been mitigated because it would be expected that those who are lower in functioning and could not hold still may also be the ones who have more disrupted white matter integrity. This sample is also a homogeneous representation from one location of survivors of pediatric brain tumor and may not be generalizable. A larger, multisite study would be beneficial to determine if these same findings are seen in other survivors of pediatric brain tumor.

Future research in this area is still necessary. Specifically, a larger multisite study investigating outcomes in survivors of pediatric brain tumor would be beneficial to include a more diverse sample population. Such a study would also allow subgroup analyses based on type of treatment, a necessary step to determining which children are most at risk of long-term neurocognitive morbidities. Research has shown that survivors of pediatric brain tumor show deficits in a variety of neurocognitive domains as well as quality of life, but fewer have focused on how survivors are functioning in daily life (e.g., in adaptive behaviors). Moreover, studies integrating neuroimaging methods with more ecologically-valid assessments of day-to-day functioning in survivors could further elucidate the neurobiological underpinnings of executive and social functioning among this population.

This study reinforces current literature that survivors of pediatric brain tumor are at higher risk for late effects including deficits in neurocognitive domains and diminished white matter integrity in brain pathways. Additionally, this study offers further insight into associations among white matter pathways and neurocognitive domains in survivors of pediatric brain tumor. Research in this area can help inform a long-term goal to help survivors post-treatment after pediatric brain tumor.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by gifts from Patricia and Rodes Hart and an anonymous donor to Bruce E. Compas, PhD.

References

Ailion, A. S., Hortman, K., & King, T. Z. (2017). Childhood brain tumors: A systematic review of the structural neuroimaging literature. *Neuropsychology Review*, *27*(3), 220–244. doi:10.1007/s11065-017-9352-6

Anderson, F. S., & Kunin-Batson, A. S. (2009). Neurocognitive late effects of chemotherapy in children: the past 10 years of research on brain structure and function. *Pediatric Blood and Cancer*, *52*(2), 159–164. doi: 10.1002/pbc.21700

Aukema, E. J., Caan, M. W. A., Oudhuis, N., Majoie, C. B. L. M., Vos, F. M., Reneman, L., … Schouten-van Meeteren, A. Y. N. (2009). White matter fractional anisotropy correlates with speed of processing and motor speed in young childhood cancer survivors. *International Journal of Radiation Oncology. Biology. Physics*, *74*(3), 837–843. doi:10.1016/j.ijrobp.2008.08.060

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., … Reiss, A. L. (2005). White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study.

Cerebral Cortex, *15*(12), 1848–1854. doi:10.1093/cercor/bhi062

Briere, M. E., Scott, J. G., McNall-Knapp, R. Y., & Adams, R. L. (2008). Cognitive outcome in pediatric brain tumor survivors: delayed attention deficit at long-term follow-up. *Pediatric Blood and Cancer*, *50*(2), 337–340. doi:10.1002/pbc.21223

Brinkman, T. M., Reddick, W. E., Luxton, J., Glass, J. O., Sabin, N. D., Srivastava, D. K., … Krull, K. R. (2012). Cerebral white matter integrity and executive function in adult survivors of childhood medulloblastoma. *Neuro-Oncology*, *14*(Suppl 4), iv25–36. doi:10.1093/neuonc/nos214

Cohen, M. (1997). *Children's memory scale*. San Antonio, TX: Psychological Corporation.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan executive function system (D-KEFS)*. San Antonio, TX: Psychological Corporation.

Hardy, K. K., Bonner, M. J., Willard, V. W., Watral, M. A., & Gururangan, S. (2008). Hydrocephalus as a possible additional contributor to cognitive outcome in survivors of pediatric medulloblastoma. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*, *17*(11), 1157–1161. doi:10.1002/pon.1349

Kahalley, L. S., Conklin, H. M., Tyc, V. L., Hudson, M. M., Wilson, S. J., Wu, S., … Hinds, P. S. (2013). Slower processing speed after treatment for pediatric brain tumor and acute lymphoblastic leukemia. *Psychooncology*, *22*(9), 1979–1986. doi:10.1002/pon.3255

King, T. Z., Wang, L., & Mao, H. (2015). Disruption of white matter integrity in adult survivors of childhood brain tumors: Correlates with Long-Term intellectual outcomes. *PLoS One*, *10*(7), e0131744. doi:10.1371/journal.pone.0131744

Levin, H. S., Wilde, E. A., Chu, Z., Yallampalli, R., Hanten, G. R., Li, X., … Hunter, J. V. (2008). Diffusion tensor imaging in relation to cognitive and functional outcome of traumatic brain injury in children. *Journal of Head Trauma Rehabilitation*, *23*(4), 197–208. doi:10.1097/01.HTR.0000327252.54128.7c

Mabbott, D. J., Rovet, J., Noseworthy, M. D., Smith, M. L., & Rockel, C. (2009). The relations between white matter and declarative memory in older children and adolescents. *Brain Research*, *1294*, 80–90. doi:10.1016/j.brainres.2009.07.046

Makola, M., Douglas Ris, M., Mahone, E. M., Yeates, K. O., & Cecil, K. M. (2017). Long-term effects of radiation therapy on white matter of the corpus callosum: a diffusion tensor imaging study in children. *Pediatric Radiology*, *47*(13), 1809–1816. doi:10.1007/s00247-017-3955-1

McGrath, J., Johnson, K., O'Hanlon, E., Garavan, H., Gallagher, L., & Leemans, A. (2013). White matter and visuospatial processing in autism: a constrained spherical deconvolution tractography study. *Autism Research*, *6*(5), 307–319. doi:10.1002/aur.1290

Mulhern, R. K., Merchant, T. E., Gajjar, A., Reddick, W. E., & Kun, L. E. (2004). Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncology*, *5*(7), 399–408. doi:10.1016/S1470-2045(04)01507-4

Ostrom, Q. T., Gittleman, H., Truitt, G., Boscia, A., Kruchko, C., Barnholtz-Sloan, J. S. (2018). CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2011–2015. *Neuro-Oncology*, 20(suppl 4), iv1–iv86. doi:10.1093/neuonc/noy131

Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience*, *16*(7), 1227–1233. doi:10.1162/0898929041920441

Nelson, M. B., Macey, P. M., Harper, R. M., Jacob, E., Patel, S. K., Finlay, J. L., … Compton, P. (2014). Structural brain alterations in children an average of 5 years after surgery and chemotherapy for brain tumors. *Journal of Neuro-Oncology*, *119*(2), 317–326. doi:10.1007/s11060-014-1480-8

Palmer, S. L., Glass, J. O., Li, Y., Ogg, R., Qaddoumi, I., Armstrong, G. T., … Reddick, W. E. (2012). White matter integrity is associated with cognitive processing in patients treated for a posterior fossa brain tumor. *Neuro-Oncology*, *14*(9), 1185–1193. doi:10.1093/neuonc/nos154

Peters, B. D., Ikuta, T., DeRosse, P., John, M., Burdick, K. E., Gruner, P., … Malhotra, A. K. (2014). Age-related differences in white matter tract microstructure are associated with cognitive performance from childhood to adulthood. *Biological Psychiatry*, *75*(3), 248–256. doi:10.1016/j.biopsych.2013.05.020

Riggs, L., Bouffet, E., Laughlin, S., Laperriere, N., Liu, F., Skocic, J., … Mabbott, D. J. (2014). Changes to memory structures in children treated for posterior fossa tumors. *Journal of the International Neuropsychological Society*, *20*(2), 168–180. doi:10.1017/S135561771300129X

Robinson, K. E., Fraley, C. E., Pearson, M. M., Kuttesch, J. F., Jr., & Compas, B. E. (2013). Neurocognitive late effects of pediatric brain tumors of the posterior fossa: A quantitative review. *Journal of the International Neuropsychological Society*, *19*(1), 44–53. doi:10.1017/S1355617712000987

Robinson, K. E., Kuttesch, J. F., Champion, J. E., Andreotti, C. F., Hipp, D. W., Bettis, A., … Compas, B. E. (2010). A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatric Blood and Cancer*, *55*(3), 525–531. doi:10.1002/pbc.22568

Rueckriegel, S. M., Driever, P. H., Blankenburg, F., Ludemann, L., Henze, G., & Bruhn, H. (2010). Differences in supratentorial damage of white matter in pediatric survivors of posterior fossa tumors with and without adjuvant treatment as detected by magnetic resonance diffusion tensor imaging. *International Journal* of *Radiation Oncology Biology Physics*, *76*(3), 859–866. doi:10.1016/j.ijrobp.2009.02.054

Schaeffer, D. J., Krafft, C. E., Schwarz, N. F., Chi, L., Rodrigue, A. L., Pierce, J. E., … McDowell, J. E. (2014). The relationship between uncinate fasciculus white matter integrity and verbal memory proficiency in children. *Neuroreport*, *25*(12), 921–925. doi:10.1097/WNR.0000000000000204

Shortman, R. I., Lowis, S. P., Penn, A., McCarter, R. J., Hunt, L. P., Brown, C. C., … Sharples, P. M. (2014). Cognitive function in children with brain tumors in the first year after diagnosis compared to healthy matched controls. *Pediatric Blood and Cancer*, *61*(3), 464–472. doi:10.1002/pbc.24746

Tan, K., Meiri, A., Mowrey, W. B., Abbott, R., Goodrich, J. T., Sandler, A. L., … Wagshul, M. E. (2018). Diffusion tensor imaging and ventricle volume quantification in patients with chronic shunt-treated hydrocephalus: a matched case-control study. *Journal of Neurosurgery*, *129*, 1–12. doi:10.3171/2017.6.jns162784

Treit, S., Chen, Z., Rasmussen, C., & Beaulieu, C. (2014). White matter correlates of cognitive inhibition during development: a diffusion tensor imaging study. *Neuroscience*, *276*, 87–97. doi:10.1016/j.neuroscience.2013.12.019

Wechsler, D. (2003). *Wechsler intelligence scale for children–Fourth Edition (WISC-IV)*. San Antonio, TX: The Psychological Corporation.

Winter, A. L., Conklin, H. M., Tyc, V. L., Stancel, H., Hinds, P. S., Hudson, M. M., & Kahalley, L. S. (2014). Executive function late effects in survivors of pediatric brain tumors and acute lymphoblastic leukemia. *Journal of Clinical and Experimental Neuropsychology*, *36*(8), 818–830. doi:10.1080/13803395.2014.943695

Witelson, S. F., Kigar, D. L., Scamvougeras, A., Kideckel, D. M., Buck, B., Stanchev, P. L., … Black, S. (2008). Corpus callosum anatomy in right-handed homosexual and heterosexual men. *Archives of Sexual Behavior*, *37*(6), 857–863. doi:10.1007/s10508-007-9276-y

Wolfe, K. R., Madan-Swain, A., & Kana, R. K. (2012). Executive dysfunction in pediatric posterior fossa tumor survivors: a systematic literature review of neurocognitive deficits and interventions. *Developmental Neuropsychology*, *37*(2), 153–175. doi:10.1080/87565641.2011.632462

Wozniak, J., Krach, L., Ward, E., Mueller, B., Muetzel, R., Schnoebelen, S., … Lim, K. (2007). Neurocognitive and neuroimaging correlates of pediatric traumatic brain injury: a diffusion tensor imaging (DTI) study. *Archives of Clinical Neuropsychology*, *22*(5), 555–568. doi:10.1016/j.acn.2007.03.004

Yeh, F. C., Verstynen, T. D., Wang, Y., Fernandez-Miranda, J. C., & Tseng, W. Y. (2013). Deterministic diffusion fiber tracking improved by quantitative anisotropy. *PLoS One*, *8*(11), e80713. doi:10.1371/journal.pone.0080713