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Diffusion Tensor Imaging of Deep Gray Matter in Children Treated for Brain Malignancies

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Abstract

Purpose—Previous DTI studies reported microstructural changes in white matter of patients receiving treatment for brain malignancies. The primary aim of this prospective pilot longitudinal study was to examine if DTI can detect microstructural changes in deep gray matter (as evaluated by the apparent diffusion coefficient, ADC) between pediatric patients treated with cranial radiation therapy (CRT) and typically developing healthy children. The relationship between ADC and neurobehavioral performance was also examined.

Methods—ADC was measured at 1.5T in the caudate, putamen, globus pallidus, thalamus, and hippocampus in 9 patients (mean age 11.8 years) and 9 age-matched healthy controls. The study was designed with 4 visits: baseline, 6-month, 15-month, and 27-month follow-ups.

Results—Patients had 24% higher overall mean ADC in the hippocampus compared with controls (p=0.003). Post-hoc analyses revealed significantly elevated ADC at baseline (p=0.003) and at the 27-month follow-up (p=0.006). Nevertheless, patients performed normally on a verbal memory test, considered to be a hippocampus-related function. Relative to controls, patients' performance on the tests of the visual-spatial working memory decreased over time (group by visit: p=0.036). Both patients and controls showed a decline in motor speed with increasing ADC in the globus pallidus and putamen.

Conclusions—Childhood brain malignancies and their treatment may affect gray matter microstructure as measured by water diffusion. Significant findings in the hippocampus but not other regions suggest that differences in tissue sensitivity to disease- and treatment-related injury

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among gray matter regions may exist. ADC in basal ganglia may be associated with motor performance.

Keywords

Radiation therapy; children; brain; basal ganglia; hippocampus; diffusion tensor imaging

Introduction

Long-term survival of pediatric patients with brain malignancies has markedly increased over the last two decades, due to advances in treatment with cranial radiation therapy (CRT), surgery, and chemotherapy. While survival rates have increased, so have concerns about the neurotoxic effects of these treatments on healthy brain tissue. Effects of treatments involving CRT manifest as vascular and glial pathologies and are categorized based on the time of their onset [2]. Acute reactions, which are mostly transient and responsive to medication [12], occur within 1–6 weeks after therapy [2]. Early-delayed reactions occur within 3 weeks to several months, and neurotoxic late-delayed effects of treatments typically manifest within several months to years after treatment completion [2]. More than 40% of survivors of childhood brain tumors develop cognitive deficits attributed to the tumor or the treatments [28]. A well-established, influential factor related to development of cognitive impairment is CRT, particularly if administered at younger ages and with higher doses. Tumor type, size and location, surgery, and systemic chemotherapy may also contribute to neurocognitive impairment, with potentially synergistic effects [4, 28]. Long-term neurocognitive impairment can negatively impact quality of life and socioeconomic achievement in surviving patients [6].

Development of adverse neurocognitive effects has been attributed mainly to injury of healthy white matter; however, therapies may impact all brain tissues [4]. The most commonly observed neurocognitive deficits in surviving children involve attention, memory, and processing speed [4, 6], functions influenced by circuits comprising deep gray matter structures – basal ganglia, thalamus, and hippocampus. Frontal-basal ganglia-thalamic circuits are involved in control of movement and processes leading to movements [8] and may also contribute to encoding and retrieval of declarative memories [27], functions mediated by the medial temporal lobe. Considering the relevance of deep gray matter to neurocognitive domains that are impaired by treatment, studies of deep gray matter tissue with concurrent neuropsychological evaluation may further improve our understanding of pathogenesis of neuropsychological dysfunction [28].

An earlier study reviewed patterns of abnormalities typically associated with acute, early-delayed, and late-delayed effects on brain parenchyma as detected on clinical MRI scans [2]. Advanced neuroimaging techniques may detect tissue impairment even in regions with normal appearance on conventional MRI [25]. Diffusion tensor imaging (DTI), a technique that probes tissue microstructure by measuring microscopic motion of water molecules, has been used extensively in studies of brain development and has also been applied to study treatment effects in patients diagnosed with brain malignances. In healthy developing brain, DTI revealed age-related differences in FA and mean diffusivity, parameters characterizing microstructure and directionality of white matter tracts and deep gray matter regions that function as their relay stations [13]. In pediatric medulloblastoma patients treated with surgery, chemotherapy, and CRT, DTI detected white matter impairment (low fractional anisotropy, FA) even in regions demonstrating no abnormalities on conventional MRI [10]. In patients with posterior fossa tumors, administration of adjuvant therapy lead to a more pronounced damage to white matter microstructure than treatment with surgery alone [26]. In childhood cancer survivors, white matter FA has been related to motor [1] and processing

speed [1, 23]. To date, DTI studies focused mostly on white matter, which is considered more sensitive to neurotoxic treatment effects than gray matter [2, 14]. However, in a recent pilot DTI study in children previously treated for medulloblastoma, measurements were also performed in deep gray matter nuclei [16]. Apparent diffusion coefficient (ADC) was a more sensitive parameter than FA to detect differences between patients and healthy controls in all selected white matter regions and deep nuclei (thalamus and putamen) [16]. In the study cohort, higher mean ADC was associated with lower IQ; no relationship between mean FA and IQ was detected [16].

The main goal of this pilot prospective longitudinal study was to use DTI to evaluate deep gray matter microstructure in patients receiving CRT with or without adjuvant chemotherapy early in treatment (after surgery, if performed) and 6, 15, and 27 months post-CRT. ADC in the thalamus, globus pallidus, putamen, caudate, and hippocampus was measured and concurrent neuropsychological evaluation was performed in pediatric patients diagnosed with brain malignancies (primary brain tumors and leukemia) and a control group of healthy children. We hypothesized that in patients, ADC would increase and corresponding neuropsychological performance would decline following treatment. To determine if the impairment of deep gray matter microstructure is associated with deficits in neuropsychological performance, correlation analyses between neuropsychological test scores and ADC in corresponding gray matter regions were carried out.

Methods

Table 1 shows the *demographic and clinical information* on the nine pediatric patients who received brain radiation (7 boys; mean age 11.8 ± 3.7 years, all right-handed). Over a period of 2.3 years, consecutive patients with brain malignancies who completed at least 3 MRI scans were selected. The control group consisted of 9 typically developing children (2 boys; mean age 11.2 ± 1.8 years, 5 right-handed). The study was planned to include a baseline examination (in patients, after surgery and before radiation), and 6-month, 15-month and 27-month follow-up visits (in patients, after completion of CRT). All participants were free of psychiatric disease based on assessments using the Diagnostic Interview for Children and Adolescents, 4th edition. Institutional Review Board approval and a signed written informed consent were obtained.

MRI was performed at 1.5 Tesla using the standard circularly polarized birdcage transmit-receive head coil. DTI data were acquired using a single-shot diffusion-weighted spin-echo echo-planar imaging sequence with the following parameters: TE=93.7 ms, matrix size 96×96, field-of-view 240 mm, two b=0 s/mm^2 images, maximum b=1000 s/mm^2, 15 non-collinear diffusion gradient directions, 2 acquisitions, 24 axial slices parallel to the anterior commissure - posterior commissure plane, 5 mm slice thickness, no gap; 4 min 48 s scan time. The position and orientation of the DTI slices on a mid-sagittal image was used to prescribe the follow-up examinations. Diffusion tensors were computed using DTI Studio (cmrm.med.jhmi.edu); FA and ADC were calculated. The FA maps were used to draw ROIs, which were superimposed on the ADC maps using the program “DSX” (godzilla.kennedykrieger.org). Since the diffusion of water molecules in gray matter is isotropic [18] and FA, a measure of directionally restricted diffusion of water molecules, would be difficult to interpret, only ADC was analyzed. Mean ADC was evaluated in *five regions-of-interest (ROIs)* in both hemispheres: thalamus (1), globus pallidus (2), putamen (3), caudate head (4), and hippocampal head (5). The ROIs were drawn at a corresponding level for all participants, encompassing the largest portion of the cross-sectional area, according to a template (Figure 1). This approach has been shown to have excellent inter-rater and intra-rater reproducibility [3]. The measurements were performed by a single reader, a neuroradiologist (AN) two times and the measurements were averaged. The

agreement between the two measurements was excellent (pooled data from the baseline visit, intraclass correlation coefficient=0.944). To minimize partial volume effects with the cerebrospinal fluid, all pixels with FA values less than 0.15 were eliminated from the analyses [5]. The ROIs in patients showed predominantly normal appearance on conventional MRI. T_2 abnormalities in proximity to or only partially involving an ROI were noted only in patient 2 (bilaterally in the hippocampus), patient 3 (unilaterally in the caudate), and patient 5 (bilaterally in the thalamus).

Mean radiation doses to each particular region of the brain (Table 1) were calculated using the Pinnacle software (version 9) after overlaying the ROIs with the radiation treatment plan.

Neurobehavioral assessment was designed to provide a delineation of select neuropsychological functions, using nationally standardized tests with good test-rest reliability that have been validated in the age range of interest. We emphasized assessment of memory and motor speed, considered to be most sensitive to radiation effects. *Working memory* was assessed using the Bead Memory Test (Stanford-Binet Intelligence Scale, 4th edition), a measure of visual-spatial working memory; and Auditory Working Memory (Woodcock Johnson-III), an assessment of auditory verbal memory. Working memory tests are considered to be dependent on dorsolateral prefrontal-striatal circuitry, which includes the caudate nucleus. *Verbal memory* was assessed using the Memory for Words Test (Woodcock Johnson-III), a measure of short-term auditory verbal learning and declarative memory, considered to be dependent on subcortical systems including the thalamus and the hippocampus. *Motor speed* was assessed using Purdue Pegboard. The two-hand trial was analyzed for the present study, given the group differences in handedness. Measures of motor speed are considered to be dependent on frontostriatal circuitry involving the motor circuit, which includes the putamen and globus pallidus.

To account for heterogeneity and correlations in the outcome variable (ADC) resulting from individual repeated measurements over time and in different ROIs, Linear mixed-effects models (LME) analyses were applied for *statistical evaluations*. Differences in ADC between patients and controls at the four visits were examined, controlling for age and sex. The main LME analysis included fixed effects of group, sex, age, region, hemisphere, visit and the interaction terms group × region, group × age, and group × visit. Post-hoc analyses in individual ROIs included all significant terms of the main analysis (except those involving “region”) and the interaction term group × visit. In individual ROIs, LME was also applied to examine differences in ADC among patients receiving radiation doses <20 Gy, 20–50 Gy, and >50 Gy, controlling for visit and age. Post-hoc comparisons in individual ROIs at the 4 visits were performed using GLM ANOVA controlling for age and side. LME analyses were also used to assess the difference in neurobehavioral performance between patients and controls (using raw scores of the neuropsychological tests), and among the visits, controlling for age. Main effects (group, visit) and the interaction terms group × visit, group × age were used. To evaluate the relationship between neuropsychological test scores and ADC values, LME analyses of the neuropsychological scores with the terms group, visit, ADC, group × ADC, visit × ADC, and group × visit were applied. To examine if differences exist in the relationship between the neuropsychological test scores and ADC in the left and right hemispheres, the term “hemisphere” was also included in these analyses. To account for the effect of age, standard or z-scores were used. Statistical significance for all main analyses was set to $p<0.05$ and reduced to $p<0.01$ in all post-hoc tests to account for multiple comparisons (5 regions). Data are presented as means ± standard deviations.

Results

The following number of DTI and neuropsychological (NP) datasets were obtained: at visit 1 (baseline), 8/9 (patients/controls) for both DTI and NP; at visit 2, 7/8 for DTI and 9/8 for NP; at visit 3, 7/8 for both DTI and NP; at visit 4, 8/9 for DTI and 7/9 for NP. Four patients had DTI and NP data from all visits. Data from the second visit of patient 6 could not be used because of artifacts due to braces. The NP tests were completed within 3 months of the MRI examination in each subject. Due to scheduling difficulties, in 6 patients, the baseline examination was performed before the start of radiation (Table, patients 1, 2, 3, 5, 6, 7) and in 2 patients, after the radiation treatment was completed (after 2 and 8 days (patients 4 and 8)). Patient 9 missed the baseline examination. There was no significant difference in age between the patient group and the control group at baseline (T-test: $p = 0.26$). The mean time interval between the baseline and each follow-up visit were: visit 2, 0.60/0.57 years (patients/controls); visit 3, 1.4/1.4 years; and visit 4, 2.3/2.5 years.

Mean ADC in Examined Regions-of-Interest: Group Differences

Figure 2 compares mean ADC values in patients and controls in the 5 ROIs at each of the four visits. The main LME analysis included ADC data from the 5 ROIs in both hemispheres, in all subjects and at all visits, a total of 636 observations (statistical power=0.63, correlation $\rho=0.4$). Mean ADC in patients ($0.793 \pm 0.237 \cdot 10^{-3}$ mm^2/s) was 7.6% higher than in the control group ($0.737 \pm 0.243 \cdot 10^{-3}$ mm^2/s; $p=0.01$). Mean ADC and the group differences in mean ADC varied among regions (region: $p<0.0001$; group × region: $p<0.0001$). ADC decreased with age ($p=0.004$) and a 2.8% higher mean ADC was detected in the left hemisphere than in the right hemisphere ($p=0.041$). No overall ADC differences between boys and girls (sex: $p=0.48$) and among visits ($p=0.067$) were detected.

The post-hoc analyses in individual ROIs revealed a significant difference in mean ADC between patients and controls in the *hippocampus* (region 5), with an overall 24% higher mean ADC ($1.05 \pm 0.33 \cdot 10^{-3}$ mm^2/s) in patients (group: $p=0.003$) across the visits (group × visit: $p=0.25$). The group differences remained significant ($p=0.005$) even after removing data of patient 2 who had abnormal hippocampal appearance on conventional T_2 -weighted MRI (see Methods, section MRI). At individual visits, significant group differences were detected at baseline (37% higher ADC in patients, $p=0.003$) and at the 4th visit (23% higher ADC in patients, $p=0.006$) (visit 2: $p=0.014$, visit 3: $p=0.087$) (Figure 2). In the *thalamus* (region 1), *globus pallidus* (region 2), *putamen* (region 3), and *caudate* (region 4) the post-hoc LME analyses did not reveal any significant differences between patients and controls (group: $p=0.73$, 0.21, 0.037, and 0.015, respectively).

There was no difference in the mean radiation doses among the ROIs (thalamus: 33.4 ± 17.0 Gy, globus pallidus 33.1 ± 12.3 Gy, putamen 29.8 ± 11.4 Gy, caudate 30.0 ± 10.5 Gy, hippocampus 33.5 ± 11.5 Gy), between hemispheres and between younger and older patients. No differences in ADC among patients who received radiation doses <20, 20–50, and >50 Gy were detected in any ROI ($p=0.14 – 0.75$).

Neuropsychological Performance: Differences between Patients and Controls

On the test of visual-spatial working memory (Bead Memory), the main LME analysis detected a decrease in scores in patients over time (age-adjusted mean scores: 0.20 ± 0.98 (baseline), −0.58 ± 1.36 (visit 4)) and improved performance in controls (age-adjusted mean score: −0.66 ± 1.33 (baseline), 0.20 ± 1.11 (visit 4)) (group × visit: $p=0.036$), with no overall difference in performance between groups (group: $p=0.60$). The group differences in motor speed as assessed by the Purdue Pegboard test were not significant (group: $p=0.08$; controls showed a trend to a better performance at all four visits). No significant overall differences

between patients and controls were detected in verbal working memory or verbal memory, nor were the group by visit interactions for these variables significant.

Results of LME analyses showing a significant relationship between neuropsychological performance and ADC (ADC or ADC × visit: $0.0001<p\leq0.02$), including data from all visits, are presented in Figure 3. These analyses also indicated differences between controls and patients as shown by at least one significant term including group ($0.002\leq p<0.025$). Figure 3 shows that the test scores on visual-spatial working memory (Bead Memory test), auditory working memory and motor speed (Purdue Pegboard) decreased with increasing ADC in controls. In patients, a negative relationship between motor speed performance and ADC was also detected, although at overall lower scores. The relationships between the tests of visual-spatial and auditory working memory and ADC did not follow the trends observed in controls. The overall trends and statistical significance were confirmed in additional analyses performed without inclusion of the most extreme values in patients ($0.6 \cdot 10^{-3} <ADC<0.8 \cdot 10^{-3}$ mm^2/s). No relationship between memory performance and hippocampal or thalamic ADC was detected in either group. In none of the analyses, the term "hemisphere" (indicating left-right differences) reached statistical significance, suggesting that data obtained from both hemispheres accounted for the observed correlations.

Discussion

In children with brain malignancies treated with CRT, conventional MRI showed mostly normal findings in the evaluated deep gray matter regions both at baseline and post-radiation. However, DTI detected a 24% higher overall mean ADC in the hippocampal region in patients, indicating impairment in tissue microstructure. Significantly elevated ADC was detected both at baseline and 27 months post-CRT. In another DTI study evaluating long-term treatment effects (more than 1 year after therapy) in medulloblastoma and pilocytic astrocytoma patients, widespread decreases of FA were detected in both patient groups compared with controls. The abnormalities were less pronounced in the patients with pilocytic astrocytoma, who did not receive chemotherapy and CRT while the medulloblastoma patients did [26]. Our results thus complement this and other previous DTI studies of white matter [1, 23] by detecting tissue injury in the gray matter, and at an early stage of the treatment process. The data also suggest that combined adverse effects of the disease, initial treatment with surgery, and subsequent chemotherapy and CRT may have contributed to gray matter injury. This explanation is supported by our related volumetric MRI study, reporting reduced regional cerebellar volumes at a baseline visit and at similar time points relative to CRT [9]. Elevated ADC in the hippocampus in the current study was not accompanied by concurrent impairment on memory performance in the studied patient group. However, in both patients and controls, performance on the Purdue Pegboard declined with increasing ADC in the globus pallidus and putamen, suggesting a relationship between motor function and microstructure of corresponding regions of the basal ganglia.

Of the deep gray matter regions examined, ADC differences between patients and controls were observed only in the hippocampus. In an earlier longitudinal study on medulloblastoma patients, a decline in hippocampal volume was observed over the first 2 years post treatment, followed by volume increase. The pattern of volume changes was different from growth pattern previously reported in healthy children and could not be accounted for by tissue atrophy [19]. Since CRT can cause profound inhibition of hippocampal neurogenesis [17], our data may be of interest for future studies on short- and long-term effects of CRT on the hippocampal region and associated cognitive functions. Data from a larger group of pediatric patients (N=19) including those examined in this study showed that higher radiation doses to the hippocampus or the temporal lobes have a more pronounced effect on

neurocognitive decline than irradiation of the subventricular zone, which also contains neural progenitor cells [24].

DTI is a sensitive technique for studying brain development and maturation. In normal developing deep gray matter, mean diffusivity of water decreases with age. The age-related decreases in diffusivity are most pronounced until 2 years of age with a more gradual decrease thereafter [18]. Development of gray matter microstructure as detected by DTI continues until 24 years of age or later [13]. As the age-related decreases in water diffusivity in gray matter are related to decrease in water content and increase in macromolecular concentrations [18], elevated hippocampal ADC values in our patients compared with age-matched healthy controls may suggest disruption of these processes.

A previous cross-sectional study reported elevated ADC in the thalamus (by 53%) and the putamen (by 42%) in 8 children treated with cranio-spinal radiation for medulloblastoma, examined at a mean time of 2.5 years post-diagnosis [16]. In our longitudinal study, no group differences were detected in the thalamus and the putamen. This discrepancy may be explained by differences between the patient groups and by controlling for CSF (to account for potential reductions in tissue volume) in our study. Additionally, differences in radiation doses and treatment plans have to be considered. Our study included patients with both lower (<23.4 Gy) and higher doses (>36 Gy) to the thalamus than the medulloblastoma patients examined previously [16].

The findings of significant negative associations between the performance on tests of working memory and motor speed and deep gray matter ADC in healthy children are in agreement with previous MRI-based studies on functional networks involving the frontal, prefrontal, and striatal regions in the developing brain [11, 20, 21]. A similar trend of decreasing test scores with increasing ADC was also observed in patients on the test of motor speed but not on the tests of working memory, possibly suggesting disruption of the pathways linking the cortical regions with the striatum. None of the analyses on the relationship between subcortical ADC values and verbal memory, including analyses performed in controls only, provided significant results. However, in studies of adults, a significant correlation between hippocampal diffusivity and verbal memory function was reported in patients with small vessel disease [29], temporal lobe epilepsy [15], MCI, and early Alzheimer's disease [7]. In patients with small vessel disease, the relationship between hippocampal diffusivity and verbal memory performance was highly significant particularly in the subgroup of patients who had normal hippocampal volumes, suggesting that ADC may be an early marker of underlying neurodegenerative disease [29]. In the future, it may be interesting to examine if abnormal hippocampal ADC detected early in the course of treatment for brain malignancies would predict memory deficits at longer intervals from treatment completion.

While the limitation of this pilot study to a small number of patients with brain malignancies has to be acknowledged, longitudinal design and data sampling in multiple regions in both hemispheres provided a large number of ADC data. However, a larger group of patients (receiving a wide range of radiation doses) examined at a longer follow-up would be needed to study the effects of radiation doses on deep gray matter nuclei ADC in detail. Although the patient group included more males, no consistent differences in mean diffusivity in deep gray matter nuclei between males and females were reported recently [22].

Summary

Presence of brain malignancies and their treatment may lead to disruption of gray matter microstructure. The most interesting finding in our study was the detection of abnormal ADC in the hippocampal region, early in therapy. The study results suggest that a)

differences in tissue sensitivity to disease- and treatment-related impairment among deep gray matter regions may exist and b) tissue microstructure of deep gray matter nuclei, as measured with DTI, may be associated with neuropsychological performance (motor function).

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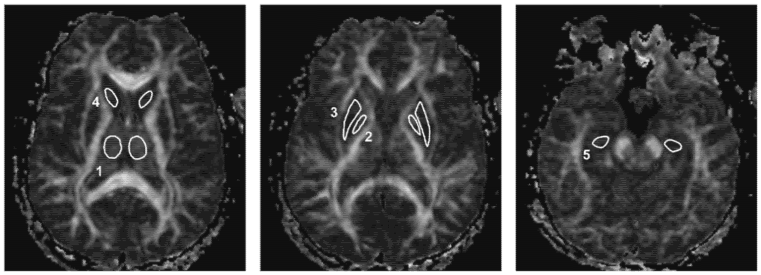

Figure 1.
Five regions of interest drawn on the FA map of a 12 year-old healthy control. Regions 1 (thalamus) and 4 (caudate head) are shown on the left image, regions 2 (globus pallidus) and 3 (putamen) are shown on the center image, and region 5 (hippocampal head) is shown on the right image.

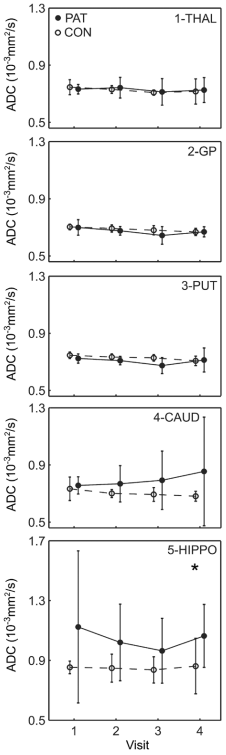

Figure 2.

Comparison of mean ADC values in the thalamus (THAL), globus pallidus (GP), putamen (PUT), caudate (CAUD), and hippocampus (HIPPO) between patients and healthy controls at the four visits. The error bars represent standard deviations. Significant group differences between patients and healthy children (hippocampus, main LME analysis: $p<0.01$) are marked by an asterisk.

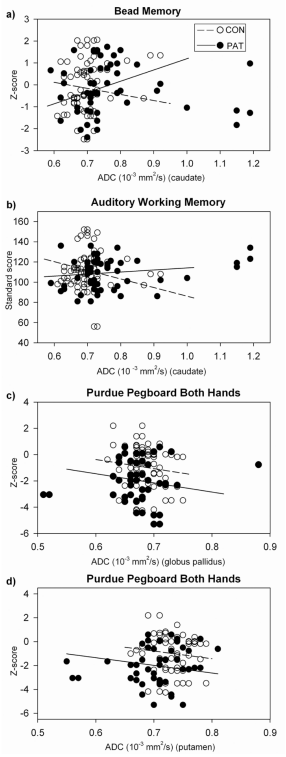

Figure 3.

Relationship between neuropsychological performance and ADC in subcortical gray matter. Data from all subjects at all visits are presented in the figure. The regression lines represent changes in neuropsychological test scores with ADC averaged across the four visits in patients and controls. The regression lines were calculated from all significant factors that comprised the final models of the respective LME analyses comparing both groups. Compared with least squares regression lines, LME regression lines take into account the variability of the data. In all LME analyses, the p values including the factor “ADC” or the interaction “ADC” by “visit” were ≤0.02. In controls, neuropsychological performance on working memory (a, b) and motor (c, d) tests improved with decreasing ADC. In patients, motor performance decreased with increasing ADC in the globus pallidus (c) and putamen (d), although at overall reduced scores. For the tests on working memory (a, b), the relationship between the test scores and ADC did not follow the trends observed in controls. We note that the calculations of the regression lines for patients in (a) and (b) included only data for ADC<1.1 $\cdot 10^{-3}$ mm^2/s; the outliers are still shown in the Figure.

Table 1

Clinical information on patients and radiation doses to the regions of interest

					Treatment Prior to CRT (Time of Administration before CRT, *months*)			Radiation Dose *(Gy)*				
	Sex	**Age *years***	**Diagnosis**	**Tumor Location**	**Surgery**	**Chemotherapy**	**Steroids**	**THAL**	**GP**	**PUT**	**CAUD**	**HIPPO**
1	M	10.2	T-cell acute lymphocytic leukemia	No CNS tumor (mediastinal mass)	No	T-cell induction chemotherapy (1.1)	Pred (0.7)	18.6	18.6	18.7	18.6	18.7
2	M	15.3	Recurrent ependymoma	Left temporal; (original tumor: lower spine)	Yes (0.9)	No	Dexa (0.8)	44.5	47.3	47.4	45.1	47.7
3	M	11.8	Malignant glioneural tumor, otherwise unclassifiable	Left frontal	Yes (5.7)	No	No	53.6	50.8	48.6	50.5	46.2
4	F	18.6	Germinoma	Suprasellar	Yes (4.1)	CsPt/VP-16/CTX/VCR (3.1)	HC (3.7)	23.1	25.7	24.8	27.0	23.7
5	M	11.8	Undiagnosed pineal mass	Pineal region	No (VP shunt, open biopsy)	No	No	54.3	44.6	29.5	26.3	20.3
6	M	11.6	Craniopharyngioma	Suprasellar	Yes (5.1)	No	Pred (4)	11.6	31.0	27.6	25.4	40.0
7	M	5.5	Pilocytic astrocytoma	Right frontal suprasellar/optic	Yes (42.7)	CaPt (35.0), TMZ (16.5)	No	12.8	16.7	15.4	26.7	*
8	F	8.7	Medulloblastoma	Posterior fossa	Yes (1.1)	No	Dexa (0.8)	42.4	34.7	29.8	25.3	32.4
9	M	12.7	Medulloblastoma	Posterior fossa	Yes (0.8)	No	Dexa (0.7)	40.0	28.2	26.5	24.7	39.3

Notes:

Abbreviations: THAL – thalamus, GP – globus pallidus, PUT – putamen, CAUD – caudate head, HIPPO – hippocampus; CaPt – Carboplatin, CsPt – Cisplatin, CTX – Cytosan, Dexa – Dexamethasone, HC – Hydrocortisone, Pred – Prednisone, VCR – Viscristine, TMZ – Temozolomide, VP -16 – Etoposide.

* The radiation dose to the hippocampal head in the patient no. 7 could not be measured (due to a surgical resection on one side and severe compression by the tumor on the contralateral side). Age at the baseline visit (patient 9, end of CRT) is reported.

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