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# Smaller White-Matter Volumes Are Associated with Larger Deficits in Attention and Learning among Long-Term Survivors of Acute Lymphoblastic Leukemia

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## Abstract

**BACKGROUND—**The primary objective of this study was to test the hypothesis that survivors of childhood acute lymphoblastic leukemia (ALL) have deficits in neurocognitive performance, and smaller white-matter volumes are associated with these deficits.

**METHODS—**The patients studied included 112 ALL survivors (84 patients who had received chemotherapy only, 28 patients who had received chemotherapy and irradiation; 63 males, 49 females; mean age ± standard deviation, 4.1 yrs ± 2.6 yrs at diagnosis; mean ± standard deviation yrs since diagnosis, 6.0 ± 3.5 yrs), and 33 healthy siblings who participated as a control group. Neurocognitive tests of attention, intelligence, and academic achievement were performed; and magnetic resonance images were obtained and subsequently were segmented to yield tissue volume measurements. Comparisons of neurocognitive measures and tissue volumes between groups were performed, and the correlations between volumes and neurocognitive performance measures were assessed.

**RESULTS—**Most performance measures demonstrated statistically significant differences from the normative test scores, but only attention measures exceeded 1.0 standard deviation from normal.

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Patients who had received chemotherapy alone had significantly larger volumes of white matter than patients who had received treatment that also included cranial irradiation, but their volumes remained significantly smaller than the volumes in the control group. Smaller white-matter volumes were associated significantly with larger deficits in attention, intelligence, and academic achievement.

**CONCLUSIONS—**Survivors of childhood ALL had significant deficits in attention and smaller white-matter volumes that were associated directly with impaired neurocognitive performance. Cranial irradiation exacerbated these deficits.

## Keywords

acute lymphoblastic leukemia; magnetic resonance imaging; image analysis; neuropsychology; neurotoxicity; attention

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With improved treatment outcomes in children with cancer, current emphasis is placed on the survivor's quality of life, including neurocognitive function. Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, affecting 2400 children annually in the United States. The 5-year event-free survival estimate for pediatric patients with ALL is approximately 80%.[1] Children who survive treatment for ALL have an increased incidence of neurocognitive impairments compared with their healthy peers.[2,3] Historically, these impairments have been characterized by declining intellectual quotient (IQ) and academic achievement test scores. However, less impairment was observed in patients who received chemotherapy only.[4,5] Replacing central nervous system (CNS) irradiation with intensive systemic and intrathecal chemotherapy has led to a reduction in late neurocognitive sequelae.[6-8] A recent focus on more basic cognitive processes has revealed milder forms of impairment that involve functional domains, such as attention, working memory, and speed of processing, that may underlie the observed declines in IQ and achievement.[9-12] The correlations between these processing deficits, CNS-directed therapy, and risk factors, such as young age at treatment and time since therapy, are well recognized now for patients who receive CNS irradiation. However, the degree and type of cognitive impairment[13] for patients who receive treatment with chemotherapy alone[14] have not been characterized well.

A correlation between decreased white-matter volumes and subtle processing deficits was demonstrated recently in brain tumor survivors who received irradiation.[15] Quantitative magnetic resonance imaging (MRI) analyses of pediatric brain tumor survivors revealed an atypical development of cerebral white matter after they received treatment with cranial irradiation, which may account for at least some of the alterations in neurocognitive function.[16] Patients with ALL who receive chemotherapy alone may have a high prevalence of leukoencephalopathy (LE), which occurs in as many as 80% of patients on some treatment regimens.[8,17] In many patients, LE can be transient and may decrease in prevalence, extent, and intensity with longer follow-up after the completion of therapy.[18] However, even after resolution of MRI-evident LE, patients may have a diminished volume of white matter.

The developing brain may be more susceptible to damage, because newly synthesized myelin has higher metabolic activity and lower stability that makes it more vulnerable to the toxic effects of therapy.[19] This assumption is supported by the finding of white-matter metabolite changes in children during treatment for ALL.[20] It is hypothesized that damage to vulnerable, long white-matter tracts may cause the neurocognitive declines in survivors.[11] There have been limited investigations relating white matter and neurocognitive function in ALL survivors who are treated without irradiation. A lack of correlation was found between subjective grading of white-matter lesions and neurocognitive performance,[19] but no quantitative measures of white-matter volume have been studied in ALL survivors.

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For the current study, we examined ALL survivors who received treatment with either chemotherapy alone or in combination with cranial irradiation. A consistent neurocognitive testing battery evaluated intellect, attention, and academic achievement. A quantitative objective measure of white-matter volumes across a transverse volume of interest that encompassed the entire corpus callosum was evaluated. The study objective was to test the hypothesis that ALL survivors with lower volumes of white matter have more severe deficits in attention and learning.

## MATERIALS AND METHODS

### Patient Population

To be eligible for participation, patients had to be between the ages of 6 years and 18 years, they had to be enrolled in school, they must have received treatment for ALL with either chemotherapy alone or in combination with radiation therapy to the CNS, they must have been off therapy for at least 12 months, and they had to have English as the primary language in the home. Written informed consent was obtained from the patient, parent, or guardian to participate in this Institutional Review Board-approved protocol.[21] Exclusionary criteria included a prior diagnosis of attention deficit hyperactivity disorder, uncontrolled seizures, tics, glaucoma, uncorrected endocrinopathies, severe sensory loss (e.g., blindness or deafness that would preclude valid psychometric testing), a history of drug abuse, current use of psychotropic medications, or recurrent tumor.

Evaluations were collected for 112 children from 2 institutions. Patients had received multiple courses of intravenous high-dose methotrexate and multiple doses of intrathecal therapy with methotrexate, hydrocortisone, and cytarabine. ALL survivors in this study were stratified by intensity of therapy according to whether the patients had ($n$ = 28 patients) or had not ($n$ = 84 patients) received cranial irradiation (18 Gray) in addition to other therapy. Demographics of the patient population are shown in Table 1.

Initial eligibility was established by medical chart review with a follow-up telephone call or introductory letter to establish interest and to schedule the clinic visit. For patients who agreed and provided informed consent, a screening battery of psychological tests was administered. An MRI examination without contrast was acquired within 3 months of the neurocognitive testing.

A group of 33 healthy sibling controls also was recruited and imaged for volumetric measures of white matter, gray matter, and cerebrospinal fluid (CSF) across the volume of interest. Participants were between ages 6 years and 16 years and were imaged without sedation or contrast. Demographics of the control population also are shown in Table 1.

### Neurocognitive Assessments

**Abbreviated wechsler intelligence scales—**All participants were given the Information (fund of factual knowledge), Similarities (verbal reasoning), and Block Design (nonverbal reasoning) subtests from either the Wechsler Intelligence Scale for Children—III[22] or the Wechsler Adult Intelligence Scale—III.[23] The screening process was used to provide age-corrected estimates of IQ (EIQ) with a mean of 100 and a standard deviation of 15. This abbreviated version reportedly is correlated highly with EIQ.[24,25]

**Conner continuous performance test—**The Conner Continuous Performance Test (CPT), which is a computer-administered test, measures selective and sustained attention, reaction time, and impulsivity[26]; and it provides age-corrected, standard scores on multiple indices of attentional abilities and impulsivity for healthy children and adolescents and for

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children who are diagnosed with attention deficit hyperactivity disorder. The CPT is approximately 15 minutes in duration and is computer scored. Eleven different age-corrected and gender-corrected indices of attention and impulsivity are derived from the individual's performance.[26] Of these, we selected the summary measures of Omissions, D' (attentiveness), and $\beta$ (risk-taking). These measures produce T-scores, which can be compared with a normative score that has a mean of 50 and standard deviation of 10. Unlike the other tests given, higher scores indicate worse performance and correspond to increased rates of omissions, inattentiveness, and less risk-taking. Less risk-taking represents a more conservative approach to decisions and is associated with slower processing speed. There are no significant practice effects from repeated administration.

**Abbreviated wechsler individual achievement test—**The Wechsler Individual Achievement Test (WIAT) is a standardized test of academic achievement that is administered individually and reportedly has acceptable reliability and validity.[27] The screening WIAT included the Reading Composite (composed of Basic Reading and Reading Comprehension subtests), Mathematics Composite (composed of Mathematics Reasoning and Numerical Operations subtests), and Spelling measures. These measures take approximately 30 minutes to administer and have standardized scores based on age-adjusted, normative samples (normative mean, 100; standard deviation, 15).

## MRI

Imaging evaluations were performed on a 1.5-T Symphony whole-body imager (Siemens Medical Systems, Iselin, NJ) by using the standard, circular, polarized volume head coil. Most of the MR images that were used in this study were acquired as 5-mm-thick (1-mm gap) oblique transverse-imaging sets that were defined by the most inferior extent of the genu and the splenium of the corpus callosum on the midline sagittal image. T1-weighted images were acquired with a gradient-echo FLASH 2-dimensional imaging sequence (repetition time between spin excitations [TR], 266 msec; echo time [TE], 6 msec; 90 ° flip angle; 3 acquisitions). Proton density-weighted and T2-weighted images were acquired simultaneously with a dual spin-echo sequence (TR/TE1/TE2 = 3500/17/102 msec; 1 acquisition). Standard positioning beams on the magnet and head immobilization devices built into the head coil by the manufacturer were sufficient to ensure adequate head positioning and immobilization in these studies.

## Quantitative MR Volumetrics

Registration methods developed by Ostuni and colleagues[28] were used to register all MRI sets within an individual examination. After registration, intensity inhomogeneity in the MR images was corrected by using a novel fast implementation of an entropy-minimization algorithm.[29] An index section was chosen as a common starting point for the volumetric studies. This single transverse section was at the level of the basal ganglia that included both genu and splenium of the corpus callosum and generally showed the putamen and the lateral ventricle. Two sections below this level and 2 sections above this level were included in the volumetric analyses to create a 3-cm-thick volume of interest that covered most of the corpus callosum. These sections allowed quantification of both interhemispheric and intrahemispheric white-matter tracts. It has been shown in other patient populations that this volume of interest is highly predictive of the full cerebral white-matter and CSF volumes.[30] The volume of regional brain parenchyma was quantified from MR images by using an automated hybrid neural network segmentation and classification method.[31] The resulting classified regions were mapped to a color scheme, as shown in Figure 1. A histogram was then completed for each color to determine the number of pixels; this value was multiplied by pixel volume to determine the sampled volume of each tissue type. Robust reliability and validity have been established for

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these methods, resulting in a predicted variance of approximately 2% in the repeated measure of white and gray matter.[31]

### Statistical Analyses

Neurocognitive assessments of intellect, attention, and academic achievement were compared with normative test averages. Performance for both patient groups, with and without irradiation, was compared with Student *t* tests. Volumetric measures also were compared between patient groups and with the healthy sibling control group by using Student *t* tests. Two-tailed probability tests of significance ($\alpha = 0.05$) were used. Assumptions of equal variance were tested with the Levene test for equality of variances. The analyses of correlations between volumes and neurocognitive performance were by assessed using linear mixed-effects models that included the potential influential factors of age at examination, time since examination, and treatment intensity. All models reported in this article were fitted appropriately by backward selection of covariate variables, and comparisons in all fitted models were tested at an $\alpha$ level of 0.05 (2-tailed).

## RESULTS

### Neurocognitive Performance

Neurocognitive assessments of intellect, attention, and academic achievement were completed, and performance was compared with normative test scores (Table 2). Most measures for both patient groups demonstrated statistically significant differences from the normative test scores. All three measures of attention were significantly deficient in patients. The average deficits on measures of $\beta$ (risk-taking) and omissions were significant clinically, with differences of > 1.0 standard deviation from normative test scores in both groups. Intellect (EIQ) also was significantly lower in patients but with deficits of approximately 0.5 standard deviation in both groups. Similarly, differences in academic achievement scores were statistically significant compared with normative test scores, except for Reading Comprehension in children who had received chemotherapy alone. Patients who had received irradiation had clinically significant impairments, consistent with previous reports.[4,5,10] For neurocognitive assessments of intellect and attention, patients who had received chemotherapy alone did not differ significantly from patients whose treatment also had included irradiation. However, performances on all measures of academic achievement were significantly more impaired in patients whose treatment also included irradiation.

### Volumetric Assessments of Brain Parenchyma

Volumetric measures of white matter, gray matter, and CSF across the volume of interest were assessed for both patient groups (Table 3). Age at examination also was assessed to determine whether it had any influence on volumetric results. Patients who had received chemotherapy alone exhibited significantly greater volumes of white matter on average compared with patients whose treatment also had included irradiation, and patients who had received chemotherapy alone were significantly younger at the time of examination. This further demonstrated the adverse impact of irradiation on white-matter volume, because older patients should have greater volumes of white matter due to normal maturation. The male-to-female ratio was equivalent for both groups of patients and would not account for volumetric differences. There were no significant differences in volumes of gray matter.

Volumetric measures of white matter, gray matter, and CSF across the volume of interest in the healthy sibling control group were assessed and compared with age-matched and gender-matched patients who had received chemotherapy only (Table 3). Although there were no significant differences in gray-matter volumes, mean white-matter volumes were significantly smaller in the patients compared with the matched healthy controls.

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### Correlations between Volumetric Assessments and Neurocognitive Performance

The most clinically significant deficits in neurocognitive performance for both groups of patients, as reported above, were in attention, with performance on the assessments of omissions and $\beta$ (risk-taking) > 1.0 standard deviation different from normative test averages. Table 4 shows the results of a general linear model analysis of neurocognitive performance, regardless of treatment, as a function of white-matter volume. Age at examination, time since examination, and treatment intensity were not significant influential factors. The slope for each model, which represented the change in the neurocognitive performance per unit volume of white matter, was negative; this implies that larger white-matter volumes corresponded to better performance on each of the measures. The models demonstrate a significant correlation between these attention measures and white-matter volume. For the intelligence measure, EIQ, the general linear models demonstrated a highly significant, positive correlation between EIQ and white-matter volume, with larger white-matter volumes corresponding to greater intelligence. For the academic achievement measures, the slope for each of the general linear models was positive, implying that larger white-matter volumes corresponded to better performance on each of the measures. The models demonstrated a significant correlation between academic achievement measures and white-matter volume for all measures except spelling.

## DISCUSSION

The results of this study confirmed the hypothesis that survivors of childhood ALL who receive treatment with or without irradiation had significant deficits in attention and smaller white-matter volumes that were associated directly with neurocognitive performance. Most neurocognitive performance measures demonstrated statistically significant deficits from normative test scores, but only the attentional measures exceeded 1.0 standard deviation from normal. Measures of academic achievement differed between the 2 patient groups, with deficits that exceeded 1.0 standard deviation only in patients who had received irradiation. Patients who had received chemotherapy alone had significantly greater volumes of white matter than patients whose treatment also included irradiation, their but volumes still were significantly smaller than the volumes observed in the age-matched and gender-matched, healthy sibling control group. Moreover, smaller white-matter volumes corresponded to larger deficits in attention, intelligence, and academic achievement.

CNS toxicity attributed to treatment for ALL has been studied extensively. Adverse effects of therapy have been observed both after chemotherapy only and after chemotherapy combined with cranial irradiation.[32] Previous studies have recognized white-matter changes in survivors[19,32] and even metabolic changes detected with $^{1}$HMR spectroscopy during therapy.[20] However, most conventional MRI studies evaluated these changes based on visual inspection of the image intensity. Those studies found only a small prevalence of MR intensity abnormalities, and no correlation was observed between neuropsychological functioning and these changes.[19] In contrast, for the current study, we evaluated white-matter volumes quantitatively and found a significant deficit compared with the volumes in the age-matched and gender-matched control group. Furthermore, strong correlations were observed between the quantitative white-matter volumes and all neurocognitive performance measurements (except attentiveness and spelling), which suggests that white-matter volume may represent a sensitive measure of neurotoxicity.

The current results demonstrated both clinically and statistically significant impairment of omissions and risk-taking, two functional domains of attention, in both groups of ALL survivors, which is consistent with previous findings by Paakko et al.[19] The $\delta$' (attentiveness) measure demonstrated some slight inattentiveness, which was not considered clinically significant and was correlated only weakly with white-matter volumes. Generally,

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attentiveness measures reflect the respondent's ability to distinguishing an object, whereas omissions and risk-taking measures reflect the respondent's ability to react or their speed of reacting to an object. Therefore, the current results showed that the ALL survivors had deficits in reacting to objects rather than in distinguishing objects. This finding is consistent with a recent reports that ALL survivors who received chemotherapy alone processed information more slowly than healthy controls, especially when more information had to be processed or when attention had to be focused precisely.[33]

Object vision is received in the visual cortex and is supported by parallel ventral pathways that convey information to the parietal and inferior temporal cortical areas. Retrieval of information requires recruitment of stored information into a special short-term store called working memory, which is located in the prefrontal cortex.[34] The impaired ability to react to an object may suggest that these survivors have deficits in conveying information, especially between lobes. This hypothesis is supported further by the strong correlation between white-matter volumes and omission and risk-taking measures. Transient hyperintensities observed during therapy extending from the frontal, temporal, and occipital lobes to the subcortical nuclei and superior longitudinal fasciculus may be precursors of later deficits in conveying information between lobes. The atypical white-matter volume development quantified in these ALL survivors suggests that even the transient hyperintensities observed during therapy may lead to permanent, subtle white-matter volume changes that are very difficult to recognize by visual inspection.

The addition of cranial irradiation played a significant role in treatment-related changes in white-matter volumes and academic achievement, but not in attention or intellect. Academic achievement measurements in patients who received irradiation therapy were significantly lower than normative means. Both white-matter volumes and academic achievement measures in patients who had received irradiation were significantly lower than the volumes in patients who had not received irradiation. However, there was no significant difference in attention measures between the two patient groups. These results suggest that patients who had received chemotherapy alone sustained less damage to the white matter and, on average, were able to compensate intellectually and academically for attentional deficits. However, patients who had received cranial irradiation had more severe impairment of white-matter volume development and were unable to compensate, resulting in more significant deficits in learning.

The mechanisms of neurotoxicity from ALL treatment remain unclear. There are two factors that may contribute to atypical white-matter volume development in these survivors: 1) damage to oligodendroglial cells and 2) damage to vascular structures. Iron contained in oligodendrocytes plays an important role in myelogenesis and the maintenance of the myelin sheath,[35] and proton magnetic relaxation times vary as a function of iron concentration.[36] Therefore, the atypical white-matter volume development observed in the current study and the white-matter intensities observed in previous studies may have been the result of demyelination caused by damage to oligodendroglial cells. This explanation is consistent with the destruction of oligodendrocytes observed in a previous postmortem study of patients with leukemia who received treatment with methotrexate.[37]

Another possible mechanism for atypical white-matter volume development is ischemia induced by damage to microvasculature. Methotrexate inhibits di-hydrofolate reductase, which is an enzyme involved in the biosynthesis of folic acid coenzymes, and, thus, reduces folate. Reduced folate causes a secondary elevation of homocysteine, which is toxic to vascular endothelium and may induce ischemic side effects.[38] This mechanism is consistent with hyperintensities observed in deep white matter during therapy extending from the frontal and occipital lobes to the subcortical nuclei and superior longitudinal fasciculus (Fig. 2). The deep white matter is most vulnerable to ischemic changes because of sparse vascularity.[39]

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Like in any study, there are limitations to the results and conclusions of the current study. Quantitative volumetric measures were conducted to assess total tissue volumes in a specific anatomic area. These measures 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 white-matter volume development and attention. However, the focus of this study was a necessary first step to establish a correlation between white-matter volumes and problems with attention and academic achievement in patients who survive ALL. Future longitudinal studies also should include diffusion tensor imaging to quantify changes in the integrity of the white matter and perfusion imaging to quantify changes in the microvasculature as possible precursors to the more macroscopic changes in volume.

In summary, the current results confirmed the hypothesis that children who survive treatment for ALL with or without cranial irradiation have significant deficits in attention and smaller white-matter volumes, which were associated directly with deficits in neurocognitive performance. Significant impairment in attention was demonstrated in both groups of ALL survivors, indicating an impaired ability to react to an object, which would be consistent with both groups of survivors having deficits in conveying information, especially between lobes. Patients who received cranial irradiation had more severe impairment of white-matter volume development and were unable to compensate, resulting in more significant deficits in learning. Patients who received chemotherapy alone apparently sustained less damage to the white matter and, on average, were able to compensate intellectually and academically for attentional deficits. Future studies of children with ALL should include longitudinal assessments of neurocognitive function and neuroimaging, even in patients who are treated without cranial irradiation.

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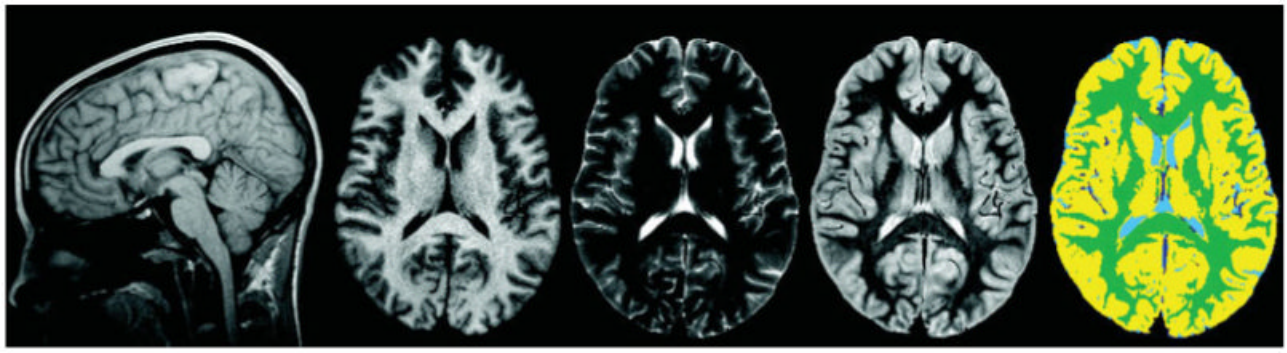

**FIGURE 1.**
The normal-appearing, sagittal, T1-weighted image on the far left shows a box that denotes the coverage of the 5 transverse sections that were used in the current study. The remaining images, from left to right, are representative transverse T1-weighted, T2-weighted, and proton density-weighted images that were used to create the segmented map on the far right.

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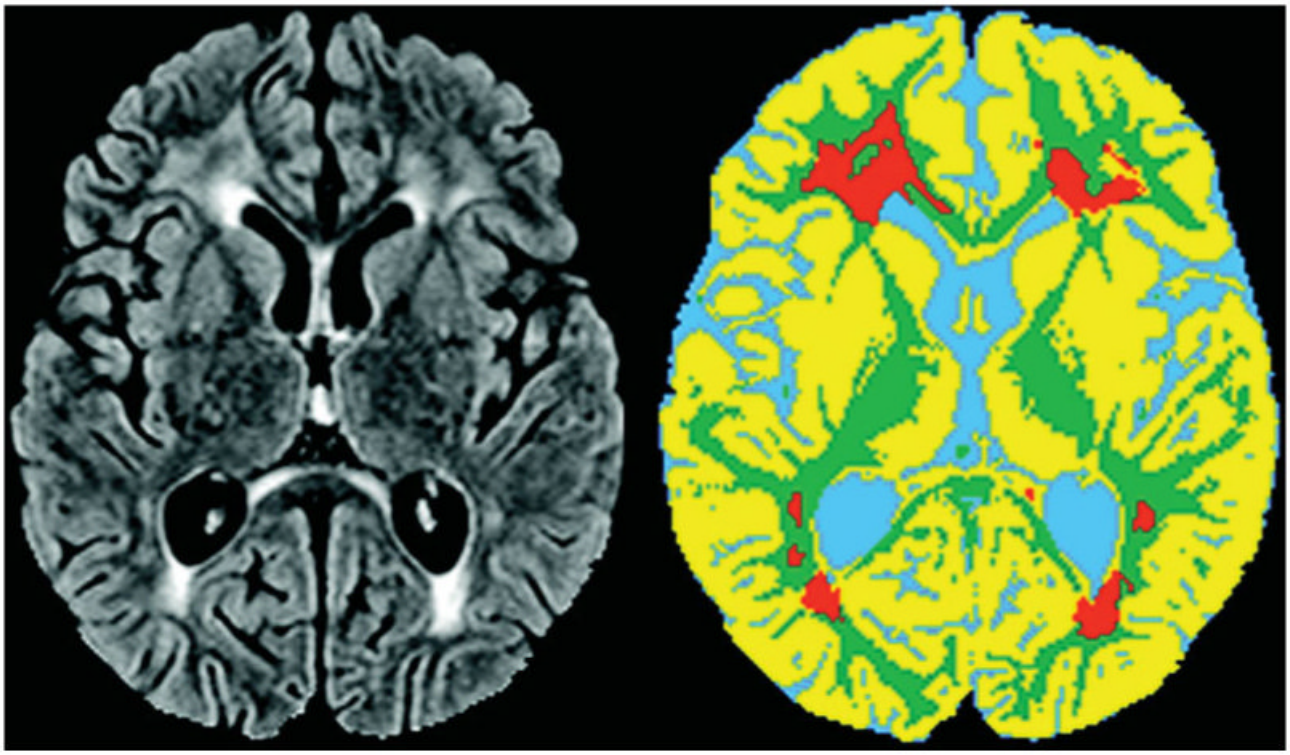

**FIGURE 2.**
A representative fluid-attenuated, inversion-recovery image (left) and the resulting segmented map (right) demonstrate the white matter hyperintensities that were observed during therapy in a patient with acute lymphoblastic leukemia who received treatment with chemotherapy alone.

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**TABLE 1**

Characteristic Variables Describing Demographics of Acute Lymphoblastic Leukemia Survivors and Healthy Sibling Controls

| Variable | Chemotherapy alone | Chemotherapy and irradiation | Healthy siblings |
|---|---|---|---|
| No. of patients | 84 | 28 | 33 |
| Gender (no.) | | | |
| Male | 47 | 16 | 15 |
| Female | 37 | 12 | 18 |
| Race (no.) | | | |
| White | 76 | 26 | 29 |
| Black | 6 | 2 | 2 |
| Other | 2 | 0 | 2 |
| Mean ± SD age at diagnosis (yrs) | 4.5 ± 2.6 | 3.1 ± 2.3 | |
| Mean ± SD time since diagnosis (yrs) | 5.3 ± 3.1 | 8.0 ± 4.0 | |
| Mean ± age at examination (yrs) | 9.8 ± 3.1 | 11.1 ± 2.6 | 12.0 ± 2.7 |

SD: standard deviation.

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## TABLE 2

Neurocognitive Performance of Acute Lymphoblastic Leukemia Survivors who Received Either Chemotherapy Alone or Combined with Cranial Irradiation

| Neurocognitive measures | Mean ± SD | | *P* |
|---|---|---|---|
| | Chemotherapy alone | Chemotherapy and irradiation | |
| Attention | | | |
| Omissions | 62.9 ± 8.7[a] | 62.9 ± 9.5[a] | 0.98 |
| D' (attentiveness) | 57.6 ± 10.4[a] | 60.8 ± 11.6[a] | 0.17 |
| *β* (risk-taking) | 72.8 ± 21.3[a] | 74.8 ± 22.3[a] | 0.67 |
| Intelligence | | | |
| EIQ | 94.2 ± 16.3[a] | 91.0 ± 16.7[a] | 0.38 |
| Academic achievement | | | |
| Math composite | 94.1 ± 15.8[a] | 84.4 ± 16.5[a] | < 0.01[b] |
| Math reasoning | 96.4 ± 14.6[c] | 88.8 ± 16.3[a] | 0.02[b] |
| Numerical operations | 93.0 ± 16.6[a] | 84.6 ± 16.3[a] | 0.02[b] |
| Reading composite | 95.4 ± 14.5[a] | 87.6 ± 16.8[a] | 0.02[b] |
| Basic reading | 95.5 ± 14.0[a] | 88.9 ± 13.1[a] | 0.03[b] |
| Reading comprehension | 98.1 ± 13.9 | 90.6 ± 17.5[a] | 0.02[b] |
| Spelling | 95.1 ± 14.6[a] | 89.2 ± 15.4[a] | 0.07 |

SD: standard deviation; EIQ: age-corrected estimates of intelligence quotient.

[a] Statistically significant differences from test norms superscript symbols ($P < 0.01$).

[b] In a statistical comparison between the two groups of survivors, the difference was significant for this variable.

[c] Statistically significant differences from test norms superscript symbols ($P < 0.05$).

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**TABLE 3**

Comparison of Tissue Volumes between Acute Lymphoblastic Leukemia Survivors who Received Either Chemotherapy Alone or Chemotherapy plus Cranial Irradiation and between a Control Group of Healthy Siblings and Age-Matched and Gender-Matched Acute Lymphoblastic Leukemia Survivors who Received Chemotherapy Alone

| | Mean ± SD tissue volume | | | |
|---|---|---|---|---|
| **Group** | **White matter (mL)** | **Gray matter (mL)** | **CSF (mL)** | **Age at examination (yrs)** |
| ALL survivors | | | | |
| Chemotherapy alone | 142.5 ± 26.4 | 315.9 ± 27.4 | 29.7 ± 8.3 | 9.8 ± 3.1 |
| Chemotherapy and irradiation | 128.8 ± 24.2 | 313.5 ± 29.8 | 37.4 ± 19.8 | 11.1 ± 2.6 |
| *P* value | 0.02[a] | 0.69 | 0.05[a] | 0.04[a] |
| Control group | | | | |
| Chemotherapy alone | 142.6 ± 23.7 | 311.2 ± 28.4 | 31.2 ± 8.2 | 11.7 ± 2.4 |
| Healthy sibling | 155.2 ± 21.0 | 310.3 ± 18.5 | 26.5 ± 4.3 | 12.0 ± 2.7 |
| *P* value | 0.03[a] | 0.87 | < 0.01[a] | 0.68 |

SD: standard deviation; CSF: cerebrospinal fluid; ALL: acute lymphoblastic leukemia.

[a]In a statistical comparison between the groups, the difference was significant for this variable.

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**TABLE 4**

General Linear Model Analysis of Neurocognitive Performance as a Function of White-Matter Volume

| Neurocognitive measures | Intercept (score) | Slope (score/mL) | *P* value[a] |
|---|---|---|---|
| Attention | | | |
| Omissions | 73.08 | - 0.073 | 0.02[b] |
| D' (attentiveness) | 68.60 | - 0.073 | 0.06 |
| $\beta$ (risk-taking) | 99.61 | - 0.19 | 0.01[b] |
| Intelligence | | | |
| EIQ | 71.05 | 0.16 | < 0.01[b] |
| Academic achievement | | | |
| Math composite | 58.76 | 0.24 | < 0.01[b] |
| Math reasoning | 64.88 | 0.21 | < 0.01[b] |
| Numerical operations | 65.97 | 0.18 | < 0.01[b] |
| Reading composite | 72.04 | 0.15 | < 0.01[b] |
| Basic reading | 75.64 | 0.13 | < 0.01[b] |
| Reading comprehension | 74.59 | 0.16 | < 0.01[b] |
| Spelling | 81.09 | 0.09 | 0.09 |

EIQ: age-corrected estimates of intelligence quotient.

[a] Patients from both treatment arms were combined for this analysis. The last column shows the significance of slope estimates that differed from zero.

[b] The *P* value was significant for this variable.