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White matter hyperintensities relate to executive dysfunction, apathy, but not disinhibition in long-term adult survivors of pediatric cerebellar tumor

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ABSTRACT

White matter hyperintensities (WMHs) have been related to executive dysfunction, apathy and disinhibition in a wide range of neurological populations. However, this relationship has not been examined in survivors of pediatric brain tumor. The goal of this study was to investigate how executive dysfunction, apathy, and disinhibition relate to WMHs in 31 long-term survivors of pediatric cerebellar brain tumor and 58 controls, using informant-report data from the Frontal Systems Behavior Scale. Total WMH volume was quantified using the Lesion Growth Algorithm. Further, periventricular, and subcortical volumes were identified based on proximity to custom ventricle masks generated in FSL. A ratio of WMH volume to whole brain volume was used to obtain normalized WMH volumes. Additionally, a multivariate regression analysis was performed. On average, informant-report scores were within normal limits and only executive dysfunction was significantly higher in survivors compared to controls ($t(47.9) = -2.4$, $p=.023$). Informants reported clinically significant levels of apathy in 32.3% of survivors. Informants also reported clinically significant executive dysfunction in 19.4 % of survivors and clinically significant disinhibition in, again, 19.4 % of survivors. Increased volume of WMHs was positively correlated with executive dysfunction ($r = 0.33$, $p = 0.02$) and apathy ($r = 0.23$, $p = .04$). Similarly, multivariate regression demonstrated correlations with executive dysfunction ($p=.05$, FDR corrected) and apathy ($p=.05$, FDR corrected). Exploratory analysis demonstrated an interaction wherein the relationship between total WMHs and executive dysfunction and apathy depends on whether the participant was a survivor. The current findings indicate that increased WMH volumes are associated with higher ratings of apathy and executive dysfunction, and that these results are likely unique to cerebellar brain tumor survivors. WMH burden may serve as a useful marker to identify survivors at risk of executive dysfunction or increased apathy.

1. Introduction

White matter hyperintensities (WMHs) are associated with impaired executive functioning, apathy, and disinhibition in a variety of populations including individuals with Parkinson's Disease, Alzheimer's Disease and depression (Zhang et al., 2020; Berlow et al., 2010; Birdsill et al., 2014; Lin et al., 2021). WMHs are areas of high signal intensity on T2-weighted or fluid-attenuated inversion recovery magnetic resonance sequences (Alber et al., 2019) (See Fig. 1). Neuropathological research indicates that WMHs in normal aging stem from chronically reduced blood flow caused by small blood vessel disease, which leads to demyelination and axonal damage, among other insults (Merino, 2019). Survivors of pediatric brain tumor are hypothesized to be at increased risk of WMHs due to life-saving treatments that damage brain vasculature. In particular, survivors treated with radiotherapy are at increased risk of WMHs and deleterious vascular outcomes compared to the general population or survivors treated without radiation (Remes et al., 2020; Miura et al., 2017). Evidence of cerebral microbleeds in pediatric brain tumor survivors that receive cranial radiation has been reported in survivors ranging from 4 months to 20 years past treatment (Peters et al., 2013; Roddy et al., 2016; Roongpiboonsopit et al., 2017). Other modifiers that increase risk of vascular injury after radiation are higher radiation dose, larger radiation field, and high blood pressure (Remes et al., 2020; Denunzio and Yock, 2020). With regard to other tumor

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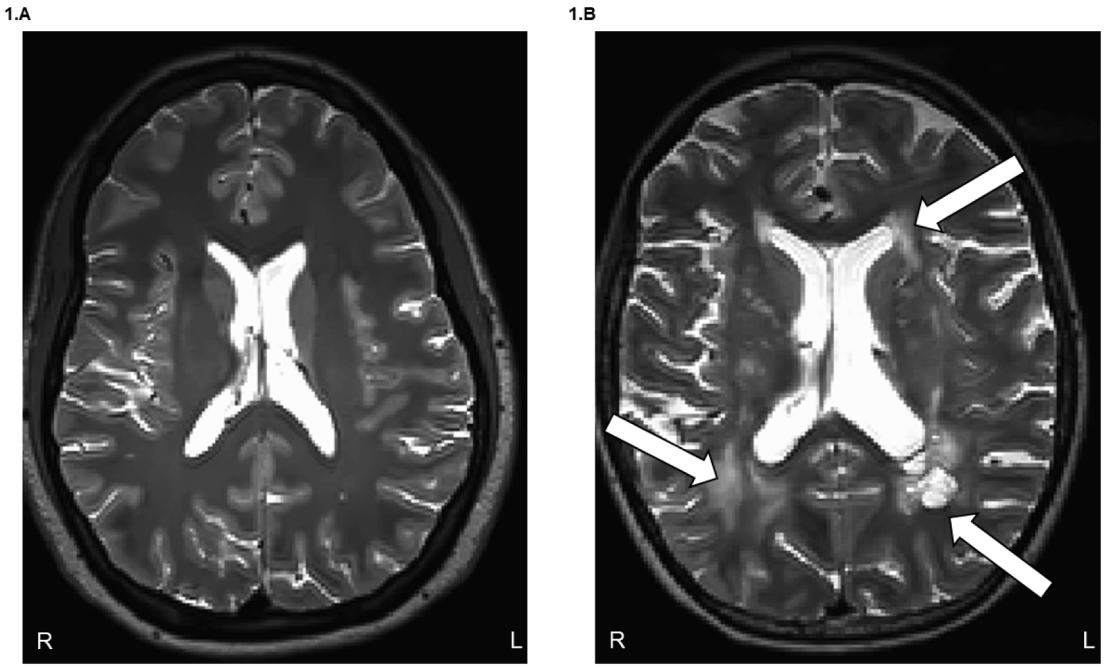

Fig. 1. Case examples from our study sample of a healthy brain and brain with WMHs. On the left (1.A) is a 31 year-old female control. On the right (1.B) is a 35 year-old female medulloblastoma survivor. WMHs appear as bright spots in T2-weighted space.

treatments, history of chemotherapy is also associated with increased prevalence of cerebral microbleeds (Roddy et al., 2016; Roongpiboonsopit et al., 2017). Additionally, survivors treated with chemotherapy without radiation had increased WMHs compared to the general population and rates increased with higher dosage and more courses of treatment (Reddick et al., 2005).

While it is established that WMHs are related to impaired cognition in the general population, there is limited literature available regarding cognitive correlates of WMHs in survivors of pediatric brain tumor. Prior work has linked WMH burden to reduced intellectual, math, and processing speed performance (Aleksonis et al., 2021; Fouladi et al., 2004), but other cognitive outcomes have not yet been explored. In particular, executive dysfunction, apathy, and disinhibition are at risk in survivors (Fox and King, 2016; Kautiainen et al., 2021; Krivitzky et al., 2016; Longaud-Valès et al., 2016), and are associated with reduced white matter integrity (Ailion et al., 2017; Ailion et al., 2019; King et al., 2019; King et al., 2015). As reduced white matter integrity is a consequence of WMHs (Alber et al., 2019; Merino, 2019), it is possible that there is a relationship between WMHs and executive functions in survivors. Therefore, we sought to extend current findings on WMHs and executive functions in brain tumor survivors by examining how informant-reported levels of executive dysfunction, apathy, and disinhibition uniquely relate to WMH burden.

Some evidence has indicated separable effects for periventricular and subcortical WMHs. Subcortical WMHs, sometimes referred to as deep WMHs, are characterized as lying below the cortex. Subcortical WMHs are thought to occur less frequently than periventricular WMHs in populations treated with radiation therapy (Kanekar and Devgun, 2014). Periventricular WMHs are differentiated from subcortical WMHs by being in contact with the ventricular wall. Locationist theories would hypothesize that the difference in location of subcortical and periventricular WMHs could translate to different behavioral sequelae. Subcortical regions consist of short-loop white matter fibers that communicate between neighboring regions, as opposed to white matter in the periventricular region which is more densely populated with long fibers that connect the cortex to subcortical nuclei and other brain regions (Filley, 1998). As such, periventricular WMHs appear to be more associated with higher-order cognitive functions such as attention and executive functioning, whereas subcortical WMHs have been related to depressive symptoms (de Groot et al., 2000; Debette and Markus, 2010). Processing speed in survivors is also primarily associated with periventricular WMHs (Aleksonis et al., 2021), but there currently is no evidence for unique relationships between subcortical WMHs and cognition in survivors. To assess any differential effects in pediatric brain tumor survivors, we chose to look at total WMHs, periventricular WMHs, and subcortical WMHs in this study.

We hypothesize that survivors will report higher levels of executive dysfunction, apathy, and disinhibition compared to controls. Additionally, we expect to see a positive relationship between total WMH load and ratings of executive dysfunction, apathy, and disinhibition. Since periventricular and subcortical WMHs have unique effects on behavior we expect to see different relationships across the domains. However, given the lack of research contrasting periventricular and subcortical WMHs with the domains, we do not predict how the relationships would differ in our sample.

2. Methods

2.1. Participant screening and recruitment

Participants were recruited as part of a parent study investigating long-term functional outcomes in pediatric brain tumor survivors. The parent study protocol was reviewed and approved by the local institutional review board, and all participants provided written informed consent. Survivors were recruited using mailings from three sources: (1) a previous longitudinal childhood brain tumor study, (2) a large hospital system database of survivors treated over 10 years ago, and (3) through the state Brain Tumor Foundation newsletter. Healthy controls were recruited through Georgia State University's undergraduate Psychology participation pool, the Center for Advanced Brain Imaging, friends of survivors, and community fliers. Participants were compensated for their time by psychological class credit, monetary compensation, or both.

Exclusion criteria for all participants included a diagnosis of neurofibromatosis, meeting diagnostic criteria for pervasive developmental disorder, history of significant neurological insult (e.g., traumatic brain

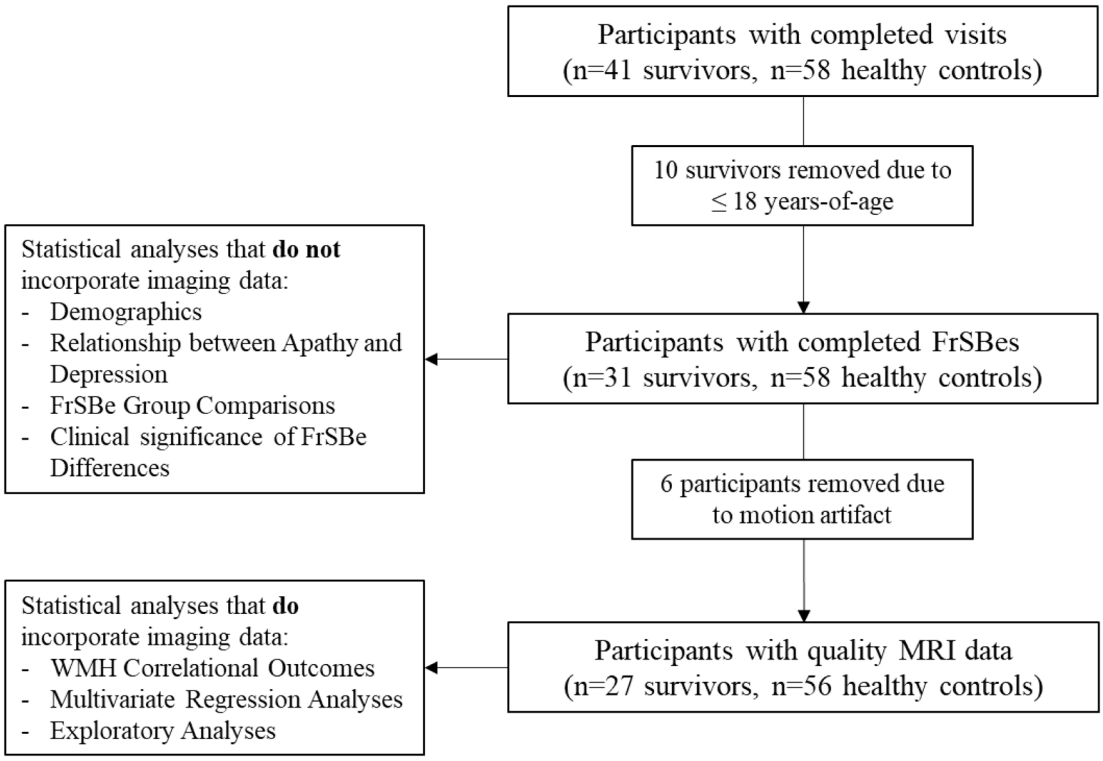

Fig. 2. Study sample flowchart. Boxes to the left of the flowchart describe which analyses were completed with what participants. Listed analyses correspond to the header titles located in the methods and results sections of this paper.

injury, stroke), lack of fluency in English, hearing or vision loss that was unable to be corrected or accommodated at the time of testing. Additional exclusion criteria for healthy control participants included presence of current mood disorders, anxiety disorders, and alcohol or substance dependence disorders as evaluated with the Structured Clinical Interview for DSM-IV-TR Axis 1 and meeting criteria for a psychiatric disorder (First et al., 2002).

The original sample of participants eligible to be used in the analyses for this study included 41 long-term survivors of childhood cerebellar tumor and 58 healthy controls. Ten survivors were removed because they were under the age of 18 and the executive functioning measure is created for participants 18 years or older. A further four survivors and two healthy controls were excluded from imaging analysis due to motion artifact. In total, 83 participants, including 27 survivors of pediatric cerebellar tumor and 56 healthy controls were used in all analyses (See Fig. 2). To address issues with restriction of range, survivors and controls were pooled into one group for WMH analyses.

2.2. Assessment of executive Dysfunction, Apathy, and disinhibition

The Frontal Systems Behavior Scale (FrSBe) was used to measure executive function (Stout et al., 2003; Grace et al., 1999). For this study, we used the informant version. The FrSBe is a 46-item questionnaire developed to assess apathy, disinhibition, and executive dysfunction with corresponding subscales in adult neurological populations. Examples of items on the Apathy subscale include "lacks energy," "speaks only when spoken to," and "lacks initiative"; examples from the Executive Dysfunction subscale include "pays attention," "is able to plan ahead," and "cannot do two things at once"; examples from the Disinhibition subscale include "is easily angered," "makes up stories when unable to remember something," and "thinks things through before acting." Raw scores were age and education normed to produce a T-score with $M = 50$ and $SD = 15$ for each subscale. A T-score ≥ 65 indicates a clinically significant score. The informant was a person knowledgeable of the participant's daily living skills for at least the past year. Of the 89 informants, 39 were a parent, 8 were a family member who was not a parent (e.g., grandparent or sibling), 18 were a significant other, and 23 were an unrelated friend/roommate, 1 informant's relationship was not specified.

Independent samples t-tests were used to compare groups on average subscale score. Chi-square tests were used to compare groups on the percentage of participants with clinically elevated scores.

2.3. Relationship between apathy and depression

While apathy and depression do co-occur, it should be noted that apathy is a unique disorder that is distinct from depression. To demonstrate that the presence of apathy as measured on the FrSBe is not dependent on presence or history of depression, the Structured Clinical Interview for DSM-IV-TR (SCID) was administered to participants by a qualified graduate student and reviewed by a licensed clinician (TZK). As noted previously, healthy controls were not considered eligible if they were currently experiencing a major depressive episode (MDE), but history of past episode(s) was not considered exclusionary. Survivors were considered regardless of current or past MDE. The graduate student who administered the SCID was blind to participants' FrSBe scores as well as any related hypotheses. Participants were later coded as having had at least one past MDE and/or a present MDE (yes/no). Presence of clinically significant apathy was coded based on the recommend FrSBe score of $T \geq 65$.

Chi-square tests of independence were used to evaluate the relationship between presence of clinically significant apathy and a history of MDE. As the norms provided by the FrSBe manual correct for age and sex, these variables were not controlled for in analyses.

2.4. MRI data acquisition

All participants were scanned using a 3 Tesla Siemens Tim Trio MRI scanner using the body coil for FR transmission and a 12 channel phased array head coil for RF receiving. Participants were outfitted with

Table 1
Demographics of Controls, Survivors, and Group Comparisons.

	Controls (n = 58)	All Survivors (n = 31)	χ^2
Sex	53.4% Female	51.6% Female	0.869
Race	44.8% Caucasian	67.7% Caucasian	0.133
	29.3% African-American	12.9% African-American	
	13.8% Asian	3.2% Asian	
	5.1% Other	16.2% Other	
Handedness	90.7% Right	83.9% Right	0.114
	M (SD)	**M (SD)**	***p***
Age (years)	22.51	23.77	0.224
	(4.36)	(5.14)	
Education (years)	14.48	13.77	0.113
	(1.70)	(2.46)	

protective earplugs to reduce scanner noise. Two types of high-resolution (1.0 mm × 1.0 mm × 1.0 mm) structural MRI scans of the brain were acquired by collecting 176 contiguous sagittal slices for each subject: (1) a T1-weighted MPRAGE, and (2) a T2-weighted SPACE. The T1 MPRAGE sequence was used with the following parameters: repetition time (TR) = 2,250 ms, echo time (TE) = 3.98 ms, inversion time (TI) = 850 ms, flip angle (FA) = 9°, isotropic resolution = 1x1x1 mm^3, acquisition bandwidth = 160 Hz. The T2 SPACE had the following acquisition parameters: TR = 3,200 ms, TE = 402 ms, isotropic resolution = 1x1x1 mm^3, acquisition bandwidth = 751 Hz.

2.5. Image processing

The T1w and T2w images are analyzed together to obtain WMH volumes. First, high-resolution T1w and T2w images are denoised with an optimized nonlocal means (ONLM) filter (https://sites.google.com/site/pierrickcoupe/softwares/denoising-for-medical-imaging/mri-denoising) to remove Rician noise from magnitude images (Gudbjartsson and Patz, 1995; Wiest-Daessle et al., 2008; Coupe et al., 2008). The denoised T1w image is bias field corrected with FSL's FAST (Smith et al., 2004; Zhang et al., 2001), followed by skull stripping using optiBET (Lutkenhoff et al., 2014), and manually touched up if necessary, using ITK-Snap to remove meninges and areas of calcification (Smith et al., 2004; Zhang et al., 2001; Lutkenhoff et al., 2014; Yushkevich et al., 2006). An estimated initial binary lesion mask of cerebellar surgical resections was created in native space using LINDA (Pustina et al., 2016). The denoised T1w and T2w images are then coregistered together via Freesurfer's boundary-based registration (bbregister) (Greve and Fischl, 2009), resulting in good alignment between the two modalities.

2.5.1. Quantification of Total WMH Volumes

Utilizing bias field corrected T1- and T2-weighted images in native space, segmentation of WMH was done using the Lesion Growth Algorithm in the Lesion Segmentation Tool toolbox for SPM12 with a threshold of 0.25 (Schmidt et al., 2012). Participants with total WMH volumes that were two standard deviations above or below the group mean were visually checked and false positives were manually fixed using ITK-Snap (as described above). Whole brain volumes were calculated using SPM12 by summing grey and white matter volumes. A ratio of WMH volume to whole brain volume was used to obtain normalized WMH volume in native space.

2.5.2. Classification of WMHs

Classification of periventricular and subcortical WMH volumes were identified through methods developed in-house. The right and left lateral ventricles of the MPRAGE image in MNI space were segmented for each participant using FSL FIRST (Patenaude et al., 2011). These images were combined to create a mask that was dilated out by 2 voxels. Any cluster of voxels previously identified as WMH that intersected or bordered the dilated ventricle mask were identified as periventricular WMH. All other clusters previously identified as WMH and not included as periventricular were identified as subcortical. We visually inspected the WMH to ensure proper classification using this algorithm.

2.5.3. Prep for Multivariate Analyses

To compare WMH maps across subjects and generate brain-behavior relationships, the T1w and T2w images were spatially normalized in a non-linear fashion to MNI template space through chimera spatial normalization using FSL's flirt and fnirt functions (Jenkinson et al., 2002; Jenkinson and Smith, 2001). Chimera spatial normalization creates "chimeric" brain that is created by artificially stitching healthy tissue from non-lesioned space into the lesion (Yourganov et al., 2018). In final analyses, the cerebellar was excluded in all subjects to ensure sensitivity to WMH.

2.6. Confound analyses

Level of education, age at examination, sex, handedness and race were compared across control and survivor groups. Independent samples t-tests were used to compare groups on level of education and age at examination. Chi-square tests were used to compare groups on sex, handedness, and race.

Normalized WMH volumes were further log-transformed to reduce notable skewness and kurtosis. This procedure was applied to all subsequent analyses for total WMH volume, periventricular volume, and subcortical volume. In addition, when examining relationships with subcortical WMH volumes, periventricular WMH volumes were controlled for, and vice versa when examining relationships with periventricular WMH volumes. We chose to control for subcortical and periventricular volumes in their respective analyses because there is evidence that they are highly correlated with each other in older adult populations (DeCarli et al., 2005).

2.7. Correlational analyses

A bivariate correlation was utilized to determine if there are any significant relationships between FrSBe scores and total WMH volume. Holm's sequential Bonferroni procedure was applied to correct for multiple comparisons.

We conducted partial correlations controlling for subcortical WMH volume ratios to examine the relationships among normalized periventricular WMH volumes and FrSBe scores. The same procedure was used to evaluate if normalized subcortical WMH volumes were related to FrSBe scores. We again utilized Holm's sequential Bonferroni procedure to correct for multiple comparisons. A Fisher r-to-z transformation was used to determine if the strength of relationships were significantly different from each other.

2.8. Multivariate regression analyses

The relationship between FrSBe scores and voxel-wise WMH in MNI space were computed using a multivariate sparse canonical correlation analysis (scaan) as implemented in LESYMAP and threshold at a FDR corrected $p = .05$ (Pustina et al., 2018). Lesions of the cerebellum (i.e., areas of resection) computed with LINDA were excluded in this analysis to focus on the effects of WMH in behavior.

2.9. Exploratory analyses

As previously noted, survivors and controls were pooled together for our correlational and multivariate regression analysis. However, we hypothesized differential relationships between WMH volume and FrSBe scores based on group. Therefore, we completed the same bivariate and partial correlations described previously between WMH volumes and FrSBe, but separated by group. Further, regression analysis tested for an interaction between total WMH volume and group

Table 2
Survivor Tumor and Treatment-Related Characteristics

	Survivors (n = 31) % (n)	
Tumor Type	25.8 (8) JPA 48.4 (15) MB 25.8 (8) Other	
Presence of Surgery	100 (31)	
Presence of Chemotherapy	54.8 (17)	
Presence of Radiation	58.1 (18)	
Radiation Field	0 (0) Whole Brain Only 6.5 (2) Focal Radiation Only 51.6 (16) Craniospinal Irradiation with Boost to Site	
Presence of Hydrocephalus	74.2 (23)	
Presence of Seizure(s)	6.5 (2)	
	M (SD)	**Range**
Duration of Chemotherapy (days)	311.94 (173.74)	32–681
Duration of Radiation (days)	46.11 (12.30)	29–75
Radiation Dosage (rads)	5515.56 (261.54)	5040–6300

Note. MB = Medulloblastoma; JPA = Juvenile Pilocytic Astrocytoma

Table 3
Relationship between History of Major Depressive Episode and Presence of Apathy

	MDE	No MDE	χ^2
Clinical Apathy	6	12	0.247
No Apathy	13	51	

Note. MDE = Major Depressive Episode

membership on FrSBe scores using a centered interaction term.

3. Results

3.1. Demographics

Groups did not differ in level of education (p =.11), or age at examination (p =.22). Survivors and controls did not differ in sex χ^2 (1, n = 89) = 0.49, p =.49 or race χ^2 (1, n = 89) = 9.41, p =.09. Therefore, we did not be control for any of these variables in analyses. Demographics of the sample can be found in Table 1. Survivors (51.6 % female) had a mean age of 23.8 (SD = 5.1; range: 17–35) and controls (53.4% female) had a mean age of 22.5 (SD = 4.4; range: 18–41) at the time of study participation. Survivors were on average 8.7 (SD = 5.0; range: 1–19) years old at diagnosis and an average of 15.1 (SD = 6.6) years since diagnosis, and an average of 14.1 (SD = 6.5) years since their last treatment. In this sample of survivors, 41.9% had a low-grade tumor and 58.1% had a high-grade tumor.

This sample includes only those with tumors located in the cerebellar region. Information about tumor types and treatment variables can be found in Table 2. 54.8% of the survivors received chemotherapy and 58.1% received radiation therapy with an average of 32.03 Gy. Of those who received either chemotherapy or radiation therapy treatments, 84.2% received both during the course of their treatment. All the survivors in this sample had surgical resection of their tumor.

Those excluded from the study and analyses did significantly differ from the group averages in age at examination, and years of education, but did not differ on sex, or ratings on the FrSBe. Differences in age at examination and years of education were expected as 10 survivors were unable to complete the FrSBe because they were under 18 years of age.

3.2. Relationship between apathy and depression

Details of our chi-squared analysis for history of past or current MDE and clinical levels of apathy can be found in Table 3. Participant history of MDE did not predict informant-reported clinically significant apathy, χ^2 (1, n = 82), p = 0.25.

3.3. Group comparisons for FrSBe

Informants for survivors reported significantly higher levels of executive dysfunction (M = 51.8, SD = 12.8) than informants for healthy controls (M = 45.7, SD = 9.4), t(47.91) = -2.35, p = .02, with a medium effect size = -0.57. All other score differences between brain tumor survivors and controls were non-significant. Details for remaining subscales and totals can be found in Table 4.

3.4. Clinical significance of FrSBe differences

The number and percentage of clinically significant apathy, disinhibition or executive dysfunction scores are presented in Table 4. There was a trend for informants of survivors to report clinical levels at a higher rate compared to control informants, and this reached statistical significance for informant reported executive dysfunction, χ^2 (1, n = 89) = 8.66, p = .003 and disinhibition, χ^2 (1, n = 89) = 4.94, p = .03. Our chi-squared analysis for apathy was not significant.

3.5. WMH correlational outcomes

Higher total volumes of WMHs were significantly correlated with higher executive dysfunction scores (r = 0.33, p = .02). Subcortical WMH volumes were positively correlated with apathy (r = 0.23, p = .04) and executive dysfunction (r = 0.23, p = .04) when controlling for periventricular WMH volumes. Periventricular WMH volumes were positively correlated with scores on executive dysfunction (r = 0.25, p = .02) when controlling for subcortical WMH volumes. See Table 5 for further information.

3.6. Multivariate regression analyses

In our multivariate correlation analysis, we showed significant brain-behavior relationships for apathy (p=.05, FDR corrected) and executive dysfunction scores (p=.05, FDR corrected) when using a WMH overlap of at least two participants. Significant voxel clusters were in similar

Table 4
Frontal Systems Behavior Scale Survivor and Control Group Comparisons

	Survivors		Healthy Controls					
	Scores M (SD)	**Clinically Impaired % (n)**	**Scores M (SD)**	**Clinically Impaired % (n)**	***t***	***p***	***d***	***X²***
Apathy	57.8 (16.9)	32.3 (10)	52.9 (12.5)	17.2 (10)	−1.42	0.164	−0.35	0.106
Disinhibition	42.3 (10.8)	19.4 (6)	46 (10.6)	5.2 (3)	1.52	0.133	0.34	**0.034**
Executive Dysfunction	51.8 (12.8)	19.4 (6)	45.7 (9.4)	1.7 (1)	−2.35	**0.023**	−0.57	**0.003**

Note. Significant differences are in bold.

Table 5
Correlations Between Frontal Systems Behavior Scale Scores and WMH Volumes Based on Location.

	Apathy	Disinhibition	Executive Dysfunction
Log Transformed Normalized Total WMH Volume	0.184 *p*=.096	-0.071 *p*=.521	**0.334** ***p*=.002**
Log Transformed Normalized Periventricular WMH Volume	0.154 *p*=.167	0.134 *p*=.230	**0.250** ***p*=.023**
Log Transformed Normalized Subcortical WMH Volume	**0.232** ***p*=.036**	-0.091 *p*=.416	**0.232** ***p*=.036**

Note. WMH = white matter hyperintensities. Significant correlations are in bold.

locations, predominately periventricular, for both apathy and executive dysfunction (see Fig. 3). Significant clusters were larger for the apathy subscale (e.g., largest cluster: 1,048 voxels) compared to the executive dysfunction subscale which were approximately half the size (e.g., largest cluster: 496 voxels).

3.7. Exploratory analyses

Total WMH volumes were positively correlated with apathy (r = 0.528, $p = .005$) and executive dysfunction scores (r = 0.490, $p = .01$) for survivors. Subcortical WMHs were also positively associated with apathy (r = 0.489, $p = .01$) for survivors. No other relationships were significant for survivors. No correlations between WMHs and FrSBe scores were significant for controls (See Table 6).

Regression analyses (Fig. 4, Table 7) revealed a significant, predicted interaction between total WMH volume and group membership on executive dysfunction, ($\beta = 16.00$, $p = .01$, unique $R^2 = 0.07$) To interpret this interaction, we assessed the simple effect of total WMH volume among survivors and controls. As expected, in survivors, a significant positive relationship was seen between total WMH volume and executive dysfunction scores ($\beta = 13.11$, $p = .003$, unique $R^2 = 0.09$). However, this relationship was no longer significant in controls ($\beta = -2.22$, $p = .60$, unique $R^2 = 0.003$). We found the same pattern for apathy scores. There was a significant interaction between total WMHs and group membership ($\beta = 26.82$, $p = .001$, unique $R^2 = 0.12$), and when probed, a positive relationship between WMHs and apathy scores was seen in survivors ($\beta = -16.41$, $p = .004$, unique $R^2 = 0.09$), but not controls ($\beta = -9.29$, $p = .09$, unique $R^2 = 0.03$). Like our correlational analyses, there was no main effect using disinhibition scores nor was there a significant interaction.

4. Discussion

This study aimed to investigate relationships between apathy, executive dysfunction, and disinhibition and WMH volumes in survivors of pediatric brain tumor. We expected survivors to have higher executive dysfunction, apathy, and disinhibition scores compared to controls. Additionally, we hypothesized that there would be a positive relationship between total WMH load and reported executive dysfunction, apathy, and disinhibition, and these relationships would be stronger in survivors compared to controls. Lastly, we expected differential relationships for subcortical and periventricular WMHs.

4.1. Executive dysfunction

Executive dysfunction as reported by informants on the FrSBe was the most strongly related to WMH burden. Total, periventricular, and subcortical WMH volumes were all positively correlated with informant-reported executive dysfunction in our analysis. Additionally, in the multivariate regression approach, executive dysfunction was significantly related to WMH lesions located primarily in the frontal periventricular regions. Frontal-subcortical-cerebellar systems support executive functions (Clark et al., 2021). Therefore, it is not surprising to observe the WMHs related to executive dysfunction to be predominately frontal periventricular regions. No other component of the FrSBe was as consistently related to WMH load. While both survivors and controls were combined in the correlation analysis, exploratory analysis revealed that the direction and strength on the relationship was likely driven by survivors. Additionally, group comparisons on the FrSBe showed that informant-reported executive dysfunction scores were significantly greater for brain tumor survivors than healthy controls. Taken together, these results suggest that pediatric brain tumor survivors experience higher levels of executive dysfunction and that increased executive dysfunction is related to an increased volume of WMHs. Executive dysfunction measured on the FrSBe covers a wide range of cognitive

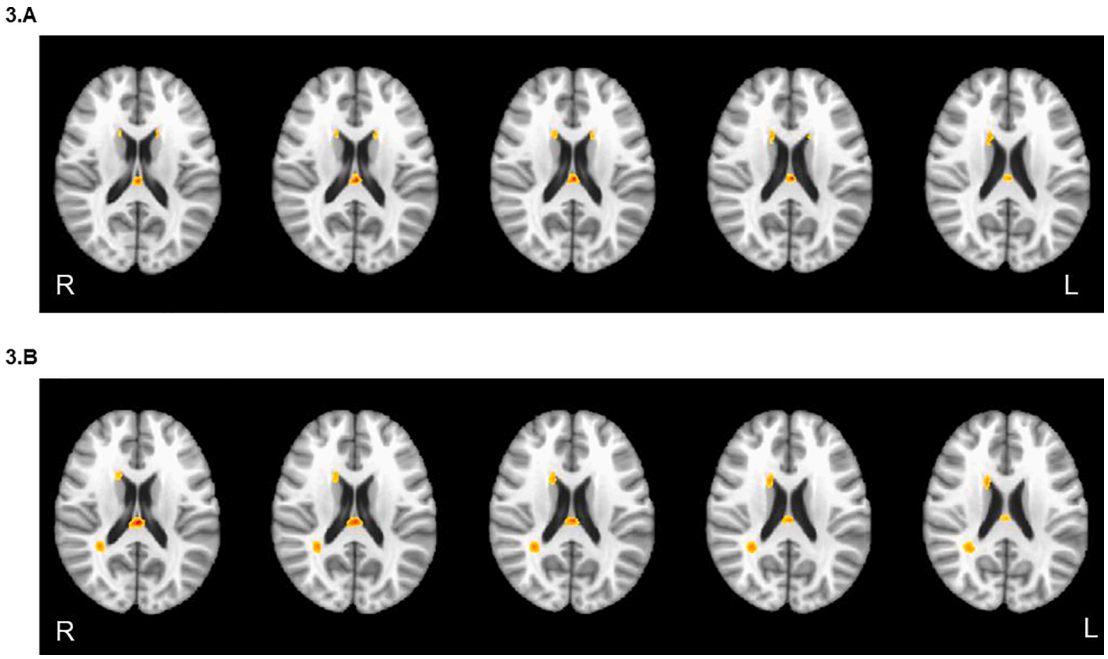

Fig. 3. Multivariate Regression Results of Significant Voxels Related to Informant-Reported A.) Executive Dysfunction and B.) Apathy Scores.

Table 6
Exploratory Correlations Between Frontal Systems Behavior Scale Scores and WMH Volumes Separated by Group.

	Apathy	Disinhibition	Executive Dysfunction
Survivors			
Log Transformed Normalized Total WMH Volume	**0.528** ***p*=.005**	0.304 *p*=.124	**0.490** ***p*=.010**
Log Transformed Normalized Periventricular WMH Volume	0.258 *p*=.203	0.251 *p*=.216	0.373 *p*=.061
Log Transformed Normalized Subcortical WMH Volume	**0.489** ***p*=.011**	0.128 *p* =.532	0.280 *p*=.167
Controls			
Log Transformed Normalized Total WMH Volume	-0.167 *p*=.217	-0.100 *p*=.462	-0.005 *p*=.972
Log Transformed Normalized Periventricular WMH Volume	-0.040 *p*=.772	-0.010 *p*=.942	0.037 *p*=.791
Log Transformed Normalized Subcortical WMH Volume	-0.081 *p*=.557	-0.092 *p*=.505	-0.004 *p*=.974

Note. WMH = white matter hyperintensities. Significant correlations are in bold.

processes. Schienser and colleagues (Schiehser et al., 2011), characterize the executive dysfunction subscale as "…problems with sustained attention, working memory, organization, planning, future orientation, sequencing, problem solving, insight, mental flexibility, self-monitoring of ongoing behavior, and/or ability to benefit from feedback or modify behavior following errors". Therefore, it is possible that executive dysfunction was more consistent than the other subscales because it covers such a wide range of higher-order processes.

4.2. Apathy

Apathy scores were positively related to subcortical WMHs in our partial correlation. Additionally, apathy was again related to WMHs in the multivariate regression. Indicating that increased apathy is associated with increased WMH volumes. Similar to executive dysfunction, we noted an interaction between WMHs and group membership, wherein the relationship between total WMHs and apathy was significant for survivors at the group level, but they were not related when looking at controls. These results indicate that WMHs and apathy are uniquely related in survivors compared to controls.

Unlike executive dysfunction, in our correlational analysis, apathy was only correlated with subcortical WMHs, supporting separable effects of subcortical and periventricular WMHs. This is consistent with literature linking apathy to subcortical WMHs in other populations (Zhang et al., 2020). In our multivariate regression analysis, WMHs related to apathy were lateralized to the right hemisphere. Interestingly, apathy is more common in stroke patients with right-hemisphere WMHs (Moretti and Signori, 2016), suggesting a novel role for right subcortical lesions in apathy. Greater apathy in survivors in comparison to healthy samples has been reported previously (Fox and King, 2016; Mehren et al., 2018), but this finding was not replicated in our analysis. The proportion of survivors in clinically impaired range for apathy was 32.3%, which are similar to rates reported in other studies of pediatric tumor survivors (Carroll et al., 2013). It was unclear why a modest proportion (17.2%) of our controls had clinically significant apathy as reported by their informants. Further examination of our data revealed that only three controls with significant apathy had a history of psychopathology. Two controls had a history of MDE, and one had a history of panic disorder. Thus, indicating that psychopathology could not explain rates of clinical apathy among our controls. There is a paucity of literature available on rates of general apathy in young adults. However, some literature has suggested increased apathy for individuals enrolled in college, which made up the majority of our control population (Bjornsen et al., 2007).

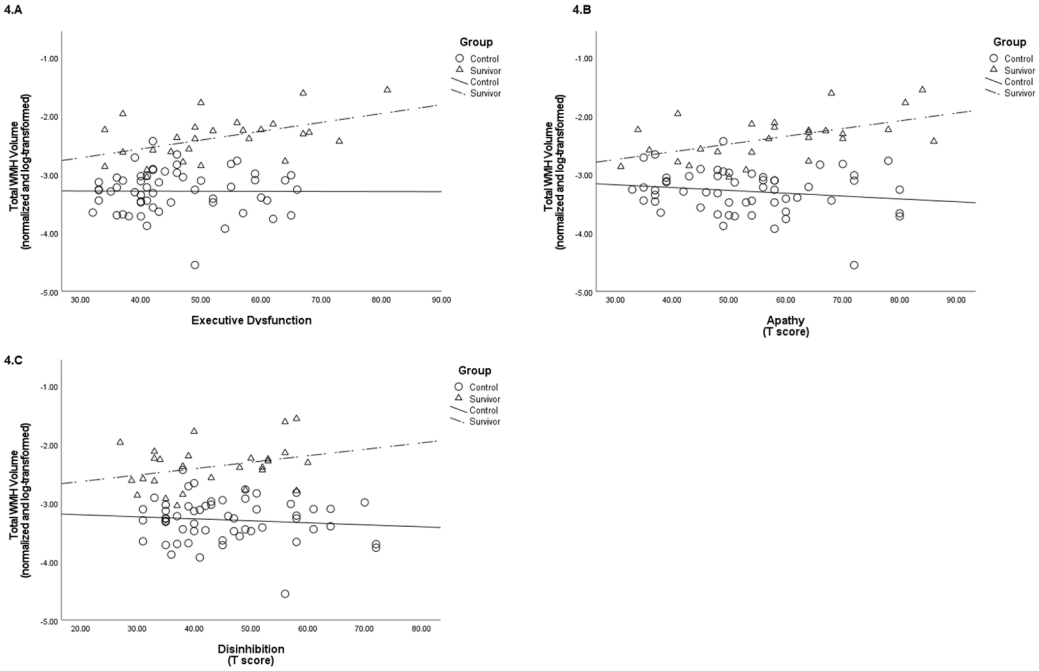

Fig. 4. Scatterplot showing interaction effect of group membership on the relation between total WMH volume and A.) executive dysfunction, B.) apathy, and C.) disinhibition. Significant interactions were found for executive dysfunction and apathy as predictors.

Table 7
Exploratory Regressions Between Frontal Systems Behavior Scale Scores, Total WMH Volume, and Group Membership

	β	Standard Error	*p*-value	Unique R^2
Apathy				
Total WMH Volume	3.56	3.82	0.354	0.009
Group	−6.26	5.23	0.227	0.02
Total WMH Volume × Group	**26.82**	**8.09**	**0.001**	**0.12**
Total WMH x Controls	−9.29	5.37	0.088	0.03
Total WMH x Survivors	**16.41**	**5.51**	**0.004**	**0.09**
Disinhibition				
Total WMH Volume	1.00	3.18	0.775	0.001
Group	−7.00	4.35	0.112	0.03
Total WMH Volume × Group	11.33	6.74	0.097	0.03
Total WMH x Controls	−4.43	4.47	0.325	0.01
Total WMH x Survivors	6.42	4.59	0.166	0.02
Executive Dysfunction				
Total WMH Volume	5.45	3.02	0.075	0.03
Group	−3.04	4.13	0.463	0.006
Total WMH Volume × Group	**16.00**	**6.38**	**0.014**	**0.05**
Total WMH x Controls	−2.22	4.24	0.603	0.003
Total WMH x Survivors	**13.11**	**4.35**	**0.003**	**0.09**

Note. WMH = white matter hyperintensities. Significant relationships are in bold.

4.3. Disinhibition

Contrary to our expectations, survivor disinhibition scores were on average lower than controls. However, the proportion of survivors with reported clinical impairment was significantly greater than the number of controls with clinically significant disinhibition. In our imaging analyses, disinhibition was not associated with WMHs. Therefore, it is likely that the difference in disinhibition scores observed in our group comparisons are unrelated to WMHs or were obscured by a lack of power. While we did not expect this finding, a review of the literature suggests that survivors do not consistently display increased disinhibition (Krivitzky et al., 2016). Interestingly, in a sample of school-age pediatric tumor survivors, researchers found that survivors' behavior was more inhibited compared to their peers, despite also being rated as having worse effortful control (Salley et al., 2015). It may be that these inconsistencies regarding disinhibition stem from differences in measures, with some measures capturing more internalizing symptoms and others externalizing behaviors. Additionally, effortful control evaluates for issues with both restraint and initiation. Initiation plays an important role in both inhibited and apathetic behaviors, a skill impaired in survivors (Wochos et al., 2014; Wolfe et al., 2013). Dysregulated initiation may therefore manifest as behavioral inhibition depending on the context in which the individual has failed to initiate.

4.4. Strengths and weaknesses

A major strength of this study is the use of semi-automated multivariate methodology. Multivariate approaches are advantageous over univariate forms of imaging analysis because they consider all voxels at once rather than examining each voxel independently. Additionally, this study investigated brain-behavior relationships based on WMH location. Our differential outcome between subcortical and periventricular WMH volumes illustrates how consideration of WMH location improves the precision of research findings. Beyond strengths, there were some limitations to this study. First, due to our limited sample size, this study was only able to separately evaluate correlations between WMH volumes and FrSBe scores for survivors and controls on an exploratory basis. It is highly likely that these relationships differ for survivors and controls based on our exploratory analysis. Second, participants in this study were all young adults. Wang et al. (Wang et al., 2019) report a prevalence of WMHs to be 25.94% in adults under the age of 45 and, the vast majority of these WMHs were graded as mild. Since occurrence of WMHs increase with age, it is possible that our sample was too young to fully assess WMH load. However, as reported previously (Aleksonis et al., 2021), we did see high WMH burden is a subset of our survivors. Future prospective studies may wish to address this limitation by investigating the development of WMHs in pediatric brain tumor survivors later in life beyond young adulthood. Third, this study utilized a single, informant-based, rating scale of executive dysfunction, apathy, and disinhibition. While interrater reliability between self-report and informant-report on the FrSBe appears to be good in other populations with neurological injury (Schiehser et al., 2011), additional work is needed to characterize the utility of the FrSBe in brain tumor survivors. Our sample of informants had varied relationships with the participants, which may impact the level of insight into participants' abilities and consequently their ratings. Additionally, significant relationships between WMHs and several executive functioning measures would provide stronger support for our findings.

4.5. Conclusion

In conclusion, this study found brain tumor survivors have higher levels of executive dysfunction compared to controls, and that increased WMH volumes are associated with greater levels of apathy and executive dysfunction. While this study primarily demonstrates the consistent relationship between executive dysfunction and WMHs in a unique neurological population, it also highlights the wide range of functioning that survivors and their peers have in young adulthood. As survivors continue to age, it will be imperative that both survivors and their loved ones are attentive to survivors' cognitive risks so that survivors may continue to participate in daily living to the fullest of their abilities. It is plausible that the survivors will experience signs of early cognitive and brain aging, and early identification of these occurrences will be crucial for optimal intervention. WMHs may serve as a useful marker for cognitive risks including development of executive dysfunction and apathy in survivors. Future work should consider the impact of informant relationship on executive functioning reports. Additional research may also wish to examine the relationship between WMHs and other measures of executive functioning, and reports of survivors' outcomes, such as quality of life and adaptive functioning. Further, it would be useful to investigate whether tumor location, tumor type, and treatment type influence the presence, volume and location of WMHs. Lastly, longitudinal research is needed to test whether occurrence of WMHs predate cognitive impairments in this population.

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CRediT authorship contribution statement

Olivia C. Haller: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Holly A. Aleksonis:** Conceptualization, Formal analysis, Writing – review & editing. **Lisa C. Krishnamurthy:** Methodology, Writing – review & editing. **Tricia Z. King:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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