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Prognostic Factors that Increase the Risk for Reduced White Matter Volumes and Deficits in Attention and Learning for Survivors of Childhood Cancers

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Abstract

OBJECTIVE—In children, CNS-directed cancer therapy is thought to result in decreased cerebral white matter volumes (WMV) and subsequent neurocognitive deficits. This study was designed as a prospective validation of the purported reduction in WMV, associated influential factors, and its relationship to neurocognitive deficits in a very large cohort of both acute lymphoblastic leukemia (ALL) and malignant brain tumors (BT) survivors in comparison to an age similar cohort of healthy sibling controls.

PROCEDURES—The effects of host characteristics and CNS treatment intensity on WMV were investigated in 383 childhood cancer survivors (199 ALL, 184 BT) at least 12 months post-completion of therapy and 67 healthy siblings that served as a control group. T-tests and multiple variable linear models were used to assess cross-sectional WMV and its relation with neurocognitive function.

RESULTS—BT survivors had lower WMV than ALL survivors, who had less than the control group. Increased CNS treatment intensity, younger age at treatment, and greater time since treatment were significantly associated with lower WMV. Additionally, cancer survivors did not perform as well as the control group on neurocognitive measures of intelligence, attention, and academic achievement. Reduced WMV had a larger impact on estimated IQ among females and children treated at a younger age.

CONCLUSIONS—Survivors of childhood cancer that have undergone higher intensity therapy at a younger age have significantly less WMV than their peers and this difference increases with

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time since therapy. Decreased WMV is associated with significantly lower scores in intelligence, attention, and academic performance in survivors.

Keywords

Childhood ALL; Malignant Primary Brain Tumors; Cancer Survivors; Magnetic Resonance Imaging; Neuropsychology; Computer-Assisted Image Analysis

INTRODUCTION

Among the most common childhood cancers, leukemia/lymphoma and CNS tumors account for the majority of new cases. In the United States, acute lymphoblastic leukemia (ALL), the most common malignancy of childhood and adolescence, accounts for two-thirds of childhood cancers diagnosed annually [1]. Recent studies have found the 5-year event-free survival rate to be as high as 94% [2]. Brain tumors (BT) are the second most frequently diagnosed childhood malignancy and the most common pediatric solid tumor [3]. Medulloblastoma is the most common malignant BT with 5-year event-free survival rates of 83% for average-risk and up to 70% for high-risk disease [4, 5]. Progress in cure rates has allowed for a shift of focus towards the management of the long-term effects of disease and treatment to improve quality of life for survivors. Over two-thirds of the survivors experience treatment-related consequences such as developing secondary malignancies or neurocognitive deficits [6, 7].

Neurocognitive deficits are among the most common sequelae observed in childhood cancer survivors receiving CNS-directed therapy. Risk factors associated with neurocognitive decline most reliably include younger age at treatment, longer time since treatment, and treatment intensity. Younger age at treatment and intensity of CNS therapy have been associated with worse neurocognitive outcomes in both childhood ALL [8, 9] and BT [10], most likely resulting from greater vulnerability of the developing brain to neurotoxic agents [11] with or without irradiation [12-14]. Investigations in both ALL and BT survivors have begun to identify specific areas of neurocognitive impairment including attention, working memory and processing efficiency that may be more sensitive to central nervous system-directed therapy and more proximal contributors to global declines in IQ and academic achievement [15-17]. These core deficits may be amplified by increased intensity of CNS-directed therapy, younger age at treatment, or greater time from completion of therapy [18].

White matter volume (WMV) changes provide a context for understanding factors that place children at greatest risk for neurocognitive impairment. Radiation therapy is a primary component of treatment for childhood BTs and is a well-established cause of change in WMV [19] associated with neurocognitive declines [20-23]. As many as 80% of patients treated for ALL without irradiation may develop chronic or transient leukoencephalopathy [24, 25]. Adverse effects of younger age at treatment may be due to toxic effects of therapy on newly synthesized myelin which is more metabolically active and less stable [26, 27].

While studies have reported decreased WMV in childhood cancer survivors and associated these reduced volumes with neurocognitive deficits, most are based on relatively small samples of patients, often with a retrospective design and seldom with a control cohort

[20-23]. This current study was designed as a prospective validation of the purported reduction in WMV, associated influential factors, and its relationship to neurocognitive deficits in a very large cohort of both ALL and malignant BT survivors in comparison to an age similar cohort of healthy sibling controls. A quantitative objective measure of brain parenchyma was evaluated across a transverse volume of interest at the level of the basal ganglia combined with a consistent neurocognitive testing battery which evaluated intellect, attention, and academic achievement. Survivors were hypothesized to be at greater risk for abnormally low WMVs because of higher CNS treatment intensity, female sex, younger age at treatment, and greater time since treatment. Additionally, lower WMV was hypothesized to correspond to more severe deficits in IQ, attention, and learning measures.

MATERIALS AND METHODS

Patients

Data for this study were collected during the screening phase of a multi-institutional trial of learning impairments among survivors of childhood cancer with a methylphenidate intervention (NCT00576472). No significant differences were found between the participating institutions; therefore, data was collapsed across the sites and analyzed together. Data collection occurred between January of 2000 and February of 2009. Study participants were at least 12 months post-completion of anti-neoplastic therapies for either ALL or a malignant BT, between 6 and 18 years of age, enrolled in school, and spoke English as their primary language. Subjects were required to be at least 6 years of age in order to ensure consistent neurocognitive testing with a single battery. In order to participate in the Institutional Review Board-approved protocol, written informed consent was obtained from the patient, the parent or guardian [28].

This cross-sectional study reports on 450 subjects: 67 healthy sibling controls (33 males, 34 females) and 383 cancer survivors who completed a single MRI examination and neurocognitive evaluation within three 3 month window as part of the screening assessment to determine eligibility for the intervention in the clinical trial. Survivors were categorized based on their diagnosis of ALL (112 males, 87 females) or malignant BT (101 males, 83 females). CNS therapy was categorized into four levels based on well-established increasing levels of neurocognitive impairment in children associated with the addition of cranial irradiation and the even greater impairments associated with dose levels greater than 24 Gy: no CNS therapy (sibling control group), mildly intense CNS therapy (systemic and/or intrathecal chemotherapy only), moderately intense CNS therapy (≤ 24 Gy CRT with or without systemic and/or intrathecal chemotherapy), and high intensity CNS therapy (> 24 Gy CRT with or without systemic and/or intrathecal chemotherapy) (Table 1).

Neurocognitive Assessments

Abbreviated Wechsler Intelligence Scale—The Wechsler Intelligence Scale for Children-Third Edition (WISC-III) [29] was used for children between the ages of 6 and 16, and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) [30] was used for those 17 and older. For this study, participants were given an abbreviated battery of subtests that

included Information, Similarities, and Block Design components resulting in an estimated IQ (EIQ) that was adjusted for age [22, 31].

Conner's Continuous Performance Test—The Conners' Continuous Performance Test (CPT) [32] is a computer-administered test that measures sustained and selective attention, reaction time, and impulsivity. Scores for omission errors (failing to respond to targets- inattention), commission errors (responding to nontargetsimpulsivity), reaction time (processing speed), reaction time variability, d' (attentiveness or vigilance), β (risk taking) and a CPT Index (weighted sum of all indices) were collected. Beta was bi-directionally scored with higher scores indicative of overly cautious responding while lower scores indicate impulsivity. This study focused on higher scores being indicative of worse performance and corresponding to increased rates of omissions, inattentiveness, and less risk-taking which represented a more conservative approach to decisions and was associated with slower processing speed.

Wechsler Individual Achievement Test—The Wechsler Individual Achievement Test (WIAT-I) [33] is a standardized test of academic achievement that is administered individually. A Reading Composite (composed of Basic Reading and Reading Comprehension subtests), a Mathematics Composite (composed of Mathematics Reasoning and Numerical Operations subtests), and Spelling measures were examined.

MR Imaging

MRI evaluations were performed on a 1.5-T Symphony (Siemens Medical Systems, Iselin, NJ) whole-body imager. Oblique transverse T1-weighted, T2-weighted, and proton-density-weighted images were obtained as 5 mm-thick slices with a 1 mm gap. Participants underwent MRI examination at screening before any intervention. MR examinations of patients were incorporated into their routine annual follow-ups.

Quantitative MR Volumetrics

A representative five slice volume (3 cm-thick) at the level of the basal ganglia including the genu and splenium of the corpus callosum, the putamen, and lateral ventricles, was selected for the volumetric studies [34-36]. All MRI sets within an individual examination were registered, intensity inhomogeneity corrected [37], and tissues were segmented using an automated hybrid neural network segmentation and classification method [38]. Considerable reliability and validity have been established for these methods, resulting in a predicted variance of approximately two percent in the repeated measure of white and gray matter [38].

Statistical Analyses

Neurocognitive evaluations of intelligence, attention, and academic achievement were contrasted with normative test averages. Performance for both patient groups and the healthy sibling control group were compared with two-sided *t* tests, as were volumetric measures. A Chi-squared test was used to test for sex distribution differences between the groups. Multiple variable linear models, able to account for unequal sample sizes when needed, were used to assess the effects of host characteristics and CNS treatment intensity on WMV; and

subsequently the effects of WMV on measures of neurocognitive performance. Effect sizes for influential variables identified in the linear models were evaluated using the Cohen's F statistic. Due to the heterogeneity of the sample cohort and the design and objectives of this study within the large prospective interventional trial, all patient data available were used in generating the models as a discovery phase result and should be followed by a separate validation study with an independent sample. All statistical tests were performed using SAS version 9.3. The level of significance (α) was 0.05.

RESULTS

Volumetric Assessment

Volumetric measures of white matter, gray matter, and CSF were assessed for both the patient and control populations (Table 2). WMV was significantly reduced in patients compared to controls with a corresponding significant increase in CSF volume. Head size, as assessed by ICV, was slightly smaller in patients than controls but was not significant. Additional evaluations of WMV as a function of sex, diagnosis, and CNS TX intensity were conducted to further characterize these differences (Table 3). Males phenotypically have a larger head size and subsequently did display significantly greater WMV than females. While the control group was recruited with a balanced sex distribution for each age range, the ALL and BT survivors had similar sex distributions with slightly more males than females (1.29 and 1.22, respectively). Further Chi-squared testing of the sex distributions between all three groups revealed no significant differences (P=0.60). Given the lack of significant differences, statistical analyses of WMV were not controlled for ICV or sex.

Analysis of the groups by diagnosis revealed that BT survivors had significantly less WMV than ALL survivors, who had significantly less than the control group (P<0.001). Most ALL patients (82%) received mildly intense CNS therapy with only high-risk subjects receiving moderately intense CNS therapy. Almost all BT patients (94%) received high intensity CNS therapy. To eliminate the confounding influence of diagnosis within the intensity groups, we restricted the sample of ALL survivors to those that had undergone mild intensity treatment only and BT survivors to those that had undergone high intensity treatment only. While this effectively eliminated the moderate intensity group, no significant differences in WMV between moderate and high intensity treatment levels were detected and no further analyses of this group were performed. All subsequent reference to BT or ALL survivors refer to this new modified grouping. While BT and ALL survivors both received chemotherapy, the BT survivors also received irradiation, surgery, and potentially had experienced hydrocephalus. The difference between the two groups of survivors was more than simply with or without irradiation since the groups differed in both diagnosis, with its associated complications, and treatment intensity. With this modified grouping, BT survivors had significantly less WMV than ALL survivors, who had significantly less than the control group.

Analysis of the effects of age at treatment, and time since treatment on WMVs was then conducted using multiple variable linear models. Separate models were created for the high intensity BT group and the mild intensity ALL group (Figure 1). Each model generates a 3D-plane which relates the independent variable of WMV (represented by the color bans in the figures) with the two significant (P < 0.03) dependent variables of age at treatment and

time since treatment shown on the two axes. The equations for the models are shown in Equations 1 and 2. The effect size from the Cohen F tests were 0.26 for age at treatment and 0.32 for time since treatment in the ALL survivors, and 0.26 for age at treatment and 0.15 for time since treatment in the BT survivors. Age at treatment for the ALL survivors was younger than the average age for the BT survivors. ALL survivors were also slightly further out from therapy compared to the BT survivors.

$$WMV\,(\mathrm{ALL-mild}) = 105.46 + 3.43^{*}\mathrm{age\_at\_TX} + 3.75^{*}\mathrm{time\_since\_TX} \quad (1)$$

$$WMV\,(\mathrm{BT-high}) = 108.72 + 1.53^{*}\mathrm{age\_at\_TX} + 1.53^{*}\mathrm{time\_since\_TX} \quad (2)$$

High intensity CNS treatment had a larger adverse effect on WMVs than did mild intensity therapy. Earlier age at treatment also had a significant adverse impact on WMV. However, longer time since therapy corresponded to larger WMV demonstrating continued maturation but at a much slower rate in the high intensity therapy group. The model showed that BT patients cannot reach the same WMV over the same number of years as their counterparts treated for ALL. In addition to the difference in potential WMVs, at the end of treatment, an ALL survivor's rate of WMV increase with time since treatment was higher, resulting in a greater divergence over time which appears to approach the control values.

Neurocognitive Performance

Neurocognitive evaluation of intellect, attention, and academic achievement were analyzed for patients and controls (Table 4). Of the 338 survivors in the modified grouping, 321 (154 ALL, 167 BT) and all 67 controls were assessed for neurocognitive function. Neurocognitive measures were presented in a random order based on clinical availability of measures, child's schedule, and building rapport to minimize any practice or fatigue affects across the groups. EIQ was significantly lower in ALL survivors and even lower in BT survivors. Of the attention measures assessed with the CPT, both patient groups demonstrated significant decreases in risk taking, significantly slower hit reaction times, and increasing variance in hit reaction times. For hit reaction times, ALL survivors were slower than controls and BT survivors even slower. Reaction time variance increased from control to ALL survivor to BT survivor. The two groups of survivors demonstrated similar significant decreases in risk taking. The BT survivors performed significantly worse on reading, spelling and math compared to controls.

Pearson correlation analysis of the relationship between WMV and neurocognitive measures first demonstrated that decreased WMV volume was significantly correlated ($P < 0.05$) with worse performance on all measures except the CPT measure of commissions. To further characterize this relationship, the effects of sex, age at treatment, and time since treatment on WMVs were then conducted using multiple variable linear models. Smaller WMV in female survivors corresponded to lower IQs than male survivors with comparable amounts of WMV. The linear model is shown below for sex equal to 1 for males and 0 for females.

$$IQ = 64.4 + 18.6^{*}\mathrm{sex} + 0.2^{*}WMV - 0.1^{*}\mathrm{sex}^{*}WMV \quad (3)$$

A younger age at treatment corresponded to smaller WMV and the linear model shown below illustrated that reduced WMV had a larger impact on the IQ of children treated at a younger age. As age at treatment increased, the influence of WMV decreased.

$$IQ = 59.1 + 3.4^{*}\text{age\_at\_}TX + 0.2^{*}WMV - 0.01^{*}\text{age\_at\_}TX^{*}WMV \quad (4)$$

Combined effects of age at treatment and smaller WMV were also predictive of academic performance measures of reading and mathematics which have been shown to be significantly lower in this cohort of survivors.

$$\text{Reading} = 60.2 + 3.2^{*}\text{age\_at\_}TX + 0.2^{*}WMV - 0.02^{*}\text{age\_at\_}TX^{*}WMV \quad (5)$$

$$\text{Math} = 47.9 + 3.5^{*}\text{age\_at\_}TX + 0.3^{*}WMV - 0.02^{*}\text{age\_at\_}TX^{*}WMV \quad (6)$$

Combined effects of time since treatment and smaller WMVs were not significantly predictive of any of the neurocognitive measures.

DISUSSION

Childhood cancer survivors of ALL and malignant BTs that received chemotherapy with or without irradiation demonstrate significant declines in WMV; these declines are directly associated with neurocognitive performance including both global neurocognitive declines on measures of intellectual functioning and academic skills as well as underlying deficits in specific areas of attention. Patients that received chemotherapy alone had significantly less WMV than age similar healthy sibling controls but significantly greater WMV than patients whose treatment also included CNS-targeted irradiation. Moreover, a reduced amount of WMV corresponded to larger deficits in attention, intelligence, and academic achievement. These strong associations observed between the quantitative WMV and the neurocognitive performance measurements suggest that WMV may represent a sensitive measure of neurotoxicity.

In both groups of cancer survivors, the current outcome demonstrated statistically significant slowing of hit reaction time which was consistent with previous findings by Paakko et al. [26] Hit reaction time reflects the respondent's speed of reacting to an object. Slowed ability to react to an object may suggest that cancer survivors have deficits in efficiently conveying information, especially between lobes. This hypothesis is supported further by the strong correlation between WMV and risk-taking measures. The decreased WMV development quantified in these survivors suggests that even subtle WMV changes that are very difficult to recognize by visual inspection can lead to notable differences in neurocognitive behaviors.

The addition of cranial irradiation played a significant role in treatment-related changes in WMV and neurocognitive performance. Both WMV and academic achievement measures were higher in ALL survivors relative to BT survivors. This leads us to believe that patients who received chemotherapy alone sustained less damage, and therefore had less loss of WMV.

The mechanisms of neurotoxicity from cancer treatment remain unclear. There are two factors that may contribute to atypical WMV development in these survivors. The first is damage to oligodendroglia cells and the second is damage to vascular structures. Iron contained in oligodendrocytes plays an important role in myelogenesis and the maintenance of the myelin sheath [39], and T2 relaxation times vary as a function of iron concentration [40]. Therefore, the atypical WMV development observed in the current study may have been the result of demyelination caused by damage to oligodendroglia cells [41].

There were some limitations to the results and conclusions of the current study. Quantitative assessments of WMV were conducted across a limited volume to assess total tissue volumes in a specific anatomical area. This approach is highly reproducible but may be relatively insensitive to regional changes, which may have a more dramatic impact on specific neurocognitive tasks. Another limitation of the study was the cross-sectional design, which does not yield information on the temporal evaluation of deficits in either WMV development or neurocognitive performance. The model equations listed were based on cross-sectional data and should be used with caution when applied to longitudinal trajectories of an individual subject. However, the focus of this study was to prospectively demonstrate first that survivors of ALL and malignant brain tumors are at risk for abnormally low WMV because of CNS treatment intensity and host characteristics, and secondly to establish that survivors with lower WMV have more severe problems with attention and learning. Future longitudinal studies should also include additional advanced imaging sequences such as diffusion tensor imaging (DTI) to quantify changes in the integrity of the white matter as a possible precursor to the more macroscopic changes in volume.

It would have been desirable to have included DTI in the current study given the findings demonstrating decreased reaction time and increased reaction time variance implicating an impairment of information transfer but DTI was not a routine part of MRI follow-up for cancer survivors at our institution when this clinical trial opened. However, other smaller studies have more recently demonstrated decreased fractional anisotropy (FA) compared to age matched peers associated with younger age at diagnosis, higher irradiation dose, decreased IQ, and speed of neurocognitive processing in patients treated for ALL and BT [42-44].

In summary, the current results confirm the hypothesis that childhood survivors of ALL and malignant BTs treated with or without cranial irradiation have significantly decreased WMV, which were associated directly with lower scores in intelligence, attention, and academic performance. Patients receiving higher intensity therapy at a younger age had significantly less WMV than their peers and this difference increased with time since therapy. Furthermore, both groups of cancer survivors demonstrated statistically significant slowing of hit reaction time which may suggest that cancer survivors have deficits in conveying information, especially between lobes.

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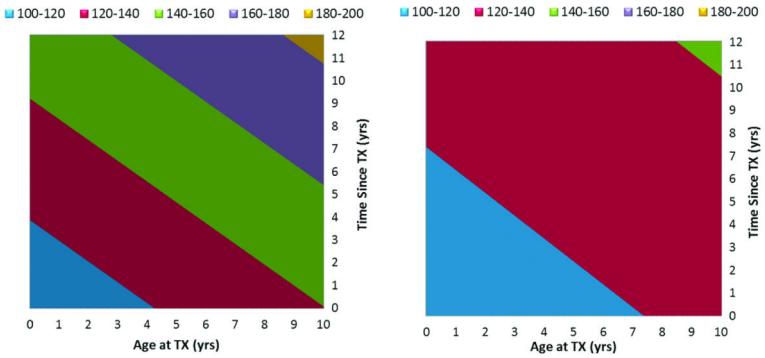

Figure 1.

Table 1

Demographics of gender, diagnosis, and treatment intensity for all 450 subjects.

	N
Gender	
Male	246 (55%)
Female	204 (45%)
Diagnosis [a]	
ALL	199 (44%)
BT	184 (41%)
Control	67 (15%)
Treatment Intensity	
Control	67 (15%)
Mild	173 (38%)
Moderate	34 (8%)
High	176 (39%)

[a] Patient groups include acute lymphoblastic leukemia (ALL), brain tumor (BT), and age-similar healthy sibling controls.

Table 2

Descriptive statistics and comparisons between patients and controls.

	Patients (N=383) Mean ± SD	Controls (N=67) Mean ± SD
Age at treatment (years) [a]		
ALL	4.7 ± 2.7	-
BT	6.5 ± 3.6	-
Time since treatment (years)		
ALL	5.4 ± 3.0	-
BT	4.7 ± 2.3	-
Age at MRI (years)	12.4 ± 3.3	11.9 ± 3.4
Tissue Volumes (cc) [b]		
WMV **	132.8 ± 27.8	151.8 ± 20.0
GMV	320.4 ± 31.6	318.4 ± 24.4
CSF **	35.7 ± 15.9	26.4 ± 5.4
ICV	492.4 ± 44.9	500.3 ± 35.6

[a] All values are presented as mean ± standard deviation. Patient groups included survivors of acute lymphoblastic leukemia (ALL) or brain tumor (BT). Significant differences between patients and controls were identified through independent sample Student's T-tests (note: significant *P*-values are noted by

* $P \leq 0.05$ and

** $P \leq 0.01$).

[b] Tissue volumes included white matter volume (WMV), gray matter volume (GMV), cerebrospinal fluid (CSF), and intracranial volume (ICV).

Table 3

White matter volumes by gender, diagnosis, and treatment intensity.

	N	Mean ± SD [a]	*P*-value [b]
Gender			
Male	246	140.8 ± 30.8	
Female	204	129.4 ± 21.8	<0.001
Diagnosis [c]			
Control	67	151.8 ± 20.0	
ALL	199	138.8 ± 32.2	<0.001
BT	184	126.3 ± 20.3	<0.001
Treatment Intensity			
Control	67	151.8 ± 20.0	
Mild	173	141.6 ± 32.6	0.004
Moderate	34	125.8 ± 24.7	<0.001
High	176	125.6 ± 19.9	<0.001
Modified Treatment Intensity Groups			
Control	67	151.8 ± 20.0	
ALL – Mild	164	141.8 ± 32.8	0.006
BT – High	174	125.9 ± 19.8	<0.001

[a] All values are presented as mean ± standard deviation (SD).

[b] *P*-value indicates significant differences in gender relative to male and between patient groups relative to controls identified through independent sample Student's T-tests.

[c] Patient groups included survivors of acute lymphoblastic leukemia (ALL) or brain tumor (BT), and age-similar healthy sibling controls.

Table 4

Neurocognitive measures of patients and sibling controls compared between groups and correlated with white matter volumes.

	Control (N=67)	ALL (N=154)	Brain Tumor (N=167)	Pearson's Correlations[a]
WISC III [b]				
Estimated IQ (SS)	103.6 ± 19.4	97.6 ± 17.1*	93.7 ± 18.5**	0.20**
WIAT				
Reading Composite (SS)	100.6 ± 17.2	98.4 ± 14.7	91.0 ± 17.9**	0.16**
Spelling Composite (SS)	99.7 ± 16.8	98.7 ± 14.2	91.8 ± 16.3**	0.12*
Math Composite (SS)	101.3 ± 16.6	97.6 ± 16.5	90.0 ± 19.1**	0.24**
CPT				
Omissions (percentile)	78.3 ± 23.0	84.1 ± 19.9	83.0 ± 23.0	−0.18**
Commissions (T-score)	51.5 ± 10.7	49.4 ± 10.2	49.9 ± 10.5	−0.00
Hit Reaction Time (T-score)	51.3 ± 14.0	46.5 ± 12.5**	43.5 ± 14.8**	0.15**
Reaction Time Variability (T-score)	54.6 ± 10.8	56.8 ± 12.8	59.2 ± 12.5**	−0.19**
Attentiveness (T-score)	57.5 ± 9.4	58.1 ± 10.7	59.0 ± 10.6	−0.19**
Risk Taking (T-score)	65.6 ± 16.8	73.9 ± 20.8**	73.7 ± 20.3**	−0.18**
CPT Index [c]	8.1 ± 6.4	7.8 ± 6.5	8.9 ± 6.5	−0.11*

[a] Pearson's correlation coefficients are listed for correlations between neurocognitive measures and white matter volume across all patients and controls combined.

[b] Neurocognitive evaluations included the Wechsler Intelligence Scale for Children (WISC III - third edition), Wechsler Individual Achievement Test (WIAT), and the Conners' Continuous Performance Test (CPT). Scores on the neurocognitive tests were reported as either standard scores (SS) with a mean of 100 ± 15 or as a T-score with a mean of 50 ± 10. Higher scores indicated better performance for WISCIII and WIAT measures but higher scores are generally worse for CPT measures with the exceptions of Risk Taking and Hit Reaction Time. All values are presented as mean ± standard deviation. Significant differences between patients and controls were identified through independent sample Student's T-tests (note: significant *P*-values are noted by

* $P \leq 0.05$ and

** $P \leq 0.01$).

[c] The CPT index score is an overall composite score where a score < 8 is normal, 8-11 is borderline, and > 11 is considered impaired.