Vulnerability of white matter to insult during childhood: evidence from patients treated for medulloblastoma

Iska Moxon-Emre, MSc, MA,^{1–3} Eric Bouffet, MD,⁴ Michael D. Taylor, MD, PhD,^{5,6} Normand Laperriere, MD,^{7,8} Michael B. Sharpe, PhD,^{7,8} Suzanne Laughlin, MD,⁹ Ute Bartels, MD,⁴ Nadia Scantlebury, PhD,¹ Nicole Law, PhD,^{1,2} David Malkin, MD,^{3,4,10} Jovanka Skocic, BA,¹ Logan Richard, MSc,^{1,2} and Donald J. Mabbott, PhD^{1,2}

¹Program in Neuroscience and Mental Health and Divisions of ⁴Hematology/Oncology, ⁵Neurosurgery, and ⁹Diagnostic Imaging, Hospital for Sick Children, Toronto; Departments of ²Psychology, ⁶Neurosurgery, ⁸Radiation Oncology, and ¹⁰Paediatrics, University of Toronto; ³Pediatric Oncology Group of Ontario, Toronto; and ⁷Radiation Oncology, Ontario Cancer Institute, Princess Margaret Hospital, Toronto, Ontario, Canada

OBJECTIVE Craniospinal irradiation damages the white matter in children treated for medulloblastoma, but the treatment-intensity effects are unclear. In a cross-sectional retrospective study, the effects of treatment with the least intensive radiation protocol versus protocols that delivered more radiation to the brain, in addition to the effects of continuous radiation dose, on white matter architecture were evaluated.

METHODS Diffusion tensor imaging was used to assess fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity. First, regional white matter analyses and tract-based spatial statistics were conducted in 34 medulloblastoma patients and 38 healthy controls. Patients were stratified according to those treated with 1) the least intensive radiation protocol, specifically reduced-dose craniospinal irradiation plus a boost to the tumor bed only ($n = 17$), or 2) any other dose and boost combination that delivered more radiation to the brain, which was also termed the “all-other-treatments” group ($n = 17$), and comprised patients treated with standard-dose craniospinal irradiation plus a posterior fossa boost, standard-dose craniospinal irradiation plus a tumor bed boost, or reduced-dose craniospinal irradiation plus a posterior fossa boost. Second, voxel-wise dose-distribution analyses were conducted on a separate cohort of medulloblastoma patients ($n = 15$).

RESULTS The all-other-treatments group, but not the reduced-dose craniospinal irradiation plus tumor bed group, had lower fractional anisotropy and higher radial diffusivity than controls in all brain regions (all $p < 0.05$). The reduced-dose craniospinal irradiation plus tumor bed boost group had higher fractional anisotropy ($p = 0.05$) and lower radial diffusivity ($p = 0.04$) in the temporal region, and higher fractional anisotropy in the frontal region ($p = 0.04$), than the all-other-treatments group. Linear mixed-effects modeling revealed that the dose and age at diagnosis together 1) better predicted fractional anisotropy in the temporal region than models with either alone ($p < 0.005$), but 2) did not better predict fractional anisotropy in comparison with dose alone in the occipital region ($p > 0.05$).

CONCLUSIONS Together, the results show that white matter damage has a clear association with increasing radiation dose, and that treatment with reduced-dose craniospinal irradiation plus tumor bed boost appears to preserve white matter in some brain regions.

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KEY WORDS medulloblastoma; craniospinal irradiation; dose-response relationship; white matter; diffusion tensor imaging; oncology

A CRITICAL issue in cancer therapy is characterizing the trade-off between the intensity of treatment and its long-term effects. This understanding is integral to providing care that maximizes cure rates while mini-

mizing negative sequelae. Children with brain tumors are a particularly informative population in which to study this interplay, and they stand to benefit from treatment adjustment. In 2 medulloblastoma patient cohorts, we evalu-

ABBREVIATIONS AD = axial diffusivity; CSI = craniospinal irradiation; CSI+PF = CSI plus posterior fossa; CSI+TB = CSI plus tumor bed; DTI = diffusion tensor imaging; FA = fractional anisotropy; FOV = field of view; FSL = Functional MRI of the Brain Software Library; MD = mean diffusivity; MNI = Montreal Neurological Institute; RD = radial diffusivity; ROI = region of interest; TBSS = tract-based spatial statistics.

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ated the relations between white matter architecture and 1) radiation treatment intensity (i.e., protocols that deliver varying degrees of radiation to the brain) and 2) radiation dose distributions.

Medulloblastoma is the most common childhood malignant CNS tumor, accounting for 50% of all posterior fossa tumors.²³ Current treatment protocols include surgery, craniospinal irradiation (CSI) with a boost to the tumor site, and chemotherapy. Although this therapeutic combination is life-saving, it contributes to long-term physical, endocrinological, and neuropsychological impairments in the survivors.²⁰ CSI treatment for medulloblastoma contributes to white matter damage, and dose-dependent volumetric and structural changes have been reported.^{11,15,21,26} However, the impact of clinically relevant CSI dose and boost volume combinations on region-specific white matter architecture is unknown. It is also unclear if reduced radiation preserves white matter. To bridge these gaps, we used diffusion tensor imaging (DTI) to compare white matter architecture as a function of the radiation treatment protocol and radiation dose.

Historically, patients with medulloblastoma were stratified into average- or high-risk disease groups.²³ A lack of neuraxis dissemination and/or no minimal residual tumor following surgery characterizes average-risk disease.¹⁸ Typically, average- and high-risk patients receive reduced- (i.e., 2340 cGy) or standard-dose CSI (i.e., 3600 cGy) to the neuraxis, respectively.²³ Initially, CSI was followed by a boost to the entire posterior fossa, but the past 2 decades have seen the development of conformal techniques that limit radiation delivery to the tumor bed.³⁵ Event-free survival in children treated with posterior fossa boost compared with tumor bed boost is uncertain, but this is the focus of The Children's Oncology Group ACNS0331 trial. The posterior fossa boost delivers more radiation to structures located outside the targeted area, especially the temporal lobes, than a boost to the tumor bed.³⁵ Thus, with these CSI doses and boosts, there is only 1 combination that considerably limits radiation exposure to the brain: reduced-dose CSI plus tumor bed (CSI+TB) boost. Although overall white matter volume changes have been documented as a function of conventional versus reduced radiation dose,²⁶ we are the first to use DTI to evaluate the impact of radiation on white matter according to treatment protocols that differ in terms of boost volume and to also consider the dose distributions.

DTI generates quantifiable indices based on the displacement and directionality of water, and its properties are thought to reflect white matter organization.³ These indices include fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD).⁹ Lower FA and higher MD/AD/RD values are thought to signify compromised myelin sheath integrity and axonal degeneration.³¹ For instance, as white matter becomes less organized, diffusion perpendicular to the fiber increases and the FA value decreases.²² Moreover, increasing AD correlates with axonal damage,³² and increasing RD is a sensitive marker of demyelination.⁸ This level of architectural detail cannot be gleaned from volumetric studies of white matter.

Regional differences must be considered to appropri-

ately capture the effect of radiation on white matter. During CSI, no brain regions are shielded from radiation; however, not all structures are equally susceptible to radiation-induced damage. Brain regions that harbor stem and progenitor cells that continue to undergo neurogenesis are known to be particularly sensitive.⁴ Structures and tracts with long periods of development may also be especially vulnerable to insult during childhood. Whole-brain white matter volume increases during childhood and adolescence,¹³ and prefrontal cortex myelination continues into the 3rd decade of life.³⁴

To the best of our knowledge, the present study is the first to evaluate the effect of clinically relevant CSI dose and boost volume combinations and to consider the continuous effect of radiation dose distribution on white matter architecture using DTI. We expect that treatment with reduced-dose CSI+TB boost will be accompanied by less white matter damage^{11,15,21,26} and possibly white matter sparing.

Methods

Participants

Thirty-four children treated for medulloblastoma between 1998 and 2012 at the Hospital for Sick Children (SickKids; Toronto, Ontario, Canada) and 38 healthy control children participated. We evaluated the impact of the treatment intensity protocols in this cohort. In a separate cohort of 15 patients, we evaluated the dose-distribution effects. The demographic variables of these cohorts are summarized in Tables 1 and 2. Patients were excluded if they had recurrent disease or premorbid neurological disorders or were receiving palliative care. Controls were free of neurological or clinical disorders and had normal findings on MRI scans (confirmed by a neuroradiologist [S.L.]). Patients were informed of this study via mailed letters, or during routine clinic visits when applicable. Controls were recruited from the community, were siblings of patients, or were family members of the SickKids staff. This study was approved by our research ethics board. Prior to participation, parents provided written informed consent and children provided assent.

Patient Treatment Information

Radiation Therapy

All patients were treated with photon beam CSI and received either a standard (3060–3940 cGy) or reduced (1800–2340 cGy) dose. Due to treatment protocol changes, patients seen before 2006 received a lateral-beam boost to the posterior fossa, whereas from 2006 onwards patients routinely received an intensity-modulated radiation therapy boost with a 1-cm margin around the tumor bed (SJMB03 protocol). We leveraged this protocol change and divided patients into those treated with 1) the least intensive radiation protocol (i.e., reduced-dose CSI+TB boost) and 2) any other dose and boost combination that delivered more radiation to the brain (i.e., “all-other-treatments” [standard-dose CSI plus posterior fossa (CSI+PF) boost, reduced-dose CSI+PF boost, and standard-dose CSI+TB boost]). The medical variables are summarized in Table 1.

TABLE 1. Demographic and medical variables of the treatment intensity protocol cohort*

Variable	Healthy Controls	Reduced-Dose CSI+TB Boost	All Other Treatments	p Value†
No. of patients	38	17	17	
Male sex	20 (52.6)	8 (47.1)	11 (64.7)	0.57
Age at diagnosis in yrs‡				0.001
Mean (SD)		8.68 (2.74)	5.70 (2.06)	
Range		4.1–15.2	1.3–9.6	
Age at scan in yrs				0.03
Mean (SD)	12.55 (2.91)	11.26 (2.62)	14.08 (3.39)	
Range	6.9–18.6	7.9–16.4	8.2–18.7	
Time since diagnosis in yrs				<0.001
Mean (SD)		2.74 (1.55)	8.37 (3.12)	
Range		1.1–5.7	3.0–13.6	
CSI				<0.001
Standard+PF boost			6	
Standard+TB boost			3	
Reduced+PF boost			8	
Reduced+TB boost		17		
Chemotherapy§				<0.001
Protocol (no. of patients treated)		SJMB03 (17)	SJMB03 (2), POG9631 (5), CCG9961 (7), MOPP (1), ACNS0331 (1)	
Gross-total resection		17 (100)	14 (82.4)	0.07
Clinical risk (average risk)		17 (100)	8 (47.1)	<0.001
Hydrocephalus				
Presence at diagnosis		15 (88.2)	12 (70.6)	0.20
Hydrocephalus requiring CSF diversion		12 (70.6)	8 (47.1)	0.16
3rd ventriculostomy		3 (17.6)	2 (11.8)	0.63
EVD only		7 (41.2)	4 (23.5)	0.27
VPS		3 (17.6)	4 (23.5)	0.67
≥1 revision		1 (5.9)	3 (17.6)	0.29
Mutism¶		3 (17.6)	7 (41.2)	0.13
Motor deficits**		14 (82.4)	11 (64.7)	0.24
Cranial nerve deficits††		4 (23.5)	3 (17.6)	0.67
Multiple postop complications		11 (68.8)	10 (58.8)	0.55
MRI scan type				0.29
1.5 T	22 (57.9)	8 (47.1)	6 (35.3)	
3.0 T	16 (42.1)	9 (52.9)	11 (64.7)	
Tumor size in mm²‡‡				0.14
Mean (SD)		2227.4 (894.66)	1753.77 (696.33)	
Range		1050–3770	957–3000	

EVD = external ventricular drain; VPS = ventriculoperitoneal shunt.

* Values are shown as number (%) for each group unless otherwise indicated.

† The p values were determined using the chi-square test for categorical variables, t-test for comparisons of patient groups, or 1-way ANOVA for comparisons between the 3 groups.

‡ For the entire patient sample, the mean age (SD) at diagnosis was 7.18 (2.83) years and the range was 1.32 to 15.16 years, whereas the mean age (SD) at CSI was 7.30 (2.87) years and the range was 1.99 to 15.31 years. The patient diagnosed at 1.3 years received CSI at 2 years. In most instances, the time between diagnosis and CSI was shorter (mean [SD] 0.11 [0.21]).

§ Chemotherapy protocols and their associated agents included the following: SJMB03 (vincristine, cisplatin, and cyclophosphamide); POG9631 (etoposide, cisplatin, cyclophosphamide, and vincristine); CCG9961 (vincristine, lomustine/cyclophosphamide, and cisplatin); MOPP (mechlorethamine, vincristine, procarbazine, and prednisone); and ACNS0331 (vincristine, cisplatin, lomustine, and cyclophosphamide).

¶ Mutism includes diminished speech output, linguistic difficulties, or dysarthria following surgery.

** Motor deficits includes ataxia, dysmetria, or hemiparesis on neurological examination.

†† Cranial nerve deficits include cranial nerve palsy on neurological examinations.

‡‡ Tumor size was calculated by multiplying the 2 largest measurements of the tumor on an anatomical MRI scan. Data were unavailable for 6 patients (2 patients in the reduced dose CSI+TB group, and 4 patients in the all-other-treatments group).

Chemotherapy

Patients were treated with a number of different protocols (SJMB03, POG9631, CCG9961, MOPP, and ACNS0331) and received different chemotherapeutic agents as a result. The number of patients treated with each protocol, and the agents used in each, are provided in Tables 1 and 2. During radiation therapy, patients treated with the POG9631 protocol received oral etoposide, patients treated with the CCG9961 protocol received weekly vincristine, and patients treated with the ACNS0331 protocol received weekly vincristine. Patients treated with the SJMB03 and MOPP protocols did not receive concurrent chemotherapy during radiation therapy. All patients received chemotherapy after radiation therapy.

Neuroimaging Protocol

MRI was performed at SickKids using either a GE LX 1.5-T MRI scanner with an 8-channel head coil or a Siemens 3-T whole-body MRI scanner (Trio Tim syngo MR B17 system) with a 12-channel head coil. The GE LX 1.5-T MRI protocol included a 3D T1-weighted, fast spoiled, gradient-echo, inversion recovery-prepared sequence (TI 400 msec; TE/TR 4.2/10.056 msec; 116–124 contiguous axial slices; flip angle 20°; 256 × 192 matrix interpolated to 256 × 256; FOV 240 × 240 mm; slice thickness 1.5 mm) and a diffusion-weighted single-shot spin-echo DTI sequence with an echo planar imaging readout (25–31 directions; b = 1000 s/mm²; TE/TR 85.5/15,000 msec; 45–50 contiguous axial slices, flip angle 90°; 128 × 128 matrix interpolated to 256 × 256; FOV 240 × 240 mm; slice thickness 3 mm). The Siemens 3-T MRI protocol used a T1 AX 3D MPRAGE Grappa 2 protocol (TI 900 msec; TE/TR 3.91/2300 msec; 160 contiguous axial slices; flip angle 9°; 256 × 224 matrix; FOV 256 × 224 mm; voxel size = 1 mm isotropic) and diffusion-weighted, single-shot, spin-echo DTI sequence with an echo planar imaging readout (30 directions; b = 1000 s/mm²; TE/TR 90/9000 msec; 70 contiguous axial slices; flip angle 90°; 122 × 122 matrix interpolated to 244 × 244; FOV 244 × 244 mm; voxel size = 2 mm isotropic). The MRI images were eddy-corrected for current distortions, and the DTI indices (FA/MD/AD/RD) were calculated using the Functional MRI of the Brain (FMRIB) Software Library (FSL) (version 4.1.8).³⁰ Patients underwent scanning at 1.5 T or 3 T based on their radiological indications or cohort. Scanning 1 individual at both 1.5 T and 3 T revealed signal-to-noise ratios of 28.5 and 70.7, respectively, for the zero diffusion-weighted images. We thus matched the groups for scanner type, and we included the MRI scanner type as a covariate in the regional and TBSS analyses of the imaging data to control for signal-to-noise ratio differences across the 1.5-T and 3-T scanners.

Analytical Plan

First, medical and demographic variables were compared between groups using chi-square tests, t-tests, or 1-way ANOVA, as appropriate. The p values for all comparisons are provided in Table 1. Next, we evaluated the relationship between white matter and clinically relevant protocols using regional white matter and tract-based spa-

TABLE 2. Demographic and medical variables of the dose-distribution cohort

Variable	Medulloblastoma Patients
No. of patients	15
Male sex	9 (60%)
Age at diagnosis in yrs	
Mean (SD)	8.2 (2.93)
Range	4.8–15.0
Age at scan (yrs)	
Mean (SD)	10.5 (2.58)
Range	6.2–15.4
Time since diagnosis in yrs	
Mean (SD)	2.3 (1.36)
Range	0.3–5.0
CSI	
Standard+PF boost	1
Standard+TB boost	2
Reduced+PF boost	2
Reduced+TB boost	10
Chemotherapy*	
Protocol (no. of patients treated)	SJMB03 (12), POG9631 (1), CCG9961 (1), ACNS0331 (1)
Gross-total resection	13 (86.7%)
Clinical risk (average risk)	12 (80%)
Hydrocephalus	
Present at diagnosis	9 (60%)
Hydrocephalus requiring CSF diversion	7 (46.7%)
3rd ventriculostomy	1 (6.7%)
EVD only	6 (40%)
VPS	0
≥1 revision	0
Mutism†	4 (26.7%)
Motor deficits‡	7 (46.7%)
Cranial nerve deficits§	0
Multiple postop complications	6 (40%)
MRI scan type	
1.5 T	15

* Chemotherapy protocols and their associated agents included SJMB03 (vincristine, cisplatin, and cyclophosphamide), POG9631 (etoposide, cisplatin, cyclophosphamide, and vincristine), CCG9961 (vincristine, lomustine/cyclophosphamide, and cisplatin), MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), and ACNS0331 (vincristine, cisplatin, lomustine, and cyclophosphamide).

† Mutism includes diminished speech output, linguistic difficulties, or dysarthria following surgery.

‡ Motor deficits include ataxia, dysmetria, or hemiparesis on neurological examinations.

§ Cranial nerve deficits include cranial nerve palsy on neurological examinations.

tial statistics (TBSS) analyses, controlling for variables that differed between groups where appropriate. Lastly, we evaluated the relationship between FA, dose, age at diagnosis, and time since diagnosis in a voxel-wise manner.

Regional Analyses

T1-weighted images were segmented into gray matter, white matter, and CSF using FSL-FMRIB's Automatic Segmentation Tool.³⁹ White matter segmentations included 8 cerebral regions (i.e., bilateral frontal, parietal, temporal, and occipital) and 4 posterior fossa regions (i.e., pons, vermis, and bilateral cerebellar hemispheres) based on a template modified from Kabani et al.¹⁰ as defined by Mabbott et al.¹⁶ Using affine transformation, this template was applied to produce white matter segmentations for all participants, then transformed into DTI space using linear and nonlinear transformations.^{36,37} Collapsing across hemispheres for the frontal, temporal, parietal, and occipital regions and across posterior fossa regions yielded 5 regions of interest (ROIs). Due to individual variations in brain volume, the total number of voxels in each ROI differed across participants.

As DTI indices are non-orthogonal, we conducted multivariate ANOVA to compare FA/MD/AD/RD for each white matter ROI between healthy controls and both patient groups. We followed up with a series of univariate ANOVA analyses between the patient groups, as defined above, and between patients treated with a reduced dose only to directly compare the tumor bed and posterior fossa boosts. Including covariates was deemed an appropriate method to correct for the effects of the demographic and treatment variables on our outcome measures because they overlapped in our groups.¹⁴ All post hoc pairwise comparisons were Bonferroni corrected.

TBSS Analyses

Voxel-wise analyses were conducted with TBSS.²⁹ All subjects' FA data were aligned into a common space (MNI152; Montreal Neurological Institute [MNI]) using the nonlinear registration tool FNIRT.^{1,2} Then, a cross-subject mean FA image was created and used to generate a "skeleton" FA map to represent the center that was common to all tracts and thresholded at $FA > 0.20$. Finally, participant-specific FA maps were aligned with the skeleton, and values along the width of each tract were considered in the cross-subject voxel-wise statistics with clusters defined by $T > 3$.

TBSS controls for family-wise errors by using a permutation methodology. The null distribution of the cluster-size statistic was built up over 5000 random permutations. Cluster size was thresholded at $p < 0.05$, which is fully corrected for multiple comparisons. A mask was made for each significant cluster, and the anatomical extent of each was labeled with reference to MNI's structural atlas and Johns Hopkins University's white matter tractography atlas.^{7,17}

Voxel-Wise Dose-Distribution Analyses

White matter was segmented as described in the regional analyses section above. The dose-distribution maps from treatment planning were coregistered with the patients' FA images and then aligned into the common space. Each voxel thus had a corresponding radiation dose and FA value. Each brain region was exposed to a different range of radiation doses, as follows: frontal, 1871 to 5423 cGy; temporal, 2013 to 5755 cGy; parietal, 1863 to

5557 cGy; occipital, 1912 to 5820 cGy; and posterior fossa, 2450 to 5987 cGy. There was considerable variation in the number of voxels exposed to the different doses within each region (Fig. 1). We performed linear mixed-effects analyses to evaluate the relationships between dose, age at diagnosis, time since diagnosis, and FA in the temporal and occipital regions only (i.e., brain regions containing sufficient voxels that were exposed to a wide range of radiation doses) (see Fig. 1). Dose, age at diagnosis, and time since diagnosis were entered as fixed effects, and random intercepts were included for participants. We conducted a series of model comparisons and evaluated the added contribution of each significant fixed effect. The p values were obtained from the likelihood ratio tests that compared the full model with the effect of interest to a model without these effects.

Results

Participant and Treatment Information

Age at scan differed between the 3 groups ($p = 0.03$), and age at diagnosis and time since diagnosis differed between the patient groups (all $p < 0.005$). Given that DTI indices change with age³⁸ and that age at diagnosis and time since diagnosis may contribute to poor outcome in patients,²³ we controlled for these variables in the subsequent analyses where appropriate. Because we deliberately stratified patients according to treatment protocol, the patient groups differed in terms of clinical risk, craniospinal irradiation, and chemotherapy (all $p < 0.001$). These variables were not controlled for in the subsequent analyses.

Regional Analyses

White Matter of Patients Treated With Higher Intensity Radiation Protocols Differs From Healthy Controls in All Brain Regions

Significant multivariate main effects were found for the DTI indices in all brain regions (all $F(8,130) > 2.19$; all $p < 0.03$) and were qualified by the significant univariate effects and pairwise comparisons. The all-other-treatments group had lower FA and higher RD relative to controls in all brain regions (all $p < 0.05$; Fig. 2A) and higher MD in the temporal, occipital, and posterior fossa regions (all $p < 0.05$). The reduced-dose CSI+TB boost group had higher FA values relative to the all-other-treatments group in the temporal, parietal, occipital, and posterior fossa regions (all $p < 0.005$), lower RD in the temporal and occipital regions (all $p < 0.005$; Fig. 2A), and lower MD in the temporal region ($p < 0.001$). Notably, FA did not differ between the controls and patients in the reduced-dose CSI+TB boost group in any brain region (all $p > 0.05$). RD and MD were higher in the reduced-dose CSI+TB boost group than in controls in only the posterior fossa (all $p < 0.05$; Fig. 2A). No group differences in AD emerged. MRI scanner type and age at scan were included as covariates in these analyses.

White Matter Differs Between Patient Groups

We limited our analyses to FA and RD, as these indices showed the most robust differences in the analyses, including controls. Relative to the patients in the all-other-treatments group, patients treated with reduced-dose CSI+TB

FIG. 1. Histograms depicting the number of voxels exposed to specific radiation doses in each brain region. **A:** The temporal and occipital regions contained many voxels that were exposed to different doses of radiation. These brain regions were included in the linear mixed-effects model comparisons designed to evaluate the continuous effect of dose on FA (see Table 4). **B:** The majority of the voxels in the frontal, parietal, and posterior fossa regions were exposed to the same dose, and the linearity assumption was violated as a result. These brain regions were not included in the linear mixed-effects model comparisons. Each brain region contained all the voxels from the patients in our sample ($n = 15$; see Table 2). For each graph, the upper limit of the y-axis was set to the total number of voxels included for that brain region.

boost had higher FA ($F = 4.2$; $p = 0.05$) and lower RD ($F = 4.68$; $p = 0.04$) in the temporal region and higher FA in the frontal region ($F = 4.78$; $p = 0.04$; Fig. 2B). Comparing patients treated with reduced doses revealed that receiving a tumor bed versus a posterior fossa boost was associated with higher FA in the occipital region ($F = 4.42$; $p = 0.05$) and lower RD in the frontal ($F = 5.07$; $p = 0.04$), temporal ($F = 5.22$; $p = 0.03$), and occipital ($F = 10.24$; $p = 0.005$) regions (Fig. 2C). MRI scanner type, age at scan, age at diagnosis, and time since diagnosis were included as covariates in these analyses.

TBSS

Treatment With Reduced-Dose CSI+TB Boost Spares White Matter

FA and RD differed between the patients and controls in many white matter tracts throughout the brain (all $F > 9$; all $p < 0.001$). Post hoc pairwise comparisons revealed that many voxels in the all-other-treatments group had lower FA and higher RD values when compared with controls (all $T > 2.05$; all $p < 0.001$; Fig. 3A; Table 3), and patients treated with reduced-dose CSI+TB boost had lower FA and higher RD values when compared with controls (all $T > 1.9$; all $p < 0.01$; Fig. 3B; Table 3). Patients in the reduced-dose CSI+TB boost group had many voxels with higher FA and lower RD than patients in the all-other-treatments group (all $T > 1.84$; $p < 0.01$; Fig. 3C; Table 3), but there were no instances where the reverse was true. This last comparison did not remain significant when age at diagnosis and time since diagnosis were included as covariates. For visualization purposes, TBSS maps were overlaid on representative dose distributions, highlighting that differences between patient groups were largely confined to the brain regions that were exposed to the maximum dose (i.e., ~5500 cGy)

following posterior fossa boost. Identical brain regions were exposed to less radiation (i.e., ~3200 cGy) following tumor bed boost (Fig. 4).

Voxel-Wise Dose-Distribution Analyses

Across voxels in the temporal and occipital regions, decreasing dose and increasing age at diagnosis were associated with increasing FA (all $T > 2.47$; all $p < 0.05$; Table 4). In the temporal region, the model that included age at diagnosis and dose together was a better predictor of FA than models that included either variable alone (all $p < 0.005$). In the occipital region, the model that included age at diagnosis and dose together was a better predictor of FA than age at diagnosis alone (all $p < 0.001$), but not a better predictor than dose alone (all $p > 0.05$; Table 4). Time since diagnosis never predicted FA.

Discussion

As new stratification and dose de-escalation strategies are considered in the treatment of medulloblastoma, it is important to understand the implications of reducing treatment. We evaluated the relation between radiation exposure and white matter architecture by comparing the following: 1) DTI indices between healthy controls and a cohort of patients treated with different clinically relevant protocols and 2) voxel-wise dose-distribution effects in the temporal and occipital regions in a separate patient cohort. We observed that 1) treatment with reduced-dose CSI+TB boost may spare white matter and that 2) decreasing radiation dose predicts white matter sparing.

Regional white matter analyses revealed that reduced-dose CSI+TB treatment was associated with higher FA and lower RD in the temporal region and higher FA in the

FIG. 2. Reduced-dose CSI+TB boost treatment is less damaging to the white matter than higher intensity protocols. **A:** The means and standard errors of FA and RD for the 5 brain regions examined (collapsed across hemispheres) in healthy controls, patients treated with reduced-dose CSI+TB boost, and patients in the all-other-treatments group after controlling for scanner and age at scan. The following are not shown: mean (standard errors) of MD in 1) the all-other-treatments group versus healthy controls in the temporal region (0.000847 [0.0000094] vs 0.000799 [0.0000061]; $p < 0.001$), occipital region (0.000789 [0.0000094] vs 0.00076 [0.0000061]; $p = 0.04$), and posterior fossa region (0.000816 [0.000014] vs 0.000747 [0.0000093]; $p < 0.001$); 2) patients treated with reduced-dose CSI+TB versus all-other-treatments in the temporal region (0.00079 [0.0000093] vs 0.000847 [0.0000094]; $p < 0.001$); and 3) patients treated with reduced-dose CSI+TB versus healthy controls in the posterior fossa region (0.000791 [0.000014] vs 0.000747 [0.0000093]; $p = 0.03$). **B:** The means and standard errors of FA and RD for the 5 brain regions examined (collapsed across hemispheres) in patients treated with reduced-dose CSI+TB boost and all other treatments after controlling for scanner, age at scan, and 2 additional covariates that were not applicable to healthy controls (age at diagnosis and time since diagnosis), and **(C)** in patients treated with reduced-dose CSI+TB boost and reduced dose CSI+PF boost after controlling for scanner, age at scan, age at diagnosis, and time since diagnosis. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

frontal region than all other treatments, even when controlling for variables that differed between patient groups. Specifically, we controlled for time since diagnosis and age at diagnosis, as these variables have the capacity to influence outcome.²³ As expected, reduced-dose CSI+TB boost treatment appears less damaging to white matter than treatment with protocols that deliver more radiation to the brain. Notably, FA and RD may not have differed in the posterior fossa between patient groups, as the trauma associated with surgical excision and radiation delivery is maximal in this region in both groups.

TBSS revealed that patients treated with reduced-dose CSI+TB boost differed less from the controls than the all-other-treatments group. There were also many voxels where the reduced-dose CSI+TB boost group did not differ from the controls. Because this patient group was treated homogeneously, we can infer that treatment with reduced-dose CSI+TB boost has the capacity to spare the white matter in some structures, in particular the temporal lobes, internal capsule, and splenium of the corpus callosum. TBSS also revealed many voxels where patient groups differed in FA and RD. However, the potential contributions

of age at diagnosis and time since diagnosis could not be ruled out in this analysis.

To consider more directly the impact of dose, age at diagnosis, and time since diagnosis, we conducted voxel-wise dose-distribution analyses in a separate cohort of patients. These data provide evidence that decreasing dose and increasing age are associated with white matter sparing.

Unlike volumetric white matter analyses, DTI can be used to evaluate the architecture of neuronal tissue and its pathological changes. FA and RD are thought to reflect the overall white matter and myelin architecture, respectively.^{31,32} Myelin synthesis actively occurs during childhood,³³ and radiation disrupts oligodendrocyte mitosis.²⁸ Because RD is thought to correspond to demyelination,^{12,32} it is logical that RD differed according to the treatment intensity protocol. In contrast, AD did not differ between the patient groups and controls. This may suggest that axons are less susceptible than myelin to treatment with radiation. Moreover, our TBSS results are consistent with studies that found frontal white matter to be especially vulnerable following whole-brain CSI.^{24,25}

FIG. 3. Treatment with less radiation spares the white matter in the temporal region. Differences in FA between the medulloblastoma treatment groups and healthy control children are shown. Clusters of voxels with significantly reduced FA ($p < 0.05$) in patients treated in the all-other-treatments group compared with controls (**A**), patients treated with reduced-dose CSI+TB boost compared with controls (**B**), and patients treated in the all-other-treatments group compared with patients treated with reduced-dose CSI+TB boost (**C**). Clusters are displayed in red and superimposed on the FMRIB FA template. Images are shown in radiological convention. Numbers represent MNI z-coordinates. White arrows indicate areas where the patients in the all-other-treatments group differ from controls, but patients treated with reduced-dose CSI+TB boost do not differ. **Right:** A coronal section from each comparison is provided. Note that there are greater differences between controls and patients in the all-other-treatments group than between controls and patients treated with reduced-dose CSI+TB boost, particularly in the temporal lobes. Only FA is shown, but similar patterns of differences were observed with RD. Cluster details are provided in Table 3. L = left; R = right.

The white matter sparing we observed is exciting as it may help explain the preserved intellectual function in patients treated with reduced-dose CSI+TB boost.¹⁹ Temporal white matter may be critical to performing cognitive tasks. Indeed, a recent study found an association between radiation dose to the hippocampus and temporal lobes in pediatric patients and a decline in their neurocognitive skills.²⁷

The present study should be considered in light of some limitations. First, patients treated with reduced-dose CSI+TB boost had the shortest follow-up time from treatment. The degree to which white matter sparing remains over time is unknown; it is possible that white matter indices change slowly over time and that this apparent white matter sparing would gradually diminish. However, we note that time since diagnosis did not predict FA in our

voxel-wise dose-distribution analyses. Second, although our sample size was large, it became smaller when stratified by treatment protocol. Third, our sample included participants with various treatment histories. For instance, chemotherapy protocols have changed over the captured time period, and this may be an unavoidable confounding factor. Patients in the reduced-dose CSI+TB group received vincristine, cisplatin, and cyclophosphamide. Patients in the all-other-treatments group were treated on several different protocols and received differing combinations of vincristine, cisplatin, cyclophosphamide, lomustine, etoposide, mechlorethamine, procarbazine, and prednisone. Although chemotherapy has been associated with reduced white matter volume,⁵ white matter pathology has not consistently been reported.⁶ Lastly, the different image-processing protocols may explain some of the

TABLE 3. FA and RD TBSS analysis of the clusters that differed between groups

Contrast	Cluster (no. of voxels)*	Cluster Family-Wise Error-Corrected p Value	Brain Regions Encompassed†‡	White Matter Structures Encompassed‡§	Mean t Value
FA					
All other treatments < healthy controls	93,202	<0.001	Cerebellum, parietal lobe, temporal lobe, occipital lobe, frontal lobe, thalamus, putamen, caudate, insula	Forceps minor, IFOF, SLF, ATR, ILF, forceps major, CST, SLF (temporal part), UF, cingulum (cingulate gyrus + hippocampus)	2.24
Reduced+TB boost < healthy controls	29,860	<0.001	Parietal lobe, frontal lobe, occipital lobe, temporal lobe, insula, caudate	Forceps minor, SLF, forceps major, SLF (temporal part), CST, IFOF, ILF, ATR, cingulum (hippocampus), UF	1.93
	12,994	0.003	Cerebellum, thalamus, temporal lobe, frontal lobe, putamen, caudate, insula, parietal lobe, occipital lobe	ATR, IFOF, CST, ILF, UF, SLF, SLF (temporal part), forceps minor, cingulum (hippocampus), rt cingulum (cingulate gyrus)	2.17
All other treatments < reduced+TB boost	17,769	0.005	Temporal lobe, occipital lobe, parietal lobe, cerebellum, putamen, frontal lobe, thalamus, caudate, insula	IFOF, rt ILF, forceps minor, CST, ATR, forceps major, SLF, SLF (temporal part), cingulum (hippocampus + cingulate gyrus), UF	1.85
	11,193	0.006	Temporal lobe, occipital lobe, parietal lobe, putamen, thalamus, frontal lobe, insula, caudate	ILF, IFOF, ATR, SLF (temporal part), forceps major, lt CST, lt UF, lt cingulum (cingulate gyrus + hippocampus), forceps minor	1.99
RD					
All other treatments > healthy controls	80,716	<0.001	Cerebellum, parietal lobe, temporal lobe, thalamus, frontal lobe, occipital lobe, putamen, caudate, insula	Forceps minor, SLF, IFOF, ATR, ILF, forceps major, SLF (temporal part), CST, UF, cingulum (cingulate gyrus + hippocampus)	2.06
Reduced+TB boost > healthy controls	17,163	0.002	Parietal lobe, frontal lobe, temporal lobe, occipital lobe, insula, caudate	SLF, forceps minor, SLF (temporal part), CST, forceps major, cingulum (cingulate gyrus & hippocampus), ILF, IFOF, ATR, UF	2.09
	2280	0.005	Thalamus, caudate, parietal lobe, temporal lobe	ATR, rt CST, rt cingulum (cingulate gyrus + hippocampus), forceps minor, rt SLF, rt IFOF	3.22
All other treatments > reduced+TB boost	25,909	0.001	Temporal lobe, occipital lobe, parietal lobe, putamen, thalamus, frontal lobe, caudate, insula, cerebellum	IFOF, ILF, forceps major, CST, SLF (temporal part), ATR, UF, cingulum (cingulate gyrus + hippocampus), forceps minor	1.97

ATR = anterior thalamic radiation; CST = corticospinal tract; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; TB = tumor bed; UF = uncinate fasciculus.

* Significant clusters containing < 100 voxels were excluded.

† Brain regions defined by the MNI structural atlas.

‡ All structures are listed in order from greatest to least probability of being a member of the labeled regions within the respective atlas.

§ White matter structures defined by the Johns Hopkins University white matter tractography atlas. Unless otherwise specified, the structures listed refer to bilateral counterparts.

apparent inconsistencies between the regional and TBSS analyses; regional analyses are based on the DTI indices calculated from each participant's anatomical white matter segmentations, whereas TBSS is performed in reference to the white matter skeleton that is common to all participants.

Future directions include 1) understanding how structural changes predict neurocognitive function; 2) clarifying the unique effects of radiation by evaluating children treated with chemotherapy only (e.g., acute lymphocytic

leukemia patients); and 3) assessing the implications of medical complications such as mutism and hydrocephalus.

Conclusions

We have demonstrated that radiation, whether evaluated according to the treatment intensity protocols or dose-distribution maps, compromises white matter. We also show, not surprisingly, that a younger age at diagnosis is an important factor. We found that reduced-dose CSI+TB

FIG. 4. The white matter appears spared in the brain regions exposed to less radiation following a TB boost. **A and B:** Note that the clusters (displayed in yellow) are identical. This figure demonstrates that a lower dose/smaller field of radiation is delivered to the brain following a TB boost (B) compared with a posterior fossa boost (A). Radiation dose distributions depict a gradient of radiation doses ranging from 2300 (blue) to 5500 cGy (pink). Clusters indicate where RD is decreased ($p < 0.05$) in patients treated with reduced-dose CSI+TB boost versus the all-other-treatments group. Clusters are superimposed on radiation dose distributions (shown in blue, purple, and pink). Images are shown in radiological convention. Numbers represent MNI x-, y-, and z-coordinates for the sagittal, coronal, and axial planes, respectively. Dose distributions, as determined during treatment planning, were first coregistered with the patient's FA image, then aligned into a common space. For visualization purposes, 2 dose distributions, each from a single patient treated with reduced-dose CSI, are shown. Boxed areas are magnified and placed side by side to emphasize the relation between the voxels that differed between patient groups and the corresponding doses administered to those exact brain regions. The clusters of difference in RD between the 2 patient groups correspond to areas where the delivered dose is ~ 3200 cGy (purple areas) in the reduced-dose CSI+TB boost group, and ~ 5500 cGy (pink areas) in patients treated with a larger boost volume. White matter may have been relatively "spared" in the group treated with reduced dose CSI+TB boost. Only RD is shown, but similar patterns of difference were observed with FA. Cluster details are provided in Table 3. L = left; R = right.

boost appears to preserve white matter in some brain regions. The posterior fossa boost delivers more radiation to the temporal lobes than a boost to the tumor bed;³⁵ our regional and TBSS analyses suggest white matter damage accompanies this increase in exposure. In the context of excellent survival with the tumor bed boost,¹⁹ our findings suggest that the posterior fossa boost be reconsidered. Our study is the first to characterize the regional effects of treatment intensity protocols on white matter and evaluate voxel-wise dose effects in parallel. Our findings provide

a better understanding of radiation-induced white matter vulnerability and suggest there may be a threshold beyond which toxicity increases substantially. Importantly, our findings offer the possibility of superior outcomes for patients eligible for treatment with reduced-dose CSI+TB boost.

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TABLE 4. Predicting FA with linear mixed-effects models*

Region	Fixed Effect Included in the Model	Estimate	Standard Error	t Value	p Value†	p Value‡
Temporal	Dose	-0.000016	0.0000004	-44.20	<0.001	0.004
	Age at diagnosis	0.008	0.002	4.37	<0.001	<0.001
Occipital	Dose	-0.00002	0.0000006	-40.94	<0.001	0.10
	Age at diagnosis	0.007	0.003	2.47	0.03	<0.001

* A series of linear mixed-effects models and model comparisons were conducted to evaluate the continuous effects of dose and age at diagnosis, on FA.

† The p values correspond to the significance of the model with either fixed effect alone.

‡ The added benefit of a model that includes both the dose and age at diagnosis was evaluated. The p values were obtained from the likelihood ratio test of the model that included both fixed effects against models that included either fixed effect alone.

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References

- Andersson JLR, Jenkinson M, Smith SM: Non-linear optimisation. **FMRIB Technical Report TR07JA1**. (<http://www.fmrib.ox.ac.uk/analysis/techrep/tr07ja1/tr07ja1.pdf>) [Accessed January 20, 2016]
- Andersson JLR, Jenkinson M, Smith SM: Non-linear registration, aka spatial normalisation. **FMRIB Technical Report TR07JA2**. (<http://www.fmrib.ox.ac.uk/analysis/techrep/tr07ja2/tr07ja2.pdf>) [Accessed January 20, 2016]
- Basser PJ: Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. **NMR Biomed** **8**:333–344, 1995
- Blomstrand M, Brodin NP, Munck Af Rosenschöld P, Vogelius IR, Sánchez Merino G, Kiil-Berthlesen A, et al: Estimated clinical benefit of protecting neurogenesis in the developing brain during radiation therapy for pediatric medulloblastoma. **Neuro Oncol** **14**:882–889, 2012
- Edelmann MN, Krull KR, Liu W, Glass JO, Ji Q, Ogg RJ, et al: Diffusion tensor imaging and neurocognition in survivors of childhood acute lymphoblastic leukaemia. **Brain** **137**:2973–2983, 2014
- Genshaft M, Huebner T, Plessow F, Ikonomidou VN, Abolmaali N, Krone F, et al: Impact of chemotherapy for childhood leukemia on brain morphology and function. **PLoS One** **8**:e78599, 2013
- Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, et al: Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. **Neuroimage** **39**:336–347, 2008
- Janve VA, Zu Z, Yao SY, Li K, Zhang FL, Wilson KJ, et al: The radial diffusivity and magnetization transfer pool size ratio are sensitive markers for demyelination in a rat model of type III multiple sclerosis (MS) lesions. **Neuroimage** **74**:298–305, 2013
- Jones DK, Leemans A: Diffusion tensor imaging. **Methods Mol Biol** **711**:127–144, 2011
- Kabani NJ, Sled JG, Chertkow H: Magnetization transfer ratio in mild cognitive impairment and dementia of Alzheimer's type. **Neuroimage** **15**:604–610, 2002
- Khong PL, Kwong DL, Chan GC, Sham JS, Chan FL, Ooi GC: Diffusion-tensor imaging for the detection and quantification of treatment-induced white matter injury in children with medulloblastoma: a pilot study. **AJNR Am J Neuroradiol** **24**:734–740, 2003
- Klawiter EC, Schmidt RE, Trinkaus K, Liang HF, Budde MD, Naismith RT, et al: Radial diffusivity predicts demyelination in ex vivo multiple sclerosis spinal cords. **Neuroimage** **55**:1454–1460, 2011
- Lebel C, Beaulieu C: Longitudinal development of human brain wiring continues from childhood into adulthood. **J Neurosci** **31**:10937–10947, 2011
- Li L, Kleinman K, Gillman MW: A comparison of confounding adjustment methods with an application to early life determinants of childhood obesity. **J Dev Orig Health Dis** **5**:435–447, 2014
- Mabbott DJ, Noseworthy MD, Bouffet E, Rockel C, Laughlin S: Diffusion tensor imaging of white matter after cranial radiation in children for medulloblastoma: correlation with IQ. **Neuro Oncol** **8**:244–252, 2006
- Mabbott DJ, Rovet J, Noseworthy MD, Smith ML, Rockel C: The relations between white matter and declarative memory in older children and adolescents. **Brain Res** **1294**:80–90, 2009
- Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, et al: A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). **Philos Trans R Soc Lond B Biol Sci** **356**:1293–1322, 2001
- Merchant TE, Kun LE, Krasin MJ, Wallace D, Chintagumpala MM, Woo SY, et al: Multi-institution prospective trial of reduced-dose craniospinal irradiation (23.4 Gy) followed by conformal posterior fossa (36 Gy) and primary site irradiation (55.8 Gy) and dose-intensive chemotherapy for average-risk medulloblastoma. **Int J Radiat Oncol Biol Phys** **70**:782–787, 2008
- Moxon-Emre I, Bouffet E, Taylor MD, Laperriere N, Scantlebury N, Law N, et al: Impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in patients with medulloblastoma. **J Clin Oncol** **32**:1760–1768, 2014
- Mueller S, Chang S: Pediatric brain tumors: current treatment strategies and future therapeutic approaches. **Neurotherapeutics** **6**:570–586, 2009
- Nagesh V, Tsien CI, Chenevert TL, Ross BD, Lawrence TS, Junick L, et al: Radiation-induced changes in normal-appearing white matter in patients with cerebral tumors: a diffusion tensor imaging study. **Int J Radiat Oncol Biol Phys** **70**:1002–1010, 2008
- Pierpaoli C, Basser PJ: Toward a quantitative assessment of diffusion anisotropy. **Magn Reson Med** **36**:893–906, 1996
- Pollack IF: Multidisciplinary management of childhood brain tumors: a review of outcomes, recent advances, and challenges. **J Neurosurg Pediatr** **8**:135–148, 2011
- Qiu D, Kwong DL, Chan GC, Leung LH, Khong PL: Diffusion tensor magnetic resonance imaging finding of discrepant fractional anisotropy between the frontal and parietal lobes after whole-brain irradiation in childhood medulloblastoma survivors: reflection of regional white matter radiosensitivity? **Int J Radiat Oncol Biol Phys** **69**:846–851, 2007
- Qiu D, Leung LH, Kwong DL, Chan GC, Khong PL: Mapping radiation dose distribution on the fractional anisotropy map: applications in the assessment of treatment-induced white matter injury. **Neuroimage** **31**:109–115, 2006
- Reddick WE, Russell JM, Glass JO, Xiong X, Mulhern RK, Langston JW, et al: Subtle white matter volume differences in children treated for medulloblastoma with conventional or reduced dose craniospinal irradiation. **Magn Reson Imaging** **18**:787–793, 2000
- Redmond KJ, Mahone EM, Horska A: Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: a prospective study. **Neuro Oncol** **15**:1455, 2013
- Sheline GE, Wara WM, Smith V: Therapeutic irradiation and brain injury. **Int J Radiat Oncol Biol Phys** **6**:1215–1228, 1980
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al: Tract-based spatial statistics:

- voxelwise analysis of multi-subject diffusion data. **Neuroimage** **31**:1487–1505, 2006
30. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al: Advances in functional and structural MR image analysis and implementation as FSL. **Neuroimage** **23** (Suppl 1):S208–S219, 2004
 31. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH: Demyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. **Neuroimage** **17**:1429–1436, 2002
 32. Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, et al: Demyelination increases radial diffusivity in corpus callosum of mouse brain. **Neuroimage** **26**:132–140, 2005
 33. Spreen O, Risser AT, Edgell D: **Developmental Neuropsychology**. New York: Oxford University Press, 1995
 34. Teffer K, Semendeferi K: Human prefrontal cortex: evolution, development, and pathology. **Prog Brain Res** **195**:191–218, 2012
 35. Wolden SL, Dunkel IJ, Souweidane MM, Happersett L, Khakoo Y, Schupak K, et al: Patterns of failure using a conformal radiation therapy tumor bed boost for medulloblastoma. **J Clin Oncol** **21**:3079–3083, 2003
 36. Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC: Automated image registration: I. General methods and intrasubject, intramodality validation. **J Comput Assist Tomogr** **22**:139–152, 1998
 37. Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC: Automated image registration: II. Intersubject validation of linear and nonlinear models. **J Comput Assist Tomogr** **22**:153–165, 1998
 38. Yoshida S, Oishi K, Faria AV, Mori S: Diffusion tensor imaging of normal brain development. **Pediatr Radiol** **43**:15–27, 2013
 39. Zhang Y, Brady M, Smith S: Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. **IEEE Trans Med Imaging** **20**:45–57, 2001

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or in the findings specified in the paper.

Author Contributions

Conception and design: Mabbott, Moxon-Emre. Acquisition of data: Mabbott, Moxon-Emre, Bouffet, Taylor, Laperriere, Sharpe, Bartels, Scantlebury, Law. Analysis and interpretation of data: Mabbott, Moxon-Emre, Skocic. Drafting the article: Mabbott, Moxon-Emre. Critically revising the article: Mabbott, Moxon-Emre, Bouffet, Taylor, Laperriere, Sharpe, Bartels, Scantlebury, Law, Malkin, Skocic, Richard. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mabbott. Statistical analysis: Mabbott, Moxon-Emre, Scantlebury, Law, Skocic. Administrative/technical/material support: Mabbott, Bouffet, Taylor, Laperriere, Sharpe, Laughlin, Bartels. Study supervision: Mabbott.

Supplemental Information

Previous Presentations

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Correspondence

Donald J. Mabbott, The Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada. email: donald.mabbott@sickkids.ca.