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CLINICAL INVESTIGATION **Pediatric**

WHITE MATTER FRACTIONAL ANISOTROPY CORRELATES WITH SPEED OF PROCESSING AND MOTOR SPEED IN YOUNG CHILDHOOD CANCER SURVIVORS

Eline J. Aukema, M.Sc.,* Matthan W. A. Caan, M.Sc.,†‡ Nienke Oudhuis, M.Sc.,* Charles B. L. M. Majoie, M.D.,† Frans M. Vos, Ph.D.,†‡ Liesbeth Reneman, M.D.,† Bob F. Last, Ph.D.,*§ Martha A. Grootenhuis, Ph.D.,* and Antoinette Y. N. Schouten-van Meeteren, M.D.‖

*Pediatric Psychosocial Department and ‖Department of Pediatric Oncology, Emma Children's Hospital/Academic Medical Center, and †Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; ‡Delft University of Technology, Delft, The Netherlands; and §Department of Developmental Psychology, Free University of Amsterdam, Amsterdam, The Netherlands

Purpose: To determine whether childhood medulloblastoma and acute lymphoblastic leukemia (ALL) survivors have decreased white matter fractional anisotropy (WMFA) and whether WMFA is related to the speed of processing and motor speed.

Methods and Materials: For this study, 17 patients (6 medulloblastoma, 5 ALL treated with high-dose methotrexate (MTX) (4×5 g/m^2) and 6 with low-dose MTX (3×2 g/m^2)) and 17 age-matched controls participated. On a 3.0-T magnetic resonance imaging (MRI) scanner, diffusion tensor imaging (DTI) was performed, and WMFA values were calculated, including specific regions of interest (ROIs), and correlated with the speed of processing and motor speed.

Results: Mean WMFA in the patient group, mean age 14 years (range 8.9 – 16.9), was decreased compared with the control group ($p = 0.01$), as well as WMFA in the right inferior fronto-occipital fasciculus (IFO) ($p = 0.03$) and in the genu of the corpus callosum (gCC) ($p = 0.01$). Based on neurocognitive results, significant positive correlations were present between processing speed and WMFA in the splenium (sCC) ($r = 0.53$, $p = 0.03$) and the body of the corpus callosum (bCC) ($r = 0.52$, $p = 0.03$), whereas the right IFO WMFA was related to motor speed ($r = 0.49$, $p < 0.05$).

Conclusions: White matter tracts, using a 3.0-T MRI scanner, show impairment in childhood cancer survivors, medulloblastoma survivors, and also those treated with high doses of MTX. In particular, white matter tracts in the sCC, bCC and right IFO are positively correlated with speed of processing and motor speed.

DTI, Children, Cancer, Neuropsychology, MTX.

INTRODUCTION

Today, in developed countries such as the United States, about one in every 450 adolescents reaching the age of 20 will be a long-term cancer survivor (1). Because of multimodal treatment strategies, the overall survival rate of children with brain tumors has increased dramatically (2). Unfortunately, progress in treatment strategies has not been able to prevent treatment-related side effects, such as neurotoxicity. For instance, children treated with craniospinal radiotherapy (CSRT) and chemotherapy for a medulloblastoma often experience serious neurocognitive impairments. Deficits in attention, memory, and speed of processing are commonly found in survivors (2–5). Children treated for acute lymphoblastic leukemia (ALL) have also shown treatment-induced neurotoxicity; this is probably caused by intrathecal and/or high-dose intravenous methotrexate (MTX), which is a replacement for cranial radiation therapy as central nervous system (CNS) prophylaxis, although published data are inconsistent (6–8).

Reprint requests to: Eline J. Aukema, M.Sc., Pediatric Psychosocial Department, Emma Children's Hospital (G8-224), Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: 0031205665670; Fax: 0031206091242; E-mail: e.j.aukema@amc.uva.nl

Preliminary results presented at two Dutch National Brain tumor meetings and in an oral presentation for pediatricians in 2008. Poster presented at the yearly institutional research meeting (Emma symposium 2008). Poster presented at the SIOP meeting 2008 in Berlin and at the Medical Image Computing and Computer-Assisted Intervention (MICCAI) 2008.

Conflict of interest: none.

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The neurocognitive impairments have been associated with white matter changes caused by cranial (spinal) radiation therapy (C[S]RT), some chemotherapeutic agents including MTX, and other factors, such as tumor infiltration and hydrocephalus (9–11). The treatment-induced neurotoxicity may be caused by either a failure of ''normal'' maturation and myelination of the brain at an age-appropriate rate or by damage to already-existing white matter tracts. In children treated for cancer, negative effects based on both assumptions seem likely.

Diffusion tensor imaging (DTI), an advanced brain imaging technology, enables the study of the integrity of white matter structures, which are most vulnerable to toxic treatment. The diffusion of water molecules is high along and low perpendicular to coherent white matter tracts, resulting in an anisotropic diffusion profile. The white matter fractional anisotropy (WMFA) value quantifies this anisotropy, with 0 for isotropic and 1 for fully anisotropic diffusion profiles. WMFA reflects the myelination and axonal integrity (12). Increase of WMFA during childhood and adolescence parallels the development of important basic cognitive functions (13, 14).

Diminished WMFA seems potentially useful for detecting and monitoring white matter damage. Thereby, significant positive correlations were found for WMFA in different brain regions with intelligence and neuropsychologic functions in medulloblastoma survivors (15–17). Likewise, these positive correlations have been found in children with traumatic brain injury (18) and in patients with a wide range of psychiatric disorders (19). White matter plays an important role in the speed of processing, which is crucial for learning and coping in daily life—one of the main problems for childhood cancer survivors, especially brain tumor survivors. It is unknown whether diminished WMFA is related to these problems in speed of processing; increased insight into this relationship might help to predict neurocognitive decline in the future.

The aims of this study were 1) to estimate the functioning of cancer survivors (survivors from a medulloblastoma and ALL) with respect to intelligence, speed of processing and motor speed, 2) to measure WMFA by MRI in childhood cancer survivors after treatment with CRST and/or high-dose intravenous MTX compared with peers, and 3) to relate neurocognitive function (intelligence, speed of processing and motor speed) with WMFA in different regions of interest (ROIs).

We prospectively studied WMFA using a 3.0-T MRI and neurocognitive functioning in a group of childhood cancer survivors compared with healthy peers.

METHODS AND MATERIALS

Patients

Survivors treated in the Emma Children's Hospital for a medulloblastoma or ALL, between 8 and 16 years old and at least 3 years after the end of treatment in medulloblastoma survivors or 3 years after intravenous MTX as CNS prophylaxis in ALL survivors, were eligible for this study.

To compare different treatment modalities, our study design consisted of three subgroups of childhood cancer survivors (''patient group''); 6 medulloblastoma survivors treated with surgery, radiation (whole brain and spine: total dose range, 25.2–34.5 Gy; and posterior cranial fossa boost: range, 53.3–55.4 Gy) and chemotherapy, including lomustin, vincristin, and cisplatin; 6 ALL survivors treated with 4×5 g/m^2 intravenous MTX (''high-dose ALL'') according to the DCLSG protocol 1993–1997; and 6 survivors treated with 3×2 g/m^2 intravenous MTX (''low-dose ALL'') according to the DCLSG ALL-9 protocol 1997–2004 as CNS prophylaxis (20, 21).

Parents or adolescents were first contacted by phone and then received written information about the study.

We approached 8 medulloblastoma survivors and received six positive reactions. We then searched for age- and sex-matched survivors treated for ALL with comparable time after completion of treatment. A total of 20 ALL survivors were selected, of whom 7 did not want to be confronted with their cancer history again. We received 13 approvals for participation, and they were divided into the two different treatment groups.

After inclusion of the survivors, we selected a ''control group'' of classmates of the participating survivors. A suitable classmate, matching the survivor as closely as possible according to age, sex, and level of education, was chosen by the school, unless survivors picked their own classmate for privacy reasons or a suitable classmate of a different patient was approached by us.

The survivor and control were scheduled together for the MRI and neurocognitive evaluation to reduce possible anxiety through peer support and to increase participation. Age-specific illustrated information about the MRI procedure was provided, and professional child-directed support and the possibility of using a distracting audiotape or videotape were available during the MRI. Specific requirements as described by Dutch law and the behavioral research code of the Dutch Association for Pediatricians were met in this study design, which was approved by the local medical ethics committee.

Finally, 17 survivors (6 medulloblastoma; 5 high-dose ALL, and 6 low-dose ALL) participated in this study, as 1 survivor was unable to finish his MRI session because of anxiety and 1 survivor had a steel splinter in his eye.

Measurements

Diffusion tensor imaging (DTI) was performed on a 3.0-T MRI scanner (Philips Intera, Philips Medical Systems, Best, the Netherlands). DTI acquisition was along 16 nonlinear and 16 antipodal directions. The other parameters were echo-time: 94 msec, repetition time: 4,831–6,248 msec, diffusion weighting parameter b: 1000 s/mm^2, FOV: 240 mm, scan matrix: 70×112, and slice thickness: 3 mm. Eddy current–induced morphing was corrected by a two-dimensional affine registration of the diffusion weighted images to the B_0-image (22).

The participants were informed about the MRI results only if health-related data resulted, which was not the case in any of the children.

The neurocognitive tests were individually administered by two psychologists in approximately 2.5 h. All subjects completed a test battery to assess general intelligence, speed of processing and motor speed. This battery included the Dutch version of the Wechsler Intelligence Scale for Children, 3rd Edition (23), and the Purdue pegboard (24). Participants were informed about their cognitive functioning and possible consequences for school and daily life.

The interval between neurocognitive testing and MRI ranged between 0.0 and 3.5 months.

MRI data analyses

Structural images were judged by an experienced neuroradiologist for macroscopic white matter lesions, atrophy, status of the primary tumor, if appropriate (*i.e.,* in medulloblastoma survivors), and possible other new lesions. FA-images were computed using Teem-software (http://teem.sf.net). Further analysis was performed in Matlab using Statistical Parametric Mapping (SPM5) software (Wellcome Department of Cognitive Neurology, London, England) and Matlab software (The MathWorks, Natick, MA). As an initialization, all data were co-registered to the echo planar imaging template available in the SPM toolbox.

The data were segmented into white matter, gray matter and cerebrospinal fluid (CSF) based on the B_0-image. A two-step procedure was performed. In the first iteration, the *a priori* white matter, gray matter, and CSF-maps available in SPM were used to segment the data. After this segmentation, average maps of the cohort were computed, and the second iteration was initiated using these maps. The resulting white matter mask was obtained using the following operation: i2>i1 & i2>i3 & i2>1-i1-i2-i3, where i1, i2 and i3 are the grey, white, and CSF-maps, respectively, resulting from the segmentation as shown in Fig. 1.

The WMFA volumes were smoothed using a Gaussian kernel, with a size of 6 mm (FWHM). Next, all images were spatially normalized, using both an affine and nonrigid transformation. In this way, tiny segmentation errors could be corrected through pairwise intersection of the masks.

Based on the literature (25, 26), white matter regions of interest (ROI) with a presumed relation with neurocognitive function were selected: the genu (gCC), the splenium (sCC), and the body of the corpus callosum (bCC) and the bilateral inferior fronto-occipital fasciculus (IFO). Regions of interest (ROIs) were outlined on color-coded WMFA maps. We first used a control subject and manually drew the ROIs. The ROIs identified in this subject were then used as a guide to manually define ROIs for other subjects as reproducibly as possible; subsequently, the ROIs were outlined manually by one operator. Mean WMFA was measured in each ROI.

Statistical analyses

Overall WMFA (mean WMFA and mean ROI WMFA) was calculated, and correlations with cognitive functioning were analyzed using SPSS version 14.2 (SPSS Inc., Chicago, IL).

First, demographics and cognitive functioning of the participants were described. One-sample *t* tests were performed to test whether mean scores on cognitive tests in the ''patient group'' (medulloblastoma, low-dose ALL, and high-dose ALL) and the ''control group'' differed from the normal population (23, 24). Differences in cognitive functioning between the patient subgroups were analyzed using multiple univariate analyses of variance (ANOVA).

Second, we studied group differences in overall WMFA between the patient group and the control group, using *t* tests. If overall tests for differences in WMFA were significant, we further analyzed the differences among the 3 patient subgroups with ANOVA. For assurance of the results, we also performed nonparametric Mann-Whitney *U* tests because of the non-normal distribution of WMFA in these small subgroups.

Finally, we calculated correlations of overall WMFA with intelligence, speed of processing, and motor speed in the patient group. We followed Cohen in considering correlation coefficients of 0.1 as small, 0.3 as medium, and 0.5 as large (27).

RESULTS

Participants

The characteristics of the participants are listed in Table 1. The control group was well matched for age and sex. Within the patient group, the subgroups did not differ in age at testing ($F(2, 14) = 2.04$, $p = 0.17$) or in age at diagnosis ($F(2, 14) = 1.13$, $p = 0.35$). However, ''interval since treatment'' differed significantly ($F(2, 14) = 5.36$, $p = 0.02$) between the patient subgroups. As expected, further analysis showed a longer interval for the high-dose ALL group compared with the low-dose ALL group ($t = 4.76$, $df = 9$, $p = 0.00$). These results were confirmed by nonparametric Mann-Whitney *U* tests.

Neurocognitive functioning

Neurocognitive functioning and differences from the norm population are presented in Table 2. The medulloblastoma group scored the worst on almost all cognitive measures, especially on processing speed and motor speed compared with the norm population, followed by the high-

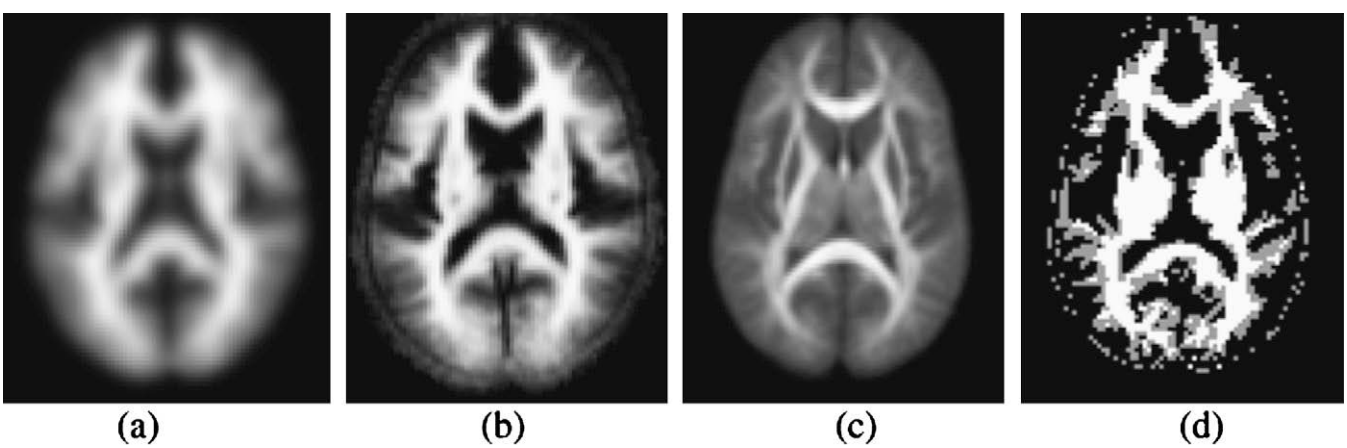

Fig. 1. Overview of magnetic resonance imaging data analyses. (a) *A priori* white matter segmentation map provided by statistical parametric mapping software and (b) based on the data in this study. (c) Fractional anisotropy values averaged over all subjects after spatial normalization. (d) Voxels segmented into white matter of one patient–control pair, gray denoting either one of the two and white denoting both subjects, the latter being used in the analysis.

Table 1. Characteristics of the participants

	MED	High-dose ALL	Low-dose ALL	Patient group	Control group
n	t6	5	6	17	17
Gender					
Female	5	0	6	11	11
Male	1	5	0	6	6
Age at study (y)					
Mean (SD)	13.6 (3.0)	15.4 (1.4)	13.2 (2.7)	14.0 (2.5)	13.9 (2.9)
Min, max	8.9, 16.8	13.4, 16.9	10.1, 16.7	8.9, 16.9	8.8, 17.0
Age at diagnosis (y)					
Mean (SD)	4.7 (1.3)	3.7 (1.5)	7.1 (4.5)	5.2 (3.1)	–
Min, max	2.9, 6.7	2.2, 5.7	2.0, 13.2	2.0, 13.2	
Interval (y)					
Mean (SD)	8.8 (4.0)	11.5 (1.2)	5.9 (2.4)	8.4 (3.5)	–
Min, max	2.7, 13.3	10.6, 13.6	3.4, 9.9	2.7, 13.6	

Abbreviations: MED = medulloblastoma group; High-dose ALL = leukemia group, high-dose MTX (4×5 g/m^2); low-dose ALL = leukemia group low-dose MTX (3×2 g/m^2); Interval = time since end of treatment.

dose ALL group and the low-dose ALL group. Lower scores were also found in the control group; moreover, cognitive functioning differed significantly from the norm scores.

Analysis of variance showed a trend toward a difference in full scale IQ (F (2, 14) = 3.19, $p = 0.07$) between the patient subgroups. Further analysis revealed significantly lower full scale IQ in the medulloblastoma group ($p = 0.04$) compared with the low-dose ALL group. The verbal comprehension index score and perceptual reasoning score did not differ between the patient subgroups.

In addition, ANOVA showed significant differences (F (2,14) = 14.50, $p = 0.00$) between the patient subgroups in the processing speed index score. Further analysis

Table 2. Cognitive functioning of the participants compared with the normal population group

	MED	High-dose ALL	Low-dose ALL	Patient group	Control group
n	6	5	6	17	17
Intelligence *					
FSIQ					
Mean (SD)	82.8 (14.8)	97.4 (12.4)	102.2 (13.7)	93.9 (15.5)	88.4 (13.8)
Min, max	61, 104	81, 111	87, 123	61, 123	68, 120
p Value	**0.04**	0.66	0.71	0.13	**0.00**
VCF					
Mean (SD)	88.8 (13.1)	96.6 (12.9)	98.0 (11.0)	94.4 (12.3)	90.1 (13.0)
Min, max	72, 109	80, 109	86, 114	72, 114	69, 120
p Value	0.09	0.59	0.67	0.08	**0.01**
POI					
Mean (SD)	88.0 (13.4)	102.8 (16.4)	106.2 (15.8)	98.8 (17.4)	89.9 (11.4)
Min, max	58, 108	80, 123	83, 123	58, 123	67, 110
p Value	0.13	0.73	0.38	0.77	**0.00**
Processing speed†					
PSF					
Mean (SD)	73.7 (11.6)	92.8(12.7)	106.5 (7.3)	90.9 (17.4)	96.9 (14.9)
Min, max	55, 91	72, 105	99, 114	55, 114	72, 124
p Value	**0.00**	0.27	0.08	0.05	0.41
Motor speed‡					
MS (Z)					
Mean (SD)	−1.79 (1.43)	−1.07 (0.95)	−1.10 (0.53)	−1.34 (1.03)	−0.56 (0.98)
Min , max	−4.0, −0.10	−1.97, 0.46	−1.88, −0.48	−4.0, 0.46	−2.62, 1.24
p Value	**0.03**	0.06	**0.00**	**0.00**	**0.03**

Abbreviations: FSIQ = full scale IQ; VCF = verbal comprehension factor; POF = perceptual organization factor; PSF= processing speed factor; MS= motor speed score in Z-scores; MED = medulloblastoma group; high-dose ALL = leukemia group, high-dose MTX (4×5 gr/m^2); low-dose ALL = leukemia group, low-dose MTX (3×2 gr/m^2).

* WISC-III-NL; mean = 100, SD = 15; results of 1-sample *t* tests with test value = 100.

† Processing speed; mean = 100, SD = 15; results of 1-sample *t* tests with test value = 100.

‡ Motor speed: total *Z* score; mean = 0, SD = 1 (−1 SD indicates worse; +1 SD indicates better); results of 1-sample *t* tests with test value = 0.

revealed significantly lower processing speed scores in the medulloblastoma group compared with the high-dose ALL group ($p = 0.03$) and the low-dose ALL group ($p = 0.00$). A trend toward a difference between the high-dose ALL group compared with the low-dose ALL group ($p = 0.05$) was found in favor of the latter group.

No group differences in motor speed were found ($F(2, 14) = 0.90$, $p = 0.43$).

All results were confirmed by nonparametric Mann-Whitney *U* tests.

Structural MR images

All controls and 11 patients (low-dose ALL and high-dose ALL) had normal findings for the T2-weighted and 3D-T1 weighted scans. Six patients, (medulloblastoma group) showed structural abnormalities on the T2-weighted and 3D-T1-weighted scans, including tissue loss of the cerebellar hemispheres ($n = 4$) or vermis ($n = 3$), hemosiderin deposits related to small previous occipital (n=2), or temporal ($n = 2$) hemorrhages and subtle signal increases in the bilateral parietal white matter ($n = 1$).

WMFA findings

WMFA is presented in Table 3. As anticipated, mean WMFA was lower in the patient group compared with the control group ($p = 0.01$). WMFA was lower in the right IFO ($p = 0.03$) and the gCC ($p = 0.01$), and a trend was found in the bCC ($p = 0.07$). These results were confirmed by nonparametric Mann-Whitney *U* tests.

Analysis of variance showed significant differences in mean WMFA ($F(2, 14) = 5.61$, $p = 0.02$), sCC WMFA ($F(2, 14) = 4.21$, $p = 0.04$) and bCC WMFA ($F(2,14) = 4.79$, $p = 0.03$) between the patient subgroups. Further analyses revealed significantly lower mean WMFA ($p = 0.01$), lower sCC WMFA ($p = 0.03$) and lower bCC WMFA ($p = 0.03$) in the medulloblastoma group compared with the high-dose ALL group. Trends toward lower sCC ($p = 0.10$) and bCC WMFA ($p = 0.07$) compared with the low-dose ALL group were found. No differences between the two ALL groups were found.

With respect to the different patient groups, the medulloblastoma group had lower mean WMFA (mean difference = 0.02, $p = 0.00$) and lower bilateral IFO WMFA (mean difference right IFO = 0.05, $p = 0.01$; and mean difference left IFO = 0.04, $p = 0.00$) compared with their age- and sex-matched controls. A trend was found toward a difference in the sCC WMFA (mean difference = 0.13, $p = 0.09$). The high-dose ALL group had significantly lower gCC WMFA (mean difference = 0.07, $p = 0.01$) compared with their controls. No significant differences between the low-dose ALL group and their controls were found. These results were confirmed by nonparametric Mann-Whitney *U* tests.

Correlations of WMFA with cognitive functioning

Correlations between WMFA and cognitive functioning in the patient group are presented in Table 4.

Mean WMFA was not significantly correlated with total intelligence in the patient group.

The sCC WMFA ($r = 0.53$, $p = 0.03$) and the bCC WMFA ($r = 0.52$, $p = 0.03$) showed a significantly positive correlation with the processing speed index score. The right IFO WMFA showed a significantly positive ($r = 0.49$, $p < 0.045$) correlation and a trend toward a positive correlation between sCC ($r = 0.46$, $p = 0.06$) and motor speed score. No correlations between other ROI WMFA values and cognitive scores were found. The correlations were strong according to Cohen ($r = \sim 0.5$).

In the control group the right IFO as well as the left IFO were also correlated to speed of processing ($r = 0.55$, $p = 0.02$ and $r = 0.58$, $p = 0.02$).

DISCUSSION

To our knowledge, this is the first study reporting WMFA changes after childhood cancer using a 3.0-T MRI scanner. The results of this study showed that WMFA is decreased in childhood cancer survivors and is associated with neurocognitive skills, including speed of processing and motor speed. Mean WMFA and WMFA in ROIs, especially right IFO and gCC, were reduced. Because WMFA reflects the myelination and axonal integrity (12), these results indicate that the integrity of the white matter tracts are affected in childhood cancer survivors of medulloblastoma and survivors of ALL treated with high-dose MTX. These findings are in agreement with a number of other studies showing white matter impairment (11, 28, 29) and, in particular, vulnerability of the frontal lobes and the corpus callosum (30, 31) after treatment for these types of cancer during childhood.

In addition, the current study showed evidence for positive correlations between detailed WMFA impairment, especially in the right IFO and in the sCC and bCC, and neurocognitive impairment, especially speed of processing and motor speed. Lower WMFA in these regions correlated with slower speed of processing and motor speed. This supports the idea that more anisotropic white matter tracts facilitate more processing and faster processing of information. The splenium and body of the corpus callosum play important roles in the communication between the different brain areas, in particular the occipital and motor regions, and this could explain the relation with visual speed of processing and motor speed (32). Mabbot *et al.* (26) found that the right frontal–parietal region contributes to the speed of visual–spatial searching (26). In a wide range of childhood neuropsychiatric illnesses, including attention deficit/hyperactivity disorder (ADHD), size differences in the corpus callosum have been reported (19). In patients with traumatic brain injury (TBI), which also usually induces diffuse axonal injury, damage in the corpus callosum is related to a poorer neurocognitive outcome (33).

Several limitations to our study can be identified. First, the compilation of our control group, derived from the same school level with a low average intelligence, hindered the generalization of the patient data. Second, because many childhood brain tumors are located infratentorially, the

Table 3. Mean white matter fractional anisotropy values in different regions of interest

	MED	High-dose ALL	Low-dose ALL	Patient group	Control Group
n	**6**	**5**	**6**	**17**	**17**
Mean WMFA	0.399**	0.418	0.408	0.407*	0.418
SD	0.072	0.010	0.011	0.012	0.010
Right IFO WMFA	0.217	0.225	0.212	0.217*	0.243
SD	0.029	0.019	0.031	0.026	0.038
Left IFO WMFA	0.221	0.230	0.212	0.220	0.235
SD	0.019	0.019	0.028	0.023	0.035
gCC WMFA	0.472	0.455	0.499	0.474*	0.517
SD	0.064	0.029	0.032	0.047	0.004
sCC WMFA	0.494**	0.666	0.623	0.590	0.615
SD	0.014	0.021	0.097	0.012	0.053
bCC WMFA	0.494**	0.666	0.623	0.590	0.615
SD	0.014	0.021	0.097	0.012	0.053

Abbreviations: MED = medulloblastoma group, high dose ALL = leukemia group high-dose MTX (4 x 5 gr/m^2), low-dose ALL = leukemia group dose MTX (3 x 2 gr/m^2), WMFA = white matter fractional anisotropy values, IFO = inferior fronto-occipital fasciculus, gCC, sCC, bCC = genu, splenium and body of the corpus callosum.

* significant (< 0.05) differences between the patient group and the control group.

** significant (<0.05) differences between MED and high-dose ALL.

Table 4. Correlations of mean WMFA values with cognitive functioning in the patient group (N = 17)

	Full scale intelligence	Processing speed factor	Motor Speed
Mean WMFA	0.22	0.35	0.07
p Value	0.40	0.17	0.78
Right IFO WMFA	0.23	0.21	0.49
p Value	0.38	0.41	**0.045**
Left IFO WMFA	0.10	0.06	0.16
p Value	0.70	0.81	0.54
gCC WMFA	-0.16	0.22	-0.33
p Value	0.55	0.40	0.20
sCC WMFA	0.16	0.53	0.46
p Value	0.54	**0.03**	**0.06**
bCC WMFA	0.10	0.52	0.33
p Value	0.71	**0.03**	0.19

Abbreviations: WMFA = white matter fractional anisotropy; IFO = inferior fronto-occipital fasciculus; gCC, sCC, bCC = genu, splenium and body of the corpus callosum.

impact of cerebellar damage and hydrocephalus in the past requires specific attention for its influence on motor speed, attention, and executive functions (34). Thus, cerebellar damage may also have contributed to the cognitive decline in our medulloblastoma subgroup. Third, we did not correct for age, as we did not find any age-related increase of overall WMFA. The WMFA increases more rapidly during the first few years; in the corpus callosum, the increase occurs up to the age of 6 years, and in the center semiovale, the increase occurs up to the age of 11 years (35). The reason that we did not find age-related increases of WMFA is likely because the majority of our patients were more than 12 years of age. However, the application of DTI at a 3.0-T MRI still enabled us to detect differences at a more specific detailed level, despite the older age of our participants.

CONCLUSION

We conclude that DTI on a 3.0-T MRI is sensitive for the detection of region-specific changes in white matter integrity in pediatric cancer survivors, and that WMFA correlates with speed of processing and motor speed—both serious problems for childhood brain tumor survivors.

The impact of different doses of MTX on neurocognitive functioning should be studied more thoroughly, not only in childhood cancer survivors but also in patient groups in which MTX is a common treatment modality. Future longitudinal studies with DTI collected from the start of the treatment for different types of malignancies and treatment, integrated with neurocognitive measures, could lead to a better understanding of causative neurotoxic factors and its relations with adverse cognitive functions. This could ultimately result in a predictive model of neurotoxicity on neurocognitive outcome—leading to changes in treatment modalities or possibly white matter protection, and thereby preventing these adverse late effects.

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