White matter integrity is associated with cognitive processing in patients treated for a posterior fossa brain tumor

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Children treated for posterior fossa tumors experience reduced cognitive processing speed and, after imaging, show damage to white matter (WM) tracts in the brain. This study explores relationships between white matter microstructure, assessed by fractional anisotropy (FA), and speed of cognitive processing using tract-based spatial statistics (TBSS). At 36 months after treatment with radiotherapy and chemotherapy, 40 patients completed an MRI examination and neuropsychological evaluation. Patients were matched with healthy control subjects based on age, sex, and race. Individual FA values were extracted from examinations for all voxels identified as having significant association between processing speed and FA using TBSS. The regions were labeled anatomically, and fiber tracts were grouped into larger fiber bundle categories based on their anatomical and functional associations. Analyses were performed between mean skeletal FA values in each of the fiber bundles and each of the cognitive processing scores controlling for age. Children 3 years after treatment for posterior fossa brain tumors demonstrate significantly lower processing speed associated with decreased FA, compared with their healthy peers. Commissural fibers in the corpus callosum were negatively affected by disease and therapy with detrimental consequence on patients’ cognitive processing. Diffusion tensor imaging of the white matter tracts in the brain is relevant to determining potential mechanisms underlying clinically meaningful change in cognitive performance. Neuroprotective strategies are needed to preserve critical functions.

Keywords: diffusion tensor imaging, FA, medulloblastoma, processing speed, TBSS.

Medulloblastoma occurs in the posterior fossa and is the most common form of malignant brain tumor diagnosed in children. Pediatric medulloblastoma can occur at any age but is typically diagnosed in children up to 10 years of age, with a peak incidence at 5 years of age.1,2 Because of the tumor’s high predilection to spread in the neuraxis, contemporary treatment protocols include maximal surgical resection, radiation therapy to the entire neuraxis and tumor bed in children ≥3 years of age, and adjuvant chemotherapy. Treatment is risk-adapted with those patients considered to be at high risk receiving higher doses of radiation therapy.3 Rates of survival have been steadily increasing. A recent report shows an overall 5-year survival rate of 85% for those patients with average-risk medulloblastoma and 70% for those with high-risk disease.3 However, successful treatment has been associated with an unacceptable number of long-term limitations in regard to function, especially as it relates to cognitive performance.4–7 An idea maintained in previous publications,8–10 slowed information processing speed may be the first cognitive deficit to emerge following treatment. The ability to process information efficiently normally increases rapidly at an early age and, among healthy children, continues to improve throughout childhood, eventually reaching adult levels of performance during late adolescence.11 Increases in knowledge and skill acquisition are associated with increases in processing speed. In contrast, children who have been treated for...
brain tumors have shown a decreased rate of knowledge and skill acquisition over time from diagnosis, leading to a decline in overall intellect.9,12 Deficits have also been found to be more prominent for those children who receive a diagnosis and are treated at a younger age.13

Recent studies have included diagnostic neuroimaging to supplement behavioral studies examining long-term impact of treatment, with results suggesting that this impaired speed of information processing may result from damage to the white matter (WM) structures of the brain.8,14,15 Myelination allows for faster conduction of electrical impulses,16 and unlike the unmyelinated gray matter that develops rapidly by 4 years of age, the process of myelination in the WM continues into the second decade of life.17 Therefore, WM maturity is directly related to age of the patient.

Consequently, WM has been found to be extremely vulnerable to injury from cranial radiation and chemotherapy, especially during periods of rapid myelination.4,18 WM volumes among children treated for medulloblastoma have been found to be reduced, compared with patients who have not received radiation.19,20 A subsequent longitudinal study14 found that, after treatment, both older and younger patients lost WM volume at a similar rate. However, because younger children begin treatment with a lower volume of mature WM, they experience greater deviation from expected developmental norms.15 In addition, studies of radiation dose-tissue response have shown that patients who received reduced doses had a slower rate of WM loss, compared with those who received the higher doses.15 This dose-tissue response among patients with medulloblastoma was also supported by Palmer et al., who found significant volume decreases in the posterior regions of the corpus callosum, the area nearest the tumor bed and receiving the highest doses of radiation.21 Thus, patients who are older at the time of treatment and, therefore, more neurologically mature may be better able to compensate for the detrimental effects of cranial radiation.

Although extremely valuable, quantitative volumetric imaging methods cannot detect changes to WM microstructure. Diffusion tensor imaging (DTI) is a magnetic resonance technique that allows researchers to examine the integrity of the WM tissue, measured as fractional anisotropy (FA). Normally, as a child ages, FA increases in a nonlinear pattern, corresponding to increasing axon myelination. In addition, the association between FA in specific brain regions and the development of cognitive functions has been established among healthy children and specific medical populations.22,23 While assessing children with traumatic brain injuries, researchers found that those with lower FA values in the corpus callosum also exhibited slower processing speed and reaction times.23,24 WM FA was also found to be associated with processing and motor speed in a small group of young cancer survivors.25

Previous studies have clearly shown that children treated for posterior fossa tumors are susceptible to WM damage and vulnerable to decreases in the ability to process information efficiently. Therefore using DTI and tract-based spatial statistics (TBSS), we explored how WM integrity may influence cognitive processing in children treated for posterior fossa tumors, compared with carefully matched, healthy control subjects.

Materials and Methods

Patients

Study participants were enrolled on an institutional review board–approved clinical trial for patients with newly diagnosed medulloblastoma or atypical teratoid rhabdoid tumor. Written consent was obtained for participation. Patients who were at least 3 years from diagnosis were eligible for the study (n = 66). At 36 months after diagnosis, patients must have completed an MRI examination, including DTI sequences, and a valid neuropsychological evaluation, including an assessment of information processing speed. Patients were excluded because of metallic artifacts (n = 2), missing DTI (n = 5), or poor quality on MRI restricting normalization (n = 3). Additional exclusion criteria included language barriers restricting valid neuropsychological evaluation (n = 2), poor physical well-being restricting valid assessment during their scheduled visit (n = 3), progressive disease for which the patient was taken off study (n = 3), pre-existing psychological deficits (n = 4), parent refusal (n = 6), and completing a partial neuropsychological evaluation that did not include information processing speed (n = 1). One additional patient was excluded because of severe residual posterior fossa syndrome.

Forty patients (27 males and 13 females) ranging in age from 3.1 to 20.3 years at diagnosis (Mean = 9.9 years, SD = 4.3), and from 6.0 to 23.5 years of age at time of evaluation (Mean = 12.8, SD = 4.4), were included in the study group. According to enrollment documents, 33 patients were white, 3 were African American, 2 were Asian, and 2 were classified as “other.”

All patients underwent maximal surgical resection, and 2 of the 40 patients received a diagnosis of post-surgery posterior fossa syndrome that resolved prior to the chemotherapy phase of treatment. All patients were treated with risk-adapted craniospinal irradiation (CSI), followed by 4 cycles of high-dose chemotherapy (cyclophosphamide, cisplatin, and vincristine) with stem cell support. High-risk (HR, n = 7) patients received 36–39.6 Gy CSI and a 3-D conformal boost of 55.8–59.4 Gy to the primary site. The HR patients included 6 who received a diagnosis of medulloblastoma and 1 patient with atypical teratoid rhabdoid tumor. Average-risk (AR, n = 33) patients received 23.4 Gy CSI and a 3-D conformal boost of 55.8 Gy to the primary site. Thirty-two patients with medulloblastoma and 1 with atypical teratoid rhabdoid tumor comprised the AR group.
Healthy Controls

Control participants were enrolled on an institutional review board–approved clinical trial examining neural substrates of reading. Written consent was obtained for participation. Those who were at least 6 years of age were eligible for the study (n = 93). Each control subject completed an MRI examination with DTI sequences and a valid neuropsychological evaluation, including an assessment of information processing speed. Forty control subjects were matched with corresponding patients based on age at the time of the MRI. Control subjects were an average of 12.86 years of age (range, 6.03–23.68 years). Thirty-nine pairs were also matched according to sex (n = 26 males) and 35 were matched according to race (n = 36 white, n = 4 African American).

Assessment of Information Processing Speed

All participants completed a protocol-driven evaluation of cognitive function using the Woodcock-Johnson Tests of Cognitive Abilities (Third Edition). The Woodcock-Johnson battery was extensively normalized, using >8800 healthy subjects in >100 geographically diverse US communities. Two subtests designed to measure speed of information processing were of particular interest: (i) decision speed developed to test processing of semantic information and (ii) visual matching developed to test speed of processing visual perceptual information. Together, these 2 subtests combine to produce the processing speed composite score, a standardized measure of overall processing speed. Age-adjusted standard scores have a population mean of 100 and a SD of 15.

Diffusion Tensor Imaging

MR Acquisition.—Diffusion tensor imaging was acquired on one of two 1.5 Tesla Avanto MR scanners (Siemens Medical Systems) using bipolar diffusion-encoding gradients to reduce gradient-induced eddy currents that cause image distortion and degradation. All images were acquired using a double-spin echo echo-planar imaging (EPI) pulse sequence (TR/TE = 10/100 ms, b = 1000 ms). Imaging sets were acquired as forty 3-mm thick contiguous axial sections with whole-head coverage, 128 square matrix, and 22-cm field-of-view (acquired resolution of 1.7 × 1.7 × 3.0 mm). Four acquisitions were acquired with 12 non-coplanar, noncplanar diffusion gradient directions to calculate the diffusion tensor for each voxel and to ensure the highest signal to noise possible in a limited amount of time to minimize the risk-benefit ratio for this young vulnerable population.

DTI Analysis.—Voxel-wise tensor calculations were performed with the DTI toolkit under SPM8 (http://www.flim.ion.ucl.ac.uk/spm/). Data from the 4 acquisitions were realigned before tensor calculation to correct for linear image drift, and the mean of the 4 realigned image sets were used for tensor calculation. After the tensors were calculated, Eigen-values were derived to calculate an FA map for the whole brain.

Tract-Based Analyses.—The quantitative DTI maps of FA were processed following the TBSS pipeline, part of FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl). TBSS is more reliable than other techniques because it minimizes inter-subject variability. TBSS registration non-linearly transformed the FA images into a standard space using the FMRIB58_FA image as the target. After registration, the tract skeletonization process was performed using an FA lower threshold of 0.25. The final WM skeleton represented the fiber bundle centers across both patients and control subjects. FA skeletons were compared between patients with medulloblastoma and control subjects with use of the randomize permutation algorithm in FSL to perform multiple regression analyses. Voxel-wise tests were performed with 5000 permutations using threshold-free cluster enhancement (TFCE) while treating age as a covariate. Multiple comparisons were accounted for by controlling for family-wise error rates. The first analysis performed was a simple group-wise Student’s t test of FA values between patients and control subjects. The contrast of interest was the FA of voxels, which were greater in control subjects than in patients.

Additional analyses performed were conducted using the following multiple linear regression,

\[ FA_i = \beta_0 + \beta_1 \text{group}_i + \beta_2 \text{PS}_i + \beta_3 (\text{group}_i \times \text{PS}_i) + \beta_4 \text{age}_i + \epsilon_i, \]

where \( i = 1, \ldots, 80 \) and \( \epsilon_i \) is a random error.

In this equation, the group variable was set to one for patients and zero for control subjects. Age was defined as the age of the subject at examination, and processing speed (PS) was the overall speed of processing standard cluster score for each subject. The second analysis evaluated voxels in which PS was significantly associated with FA including the entire subject pool, both patients and control subjects. The third analysis identified voxels that were significantly different between patients and control subjects in their FA association with overall speed of processing standard cluster score. Only fully corrected \( P \) values <.01 generated by 5000 permutations were considered to be statistically significant.

The identified regions were labeled anatomically using the JHU-ICBM-DTI-81 WM atlas. Fiber tracts were grouped according to anatomical and functional associations with larger fiber bundles.

Statistical Approach.—All statistical analyses were conducted using a statistical software package (SPSS for Windows, version 15.0, 2006; SPSS). Speed of information processing was examined for all participants. Measures of PS were also examined among the patient group with regard to risk (AR vs HR) and age at the time of diagnosis. Paired sample t tests were conducted.
to compare patients and control subjects on visual matching, decision speed, and overall processing speed. Paired sample \( t \) tests were also conducted to compare FA in each identified fiber tract.

The observed WM FA in each fiber bundle demonstrated a positive relationship with age of the patient. Therefore, post hoc regression analyses were completed to remove age-related variance. Separate models were developed for each fiber bundle to determine whether the relationship between FA and processing speed remained significant after accounting for age. Because of the exploratory nature of the study, no adjustment was made for multiple comparisons.

**Results**

**Processing Speed**

**Patients.**—Overall PS was found to be in the low average range for the patient group (Mean = 85.6, SD = 15.0). Visual matching was also in the low average range (Mean = 82.2, SD = 14.9), whereas decision speed was in the average range (Mean = 92.5, SD = 14.1; Table 1). AR patients had a mean overall PS score of 86.3 (SD = 14.4), and HR patients had a mean overall PS score of 82.0 (SD = 18.3). Patients in both risk groups were considered to be in the low average range. No statistically significant differences between the 2 groups were evident.

Visual matching and overall PS standard scores were significantly related to age of the patient at diagnosis. The younger the child at diagnosis, the lower the visual matching score at 36 months after diagnosis (\( r = 0.36, P < .05 \)). The overall PS score also showed a significant relationship to age (\( r = 0.34, P < .05 \)). There was no significant relationship between age at diagnosis and decision speed subtest scores (\( r = 0.22, NS \)). Because evaluation of PS was done 3 years after diagnosis, age of the patient at the time of evaluation showed the same relationships to outcome scores, for both strength and significance.

**Controls.**—Healthy control patients were found to be in the average range on all 3 measures of cognitive processing: overall PS (Mean = 107.4, SD = 11.5), visual matching (Mean = 101.4, SD = 10.1), and decision speed (Mean = 112.6, SD = 13.8). These scores were all significantly higher than those of the patients (\( P < .001 \); Table 1).

As expected, there were no significant relationships between age of the subject at evaluation and overall PS, visual matching, or decision speed standard scores in the healthy control group (\( r = 0.18, r = 0.11, r = 0.20 \) respectively; NS).

**White Matter Integrity**

With use of the TBSS-based analyses as described above, a simple group-wise Student’s \( t \) test of FA values between patients and control subjects was completed. The voxels in which control subjects were found to have greater FA than that of patients were of interest. FA throughout a large majority of the fiber tracts was significantly greater in control subjects than in patients (Fig. 1, top).

The second TBSS analysis evaluated voxels in which PS was significantly associated with FA, in both patients and control subjects. The multiple regression model demonstrated that overall PS was associated with widespread and numerous fiber tracts throughout the brain (Fig. 1, middle).

The third TBSS analysis identified voxels that were significantly different between patients and control subjects in their association with overall PS score (Fig. 1, bottom). FA from these identified regions were categorized into 9 fiber bundles based on anatomical and functional associations,\(^3\) including corpus callosum, cerebral peduncle, internal capsule, corona radiate, post thalamic radiation, sagittal stratum, external capsule, cingulum, and superior longitudinal fasciculus. In each of the fiber bundles, patients had significantly lower FA, compared with control subjects (Table 2). There was no significant difference in FA between AR and HR patients in any of the bundles.

**Age at Diagnosis**

In the patient group, FA in each of the 9 bundles was significantly related to age at diagnosis. As age of the patient increased, FA also increased. Given these findings, examination of the relationship between FA in each bundle and speed of information processing was completed controlling for age. Of the 9 bundles originally identified by the TBSS methodology, 3 bundles were found to remain significantly related to overall PS in the patient group after controlling for age at diagnosis: corpus callosum, post thalamic radiation, and external capsule.

| Table 1. Speed of processing for 40 patients compared with 40 matched healthy control subjects with use of paired samples \( t \) tests (Population Mean = 100, SD = 15) |
|----------------------------------|-----------|-----------|--------|--------|
| Patients Mean (SD) | Controls Mean (SD) | \( t \)-value | \( P \) value (2-tailed) |
| Overall processing speed | 85.62 (15.02) | 107.45 (11.35) | -6.79 | <.001 |
| Decision speed | 92.55 (14.13) | 112.65 (13.84) | -6.14 | <.001 |
| Visual matching | 82.22 (14.92) | 101.45 (10.13) | -6.28 | <.001 |
Results for analyses of fiber bundle FA, visual matching, and decision speed are presented in Table 3. After thalamic radiation, FA was significantly related to decision speed ($r = 0.34$, $P < .05$), whereas that of the external capsule was significantly related to visual matching ($r = 0.42$, $P < .01$). The corpus callosum FA was found to be significantly related to both visual matching ($r = 0.39$, $P < .05$) and decision speed ($r = 0.35$, $P < .05$). FA in 3 areas of the corpus callosum was examined in relation to processing outcome: genu, body, and splenium. The genu FA was significantly related to visual matching ($r = 0.35$, $P = .026$) and showed a trend toward a significant relation with overall PS ($r = 0.31$, $P = .05$). The FA in the body of the corpus callosum was significantly related to all 3 measures of PS, visual matching ($r = 0.37$, $P = .017$), decision speed ($r = 0.32$, $P = .044$), and overall PS ($r = 0.38$, $P = .016$). The splenium FA showed a significant relation to decision speed ($r = 0.37$, $P = .019$) and overall PS ($r = 0.37$, $P = .018$).

![Fractional anisotropy (FA) skeleton mask](image)

Fig. 1. Fractional anisotropy (FA) skeleton mask (green). Top: Voxels where FA is significantly higher ($P < .01$) in controls when compared to patients (red). Middle: Voxels where FA is significantly associated with overall processing speed (red). Bottom: Voxels that are significantly different between patients and controls in their association with processing speed (red).

Table 2. Mean fractional anisotropy (FA) within white matter fiber bundles associated with speed of processing and significantly different between 40 patients and 40 matched healthy control subjects

<table>
<thead>
<tr>
<th>Fiber Bundle</th>
<th>Patients Mean (SD)</th>
<th>Controls Mean (SD)</th>
<th>t value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corpus Callosum</td>
<td>0.7257 (0.047)</td>
<td>0.7624 (0.032)</td>
<td>−4.709 (**)</td>
</tr>
<tr>
<td>Cerebral peduncle</td>
<td>0.7280 (0.039)</td>
<td>0.7712 (0.036)</td>
<td>−6.416 (**)</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>0.6565 (0.033)</td>
<td>0.6897 (0.025)</td>
<td>−5.902 (**)</td>
</tr>
<tr>
<td>Corona radiata</td>
<td>0.5403 (0.040)</td>
<td>0.5647 (0.027)</td>
<td>−3.797 (**)</td>
</tr>
<tr>
<td>Post thalamic radiation</td>
<td>0.6035 (0.044)</td>
<td>0.6354 (0.031)</td>
<td>−3.829 (**)</td>
</tr>
<tr>
<td>Sagittal stratum</td>
<td>0.5734 (0.048)</td>
<td>0.6118 (0.038)</td>
<td>−4.462 (**)</td>
</tr>
<tr>
<td>External capsule</td>
<td>0.5254 (0.046)</td>
<td>0.5575 (0.033)</td>
<td>−4.079 (**)</td>
</tr>
<tr>
<td>Cingulum</td>
<td>0.5580 (0.058)</td>
<td>0.5927 (0.051)</td>
<td>−3.591 (*)</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus</td>
<td>0.5516 (0.034)</td>
<td>0.5770 (0.029)</td>
<td>−5.236 (**)</td>
</tr>
</tbody>
</table>

*Significance (2-tailed) $P < .01$.
**Significance (2-tailed) $P < .001$. 
Proposed Conceptual Model

Our results suggest that a younger age at time of diagnosis is associated with increased risk for slowed PS and reduced WM FA in the corpus callosum. Even after controlling for age-related variance, relationships between the FA of the corpus callosum and each of the PS measures remained significant. Therefore, we explored a mediational model to clarify the relationship between age at diagnosis and speed of processing. We hypothesized that age at diagnosis determines corpus callosum FA, which in turn influences overall PS (Fig. 2).

<table>
<thead>
<tr>
<th>Fiber bundle</th>
<th>Visual matching (P value)</th>
<th>Decision speed (P value)</th>
<th>Overall processing speed (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corpus callosum</td>
<td>0.39 (0.015)</td>
<td>0.35 (0.031)</td>
<td>0.41 (0.010)</td>
</tr>
<tr>
<td>Genu</td>
<td>0.35 (0.026)</td>
<td>0.21 (NS)</td>
<td>0.31 (0.050)</td>
</tr>
<tr>
<td>Body</td>
<td>0.37 (0.017)</td>
<td>0.32 (0.044)</td>
<td>0.38 (0.016)</td>
</tr>
<tr>
<td>Splenium</td>
<td>0.30 (NS)</td>
<td>0.37 (0.019)</td>
<td>0.37 (0.018)</td>
</tr>
<tr>
<td>Cerebral peduncle</td>
<td>0.22 (NS)</td>
<td>0.23 (NS)</td>
<td>0.26 (NS)</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>0.22 (NS)</td>
<td>0.15 (NS)</td>
<td>0.21 (NS)</td>
</tr>
<tr>
<td>Corona radiata</td>
<td>0.22 (NS)</td>
<td>0.21 (NS)</td>
<td>0.24 (NS)</td>
</tr>
<tr>
<td>Post thalamic radiation</td>
<td>0.26 (NS)</td>
<td>0.34 (0.033)</td>
<td>0.33 (0.042)</td>
</tr>
<tr>
<td>Sagittal stratum</td>
<td>0.26 (NS)</td>
<td>0.20 (NS)</td>
<td>0.26 (NS)</td>
</tr>
<tr>
<td>External capsule</td>
<td>0.42 (0.007)</td>
<td>0.23 (NS)</td>
<td>0.37 (0.022)</td>
</tr>
<tr>
<td>Cingulum</td>
<td>0.29 (NS)</td>
<td>0.26 (NS)</td>
<td>0.30 (NS)</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus</td>
<td>0.18 (NS)</td>
<td>0.11 (NS)</td>
<td>0.17 (NS)</td>
</tr>
</tbody>
</table>

Proposed Conceptual Model

Results of the current study are relevant in determining a potential mechanism underlying the ability to process information efficiently. Evaluation of cognitive processing and related FA clearly reveals significant differences between patients treated for a posterior fossa tumor and healthy, carefully matched control subjects. Outcomes demonstrate that patients are at risk for significant deficits in PS as early as 36 months after diagnosis. Compared with healthy matched peers, patients had significantly slower overall PS, visual matching, and decision speed. The younger the patient was at time of diagnosis, the slower their PS outcome scores. Age of the patient serves as a proxy variable for processes...
of maturation in the WM tracts throughout the brain, and therefore, the two are highly correlated.\textsuperscript{12,33} TBSS-based analyses of WM FA found significant age-related variance in both patients and control subjects. Patients were found to have significantly lower FA, compared with that of control subjects throughout widespread WM fiber tracts (Fig. 1, top), indicating pervasive disruption to patients’ WM integrity.

The TBSS methodology allowed comparison of FA in each voxel to determine WM tracts that significantly differed between patients and their matched control subjects in their association with overall PS. Even after controlling for age-related variance in FA, commissural fibers within genu, body, and splenium of the corpus callosum were found to be associated with overall PS. Further investigation resulted in a proposed conceptual model of this relationship. To our knowledge, this is the first study to demonstrate that PS performance in this patient group is mediated by the integrity of WM tracts located throughout the corpus callosum. Our findings are consistent with the hypothesis that WM integrity and associated efficiency in signal conduction intervenes the ability to process information in a timely manner.

The positive relationship found between speed of processing and corpus callosum FA in the present study coincides with previous examinations of these factors in children who have suffered a traumatic brain injury.\textsuperscript{23,34} Slowed visual matching has also been significantly associated with lower FA of the corpus callosum among children with multiple sclerosis,\textsuperscript{25} and in a group of healthy children, visual matching was dependent on the WM integrity in the frontal-parietal region, mediating age-related changes in this core cognitive skill.\textsuperscript{33} Reduced FA in the splenium has also been reported in cohorts of children with deficits of attention\textsuperscript{16} who were also found to have significantly decreased functional connectivity in the posterior cingulate cortex and lateral prefrontal cortex. An examination of cognitive function in a small group of young childhood cancer survivors, including 6 patients treated for medulloblastoma and 11 treated for leukemia, found PS to be significantly related to WM FA in the body and splenium of the corpus callosum.\textsuperscript{25} However, Aukema et al. did not find age-related increases in FA and, therefore, did not correct for age in their analyses, nor did they test for mediational relationships.

In healthy children, overall corpus callosum volume continues to increase throughout adolescence, largely driven by growth in the mid-regions and the splenium.\textsuperscript{22,37,38} This growth is thought to be attributable to myelination of the interhemispheric axons that compose the corpus callosum. Although significant gains in corpus callosum volume are expected for healthy children, those treated for medulloblastoma experience significant decreases in volume over time after treatment.\textsuperscript{21} Insult of cranial spinal irradiation to the corpus callosum may result in ≥1 processes, including injury to pre-existing myelination, disruption of ongoing myelination, ischemia, and infarction.\textsuperscript{18}

As the largest WM tract in the brain, the corpus callosum is easily identified and less susceptible to error in image processing. Together with the advent of DTI, precise mapping of corpus callosum projections in vivo is possible. Studies of cortical projection topography have found a significant number of connections through the corpus callosum to both the primary and extrastriate areas of the visual cortex (Broadman areas 17, 18, and 19) and the posterior areas of the parietal lobe (Broadman areas 5, 7, 23, 29, 30, and 31), encompassing the posterior cingulate.\textsuperscript{39} Broadman areas 17, 18, and 19 are vital to processing visual information. The PS tasks used in the present study rely heavily on the input of visually derived information. The patients were asked to visually scan rows of small diagrams and either circle the 2 matching objects or circle 2 objects that are most similar in meaning. Therefore, the integrity of the connections that flow through the corpus callosum would be critical to successfully performing these tasks.

Limitations to the present study include the use of cross-sectional methodology. Investigation of FA in the corpus callosum over time would allow for definitive conclusions with regard to change in FA from the onset of treatment. Both volumetric and diffusion imaging would be advantageous in determining whether macrostructural changes (volume) relate to microstructural changes (FA). This may help to determine the most cost-effective and efficient manner in determining a suitable biomarker for decreases in speed of processing experienced by this group of children. Future DTI studies using longitudinal methods may hold prognostic value in determining the course of information processing deficits and understanding the vulnerability of this population of children, especially for those who receive a diagnosis at a young age.

**Conclusion**

Treatment for a posterior fossa tumor is associated with slowed visual matching, semantic, and overall PS, compared with healthy matched peers. These deficits in function are associated with widespread reduction in the integrity of multiple WM tracts and are evident as early as 36 months after diagnosis. These results emphasize the need for neuroprotective strategies to preserve the structure and function of an increasing number of long-term survivors of pediatric posterior fossa tumors. Future research should incorporate examination of the role that WM integrity plays in mediating change in cognitive performance.

**Conflict of interest statement.** None declared.
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