Brain biomarkers and neuropsychological outcomes of pediatric posterior fossa brain tumor survivors treated with surgical resection with or without adjuvant chemotherapy

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Abstract

Purpose—Children with brain tumors experience cognitive late effects, often related to cranial radiation. We sought to determine differential effects of surgery and chemotherapy on brain structure and neuropsychological outcomes in children who did not receive CRT.

Methods—Twenty-eight children with a history of posterior fossa tumor (17 treated with surgery, 11 treated with surgery and chemotherapy) underwent neuroimaging and neuropsychological

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assessment a mean of 4.5 (surgery group) to 9 years (surgery + chemotherapy group) post-treatment, along with 18 healthy sibling controls. Psychometric measures assessed IQ, language, executive functions, processing speed, memory, and social-emotional functioning. Group differences and correlations between diffusion tensor imaging findings and psychometric scores were examined.

Results—Z-score mapping demonstrated fractional anisotropy (FA) values were 2 standard deviations lower in white matter tracts, prefrontal cortex gray matter, hippocampus, thalamus, basal ganglia, and pons between patient groups, indicating microstructural damage associated with chemotherapy. Patients scored lower than controls on visuoconstructional reasoning and memory (p 0.02). Lower FA in the uncinate fasciculus (R −0.82 to −0.91) and higher FA in the thalamus (R 0.73 to 0.91) associated with higher IQ scores, and higher FA in the thalamus associated with higher scores on spatial working memory (R 0.82).

Conclusions—Posterior fossa brain tumor treated with surgery and chemotherapy affects brain microstructure and neuropsychological functioning years into survivorship, with spatial processes the most vulnerable. Biomarkers indicating cellular changes in the thalamus, hippocampus, pons, prefrontal cortex and white matter tracts associate with lower psychometric scores.

Keywords

pediatric brain tumor; neuroimaging; diffusion tensor imaging; neuropsychology; survivors of childhood cancer

Introduction

Central nervous system tumors are the most common cause of cancer death in children age 0-14 years in the United States[1]. Treatment regimens of surgery, chemotherapy and irradiation are based upon risk including tumor molecular genetics, location, pathology, and age at diagnosis[2]. Cranial irradiation (CRT) is a factor in neuropsychological deficits in pediatric cancer survivors ranging from a global loss of IQ points to memory and attention deficits[3,4]. Evidence from large cohorts, such as the Childhood Cancer Survivor Study[5] and Children's Oncology Group, supports decreasing CRT dose or elimination when feasible[6]. Children under 6 years may be treated with irradiation-sparing intensive chemotherapy regimens when possible without compromising survival [7-10], as cognitive and social-emotional effects appear mitigated with this approach[11-15]. Late effects of systemic and CNS-directed chemotherapy on the developing brain in the absence of CRT are less well-defined, but in children with leukemia, include deficits in attention, executive functions, visual processing and visual motor deficits[5,16-19].

Treatment induces neurotoxicity through oxidative stress and inflammation triggered by irradiation and/or chemotherapy[3,20]. Cell membrane breakdown and death, demyelination, and loss of blood-brain barrier integrity contribute to edema and a cycle of continuing injury[3]. Magnetic resonance imaging (MRI) illustrates extent of damage and injury subtypes *in vivo*. Diffusion tensor imaging (DTI), characterizing three-dimensional water diffusion as a function of spatial location, provides indices of mean diffusivity (MD) and fractional anisotropy (FA) indices. MD reflects cell size, shape, integrity, and molecular motion across

tissues[21,22]. High MD may indicate edema or loss of axons and demyelination.[22,23]. Comparatively low FA represents loss of microstructural integrity, particularly in myelinated regions, reduced tissue organization[21,24], and axonal damage[25].

Rueckriegel et al. (2010) demonstrated that children with low-grade brain tumors treated with surgery showed decreased FA in the white matter (WM) tract skeleton, though to a lesser extent than those treated with surgery, irradiation and chemotherapy[26]. Similar populations treated with surgery and chemotherapy showed deficits in processing speed, visual sustained attention[27] and visual working memory[28], indicating that brain tumor presence, surgical resection and chemotherapy results in WM disruption. However, few such neuroimaging studies exist, and neuropsychological outcomes remain unclear.

In a pilot study, we investigated brain injury in childhood brain tumor survivors treated with surgery and chemotherapy (n=7) compared to healthy controls (n=9) using DTI[29,30]. Higher MD values indicated significant changes in the thalamus, pons, basal ganglia, and mammillary bodies in patients compared to controls[29]. Due to sample size, it could not be determined if this pattern of injury was due to tumor, surgery, chemotherapy, or a combination of the three. The purpose of the current study was to differentiate effects of surgery alone and surgery followed by chemotherapy on brain microstructure and neuropsychological function in pediatric posterior fossa tumor survivors. Our *a priori* hypotheses were 1) neuroimaging would indicate a pattern of injury to subcortical and brainstem structures in children treated with surgery and chemotherapy (S+C) compared to children treated with surgery (S) and healthy controls (HC), 2) children in the S+C group would score lower than those in the S and HC groups on neuropsychological outcomes, and 3) injury to pons, hippocampus, basal ganglia and thalamus would correlate with poorer neuropsychological outcomes.

Methods

A cross-sectional comparative design was used with participants completing MRI with DTI and neuropsychological assessment. Patient groups included children at least 12 months from last treatment for a posterior fossa brain tumor, currently 6-17 years old, treated with either surgery (S group) or surgery and chemotherapy (S+C group). The study was approved by the Institutional Review Board. Potential subjects were identified from the neuro-oncology database and clinic lists. Parents were approached in clinic or contacted by mail or phone. At the time of patient enrollment, parents were invited to enroll healthy 6-17 year old siblings as controls. Parents and participants were required to speak and read either English or Spanish.

Exclusion criteria for all participants included metal in the body precluding MRI, preterm birth, neurodevelopmental disability, and traumatic brain injury. Controls had to be able to undergo MRI without sedation. Patients with recurrent tumor or residual disease outside the posterior fossa were excluded, as were those with a history of posterior fossa syndrome, since related deficits, including lower IQ, working memory and processing speed[31] are significant confounding variables.

All data were stored in REDCap v6.14.2[32,33].

Imaging Data and Preprocessing

Three-dimensional T1-weighted images were obtained on a 3.0T Philips Achieva scanner with voxel size of $1.0 \times 1.0 \times 1.0$ mm^3 with parameters: TR 9.9 ms; TE 4.6 ms; 240×231 matrix; FOV 24 cm. DWI imaging sequence was acquired with parameters: 70 axial slices (2 mm thick), FOV = 256 mm x 256 mm x 140 mm, TR/TE 8657/86 ms, no gap, with a 128×126 acquisition matrix, 28 gradient directions collected with b-value=1500.

T1 images were bias field corrected using ANTs'[25] N4 BFC[26] tool and manually skull-stripped in Brainsuite 16[27]. Twelve-point linear registration was done using FSL's[28-30] FLIRT[31,32] tool and nonlinear registration to the McConnell Brain Imaging Centres (MBIC) natural pediatric template for children[33,34] with FSL's FNIRT tool. The overall template space is an average of three age-appropriate MBIC templates. DW images were corrected with FSL[19] for eddy current and subject motion. Resulting DWIs were skull-stripped in DSI Studio. Brainsuite's BDP Pipeline co-registered DWI images to preprocessed T1w images, then registered to the MBIC mean template space by applying combined transformations from the T1w image's registration pipeline (Figure 1).

Neuropsychological Assessment.

Participants completed a battery of well-validated measures (i.e., Wechsler scales, NEPSY II Memory for Designs, California Verbal Learning Test, Children's Version, Receptive/ Expressive One-Word Picture Vocabulary Tests, NIH Toolbox, and Achenbach Child Behavior Checklist) commonly used to assess domains potentially affected by posterior fossa brain tumors including intelligence, processing speed, memory, executive functions, language, and psychosocial functioning (Table 1). Assessments were performed by a board-certified pediatric neuropsychologist or by doctoral trainees under her supervision.

Statistical Methods

Whole-brain voxel-wise analysis was performed in AFNI[34] using 3dttest++ to generate pairwise z score maps. We masked the cerebellum from image analysis due to our focus on structures outside the surgical resection. Age at time of scan was a regression covariate. False Discovery Rate (FDR) was applied at p 0.05 to voxel-wise analyses. Within AFNI's graphical user interface output, z-maps were thresholded to show only voxels where FA had z scores 2 SD from mean. Cluster maps were exported to ITK-SNAP[35] where mean and SD of FA values in each cluster were extracted. Anatomical labels are in concordance with an MRI atlas[36].

Post hoc analyses—Using AFNI's 3dttest++, whole brain voxel T statistic maps were created for each DTI metric using group level analysis in three pairwise analyses between S, S+C, and HC groups. AFNI's 3dcalc was then used to convert each T statistic map into a Z score map. Z maps were filtered to display regions of the brain where FA was $|Z| > 2$, indicating areas with 2 SD difference between treatment groups and then between each treatment group and HCs, using a Q-value of 0.05 (hypothesis 1). White matter clusters with 100 or more surviving contiguous voxels are reported. In the thalamus, pons and basal

ganglia, we decreased the number of contiguous voxels required to 30 or more to allow analysis of areas specified in our hypotheses, since those structures are generally smaller in size than WM regions and allowed further analysis of FA findings in regions identified in *a priori* hypothesis (thalamus, basal ganglia, hippocampus).

The χ^2 test and t-test examined differences in patient demographics and medical history among groups and neuropsychological scores were compared using linear regression. ANOVA compared scores in patients to HCs with age at diagnosis as a covariate (hypothesis 2). Analyses were performed in Stata[37] using 2-sided tests. FDR was controlled by applying the Benjamini Hochberg procedure[38] (Q-value 0.012) with significance set at p   0.02.

Pearson correlation analysis using SPSS v.25.0[39] assessed the relationship of FA in the 8 clusters that significantly differed between groups to neuropsychological scores, controlling for age and time off treatment in patient groups (hypothesis 3).

Results

Demographics

131 children were potentially eligible. After excluding those treated with CRT, turning 18 during recruitment, with PFS or severe developmental delay, or no longer followed at the institution, there were 48 patients. Of those, 5 families declined participation and 15 families didn't respond to mail/telephone invitations, for a participation rate of 58%. The 20 who did not participate compared to the 28 who did were not significantly different in current age, age at diagnosis or years since treatment, but insurance status suggested a larger percentage were of higher socioeconomic status than in the final sample. However, the sample was representative of that the institution serves.

Seventeen children in the S group, 11 in the S+C group and 18 HCs participated in the study. Demographic data are presented in Table 2. Although age at study was not different between groups, age at diagnosis was, thus the distribution of current ages between patient groups varied with the S group skewed toward younger ages and the S+C group skewed toward older ages and longer time from treatment. There was also a difference between diagnoses, as most patients in the S group had pilocytic astrocytoma and most in the S+C group had medulloblastoma (p=0.0001), which was expected related to assigned treatment. For all 46 participants, there were no group differences in preschool attendance (p=0.62), receiving special education (p=0.43), family history of developmental delays, learning disabilities, psychiatric or medical illnesses (p=0.06, p=0.31, p=0.18, p=0.08, respectively). The S+C group were treated with carboplatin, etoposide and thiotepa (with 82% receiving each of these drugs), vincristine and cyclophosphamide (73%), cisplatin (64%), methotrexate (36%), temozolomide (27%), and dasatinib, lenalidomide, or irinotecan (9%).

Neuroimaging

There were no significant group differences in regional DTI after correction for multiple comparisons with the false discovery rate (FDR) procedure, permutation analysis and cluster analysis. Despite comparable mean ages of subjects in each group, age-related effects dominated the analysis. Therefore, we partialed out participant age as a regression covariate.

Areas of significantly different FA clusters by z masks between patient groups (S vs S+C) are shown in Figure 2. FA was higher in the S group in several regions, including the superior longitudinal (SLF) and uncinate fasciculi (UF), posterior thalamic radiation (PTR)/ splenium of corpus callosum, and posterior limb of the internal capsule (PLIC), as well as in the right pons, gray and white matter of the prefrontal cortex (PFC), bilateral hippocampi, right globus pallidus and putamen, and right thalamus. FA was lower in the S group in the left thalamus.

Areas of significantly different FA clusters between each patient group and HCs are shown in Supplemental Figures 1 and 2 supporting findings between patient groups, demonstrating higher FA in the pons, hippocampus and thalamus in controls than in S patients (Supp Fig 1). FA in controls was higher than S+C patients in the hippocampus, putamen, PLIC, and inferior fronto-occipital fasciculus (Supp Fig 2). FA was lower in controls in the thalamus and SLF than in both patient groups.

Neuropsychological Assessment

No monolingual Spanish-speaking children participated. Children completed the Children's Oncology Group Language Preference Survey. The single bilingual participant who was not English dominant for testing was assessed by a bilingual examiner providing instructions in both English and Spanish and completed bilingual versions of Receptive and Expressive One-Word Picture Vocabulary tests.

There were no significant differences between patient groups in neuropsychological performance. When factoring in HCs, there was no difference in FSIQ (96.50, 96.80, 102.81), though HCs performed higher on Block Design, a subtest within FSIQ (p=0.01) (Supplemental Table 1). Controls also performed higher than patients on immediate design recall and delayed recall of designs and their spatial locations on Memory for Designs (p=0.02, 0.005, respectively). Distribution of scores are shown in Supplemental Figure 3. Significant group differences on other tasks with a motor component (i.e., Spatial Span, Coding, Symbol Search, Dimensional Change Card Sort, Flanker Inhibitory Control, and Pattern Comparison Processing Speed) were not found. Children in the S group and HCs scored lower (p= 0.02) than those in the S+C group on self-reported NeuroQOL Pediatric Cognitive function, though both groups placed within the norm. Scores on depression, fatigue and interacting with peers were not different between groups; however, parent questionnaires indicated clinical concerns regarding executive functions and social-emotional functioning more frequently for patients (Supplemental Table 2). The primary difference between groups was in the Externalizing Problems Index of the CBCL, where 36% of children in S, 20% of children in S+C, and no controls had parent-proxy scores in the clinical range.

Neuroimaging & Neuropsychological Assessment

Pearson correlations determined relationships between 8 clusters of FA significance in Figure 2 and psychometric scores in children with brain tumors, controlling for age and time off treatment (Table 3). Higher FA in the right thalamus correlated with higher scores on spatial working memory, Perceptual Reasoning, Block Design, FSIQ, and Similarities in the

S+C group. Higher FA in the right pons correlated with lower scores on memory in the S+C group. Children in the S+C group demonstrated inverse correlations between FA in the UF and FSIQ, Vocabulary, and Similarities. In the S group, higher FA in the left hippocampus and right PLIC correlated with improved scores in spatial working memory, while lower FA in prefrontal GM correlated with higher scores in spatial working memory.

The sole significant correlation in HCs was between spatial working memory and left thalamus FA (R=0.63, p=0.01).

Data available on request from authors

Discussion

This study demonstrated FA differences indicating microstructural injury in brain areas, many distant from the tumor site, in children treated with surgery and chemotherapy compared to those treated with surgery only, accompanied by minor differences in cognitive performance. FA differences were found in WM association pathways connecting temporal lobes with orbitofrontal and prefrontal cortices (UF)[40,41], and those connecting parietal lobes to prefrontal cortices (SLF)[41]; in the PLIC, PTR/CC; pons and hippocampi; basal ganglia and thalami; and the PFC. These findings both confirm and expand upon results of our pilot study, where MD differences indicated injury to subcortical GM and pons in children treated with S+C for brain tumors[29,30], also in the absence of major cognitive deficits[30].

Lower FA in certain brain structures of children in the S+C group may indicate increased vulnerability of healthy tissue to chemotherapy apart from tumor or surgery effects. White matter in the PFC and association pathways continues to develop past adolescence[42] and structures such as the UF develop later in life[43], possibly rendering these tracts more vulnerable to neurotoxicity when injured earlier in development. Children in the S+C group were younger at diagnosis than children in the S group.

Lower mean FA in WM compared to HCs is common to many neuropathological conditions, including multiple sclerosis[44], stroke[45], epilepsy[46], Alzheimer's disease[47], and brain tumors including meningiomas, low-grade gliomas, and glioblastoma multiforme[48] indicating demyelination, edema, and/or inflammation[49]. It is a marker of WM damage, but nonspecific as to exact underlying pathology.

Other pediatric brain tumor studies found decreased mean FA in WM areas identified in our study, including the UF[43,50], internal capsule, PTR/splenium of CC, SLF[51], and frontal WM[52]. However, unlike this study, most did not control for tumor location and included children treated heterogeneously with combinations of surgery, CRT, and/or chemotherapy.

The additional neuronal damage in patients who received chemotherapy was expected, as all patients in the S+C group received chemotherapeutic agents known to cross the BBB (methotrexate, cisplatin, thiotepa, and temozolomide)[20] and cause neurotoxicity[53]. While direct effects of chemotherapy in the developing brain are not fully understood, hypothesized mechanisms include neurotoxic injury to cerebral parenchyma, induction of a

secondary inflammatory response, microvascular injury, indirect chemical toxicity, increased oxidative stress, altered neurotransmitter levels[20], DNA damage, decreased neurogenesis, and shortening of telomeres[53]. These disruptions interfere with normal myelination, synaptogenesis, and pruning, all of which could contribute to our findings.

The S+C group demonstrated inverse correlations between FA in the UF and general intelligence. One would not expect that lower FA in WM, indicative of myelin disruption, would correlate with higher intelligence scores. One explanation is that FA in the UF is lower than expected where the UF crosses the SLF[54], as crossing fibers cause the diffusion tensor to become more spherical or oblate[55], reducing FA even in the presence of intact myelinated fiber tracts. Our methods did not allow determination of whether the cluster of significance was within these crossing fibers.

While FA is most commonly measured in WM, we found decreased FA in the right thalamus and increased FA in the left thalamus in the S+C group compared to the S group. This contrary finding may be due to location of the FA clusters in different thalamic nuclei (right ventrolateral nucleus and left medial thalamic nucleus), although imaging resolution did not allow us to confirm location in each subject. The medial thalamic nucleus is located much closer to the lateral ventricle than the ventrolateral nucleus, and as such may have been injured from hydrocephalus, which was more prevalent in the S+C group. High FA in GM may be a biomarker of neuronal injury in patients with chemotherapy-induced toxicity. The organization of GM, primarily made up of cell bodies, unmyelinated axons, dendrites and synapses, is less directionally organized than WM, making interpretation of DTI findings less clear[56]. Increased FA in GM was associated with gliosis in an animal model of traumatic brain injury[57]. Similar patterns of increased FA in GM are noted in chronic subdural hematoma[58], where a compression-dependent increase in FA in the caudate and putamen decreased following evacuation of hematomas, suggesting increased FA in GM could indicate damage caused by tissue compression. These studies provide evidence that increased FA in the left thalamus could be a result of gliosis, damage to surrounding white matter, and/or compression of tissues from hydrocephalus.

Decreased FA in the basal ganglia, thalamus, and pons supports our earlier findings of elevated MD in these areas in children with brain tumors treated with surgery and chemotherapy[30], as both directional indices represent microstructural injury. In 5 cognitive domains assessed (IQ, language, executive functions, processing speed, and memory), group differences were visual-spatial, suggesting greater sensitivity of these measures to broad CNS dysfunction[59], commonly reported in neurologic conditions such as congenital hydrocephalus[60].

Block Design, a visuoconstructional task requiring one to analyze part-whole relationships to copy two-dimensional patterns, is sensitive to CNS dysfunction[59]. Patient groups scored significantly lower than the HC group, though all performed within normal limits. This encouraging finding suggests that although children in the S+C group were younger at diagnosis, often a risk factor for poorer outcomes, and had intensive treatment, there were more years from diagnosis in which to, at least theoretically, develop neural plasticity. On a spatial memory task, patients performed lower than controls on learning designs and on

delayed recall of both designs and locations, with those who received chemotherapy showing an additional, though non-significant, reduction in performance. This suggests patients had difficulty encoding, a process involving the hippocampus and WM connections between frontal and parietal regions via the thalamus. It could also reflect breakdown in connections involved in consolidating memory into long-term storage, a process thought to be mediated by medial temporal and diencephalic structures, as well as specific unimodal and heteromodal cortices or in retrieving it through activity in regions of neocortex without need for medial temporal or medial diencephalic involvement[61].

Finally, it is notable that the S+C group performed similarly to the S group on neuropsychological assessment, but scored higher on QOL, even compared to controls. This further supports the theory that these children are relatively functionally intact due to neuroplasticity related to treatment at a younger age.

Limitations

As is common in pediatric brain tumor research, our sample size is relatively small, making definitive conclusions difficult, and participants had a range of cognitive abilities from impaired to superior, making aggregate data less representative. While only diagnosis and age at diagnosis differed between patient groups, patients were not specifically matched by sex, age, language, handedness or tumor location/laterality.

Considerations/Conclusions

Few prior neuroimaging studies include children with brain tumors treated with chemotherapy without CRT. We found clear patterns of brain injury in children with posterior fossa tumors treated with surgery with or without chemotherapy.

While most patients performed within normal limits on neuropsychological assessment, they performed lower than healthy controls on visual-constructional reasoning and spatial memory. Earlier neurological injury in children in the S+C group could allow for reorganization/compensation with other parts of the attention network with frontal or parietal aspects of attention playing a more important role in performance. Although not tested in this study, this is an important focus for future studies.

Factors underlying vulnerability or resilience in the face of neurotoxic therapies merit further evaluation to determine effects of genetics and environment. Future studies involving multiple institutions enabling larger sample sizes over multiple time points are necessary to pinpoint periods of neuronal vulnerability amenable to intensive interventions.

Our findings illustrate that treatment of pediatric posterior fossa brain tumors results in long-term alterations to gray and white matter microstructure, and that more pronounced differences are seen when chemotherapy is used in addition to surgical intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Abbreviations Key

AFNI	Analysis of Functional Neuroimages
CC	Corpus callosum
CRT	Cranial radiation therapy
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
GM	Gray matter
MD	Mean diffusivity
MFG	Middle frontal gyrus
MRI	Magnetic resonance imaging
PFC	Prefrontal cortex
PLIC	Posterior limb of internal capsule
PTR	Posterior thalamic radiation
SLF	Superior longitudinal fasciculus
UF	Uncinate fasciculus
WM	White matter

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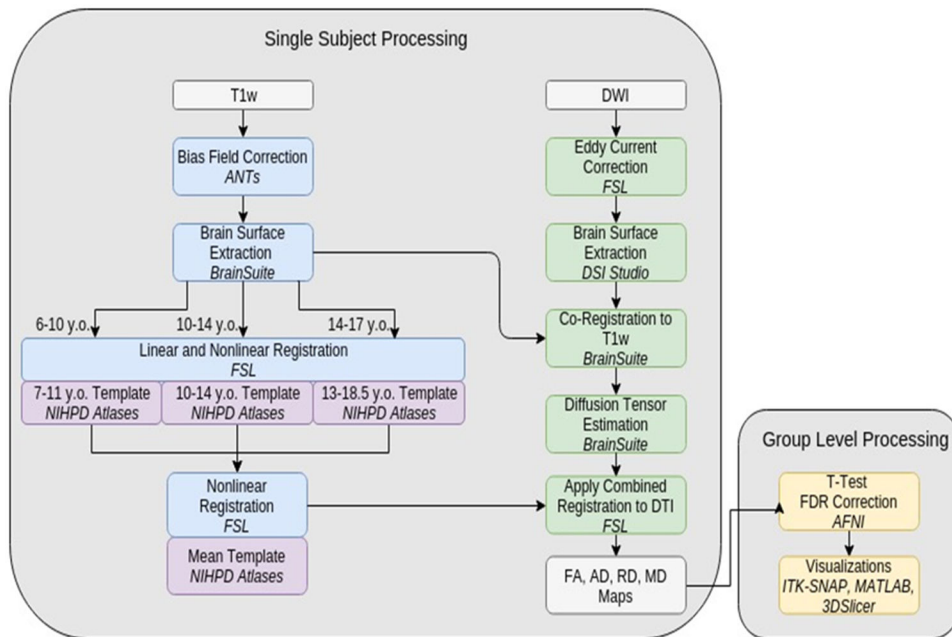61. Blumenfeld H Neuroanatomy Through Clinical Cases. Sunderland, MA: Sinauer; 2002.

Figure 1. Image processing
Details of single subject and group level image processing *Abbreviations:* AFNI, Analysis of Functional NeuroImages; ANTs, Advanced Neuroimaging Tools; DWI, diffusion-weighted imaging; FSL, FMRIB Software Library; NIHPD, NIH Pediatric MRI Data Repository
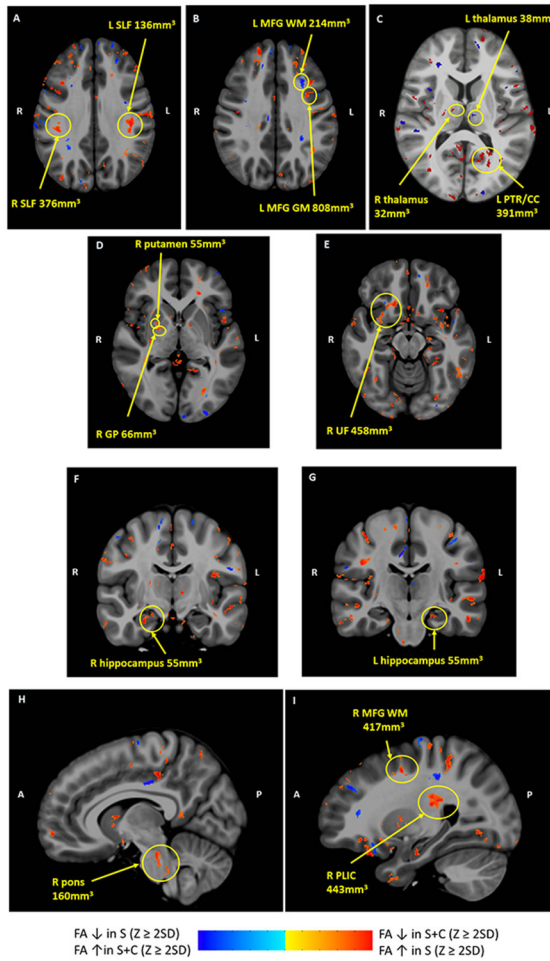
Figure 2. Areas of FA differences between patient groups in composite axial and sagittal diffusion tensor images

Red clusters indicate areas where FA z scores were 2SD lower in the S+C group than the S group; blue clusters indicate where FA z scores were 2SD lower in the S group than the S +C group. R and L indicate Right and Left on axial images; A and P indicate Anterior and Posterior. Cluster size is noted for each structure. **A** FA in bilateral SLF higher in S than S +C; **B** FA in prefrontal WM lower in S than S+C, FA in prefrontal GM higher in S than S +C; **C** FA in R thalamus higher in S than S+C, FA in L thalamus lower in S than S+C, FA in L PTR/CC higher in S than S+C; **D** FA in R putamen and GP higher in S than S+C; **E** FA in R UF higher in S than S+C; F FA higher in R hippocampus in S than S+C **G** F FA higher in L hippocampus in S than S+C; **H** FA higher in R pons in S than S+C; **I** FA higher in R PLIC and prefrontal WM in S than S+C. *Abbreviations:* CC, corpus callosum; GM, gray matter; GP, globus pallidus, MFG, middle frontal gyrus; PLIC, posterior limb of internal capsule; PTR, posterior thalamic radiation; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; WM, white matter

TABLE 1

Neuropsychological Measures

Area	Assessment	Method
General Intelligence	Full Scale Intelligence Quotient	Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II)
	Verbal Comprehension Index	
	Perceptual Reasoning Index	
	Vocabulary	
	Similarities	
	Block Design	
	Matrix Reasoning	Wechsler Intelligence Scale for Children, Fourth Edition /Wechsler Adult Intelligence Scale, 4th Edition
Processing Speed	Coding	
	Symbol Search	
	Pattern Comparison Processing Speed	HealthMeasures NIH Toolbox (NIH-T)
Memory	List A Long-Delay Free Recall	California Verbal Learning Test, Children's Version (CVLT®-C)
	Memory for Designs Content & Spatial (MD)	
	Memory for Designs Delayed Content & Spatial (MDD)	NEPSY-II
Executive Functions	Flanker Inhibitory Control & Attention	
	Dimensional Change Card Sort	NIH-T
	Digit Span	
	Spatial Span	Wechsler Intelligence Scale for Children, Fourth Edition Integrated (WISC-IV)
	List Sorting Working Memory	NIH-T
	Behavioral Regulation Index	
	Metacognition Index	
	Global Executive Composite	Behavior Rating Inventory of Executive Functions (BRIEF®) parent report questionnaire
	NeuroQOL PED Cognitive Function	HealthMeasures Neuro-QOL
Language	Expressive One-Word Picture Vocabulary Test	EOWPVT-4
	Receptive One-Word Picture Vocabulary Test	ROWPVT-4
Behavior/Mood	PED Depression	
	PED Interaction with Peers	
	PED Fatigue	HealthMeasures Neuro-QOL

Area	Assessment	Method
	Internalizing Problems	Achenbach Child Behavior Checklist (CBCL) parent report questionnaire
	Externalizing Problems	
	Total Problems	

TABLE 2

Patient demographics by treatment group compared to controls

Variable		Treatment group			Total (n = 46)	p-value
		S (n = 17)	S+C (n = 11)	HC (n = 18)		
Age – mean (SD)		10.76 (4.02)	12.18 (3.52)	10.56 (2.23)	11.02 (3.25)	0.41
Age at Diagnosis – mean (SD)		6.02 (3.57)	3.52 (3.29)	NA	5.04 (3.63)	0.07
Sex	Male	4 (24%)	6 (55%)	10 (56%)	20 (43%)	0.11
	Female	13 (76%)	5 (45%)	8 (38%)	26 (53%)	
Handedness	Right	14 (82%)	10 (91%)	17 (94%)	41 (89%)	0.78
	Left	3 (18%)	1 (9%)	1 (5%)	5 (11%)	
Patient Race/ethnicity	White	15 (88%)	10 (91%)	16 (89%)	41 (89%)	Race – 0.84
	Non-Hispanic	7 (41%)	3 (27%)	10 (63%)	20 (43%)	Ethnicity – 0.11
	Hispanic/Latino	9 (53%)	8 (73%)	6 (33%)	23 (50%)	
	Black/African American	1 (6%)	0 (0%)	0 (0%)	1 (2%)	
	Asian	1 (6%)	1 (9%)	2 (11%)	4 (9%)	
Diagnosis	medulloblastoma	0 (0%)	7 (64%)		7 (25%)	0.0001
	ependymoma	0 (0%)	1 (9%)		1 (4%)	
	Astrocytoma	2 (12%)	0 (0%)	NA	2 (7%)	
	Pilocytic Astrocytoma	14 (82%)	2 (18%)		16 (57%)	
	Other	1 (6%)	1 (9%)		2 (7%)	
Time Off Treatment (years) – mean (SD)		4.47 (3.20)	8.09 (4.71)	NA	5.89 (4.19)	0.02
Region of tumor location	Midline	6 (35%)	7 (64%)		13 (46%)	0.18
	Left	4 (24%)	3 (27%)	NA	7 (25%)	
	Right	7 (41%)	1 (9%)		8 (29%)	
Hydrocephalus at diagnosis	Yes	10 (59%)	7 (64%)		17 (61%)	0.75
	No	5 (29%)	2 (18%)	NA	7 (25%)	
	Unknown	2 (12%)	2 (18%)		4 (14%)	
Hydrocephalus severity	Mild	3 (30%)	2 (29%)	NA	5 (29%)	0.87
	Moderate	6 (60%)	3 (43%)		9 (53%)	

Variable		S (n = 17)	S+C (n = 11)	HC (n = 18)	Total (n = 46)	p-value
	Severe	0 (0%)	1 (14%)		1 (6%)	
	Unknown	1 (10%)	1 (14%)		2 (12%)	
VP shunt	Yes	1 (6%)	6 (55%)	NA	7 (25%)	**0.002**
	No	16 (94%)	5 (45%)		21 (75%)	
Bilingual	No	10 (59%)	4 (36%)	10 (56%)	24 (52%)	0.82
	Yes	5 (29%)	5 (45%)	6 (33%)	16 (35%)	
	Missing	2 (12%)	2 (18%)	2 (11%)	6 (13%)	
Annual Income	$39,999	6 (35%)	4 (36%)	7 (39%)	17 (37%)	0.80
	$40,000-$79,999	1 (6%)	1 (9%)	2 (11%)	4 (9%)	
	$80,000	7 (41%)	3 (27%)	8 (44%)	18 (39%)	
	Missing	3 (18%)	3 (27%)	1 (6%)	7 (15%)	
Did mother attend college?	No	7 (41%)	5 (45%)	8 (44%)	20 (43%)	0.12
	Yes - BS	1 (6%)	4 (36%)	2 (11%)	7 (15%)	
	Yes - Grad	6 (35%)	1 (9%)	8 (44%)	15 (33%)	
	Missing	3 (18%)	1 (9%)	0 (0%)	4 (9%)	
Did father attend college?	No	6 (35%)	5 (45%)	3 (17%)	14 (30%)	0.11
	Yes - BS	4 (24%)	4 (36%)	9 (50%)	17 (37%)	
	Yes - Grad	3 (18%)	1 (9%)	6 (33%)	10 (22%)	
	Missing	4 (24%)	1 (9%)	0 (0%)	5 (11%)	

Bold font indicates significant p-value (p 0.05)

TABLE 3.

Neuropsychological Assessment Scores & Fractional Anisotropy R values[*]

Domain/ Test	L MFG GM	R UF	R PLIC	R thalamus	L hippocampus	R pons
General Intelligence Verbal Comprehension	−0.84 S+C					
Perceptual Reasoning				0.83 S+C		
Block Design				0.91 S+C		
FSIQ		−0.91 S+C		0.88 S+C		
Vocabulary		−0.82 S+C				
Similarities		−0.84 S+C		0.73 S		
Working Memory Digit Span Total					0.98 S	
Spatial Span Total				0.82 S+C		
Spatial Span Forward	−0.98 S		0.98 S			
Memory Memory for Designs Delayed Total						−0.87 S+C
Language Expressive One Word Vocabulary Test		−0.83 S+C				

[*] p < 0.01

GM, gray matter; MFG, middle frontal gyrus; PLIC, posterior limb of internal capsule; UF, uncinate fasciculus