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# Cerebral white matter integrity and executive function in adult survivors of childhood medulloblastoma

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**Survivors of pediatric medulloblastoma are at risk for neurocognitive dysfunction. Reduced white matter integrity has been correlated with lower intelligence in child survivors, yet associations between specific cognitive processes and white matter have not been examined in long-term adult survivors. Twenty adult survivors of medulloblastoma were randomly recruited from a larger institutional cohort of adult survivors of childhood cancer. Survivors underwent comprehensive neurocognitive evaluations and MRI. Data on brain volume and cortical thickness and diffusion tensor imaging were acquired, including measures of fractional anisotropy, apparent diffusion coefficient, and axial and radial diffusivity. Observed neurocognitive scores were compared with population norms and correlated to MRI indices. Survivors were, on average, 29 years of age and 18 years postdiagnosis. Mean full-scale intelligence quotient was nearly 1 SD below the normative mean (86.3 vs 100, $P = .004$). Seventy-five percent of survivors were impaired on at least one measure of executive function. Radial diffusivity in the frontal lobe of both hemispheres was correlated with shifting attention (left: $r_s = -0.67$, $P = .001$; right: $r_s = -0.64$, $P = .002$) and cognitive flexibility (left: $r_s = -0.56$, $P = .01$; right: $r_s = -0.54$, $P = .01$). Volume and cortical thickness were not correlated with neurocognitive function. Neurocognitive impairment was common and involved many domains. Reduced white matter integrity in multiple brain regions correlated with poorer performance on tasks of executive function. Future research integrating diffusion tensor imaging should be a priority to more rigorously evaluate long-term consequences of cancer treatment and to inform cognitive intervention trials in this high-risk population.**

**Keywords:** diffusion tensor imaging, executive function, medulloblastoma, neurocognition.

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Malignancies of the central nervous system have an incidence of approximately 3.0 per 100 000 persons ≤19 years of age in the United States.[1] Primitive neuroectodermal tumors, which include medulloblastoma (MB), account for 10%–20% of all pediatric brain tumors and 40% of posterior fossa tumors.[2,3] While over 80% of children diagnosed with standard-risk MB achieve long-term survival,[4] the consequences of tumor location within the cerebellum and treatment with craniospinal irradiation (CSI) are considerable. In this paper, we review recent literature on neurocognitive outcomes and brain integrity in survivors of MB and present pilot data from adult survivors of childhood MB who are now 12–25 years postdiagnosis and post–initial treatment.

Neurocognitive deficits are among the most common sequelae observed in CSI treatment for MB. Deficits in intelligence, academics, attention, processing speed, memory, and executive function are well documented shortly following therapy completion.[5–7] Younger age at diagnosis (ie, < 7 years of age), higher dose CSI compared to reduced-dose CSI, female sex, and clinical complications such as hydrocephalus and posterior fossa syndrome have been associated with poorer cognitive outcomes, although CSI dose is most consistently implicated in neurocognitive dysfunction.[8–10] Detrimental effects of CSI on cognition at dose levels ≥36 Gy compared with doses ≤23.4 Gy have been reported,[11] yet these effects appear to be moderated by age at diagnosis.[5]

Few studies have investigated long-term neurocognitive functioning in adult survivors of childhood CNS malignancies. Edelstein and colleagues[12] reported performance-based neurocognitive outcomes for 20 adult survivors of childhood MB aged 18–47 years who were 6–42 years postdiagnosis. Compared with normative data, the survivors demonstrated global cognitive deficits and performed 1.2 SD below the expected mean in the area of working memory, 2.4 SD below in processing speed, and 3.4 SD below in executive function. Using the Childhood Cancer Survivor Study (CCSS), Ellenberg and colleagues[13] reported on the neurocognitive status in over 800 adult survivors of childhood CNS tumors. Compared with non–CNS tumor survivors and siblings, CNS tumor survivors were significantly more likely to self-report impairment in the areas of task efficiency, memory, organization, and emotional regulation. Survivors treated with whole brain cranial radiation were significantly more likely to report problems with task efficiency (effect size = 0.65) and memory (effect size = 0.63) compared with CNS tumor survivors who did not receive cranial radiation. In a follow-up CCSS investigation, Armstrong and colleagues[14] reported that region-specific cranial radiation to the temporal lobe was associated with increased likelihood of impaired task efficiency and organization in adult survivors of MB.

Cranial irradiation–induced cerebral white matter injury has been postulated to contribute to neurocognitive dysfunction in MB survivors. Mulhern et al[15] reported significantly less normal-appearing white matter and lower full-scale intelligence quotient (FSIQ) in 18 MB patients treated with CSI compared with age-matched patients treated for low-grade posterior fossa tumors with surgery alone. In MB patients, white matter volume was positively correlated with FSIQ. In a longitudinal study of 26 cases of MB treated with risk-adapted CSI, patients demonstrated significant loss of white matter relative to normally expected maturation.[16] No significant difference in rate of volume loss was observed by age at CSI treatment; however, patients treated with 23.4 Gy CSI demonstrated lower rate of volume loss compared with patients treated with 36 Gy CSI. Palmer et al[17] showed longitudinal white matter volume loss in posterior regions of the corpus callosum in 35 cases of MB treated with risk-adapted CSI; however, decline in volume was not statistically different among patients who were treated with conventional compared with reduced-dose CSI. In the first study to employ age-similar healthy controls, Reddick et al[18] reported that MB survivors treated with 35–40 Gy CSI demonstrated significantly less development of normal-appearing white matter and that younger age at CSI treatment and ventricular shunt placement were associated with reduced white matter volume in survivors.

Importantly, white matter volume loss has been associated with neurocognitive deficits in MB survivors treated with CSI. In a study of 42 survivors, 1–11 years post-treatment, Mulhern et al[19] found that white matter volume accounted for a significant amount of the variance in the relationship of age at CSI and intellectual functioning, including verbal and nonverbal reasoning, but white matter volume was not significantly associated with performance on tasks of sustained attention or verbal memory. Data from a heterogeneous sample[20] of 40 brain tumor survivors, including 18 MB patients, also revealed an association between decreased white matter volume and neurocognitive deficits, specifically global intelligence and attention. Importantly, this study further suggested that attentional abilities may mediate the observed relationship between white matter volume and IQ.

While volume loss provides an important metric for quantifying white matter injury, it does not provide insight into microscopic changes that may affect integrity of existing white matter. MRI with diffusion tensor imaging (DTI) has emerged as a useful technique to quantify water diffusion within white matter tracts. Fractional anisotropy (FA) provides an index of directionality of diffusion due to parallel organization of axonal fibers, with greater FA reflecting a higher degree of myelination and density, or white matter integrity. *Diffusivity* refers to the magnitude of diffusion of water molecules, which is restricted perpendicular to axonal fibers and can be determined by measuring the apparent diffusion coefficient (ADC) and its components of axial diffusivity (AX) and radial diffusivity (RAD), with greater diffusivity reflecting myelin-specific abnormalities. Despite the high sensitivity of this technique to pathological and functional changes within cerebral white matter, few studies have applied this method to study white matter damage in relation to neurocognitive function in survivors of MB.

Khong et al[21] utilized DTI to examine white matter integrity in 9 MB patients 1–6 years posttreatment and age-matched controls. MB survivors evidenced reduced FA in cerebral hemispheres, pons, medulla, frontal and parietal periventricular white matter, and corona radiata compared with controls. In a subsequent study of 20 MB survivors treated with CSI and boosts to the posterior fossa who were 0.2–5.8 years post-CSI, greater percentage change in FA (ie, greater loss of white matter anisotropy) was associated with younger age at diagnosis and higher CSI dose.[22] Khong et al[23] further reported an association between white matter anisotropy and neurocognitive function in child survivors of MB and acute lymphoblastic leukemia (ALL). Loss of FA was measured in 12 MB patients treated with CSI, 9 ALL patients treated with cranial radiation, and 9 ALL patients treated with chemotherapy alone. Percentage FA difference between survivors and age-matched controls was significantly associated with FSIQ as well as verbal and nonverbal reasoning.

Mabbott et al[24] used DTI to investigate white matter integrity following CSI treatment in 8 cases of MB. Relative to age-matched controls, MB patients had lower FA in several regions of interest, including the genu of the corpus callosum, posterior and anterior limbs of the internal capsule, and inferior and superior

frontal white matter. The ADC in survivors was higher in these same regions, as well as in the parietal white matter. In survivors, reduced global intelligence was correlated with decreased FA. Palmer et al[25] examined the relationship between reading skills and white matter integrity in 54 MB patients 12 months postdiagnosis. After adjusting for patient age and treatment risk status, reading decoding skills were significantly positively associated with FA in the left pons-medulla, right pons, left and right posterior limb of the internal capsule, right knee of the internal capsule, left inferior parietal, right occipital lobe, and left temporal occipital cluster.

To date, only one study has examined DTI in MB survivors in relation to more specific cognitive processes thought to underlie global intelligence. Aukema et al[26] examined white matter FA and speed of processing in childhood cancer survivors aged 8–16 years. Patients included 6 MB survivors, 5 ALL survivors treated with high-dose methotrexate, and 6 ALL survivors treated with low-dose methotrexate. Compared with age-matched controls, white matter FA was reduced in the right inferior fronto-occipital fasciculus (IFO) and the genu of the corpus callosum. White matter FA in the splenium and body of the corpus callosum was significantly positively correlated with processing speed, while white matter FA in the right IFO was positively correlated with motor speed.

DTI has been used to investigate susceptibility of specific brain regions to radiation-induced injury. Qiu et al[27] compared white matter FA in the frontal and parietal lobes of 22 MB survivors treated with equivalent doses of whole-brain radiation with age- and gender-matched controls. White matter FA was reduced in both regions in MB survivors compared with controls. Among survivors, frontal lobe white matter FA was more severely reduced than parietal lobe white matter, suggesting increased white matter sensitivity in frontal lobes. These data suggest that cognitive processes mediated by the frontal lobe, such as executive functioning, may be differentially affected following treatment-induced white matter injury. Recently, Rueckriegel et al[28] investigated supratentorial white matter damage in survivors of posterior fossa tumors, including 17 cases of MB treated with CSI and 13 cases of pilocytic astrocytoma treated with surgery alone, as well as age-matched controls. Compared with controls, MB survivors showed reduced FA in cerebellar midline structures, frontal lobes, and callosal body. No differences were apparent when comparing cases of MB with those of pilocytic astrocytoma for specific regions of interest; however, the amount of significantly reduced FA was greater in MB survivors.

Despite growing evidence implicating white matter injury as a contributing factor to the cognitive dysfunction experienced by MB survivors, no study has examined the association between white matter integrity following CSI treatment and cognition in long-term adult survivors of childhood MB. We report pilot data from such a study below.

## Methods

### *Patients*

Twenty MB survivors registered in the St Jude Lifetime Cohort Study[29] were randomly recruited. Eligibility criteria for the sample included a diagnosis of MB treated at St Jude Children's Research Hospital, tumor location within the posterior fossa, treatment with CSI, current age $\geq$18 years, and $\geq$10 years postdiagnosis. Exclusion criteria included history of developmental disorder or neurological event unrelated to cancer. All survivors provided informed written consent, and the study protocol was approved by the St Jude Children's Research Hospital Institutional Review Board.

### *Procedure*

Medical record abstraction was performed for radiation treatment (fields, doses, and energy source), all chemotherapy received (cumulative doses), and surgical procedures. Survivors underwent comprehensive assessment for neurocognitive functions in dedicated evaluation rooms. Assessed domains included intelligence (Wechsler Abbreviated Scale of Intelligence),[30] academic skills (Woodcock–Johnson Tests of Achievement III),[31] attention (Trail Making Test, Part A; Connors Continuous Performance Test II–Variability),[32,33] memory (Wechsler Adult Intelligence Scale [WAIS] III–Digits Forward; California Verbal Learning Test II; Recognition Memory Test),[34–36] processing speed (WAIS III–Digit Symbol Coding and Symbol Search; Grooved Pegboard Test),[32,34] motor function (Finger Tapping Test; Hand Dynamometer),[37] and executive function (Wisconsin Card Sorting Test; Rey–Osterrieth Complex Figure; Stroop Color Word; Trail Making Test, Part B; WAIS III–Digits Backward; Controlled Oral Word Association Test).[32,34,38–41] Survivors also completed self-ratings to assess behavioral and cognitive symptoms of executive dysfunction (Behavior Rating Inventory of Executive Function).[42] Order of testing was standardized and all assessments were completed under the supervision of a licensed psychologist. The interval between neurocognitive testing and MRI was 0–9 days.

### *Magnetic Resonance Imaging*

MRI was acquired on one of two 1.5-Tesla Avanto MR scanners (Siemens Medical Systems) using bipolar diffusion-encoding gradients. All images were acquired using a double spin echo planar imaging pulse sequence (repetition time/echo time = 10/100 ms, $b$ = 1000 ms). Imaging sets were acquired as forty 3-mm-thick contiguous axial sections with whole-head coverage, 128 square matrix, and 22-cm field of view (acquired resolution of 1.7 × 1.7 × 3.0 mm). Four acquisitions were made with 12 noncollinear, noncoplanar diffusion gradient directions to calculate the diffusion tensor for each voxel.

Voxel-wise tensor calculations were performed with the DTI toolkit under SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Data from the 4 acquisitions were realigned before tensor calculation to correct for linear image drift. FA, ADC, AX, and RAD maps were calculated for the whole brain. Parametric maps were registered to the International Consortium for Brain Mapping average 152 T2 atlas aligned in Talairach space and resampled to a 1-mm isotropic resolution. Once registered, average values were calculated for each of the parameters from white matter within each of the 6 lobular regions (left and right frontal, parietal, and temporal).

MRIs were also processed with FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) to assess brain cortical thickness. Images were aligned to correct radiofrequency inhomogeneities, brain extraction was conducted, and segmentation was used to create pial and gray/white matter surfaces to calculate the perpendicular distance or thickness. Automated parcellation of the brain was conducted to extract thickness for specific frontal, parietal, temporal, and occipital regions.

### *Statistical Analyses*

Descriptive statistics were calculated for demographic and treatment characteristics as well as neurocognitive outcomes. Scores on neurocognitive measures were transformed into age-adjusted *z*-scores using national normative data ($M = 0$, $SD = 1$). Quantile-quantile plots and the Shapiro–Wilk test were used to assess normality. To account for nonnormally distributed data, nonparametric statistical tests were employed for all analyses. Mean neurocognitive scores for the sample were compared with population norms using the one-sample Wilcoxon signed rank test. Impairment was defined as a score ≥1.3 SD below the expected population mean, corresponding to a performance consistent with the lowest 10th percentile of normative data. MRI measures were correlated with performance on executive function tasks and age at diagnosis using Spearman's rank correlation. To account for multiple comparisons, only correlations at $P \leq .01$ were considered statistically significant. All statistical analyses were completed in SAS version 9.2.

## Results

The 20 MB survivors (14 male) were, on average, 29 years of age and 18 years postdiagnosis (Table 1). Age at diagnosis ranged from 2 to 17 years. All patients were treated with >50 Gy total cumulative cranial irradiation, including a boost to the posterior fossa. Sixty percent of survivors were employed less than full time, and 50% were living dependently at the time of evaluation.

Mean FSIQ was nearly 1 SD below the normative mean (86.3 vs 100, $P = .004$). Survivors demonstrated multiple areas of impairment, with median scores in all areas falling below the expected population mean on performance based measures (Table 2). Fifty-five percent of survivors were impaired in ≥2 areas of executive function. Age at diagnosis was correlated with FSIQ ($r_s = 0.70$, $P = .001$), as well as cognitive fluency ($r_s = 0.60$, $P = .005$), shifting attention ($r_s = 0.60$, $P = .006$), working memory ($r_s = 0.77$, $P < .001$), cognitive flexibility ($r_s = 0.61$, $P = .005$), and planning and organization ($r_s = 0.57$, $P = .008$). Table 3 provides a comparison of FSIQ and performance on measures of executive function by median age at diagnosis.

Sixteen of 20 survivors (80%) showed evidence of leukoencephalopathy on MRI. Leukoencephalopathy in the basal ganglia or brainstem was present in 6 survivors. Three of these 6 survivors had only subcortical leukoencephalopathy involvement, while 3 had both cortical and subcortical involvement. Thirteen survivors

**Table 1.** Patient characteristics

| | Survivors ($n = 20$) | |
|---|---|---|
| | ***n*** | **%** |
| Sex | | |
| Female | 6 | 30 |
| Male | 14 | 70 |
| Age at evaluation, y | | |
| 21–25 | 7 | 35 |
| 26–29 | 7 | 35 |
| 30–36 | 6 | 30 |
| Educational attainment | | |
| ≤High school | 6 | 30 |
| Training beyond HS/some college | 5 | 25 |
| ≥College graduate | 9 | 45 |
| Employment | | |
| Unemployed | 7 | 35 |
| Part-time | 5 | 25 |
| Full-time/student | 8 | 40 |
| Living situation | | |
| Independent | 10 | 50 |
| Dependent | 10 | 50 |
| Age at diagnosis, y | | |
| <7 | 4 | 20 |
| 7–10 | 7 | 35 |
| 11–14 | 6 | 30 |
| 15–17 | 3 | 15 |
| Time since diagnosis, y | | |
| 12–15 | 7 | 35 |
| 16–19 | 6 | 30 |
| 20–25 | 7 | 35 |
| Chemotherapy | | |
| Yes | 15 | 75 |
| No | 5 | 25 |
| | Median | Range |
| Radiation (cGy) | | |
| Cranium | 3520 | 2340–5500 |
| Spine | 3520 | 2340–6160 |
| Posterior fossa boost | 1800 | 1100–3240 |

**Table 2.** Neurocognitive functioning

| | Median | IQ Range | % Impairment[a] | *P*-value[b] |
|---|---|---|---|---|
| Intelligence | | | | |
| Full scale | −0.90 | −2.0, 0.00 | 35 | 0.005 |
| Verbal | −1.0 | −2.2, 0.05 | 45 | 0.003 |
| Perceptual | −0.65 | −1.85, 0.1 | 30 | 0.02 |
| Academics | | | | |
| Word reading | −0.50 | −1.8, −0.37 | 35 | <0.001 |
| Calculations | −1.33 | −2.7, −0.6 | 50 | <0.001 |
| Attention | | | | |
| Focus | −1.23 | −4.73, −0.33 | 50 | <0.001 |
| Sustain | −0.20 | −1.1, 0.10 | 15 | 0.01 |
| Memory | | | | |
| New learning | −1.1 | −1.9, −0.35 | 45 | <0.001 |
| Short-term | −1.0 | −1.5, −0.50 | 35 | <0.001 |
| Long-term | −1.5 | −2.0, −1.0 | 55 | <0.001 |
| Span | −1.23 | −2.0, 0.27 | 35 | 0.01 |
| Visual | −1.67 | −2.0, −1.0 | 70 | <0.001 |
| Processing speed | | | | |
| Motor | −1.83 | −4.7, −1.16 | 75 | <0.001 |
| Information | −1.0 | −1.83, −0.33 | 45 | <0.001 |
| Visual-motor | −1.5 | −2.17, −0.83 | 60 | <0.001 |
| Motor | | | | |
| Fine | −3.37 | −5.27, −2.08 | 80 | <0.001 |
| Gross | −2.20 | −2.63, −1.5 | 80 | <0.001 |
| Executive function | | | | |
| Fluency | −0.33 | −1.17, 0.17 | 25 | 0.07 |
| Working memory | −0.67 | −1.27, −0.60 | 20 | <0.001 |
| Interference control | −0.4 | −0.5, −0.65 | 0 | 0.03 |
| Flexibility | −0.87 | −1.40, −0.43 | 35 | <0.001 |
| Shifting | −3.97 | −5.33, −0.87 | 65 | <0.001 |
| Planning and organization | −1.9 | −3.0, −0.7 | 55 | <0.001 |
| Behavior rating | | | | |
| Inhibition | 0.65 | −0.15, 1.15 | 5 | 0.01 |
| Shift | 0.30 | −1.40, 0.70 | 25 | 0.88 |
| Emotional control | 0.70 | 0.2, 1.0 | 15 | 0.07 |
| Self-monitor | 0.60 | −0.45, 0.80 | 15 | 0.37 |
| Cognitive rating | | | | |
| Initiation | 0.30 | −0.45, 0.60 | 10 | 0.78 |
| Working memory | −0.90 | −1.75, −0.30 | 35 | 0.005 |
| Planning | 0.25 | −0.85, 0.60 | 10 | 0.96 |
| Task completion | −0.20 | −0.90, 0.45 | 10 | 0.26 |
| Organization | −0.10 | −0.60, 0.50 | 20 | 0.57 |

[a]Impairment defined as performance ≤10th percentile.
[b]Comparison of observed with expected mean ($M = 0$).

demonstrated leukoencephalopathy in the cortex, 5 of whom had only frontal involvement and 7 of whom had frontal and parietal/temporal involvement, including 2 with corona radiata involvement. One survivor had leukoencephalopathy involving only the corona radiata. Figure 1 provides an axial slice image for 2 survivors, with and without evidence of multifocal leukoencephalopathy. All survivors evidenced multifocal hemosiderin deposits, suggesting prior infarcts that were likely treatment related. Eight survivors also evidenced cavernous malformations, which accounted for some of the observed infarcts, but not all in any one patient.

### *White Matter Integrity and Executive Function*

Figure 2 shows DTI images for a single patient. RAD in the frontal lobe of both hemispheres was negatively correlated

with shifting attention (left: $r_s = -0.67$, $P = .001$; right: $r_s = -0.64$, $P = .002$) and cognitive flexibility (left: $r_s = -0.56$, $P = .01$; right: $r = -0.54$, $P = .01$). The top panel of Fig. 3 shows the correlation between white matter RAD and shifting attention in the left and right hemispheres of the frontal lobe.

**Table 3.** Executive function by age at diagnosis

| | Diagnosis ≤10 y ($n = 11$) | | Diagnosis >10 y ($n = 9$) | | *P*-value[a] |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| FSIQ | −1.70 | 0.92 | 0.04 | 0.84 | 0.002 |
| Fluency | −1.30 | 1.13 | 0.37 | 1.13 | 0.009 |
| Working memory | −1.52 | 1.02 | −0.34 | 0.47 | 0.001 |
| Shifting attention | −4.58 | 1.68 | −1.4 | 1.7 | 0.002 |
| Planning/organization | −2.65 | 1.23 | −0.88 | 0.99 | 0.005 |
| Flexibility | −1.42 | 0.73 | −0.29 | 0.58 | 0.004 |

[a] Mann–Whitney *U*-test for independent samples.

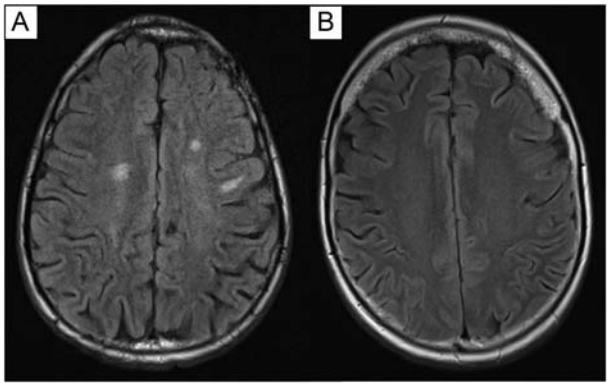


Fig. 1. Axial slices showing the presence of multifocal leukoencephalopathy in one survivor (A) and a survivor with no apparent white matter abnormalities (B).

FA in the parietal lobe was positively correlated with working memory (right: $r_s = 0.52$, $P = .017$; left: $r_s = 0.54$, $P = .01$). RAD in both parietal lobes was negatively correlated with shifting attention (left: $r_s = -0.63$, $P = .003$; right: $r_s = -0.55$, $P = .01$).

In the temporal lobe, RAD was negatively correlated with shifting attention (right: $r_s = -0.63$, $P = .003$; left: $r_s = -0.69$, $P = .0008$) and cognitive flexibility (right: $r_s = -0.52$, $P = .017$; left: $r_s = -0.56$, $P = .01$). Cognitive fluency was positively correlated with FA in the left and right temporal lobes (left: $r_s = 0.65$, $P = .002$; right: $r_s = 0.58$, $P = .007$). The bottom panel of Fig. 3 shows the correlation between RAD and shifting attention in both hemispheres of the temporal lobe.

No statistically significant correlations were found between AX and measures of executive function for any brain region. Additionally, no significant correlations emerged between white matter volume or cortical thickness and performance on measures of executive function. Table 4 provides correlations between FA and RAD and other assessed domains of neurocognitive function for the 6 lobular regions described.

## Discussion

The results of this pilot study of survivors of childhood MB treated with CSI revealed global neurocognitive impairment nearly 20 years postdiagnosis. Reduced white matter integrity was associated with observed neurocognitive dysfunction in these survivors. While past studies have reported correlations between general intelligence and white matter integrity in childhood survivors, our results suggest a relationship between specific executive function and white matter integrity in adult survivors treated with high-dose CSI for childhood MB.

Executive functions are higher-order cognitive processes that include shifting attention, working memory, cognitive fluency, cognitive flexibility, and planning and organization. The fronto-parietal network involves the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the inferior and superior parietal lobes and has been implicated in supporting the integration and

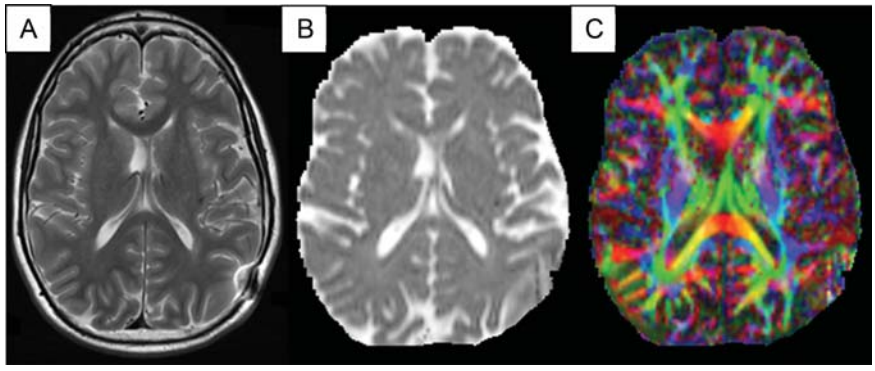


Fig. 2. DTI for one MB patient. (A) T2-weighted image, axial slice. (B) Apparent diffusion coefficient map without directional information. (C) Fractional anisotropy directional map. Red: left-right; green: anteroposterior; blue: superior-inferior.

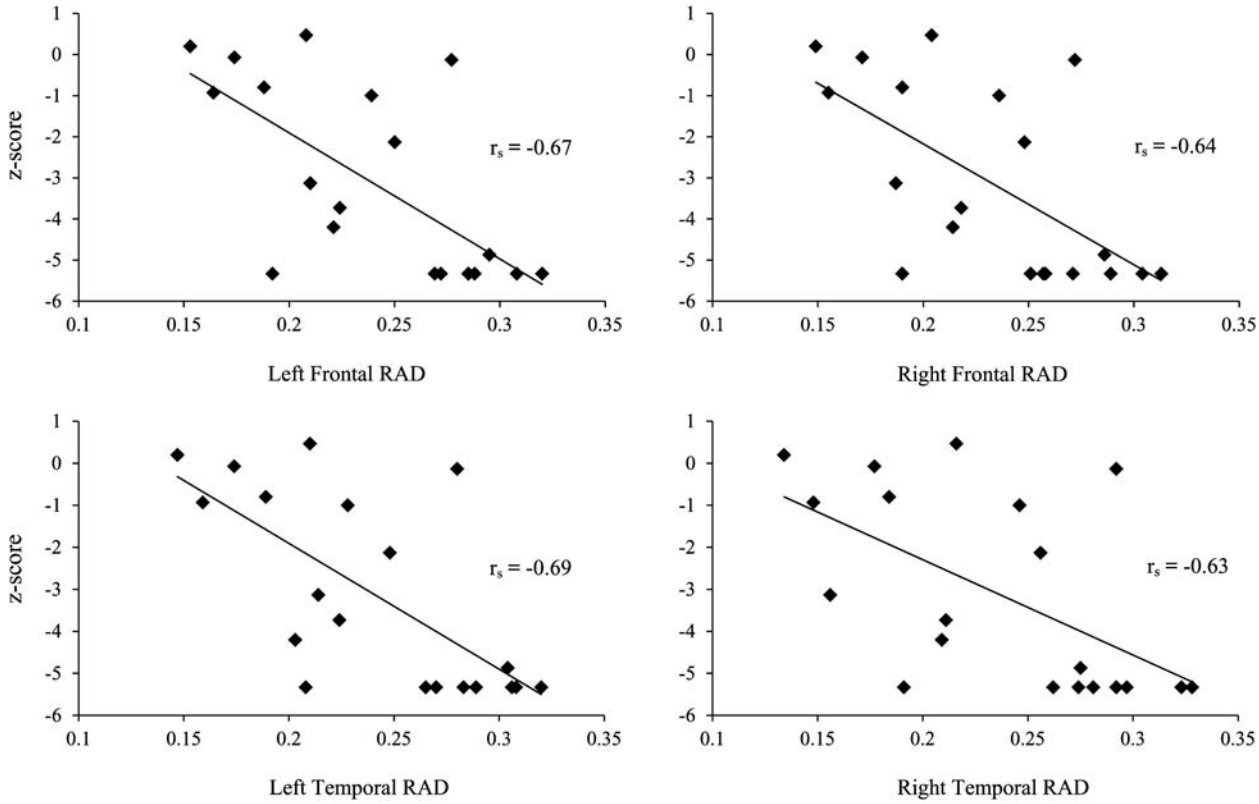


Fig. 3. Correlation between shifting attention and radial diffusivity (RAD).

control of executive processes.[43] While we did not examine white matter integrity within specific tracts known to contribute to this network, we found several significant correlations between white matter in the frontal and parietal lobes and executive processes. Specifically, white matter RAD in the frontal lobes was negatively correlated with performance on tasks of shifting attention (set shifting) and cognitive flexibility, while FA was positively correlated with working memory in the parietal lobe. Our findings suggest that loss of white matter integrity observed following CSI treatment persists for several decades and may further be associated with long-term deficits in executive function.

We also found associations between reduced white matter integrity within the temporal lobe and executive dysfunction, specifically cognitive flexibility, shifting attention, and cognitive fluency. Moreover, the observed associations between white matter integrity and executive function were generally not lateralized to a specific hemisphere. This suggests that integrated white matter pathways across several cortical regions may be responsible for the control of higher-order executive processes in MB survivors. Notably, we did not find significant associations between self-report of executive function and DTI measures. In fact, mean scores on measures of self-reported cognitive and behavior ratings did not differ from normative expectations, with the exception of working memory and inhibition. These data may suggest that performance-based measures may be more sensitive to subtle neurocognitive processes and underlying neuroanatomical changes. Alternatively, it may be that survivors adapt to their cognitive deficits over time, and self-report methods may potentiate response shift effects, whereby survivors' reporting reflects their recalibrated perceptions of cognitive function over time.

The most significant executive function deficit was observed on a task of cognitive set shifting, and poorer performance on this task was consistently correlated with reduced white matter integrity across several brain regions. Performance on executive function tasks are often multidetermined and may involve both executive and nonexecutive function components. The measure of cognitive set shifting employed in this study also required visual-motor demands (Trail Making Test, Part B). However, performance on a cognitive task requiring comparable visual scanning and motor demands (Trail Making Test, Part A) was not significantly associated with any measures of white matter integrity. Thus, our results suggest that the specific ability to shift cognitive sets is associated with reduced white matter integrity, independent of visual scanning and motor demands.

Importantly, variability in neurocognitive outcomes was evident, even in our small sample of survivors. While a greater proportion of survivors were impaired

**Table 4.** Correlations between measures of white matter integrity and neurocognitive functioning

| | Fractional Anisotropy | | | | | | Radial Diffusivity | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Left Frontal | Right Frontal | Left Temporal | Right Temporal | Left Parietal | Right Parietal | Left Frontal | Right Frontal | Left Temporal | Right Temporal | Left Parietal | Right Parietal |
| Intelligence | | | | | | | | | | | | |
| Full scale | 0.52 | 0.51 | 0.59[a] | 0.48 | 0.51 | 0.44 | −0.39 | −0.36 | −0.42 | −0.35 | −0.36 | −0.24 |
| Verbal | 0.42 | 0.40 | 0.50 | 0.44 | 0.44 | 0.42 | −0.40 | −0.37 | −0.44 | −0.39 | −0.36 | −0.27 |
| Perceptual | 0.48 | 0.49 | 0.54[a] | 0.44 | 0.48 | 0.43 | −0.30 | −0.29 | −0.31 | −0.27 | −0.28 | −0.18 |
| Academics | | | | | | | | | | | | |
| Word reading | 0.35 | 0.37 | 0.46 | 0.45 | 0.42 | 0.49 | −0.44 | −0.42 | −0.46 | −0.43 | −0.41 | −0.34 |
| Calculations | 0.34 | 0.40 | 0.47 | 0.54[a] | 0.36 | 0.52[a] | −0.48 | −0.46 | −0.52 | −0.49 | −0.45 | −0.39 |
| Attention | | | | | | | | | | | | |
| Focus | 0.28 | 0.31 | 0.43 | 0.41 | 0.26 | 0.34 | −0.41 | −0.39 | −0.44 | −0.40 | −0.37 | −0.30 |
| Sustain | −0.15 | −0.12 | −0.09 | 0.03 | −0.13 | −0.17 | −0.36 | −0.34 | −0.42 | −0.36 | −0.29 | −0.32 |
| Memory | | | | | | | | | | | | |
| New learning | 0.37 | 0.31 | 0.27 | 0.23 | 0.33 | 0.35 | −0.25 | −0.22 | −0.22 | −0.22 | −0.24 | −0.19 |
| Short-term | 0.41 | 0.38 | 0.25 | 0.24 | 0.39 | 0.40 | −0.02 | −0.01 | 0.06 | 0.03 | −0.01 | 0.03 |
| Long-term | 0.00 | 0.03 | −0.09 | 0.11 | 0.08 | 0.35 | −0.07 | −0.11 | 0.03 | −0.10 | −0.11 | −0.13 |
| Span | 0.52 | 0.45 | 0.53 | 0.28 | 0.66[a] | 0.34 | −0.26 | −0.17 | −0.31 | −0.18 | −0.25 | −0.10 |
| Visual | 0.50 | 0.59[a] | 0.57[a] | 0.66[a] | 0.58 | 0.78[b] | −0.19 | −0.15 | −0.17 | −0.02 | −0.19 | 0.13 |
| Processing speed | | | | | | | | | | | | |
| Information | 0.52 | 0.53 | 0.68[a] | 0.56[a] | 0.53 | 0.49 | −0.29 | −0.25 | −0.35 | −0.27 | −0.26 | −0.16 |
| Visual-motor | 0.44 | 0.47 | 0.61[a] | 0.57[a] | 0.47 | 0.45 | −0.28 | −0.26 | −0.34 | −0.27 | −0.24 | −0.16 |
| Motor | 0.36 | 0.41 | 0.54[a] | 0.52 | 0.35 | 0.32 | −0.30 | −0.30 | −0.34 | −0.30 | −0.25 | −0.19 |
| Executive function | | | | | | | | | | | | |
| Fluency | 0.46 | 0.44 | 0.65[a] | 0.58[a] | 0.51 | 0.44 | −0.44 | −0.39 | −0.53[a] | −0.44 | −0.38 | −0.28 |
| Working memory | 0.31 | 0.27 | 0.38 | 0.35 | 0.54[a] | 0.52[a] | −0.22 | −0.23 | −0.23 | −0.27 | −0.24 | −0.19 |
| Interference control | −0.24 | −0.42 | −0.21 | −0.36 | −0.09 | −0.19 | −0.28 | −0.28 | −0.27 | −0.25 | −0.30 | −0.26 |
| Flexibility | 0.23 | 0.24 | 0.17 | 0.19 | 0.29 | 0.22 | −0.56[a] | −0.54[a] | −0.56[a] | −0.52[a] | −0.51 | −0.44 |
| Shifting | 0.26 | 0.29 | 0.46 | 0.51 | 0.34 | 0.44 | −0.67[b] | −0.64[a] | −0.69[b] | −0.63[a] | −0.63[a] | −0.55[a] |
| Planning and organization | 0.34 | 0.39 | 0.25 | 0.46 | 0.36 | 0.46 | −0.32 | −0.31 | −0.27 | −0.27 | −0.28 | −0.25 |
| Behavior rating | | | | | | | | | | | | |
| Inhibition | 0.10 | 0.22 | 0.06 | 0.34 | 0.10 | 0.35 | 0.33 | 0.29 | 0.39 | 0.32 | 0.36 | 0.27 |
| Shift | 0.35 | 0.46 | 0.28 | 0.15 | 0.13 | 0.28 | 0.41 | 0.37 | 0.34 | 0.30 | 0.47 | 0.38 |
| Emotional control | 0.23 | 0.21 | 0.15 | 0.25 | 0.19 | 0.26 | 0.21 | 0.21 | 0.26 | 0.27 | 0.27 | 0.18 |
| Self-monitor | 0.29 | 0.38 | 0.21 | 0.48 | 0.16 | 0.40 | 0.33 | 0.30 | 0.33 | 0.25 | 0.40 | 0.30 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cognitive rating | | | | | | | | | | | | |
| Initiation | 0.24 | 0.31 | 0.24 | 0.53 | 0.17 | 0.37 | 0.17 | 0.13 | 0.10 | 0.08 | 0.27 | 0.15 |
| Working memory | 0.42 | 0.48 | 0.36 | 0.56 | 0.27 | 0.27 | 0.19 | 0.18 | 0.15 | 0.19 | 0.27 | 0.24 |
| Planning | 0.21 | 0.30 | 0.20 | 0.50 | 0.23 | 0.47 | 0.18 | 0.14 | 0.17 | 0.10 | 0.22 | 0.14 |
| Task completion | 0.29 | 0.28 | 0.15 | 0.35 | 0.16 | 0.24 | 0.37 | 0.35 | 0.40 | 0.31 | 0.41 | 0.34 |
| Organization | 0.39 | 0.48 | 0.25 | 0.43 | 0.17 | 0.33 | 0.30 | 0.27 | 0.32 | 0.26 | 0.34 | 0.32 |

[a] $P \leq .01$.
[b] $P \leq .001$.

relative to normative expectations, a sizable percentage of survivors (25%) did not evidence impairment on tasks of executive function. This finding demonstrates the need for genetic studies to understand variability in neurocognitive outcomes and/or sensitivity to CSI treatment–induced white matter damage. To date, studies have focused on polymorphisms believed to affect antioxidant enzyme activity. A study of child and adolescent MB patients demonstrated an association between glutathione s-transferase (GST)M1 null genotype and significant declines in global intelligence compared with GSTM1 nonnull genotypes following CSI.[44] Recently, Brackett et al[45] also reported associations between the GSTM1 polymorphism and greater psychological distress in adult survivors of childhood MB, though no significant associations between genotypes and self-report of neurocognitive function emerged. How genetic polymorphisms may be related to susceptibility to white matter damage following cranial irradiation in cases of MB is unknown.

A current endeavor within the field of pediatric oncology includes efforts toward remediation and/or rehabilitation of cognitive deficits that may emerge following neurotoxic cancer treatments. Several studies provide preliminary support for the effects of rehabilitation of neurocognitive deficits in childhood cancer survivors,[46–48] though only one study has examined functional brain changes as a result of systematic training efforts.[49] Thus, the neuronal mechanisms underlying the effects of cognitive intervention are largely unexplored and provide a promising area for future research. Evidence of white matter changes following cognitive intervention exists in noncancer populations, suggesting increased FA and decreased diffusivity post-intervention.[50,51] It will be important to investigate the presence of potential connectivity changes in patients with known risk for white matter abnormalities following targeted intervention efforts.

While our data, considered in the context of past findings, suggest the need for future research, there are notable limitations. First, in the absence of an age-matched control group, we are unable to discuss how observed correlations between executive function and white matter integrity may be similar or dissimilar in healthy adults of the same age. Given the small sample size in this pilot study, we had limited power to detect statistically significant associations. However, the magnitude of observed correlations is considered large for behavioral research. Finally, as the patients in our sample were treated over a decade ago, the observed white matter and neuropsychological morbidity is likely greater than that experienced in cases of MB treated on more contemporary protocols, which often involve reduced CSI dose and advanced radiation technology (eg, conformal, proton beam).

In summary, in our sample of adult survivors of childhood MB, neurocognitive impairment was common and apparent across many specific domains of function. Reduced white matter integrity, as measured by FA and RAD, was associated with poorer performance on tasks of executive function. We suggest that future

studies of neurotoxicity among MB survivors integrate DTI while also considering potential genetic predictors, to identify exposure-specific risks for adverse outcomes. Lastly, priority should be given to the design and testing of innovative cognitive interventions among this high-risk population.

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