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CLINICAL STUDY

Fronto-limbic white matter microstructure, behavior, and emotion regulation in survivors of pediatric brain tumor

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Abstract

Purpose After treatment, pediatric brain tumor survivors (PBTS) face emotional and behavioral challenges, perhaps due to tumor or treatment-related changes in brain structures involved in emotion regulation, including those with fronto-limbic connections. We hypothesized that relative to healthy controls (HCs), PBTS would exhibit greater difficulties with behavior and emotional functioning, and display reduced mean fractional anisotropy (mFA) in white matter tracts with fronto-limbic connections including the cingulum bundle (CB), inferior fronto-occipital fasciculus (IFOF), and uncinate fasciculus (UF). We further predicted that mFA would account for variance in the relationship between group and emotional/behavioral outcome.

Methods Eleven 8–16 year old PBTS and 14 HCs underwent MRI, including diffusion tensor imaging to assess white matter microstructure. Tractography quantified mFA of selected tracts. Parents rated children's emotional and behavioral functioning.

Results Compared to HCs, caregivers of PBTS reported poorer behavioral regulation and greater internalizing and externalizing symptoms. Relative to HCs, PBTS had lower mFA within the bilateral CB, IFOF, and UF ($ds = 0.59$–1.15). Across groups, several medium-to-large correlations linked tract mFA and increased internalizing, externalizing, and poor behavioral regulation. Tract mFA also accounted for significant variance in the group-outcome association.

Conclusions Reduced mFA in fronto-limbic associated tracts may be associated with reduced behavioral regulation following pediatric brain tumor. PBTS with treatment known to impact white matter may be most susceptible. Research with larger, longitudinal samples should clarify this relationship, allow for multiple mediators across time, and consider factors like tumor and treatment type.

Keywords Behavioral regulation · Children · Diffusion tensor imaging · Internalizing · Pediatric brain tumor

Introduction

Brain tumors are the most commonly diagnosed solid tumor for children in the United States, with over 4500 new cases annually [1]. Fortunately, with advancements in treatment, brain tumor survivorship has improved to roughly 74% as of 2016 [2]. With this increase in survivorship, cognitive, psychosocial, and emotional late effects are provided increased attention.

The neurocognitive sequelae of pediatric brain tumor are well documented, including declines in verbal and non-verbal intelligence, academic achievement, attention,

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and memory [3, 4]. Research on emotional and behavioral outcomes is more inconsistent, but has documented depression and anxiety [5], nervousness, and fearfulness [6]. An increased risk of internalizing and externalizing is also reported [7]. In the Childhood Cancer Survivor Study, a program of 26 collaborating institutions monitoring long term outcomes following pediatric cancer found that children with diagnoses known to impact the central nervous system (including brain tumor) were at significantly greater risk of depression, anxiety, antisocial behaviors, and diminished social competence [8]. Others have found that risk for long term withdrawal and depressive symptoms is most elevated for those with high-risk diagnoses [9]. In contrast, others found that after treatment these children are similar to peers in depressive symptoms and quality of life [10], or have found differences based on whether children rate their own mental health or parents provide proxy-report [11, 12]. Even in cases where elevated risk was found, some still documented mean scores in the average range [9]. Clearly, further research is warranted to parse the nuances of risk and resilience in this population.

Behavioral regulation is the ability to manage emotion, behavior and attention [13], and poor behavioral regulation is associated with internalizing and externalizing in healthy children [14]. Behavioral regulation may be challenging for pediatric brain tumor survivors (PBTS), thus contributing to an amalgam of symptoms phenotypically similar to attention deficit disorders [15, 16]. Behavioral regulation is one element of broader executive functioning, and includes notable skills required for social interactions and academic functioning like thinking before acting, staying focused, and controlling impulses to jump to conclusions or react emotionally [17]. However, the emotional aspects of behavioral regulation may be insufficiently tapped by traditional neuropsychological assessment measures, which tend to target cognitively-laden skills. Although behavioral regulation is measured as a single composite of measures like the Behavior Rating Inventory of Executive Function (BRIEF) [18], this index is rarely reported independently. Rather, global executive composites are used, and typically show poorer global executive function in PBTS compared to healthy peers [19] or as disproportionately impaired versus norms [20]. The extent to which poor global executive composite scores are due to poor behavioral regulation versus metacognition is worthy of exploration, especially given an abundance of evidence showing diminished neurocognitive performance in this population, which may align more closely with poor metacognition. This may improve our understanding of the broader constellation of emotional and behavioral sequelae during survivorship.

Late effects following pediatric brain tumor may be due, in part, to the impact of a tumor diagnosis and its treatment on white matter pathways [21, 22]. Recently, diffusion tensor imaging has surpassed white matter volumetrics to assess microstructural changes in white matter. One metric, mean fractional anisotropy (mFA), is highly sensitive to microstructural changes in the diffusivity of water parallel to white matter fibers [23]. Restricted diffusion, or high mFA, is thought to support greater efficiency of white matter pathways. Reduced mFA (indicative of lesser restricted diffusion) is reported in PBTS compared to healthy children in multiple tracts, including the corpus callosum, internal capsule, and frontal white matter [24].

While research on the associations among white matter and neurocognitive late effects for PBTS has advanced in recent years [25, 26], links with psychosocial outcomes remain underexplored. These links are more often studied in healthy and other clinical populations, often in adults with mood disorders. White matter pathways that support prefrontal cortical networks are involved in depressive symptoms and behavioral regulation [27]. For adults, depression is associated with lower mFA in tracts subserving the dorsolateral prefrontal cortex [28] and internal capsule [29–31], including the uncinate fasciculus (UF), the inferior fronto-occipital fasciculus (IFOF), and the cingulum bundle (CB) [29, 32]. In one study of adolescents with major depression, similar patterns of reduced mFA were documented in the subgenual anterior cingulate, right and left UF, and supragenual CB [33]. Links between the UF and anxiety symptoms have also been documented in adolescents [34].

Literature linking white matter microstructure and emotional and behavioral outcomes in the context of brain tumor is very limited. In a lone study assessing white matter and affective symptoms in adult survivors, mFA in the left internal capsule and UF were positively associated with anxiety, and mFA of these regions on the right was associated with depression [35]. These findings stand in contrast with studies showing that white matter and affective symptoms are generally negatively correlated.

The present study attempts to address the dearth of literature on the contribution of white matter microstructure to emotional and behavioral sequelae in PBTS. We identify differences in behavioral regulation, internalizing and externalizing, and white matter microstructure in PBTS relative to healthy controls, and examine interrelationships among these domains. We also explore the extent to which white matter accounts for the relationships among group and emotional and behavioral outcomes. We hypothesize that, relative to healthy controls, parents of PBTS will endorse greater symptoms of emotional and behavioral problems, and children will evidence reduced white matter microstructure. We also predict negative associations among white matter and emotional and behavioral symptoms, and white matter microstructure will account for variance in the relationships among group and emotional and behavioral outcome.

Methods

Participants and procedures

Eleven PBTS and 14 healthy controls (HCs) were included in these analyses. These survivors represent a subset of 21 PBTS identified through the cancer survivorship or neurosurgery clinics at a large southeastern children's hospital who participated in a study of neuroanatomical and neurocognitive functioning following pediatric brain tumor. Participants in the larger study were: (i) 8–16 years old at enrollment (ii) completed treatment (iii) ≥ 2 years post-diagnosis (iv) in first continuous remission, and (v) English-speaking. Exclusion criteria included: (i) pre-existing neurological/neurodevelopmental condition (e.g., neurofibromatosis, autism) (ii) history of very low birth weight (< 1500 g) (iii) secondary malignancies/relapse, and (iv) contraindications to magnetic resonance imaging (MRI). Twenty HCs, roughly matched by age and sex, were also recruited. HCs had no history of cancer or significant chronic illness, and otherwise met the same applicable inclusion and exclusion criteria. Procedures were approved by the Institutional Review Board (IRB#100316), and parental consent and child assent were obtained.

PBTS were recruited through a letter to their parents from their physician providing information about the study. After two weeks, families were contacted to determine interest and eligibility. HCs were contacted through an email solicitation to faculty and staff of the medical center. During participation, parents completed ratings of their child's emotional and behavioral functioning and children underwent a MRI session. Before scanning, all participants visited a mock scanner to ensure their comfort and readiness for neuroimaging.

For inclusion in the present analyses, children must have completed both components of the study, and the diffusion tensor imaging sequence must have met allowable motion constraints. From the original 21 PBTS, 17 completed a scan; five were excluded from these analyses due to motion and one was excluded due to missing parent ratings. Survivors that were included and excluded in analyses differed only by gender as more boys failed to complete both components ($p < 0.05$). Eighteen HCs attempted a scan, of which sixteen completed a diffusion tensor imaging (DTI) sequence and two were excluded for motion. HCs who were included versus excluded did not differ by age or sex.

Demographic data are provided in Table 1, and no significant between-group differences were found. Survivors were an average of 6.24 years post-diagnosis (SD = 3.00) and 5.70 years post-treatment completion (SD = 3.16). Six PBTS (54.5%) were diagnosed with juvenile pilocytic astrocytoma, 2 (18.2%) with dysembryoplastic neuroepithelial tumor, 2 (18.2%) with medulloblastoma, and 1 (9.1%) with germinoma. The tumors were located in the posterior fossa (8; 72.7%), optic chiasm/hypothalamus (1; 9.1%), parietal lobe (1; 9.1%), and temporal lobe (1; 9.1%). All survivors underwent some extent of resection; 4 also received chemotherapy and radiation (36.4%) with cumulative radiation dosage ranging from 54.0–56.0 Gy.

Measures

Behavioral and emotional problems

Parents rated their child's behavioral regulation, internalizing, and externalizing using the BRIEF [18] and the Child Behavior Checklist (CBCL; [36]), respectively.

The BRIEF assesses day-to-day executive function and self-regulation. Internal consistency ($\alpha = 0.80$–0.98) and test–retest reliability ($r = 0.82$) are high. In these analyses, the Behavioral Regulation Index (BRI) scale is used, which includes a child's skills with inhibition, emotional control, and shifting behaviors based on day-to-day situational demands.

The CBCL assesses a child's social, emotional, and behavioral functioning. This widely used measure has strong internal consistency ($\alpha = 0.80$) and test–retest reliability ($r = 0.88$). The Internalizing Symptoms and Externalizing Symptoms scales are used in these analyses.

Diffusion tensor imaging (DTI)

MRI acquisition

Children underwent MRI without sedation on a Philips Achieva 3 Tesla scanner dedicated to research (Philips Healthcare, Best, The Netherlands). During DTI, transverse multi-slice spin echo, single shot, echo planar imaging (EPI) sequences were used (10,000 ms TR, 60 ms TE, 2.0 mm slices, flip angle 90°), with a reconstructed voxel size of $2.0 \times 2.0 \times 2.0$ mm and a FOV of 256 mm. Diffusion was measured along 32 directions, with 2 diffusion weightings, low b-value = 0 s/mm^2, high b-value = 1000 s/mm^2. Sixty contiguous slices were obtained parallel to the anterior commissure–posterior commissure (AC–PC) plane. High resolution 3D anatomical images were acquired using an inversion-prepared spoiled gradient recalled echo sequence (IR-3D-TFE), with an inversion time T1 of 400 ms, 15 ms TR, 3 ms TE, and a FOV of $256 \times 255 \times 270$ mm with near isotropic resolution.

Table 1 Group differences

	PBTS (n = 11)	HC (n = 14)		p	Effect size[a]
Demographics					
Child age–mean (SD)	12.83 (2.51)	12.94 (2.70)		.920	0.04
Child sex (Female) (n)	7	8		.742	0.07
Child race (White/Caucasian) (n)	10	10		.194	0.43
Parent education (≥ some college) (n)	8	14		.278	0.45
Family income (≥ $50,000) (n)	8	6		.323	0.53
Child h/o behavioral treatment/therapy (yes) (n)	2	1		.399	0.17
Emotional/behavioral outcome			t (21–23)		
Behavior Regulation Index	56.20 (4.92)[b]	45.62 (6.17)[c]	3.64	.002	1.59
Internalizing symptoms	57.55 (9.06)	49.43 (9.44)	2.20	.038	0.86
Externalizing symptoms	56.09 (9.13)	45.21 (6.99)	3.06	.006	1.17
mFA					
R CB	0.44 (0.02)	0.49 (0.03)	− 2.38	.026	0.99
L CB	0.46 (0.03)	0.49 (0.02)	− 2.58	.017	1.01
R IFOF	0.46 (0.03)	0.48 (0.02)	− 2.62	.010	1.03
L IFOF	0.47 (0.02)	0.48 (0.02)	− 1.46	.159	0.59
R UF	0.42 (0.02)	0.43 (0.02)	− 1.89	.071	0.75
L UF	0.42 (0.01)	0.44 (0.02)	− 2.80	.010	1.15
R OR	0.47 (0.03)	0.47 (0.03)	− 0.76	.456	0.00
L OR	0.48 (0.04)	0.49 (0.02)	− 0.84	.410	0.32
mADC					
R CB	0.79 (0.02)	0.78 (0.04)	1.11	.281	0.32
L CB	0.78 (0.04)	0.77 (0.02)	1.26	.220	0.32
R IFOF	0.82 (0.03)	0.79 (0.03)	2.82	.010	1.00
L IFOF	0.82 (0.03)	0.79 (0.02)	2.81	.010	1.18
R UF	0.82 (0.02)	0.81 (0.02)	0.91	.373	0.50
L UF	0.83 (0.02)	0.82 (0.03)	0.64	.526	0.39
R OR	0.89 (0.09)	0.83 (0.08)	1.93	.066	0.70
L OR	0.87 (0.12)	0.81 (0.09)	1.38	.182	0.57
mAD					
R CB	1.19 (0.02)	1.20 (0.05)	− 0.92	.369	0.26
L CB	1.20 (0.04)	1.22 (0.03)	− 1.37	.184	0.57
R IFOF	1.27 (0.05)	1.26 (0.04)	0.66	.514	0.22
L IFOF	1.28 (0.04)	1.26 (0.04)	1.69	.104	0.50
R UF	1.22 (0.04)	1.23 (0.04)	− 0.66	.515	0.25
L UF	1.24 (0.03)	1.25 (0.04)	− 1.19	.248	0.28
R OR	1.37 (0.12)	1.29 (0.11)	1.67	.108	0.69
L OR	1.35 (0.14)	1.28 (0.13)	1.21	.239	0.52
mRD					
R CB	0.59 (0.02)	0.56 (0.04)	2.02	.055	0.95
L CB	0.57 (0.05)	0.54 (0.03)	2.12	.045	0.73
R IFOF	0.60 (0.03)	0.56 (0.03)	3.76	.001	1.33
L IFOF	0.59 (0.03)	0.56 (0.03)	2.73	.012	1.00
R UF	0.62 (0.02)	0.61 (0.02)	1.97	.061	0.50
L UF	0.63 (0.02)	0.61 (0.03)	1.80	.084	0.78
R OR	0.65 (0.07)	0.59 (0.07)	1.99	.058	0.86
L OR	0.63 (0.11)	0.57 (0.07)	1.56	.131	0.65

Outcome scores reported as T-scores, M = 50, SD = 10. One outlier removed from each group for Behavioral Regulation Index analysis, yielding 21 dof

PBTS Pediatric brain tumor survivor, *HC* healthy control, *R* right, *L* left, *CB* cingulum bundle, *IFOF* inferior fronto-occipital fasciculus, *UF* uncinate fasciculus, *OR* optic radiation, *mFA* mean fractional anisotropy, *mADC* mean apparent diffusion coefficient, *mAD* mean axial diffusivity; *mRD* mean radial diffusivity

[a]Effect size = Cohen's d for Child Age, Cramer's v for other comparisons

Table 1 (continued)

[b]n = 10, [c]n = 13

DTI analysis

All data were inspected for artifacts or irregularities. DTI analysis was conducted using deterministic fiber tracking algorithms via DSI Studio (https://dsi-studio.labsolver.org) [37]. Fiber tracking parameters included a step size of 0.88 mm, an anisotropy threshold of 0.16, fiber angular threshold of 80°, and minimum fiber length of 20.0 mm. Propagation directions were averaged with 20% of the previous direction to smooth individual fiber trajectories.

A multiple region-of-interest approach was used to segment white matter pathways, completed by a single rater blind to participant group (KRH). Each tract was rated twice and reliability statistics exceeded an intra-class correlation coefficient of 0.95, suggesting excellent reliability. mFA was obtained for tracts of interest, using an individualized seed-driven approach, separately for bilateral tracts. For the right and left CB, mFA was calculated using seeds placed linearly along the CB in the parasagittal planes. For the right and left UF, one seed region encompassed the temporal lobe on the posterior-most coronal plane where the sylvian fissure is visualized, and a second seed region encompassed the frontal hemisphere anterior to the genu of the corpus callosum. For the right and left IFOF, mFA was calculated using one seed region posterior to the rostrum of the corpus callosum, one encompassing the ipsilateral temporal stem, and one frontal lobe seed region, as described above. To test the specificity of the associations among white matter microstructure and behavior, control tracts (i.e., bilateral optic radiation; OR) were also processed, using seeds in the inferior occipital lobe and lateral geniculate nucleus. For each tract, a region-of-avoidance was included at the sagittal midline, to eliminate fibers crossing into the contralateral hemisphere. Composite values of mFA and other DTI metrics were calculated across voxels based on the above-mentioned parameters.

Data analysis

Data were examined for outliers (±2 SD) within group. One participant from each group exceeded criteria on the BRI, so their data were excluded from analyses involving that measure. Group differences were assessed using independent samples t-tests or Chi-square. Bivariate Pearson correlations quantified the associations among BRI, Internalizing Symptoms, Externalizing Symptoms, and mFA. Correlation magnitudes are discussed in terms of statistical significance, and based on Cohen's guidelines [38] with effect sizes assessed as: large ($r \geq 0.50$) or medium ($0.50 > r \geq 0.30$). Between-group differences in correlation were assessed using Fisher's r-to-z-transformation [39].

The PROCESS macro for SPSS [40] was used to examine the indirect effect of white matter microstructure on the association between group and emotional or behavioral outcome (see Fig. 1). Using ordinary least squares path analysis, we report unstandardized beta coefficients for each path [41]. Unstandardized path coefficients are scaled according to the measurement of specific variables in that path, and are preferable in this type of modeling, especially when independent variables are categorical [41]. As depicted in Fig. 1, this methodology results in direct effects of each pathway (a, b, c′), and the indirect effect of group on outcome via mFA (ab). Indirect effects are calculated using 10,000 bootstrap samples of products from direct effects a and b. From this a 95% bias-corrected confidence interval is assessed and if this range does not contain zero it is considered significant.

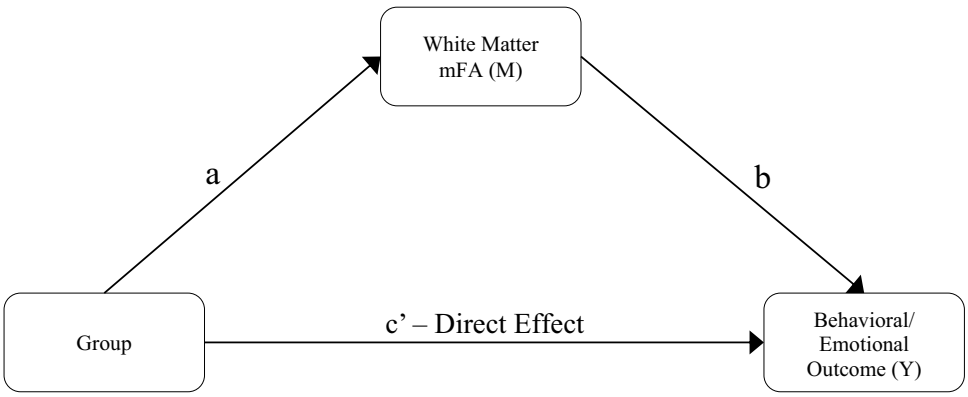

Fig. 1 Example indirect effect model

Results

Group differences

For behavioral and emotional outcomes, significant group differences were found across all domains with PBTS having worse behavioral regulation and greater internalizing and externalizing symptoms. Similar analyses for the larger participant sample have been presented previously [19, 42], though not in this specific subgroup. mFA was significantly lower in all PBTS white matter tracts of interest except the left IFOF and the right UF, with the latter approaching significance Table 1, Fig. 2). To be as comprehensive as possible, additional DTI metrics, including apparent diffusion coefficient, radial diffusivity, and axial diffusivity are also provided in Table 1. Groups did not differ on any DTI metric in the bilateral OR, although group differences in the right OR apparent diffusion coefficient and radial diffusivity approached significance.

Associations among mFA and outcomes

Correlations among outcome measures and mFA are presented in Table 2. For PBTS, internalizing symptoms were significantly negatively correlated with mFA of the bilateral IFOF and right UF. No significant relationships were observed for behavioral regulation and externalizing for this group. However, medium effect sizes were observed for the associations among mFA of the bilateral CB and internalizing and externalizing symptoms. Medium effect sizes were also noted for the associations among mFA in the bilateral OR and internalizing symptoms.

For HCs, behavioral regulation was significantly negatively correlated with mFA of the left CB. Large effect sizes were also noted, including the relationships among mFA of the right CB and both behavioral regulation and internalizing. Medium effect sizes were evident for the associations among mFA of the bilateral IFOF and behavioral regulation, and for the right IFOF and left OR and internalizing. The only group difference for the magnitude of correlation coefficients was the relationship between mFA of the right UF and internalizing, which was highly significant ($r = -0.713$) in PBTS and negligible ($r = 0.073$) in HCs.

Indirect effect of mFA on the group–outcome association

Results from indirect effect models are summarized in Table 3. Five models indicated significant indirect effect where white matter tract mFA accounts for significant variance in the relationship between group and behavioral or emotional outcome. mFA of the right CB (19.72%) and the right IFOF (20.19%) accounted for significant variance in the relationship between group and behavioral regulation. mFA of the right and left CB (13.51% and 13.26%,

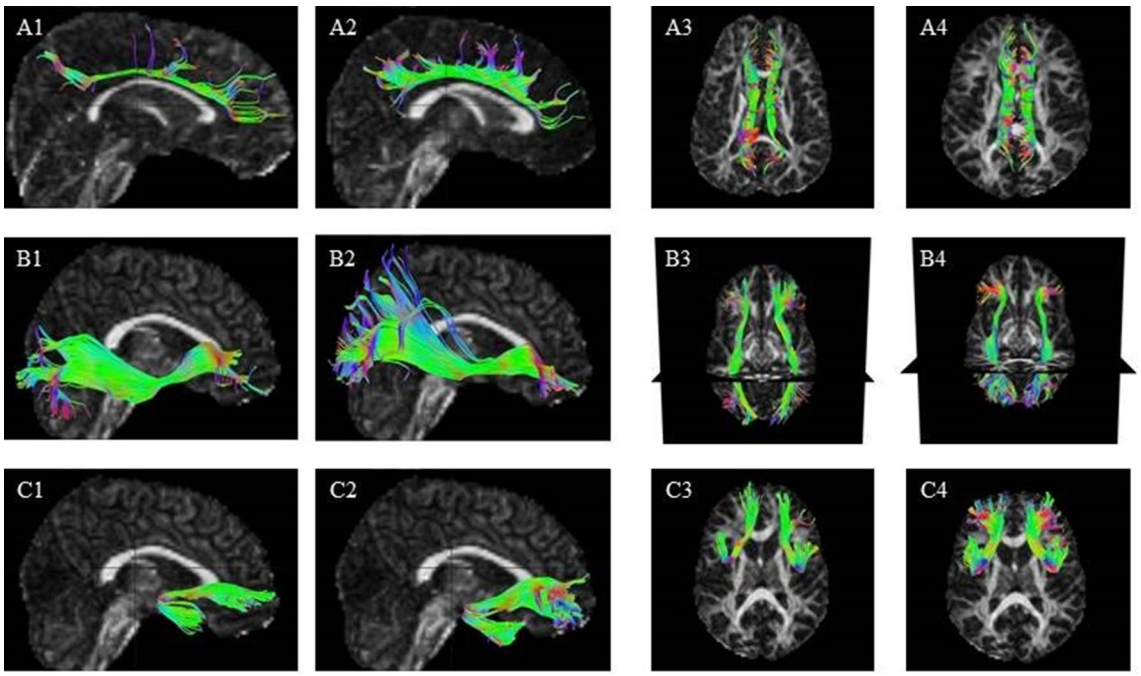

Fig. 2 DTI example images (radiological convention). *A1/A3* Prototypical PBTS of the CB. *A2/A4* Prototypical HC of the CB. *B1/B3* Prototypical PBTS of the IFOF. *B2/B4* Prototypical HC of the IFOF. *C1/C3* Prototypical PBTS of the UF. *C2/C4* Prototypical HC of the UF

Table 2 Associations among behavioral and emotional outcomes and white matter microstructure

Behavioral/emotional outcome	White matter mFA	PBTS (n = 11)	HC (n = 14)	p	Z
Behavioral regulation[a]	R CB	− .015	− .532	0.242	1.17
	L CB	− .052	− .678*	0.116	1.57
	R IFOF	− .262	− .394	0.764	0.30
	L IFOF	− .274	− .365	0.834	0.21
	R UF	− .417	.098	0.271	− 1.10
	L UF	− .115	.047	0.741	− 0.33
	R OR	− .166	.119	0.535	− 0.62
	L OR	− .041	− .145	0.818	0.23
Internalizing	R CB	− .439	− .501	0.865	0.17
	L CB	− .389	− .358	0.936	− 0.08
	R IFOF	− .626*	− .368	0.453	− 0.75
	L IFOF	− .790**	− .213	0.070	− 1.84
	R UF	− .713*	.073	0.038	− 2.08
	L UF	− .064	− .123	0.897	0.13
	R OR	− .386	.064	0.313	− 1.01
	L OR	− .467	− .324	0.356	− 0.37
Externalizing	R CB	.306	− .344	0.147	1.45
	L CB	.360	− .290	0.089	1.70
	R IFOF	.006	− .361	0.401	0.83
	L IFOF	.211	− .269	0.294	1.05
	R UF	− .040	− .182	0.757	0.31
	L UF	.325	− .164	0.280	1.08
	R OR	− .166	− .057	0.810	− 0.24
	L OR	− .031	− .183	0.741	0.33

PBTS Pediatric brain tumor survivor, *HC* healthy control, *R* right, *L* left, *CB* cingulum bundle, *IFOF* inferior fronto-occipital fasciculus, *UF* uncinate fasciculus, *OR* optic radiation

[a](BT n = 10, HC n = 13)

*p < .05. **p < .01

respectively) and the right IFOF (15.57%) accounted for significant variance in the relationship between group and internalizing. Neither the right nor left OR accounted for significant variance in the relationship between group and any behavioral or emotional outcome.

Discussion

Our objective was to examine differences in behavioral regulation, internalizing and externalizing, and white matter microstructure between PBTS and healthy peers, and to examine the interplay among these variables. Our results are amongst the first to show that certain white matter tracts predict notable variance in these poorer outcomes, above and beyond group.

Our work supports existing literature stating that PBTS are at risk for poor behavioral regulation [19, 20], and demonstrates that behavioral regulation is an important component of emotional and behavioral late effects. PBTS had greater internalizing and externalizing symptoms relative to controls [7]. However, similar to other studies, mean values were generally average, at roughly two-thirds to three-quarters of a standard deviation from the normative mean. The statistical significance of group differences also likely reflects better-than-normal functioning of HCs. Indeed, the mean parent ratings of the HCs on the BRIEF BRI and the CBCL Externalizing Symptoms scale are roughly a half standard deviation better than would be anticipated based on normative data. This finding also illustrates the considerable variability in outcomes following pediatric brain tumor, with some children struggling and others displaying remarkable resilience.

Our work also replicates that white matter mFA is reduced in this population [26], perhaps due to the direct impact of the tumor, or as a secondary consequence of surgery or treatment [24]. Indeed, although a major culprit for white matter damage, even when adjuvant chemotherapy and radiation are not required, increased intracranial pressure due to hydrocephalus and surgical interventions may also damage white matter [21]. These factors are vital to include in future studies with statistical power to do so.

Table 3 Contributions of group and white matter microstructure to behavioral and emotional outcomes

Behavioral/emotional outcome (Y)	Direct effects			Indirect effect
White matter mFA (M)	a B (SE)	b B (SE)	c' B (SE)	ab B (SE) [95% CI]
Behavioral regulation[a]				
R CB mFA	0.02 (0.01)*	− 120.20 (58.57)†	− 6.57 (2.79)*	− 2.87 (1.63) [− 6.69, − 0.43]
L CB mFA	0.03 (0.01)**	− 74.65 (47.25)	− 6.84 (2.99)*	− 2.60 (1.75) [− 6.32, 0.29]
R IFOF mFA	0.02 (0.01)*	− 91.55 (58.45)	− 7.47 (2.80)*	− 1.97 (1.26) [− 5.50, − 0.26]
L IFOF mFA	0.01 (0.01)	− 88.65 (57.94)	− 8.34 (2.61)**	− 1.10 (1.13) [− 4.37, 0.23]
R UF mFA	0.01 (0.01)*	− 31.64 (83.35)	− 8.98 (2.91)**	− 0.46 (0.96) [− 2.89, 1.13]
L UF mFA	0.02 (0.01)**	25.08 (90.95)	− 9.90 (3.14)**	0.47 (1.61) [− 2.60, 3.81]
Internalizing				
R CB mFA	0.02 (0.01)*	− 114.22 (52.97)*	− 2.67 (2.38)	− 2.40 (1.34) [− 6.13, − 0.59]
L CB mFA	0.03 (0.01)*	− 77.27 (42.55)†	− 2.81 (2.45)	− 2.27 (1.12) [− 4.83, − 0.42]
R IFOF mFA	0.02 (0.01)*	− 135.17 (58.59)*	− 1.87 (2.05)	− 3.21 (1.37) [− 6.71, − 1.01]
L IFOF mFA	0.01 (0.01)	− 132.00 (57.67)*	− 3.41 (2.11)	− 1.67 (1.14) [− 4.34, 0.18]
R UF mFA	0.01 (0.01)†	− 147.94 (91.61)†	− 3.17 (2.15)	− 1.91 (1.52) [− 6.19, > 0]
L UF mFA	0.02 (0.01)*	− 48.76 (63.11)	− 4.24 (2.75)	− 0.84 (1.09) [− 3.45, 1.00]
Externalizing				
R CB mFA	0.02 (0.01)*	− 1.02 (53.80)	− 6.80 (2.55)*	− 0.02 (0.93) [− 1.02, 2.92]
L CB mFA	0.03 (0.01)*	34.89 (41.12)	− 7.85 (2.55)**	1.03 (1.24) [− 0.85, 4.15]
R IFOF mFA	0.02 (0.01)*	− 17.04 (52.46)	− 6.42 (2.60)*	− 0.40 (1.53) [− 3.68, 2.69]
L IFOF mFA	0.01 (0.01)	13.41 (54.85)	− 6.99 (2.38)**	0.17 (0.81) [− 0.98, 2.72]
R UF mFA	0.01 (0.01)†	− 15.91 (69.78)	− 6.62 (2.45)*	− 0.21 (0.96) [− 1.58, 2.13]
L UF mFA	0.02 (0.01)*	23.52 (77.41)	− 7.23 (2.64)*	0.40 (1.27) [− 1.15, 4.33]

Unstandardized coefficients (B) and standard errors (SE). Bolded confidence intervals (CI) signify zero not included. One outlier removed from each group for Behavioral Regulation Index analysis

PBTS Pediatric brain tumor survivor, *HC* healthy control, *R* right, *L* left, *CB* cingulum bundle, *IFOF* inferior fronto-occipital fasciculus, *UF* uncinate fasciculus

[a](n = 23)

†p < .10 *p < .05 **p < .01

These findings extend existing literature on the connections among white matter and late effects by considering behavioral regulation and emotional functioning. Previous research has typically involved adults [28, 30, 31] or adolescents [29] with mood disorders, but not younger children or PBTS specifically. We selected tracts of interest based on limbic connections, including projections to the prefrontal and cingulate cortex. More robust white matter in regions related to executive function contributes to faster processing speeds [26], so we hypothesized a similar pattern with emotion and behavior. That is, as children age, they engage in increasingly complex interactions that likely require efficient responses among frontal, limbic, and cingulate regions.

To assess the specificity of our white matter tracts of interest in their links to emotional and behavioral outcomes, we also examined the extent to which white matter microstructure in the optic radiations played a role. Group differences were modest to negligible bilaterally, perhaps because development of these posterior tracts occurs prior to the maturation of the prefrontal regions [43]. It is possible that treatment after maturation is complete has a different impact on white matter microstructure than treatment that interrupts an ongoing neurodevelopmental process. This is quite speculative, yet worthy of further examination. Although most correlations among OR mFA and emotional or behavioral outcome were also negligible, medium effects were noted between the bilateral OR and internalizing symptoms. It may be that this indicates that greater global brain pathology is most closely associated with internalizing (rather than behavioral regulation or externalizing). That said, correlations were far more modest than those between the IFOF and UF and internalizing, suggesting some degree of specificity of these anterior pathways in supporting emotional functioning.

In some pathways, associations among mFA and outcomes were evident in one hemisphere (typically the right), but not the other. This pattern was most pronounced in the PBTS group, particularly the UF. Similar lateralized effects

have been observed in adults with brain tumor [35] and healthy individuals [44], specifically with links to negative emotionality. Also noteworthy is the group difference in the relationship between mFA in the right UF and internalizing. In functional neuroimaging studies, disproportionate activity in the right and left hemispheres predict symptoms of anhedonia and negative emotionality. While functional activity is outside the scope of this study, it is important to note low positive emotionality is associated with lower left hemisphere activity in the frontal region [45]. Disproportionate right prefrontal activity has been linked to depression [46]. In adults, reduced mFA in the right prefrontal and orbitofrontal cortex was associated with anxiety [47]. Further research looking at these outcomes may elucidate these lateralized findings in PBTS.

We used indirect effect models to assess the extent to which white matter microstructure explains variance in the associations among group and behavioral and emotional outcomes. Inclusion of right CB and IFOF mFA in the model further explained the relationship between group and behavioral regulation. Inclusion of the bilateral CB and right IFOF further explained the relationship between group and internalizing. Thus, while survivors are (as a whole) at risk for emotional or behavioral sequelae, damage to underlying white matter exacerbates this risk and may identify survivors in need of closer monitoring.

Clinicians should be aware that PBTS with treatment or symptoms (e.g., hydrocephalus) known to impact white matter may be at particular risk for emotional symptoms and poor behavioral regulation. Interventions that support these skills may be especially beneficial for high-risk patients. When assessing late effects, it is important to assess emotional symptoms and self-regulation, and conceptualize weaknesses within the broader context of brain-behavior relationships.

Despite several strengths, some limitations remain. Our findings are cross-sectional, so the temporal emergence and sensitive/critical time points remain unknown. Each group was quite small, limiting statistical power and our ability to consider relevant moderators. Larger samples, ideally in a longitudinal study, would allow us to examine the effects of important factors including treatment types, tumor location, histology, and lateralization, and mediators of outcome. Large samples would also allow for examination of the impact of presenting symptoms linked to brain systems (e.g., seizures, hydrocephalus) on long term outcomes. Due to our statistical power, and the limited amount of medical information abstracted during the present study, we are unfortunately unable to consider these very important factors. Furthermore, our sample of HCs displayed slightly better behavior (according to parent report) than would be expected based on normative data. It's possible this reflects the source of control participants (faculty and staff at a large university medical center), who may not completely reflect the broader population. Although our groups did not statistically differ in family income or parent education, power may have obscured small but meaningful differences, including how variability in demographic factors may affect a child's behavior. Future studies should certainly consider such socioeconomic variables. These participants were a subset of a slightly larger sample, and data may reflect those who are better able to self-regulate and remain still during MRI. While one previous study examined emotionality and white matter microstructure following brain tumor [30], this study is the first to examine this relationship in a pediatric sample. Overall, additional research remains warranted, and should examine temporal, tumor, and treatment based elements that may affect these important outcomes.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board (#IRB#100316) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Parent consent and child assent were obtained prior to participation.

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