

## Ipsilateral and Contralateral MRI Volumetric Abnormalities in Chronic Unilateral Temporal Lobe Epilepsy and their Clinical Correlates

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**Summary:** *Purpose:* To assess the presence, extent, and clinical correlates of quantitative MR volumetric abnormalities in ipsilateral and contralateral hippocampus, and temporal and extratemporal lobe regions in unilateral temporal lobe epilepsy (TLE).

*Methods:* In total, 34 subjects with unilateral left ( $n = 15$ ) or right ( $n = 19$ ) TLE were compared with 65 healthy controls. Regions of interest included the ipsilateral and contralateral hippocampus as well as temporal, frontal, parietal, and occipital lobe gray and white matter. Clinical markers of neurodevelopmental insult (initial precipitating insult, early age of recurrent seizures) and chronicity of epilepsy (epilepsy duration, estimated number of lifetime generalized seizures) were related to magnetic resonance (MR) volume abnormalities.

*Results:* Quantitative MR abnormalities extend beyond the ipsilateral hippocampus and temporal lobe with extratemporal (frontal and parietal lobe) reductions in cerebral white matter, especially ipsilateral but also contralateral to the side of seizure onset. Volumetric abnormalities in ipsilateral hippocampus and bilateral cerebral white matter are associated with factors related to both the onset and the chronicity of the patients' epilepsy.

*Conclusions:* These cross-sectional findings support the view that volumetric abnormalities in chronic TLE are associated with a combination of neurodevelopmental and progressive effects, characterized by a prominent disruption in ipsilateral hippocampus and neural connectivity (i.e., white matter volume loss) that extends beyond the temporal lobe, affecting both ipsilateral and contralateral hemispheres. **Key Words:** Temporal lobe epilepsy—Quantitative MRI.

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Quantitative volumetric magnetic resonance imaging (MRI) studies in temporal lobe epilepsy (TLE) have focused on the hippocampus because of its role in the initiation and propagation of seizures and the degree of seizure relief obtained after its resection. Volumetric abnormalities have been identified consistently in the hippocampus ipsilateral to side of seizure onset (1–4), with reduced hippocampal volumes highly correlated with histopathologic findings of hippocampal sclerosis and favorable surgical outcomes (4,5). It is now appreciated that MR volumetric abnormalities may extend beyond the hippocampus to adjacent structures including the amygdala (6,7), fornix (8), entorhinal cortex and parahippocampal region (6,9,10), thalamus (11,12), basal ganglia (13), more distal temporal lobe regions such as the temporal pole (14,15), and distant structures such as the cerebellum (16–18).

Of interest are a small number of reports suggesting the presence of generalized and diffuse cortical volume reductions in TLE (19,20). However, few of these studies have examined segmented (gray and white matter) volumes throughout the lobar regions of the cortex to characterize the nature of this broader impact. Marsh et al. (21) reported bilateral frontoparietal gray and white matter volume loss in a small sample of 14 male TLE patients compared with controls. Lee et al. (19) reported reduced whole brain volume in 27 patients with TLE, but did not examine volumes of gray and white matter. Sisodiya et al. (22) described widespread occult structural abnormalities occurring in visually normal-appearing MRIs in 27 patients with hippocampal sclerosis. Theodore et al. (23) reported that patients with localization-related epilepsy and temporal lobe onset with a history of complex febrile convulsions had significantly reduced total cerebral volume compared with that in patients without such a history. Our own prior investigation (24) reported whole brain volumetric abnormalities in TLE, most evident in cerebral white matter, but a very limited number of ictal-monitored

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unilateral TLE patients prevented a careful examination of the distribution and clinical correlates of ipsilateral versus contralateral volumetric abnormalities. Therefore, the first objective of this article is to characterize hippocampal and whole brain cortical volumetric abnormalities in temporal and extratemporal regions both ipsilateral and contralateral to the side of unilateral temporal lobe seizure onset.

The second issue to be examined concerns the potential mechanisms associated with the observed volumetric abnormalities. Once again, much of the current literature has focused on the etiology of hippocampal volume abnormalities in TLE. Findings have implicated both early neurodevelopmental factors including complex febrile convulsions and early age at onset of recurrent seizures, as well as progressive seizure-related features such as duration and estimated number of lifetime generalized seizures in hippocampal integrity (25–29). The limited examination of extratemporal volume abnormalities in TLE, especially whole brain volumes, has precluded a clear determination of their potential etiologic factors. The present study examined the clinical seizure correlates of hippocampal and extratemporal lobe volumetric abnormalities, focusing on segmented volumes of cerebral gray matter and white matter, with particular attention to markers of an early neurodevelopmental insult and markers of epilepsy chronicity.

In summary, examining patients with unilateral TLE and healthy controls, the current study addressed: (a) the extent and nature of quantitative MRI volumetric abnormalities in hippocampus, temporal lobe, and extratemporal lobe gray and white matter, both ipsilateral and contralateral to the side of seizure onset; and (b) the association of identified temporal and extratemporal lobe volumetric abnormalities to neurodevelopmental and progressive clinical seizure features.

## METHODS

### Subjects

The study sample consisted of 34 patients with unilateral TLE (15 left, 19 rights) and 65 healthy controls (Table 1). The majority of these chronic TLE patients were under consideration for surgical treatment (anterior temporal lobectomy) of their medication-resistant epilepsy. Surgical candidacy is determined by a consensus multidisciplinary group and includes review and consideration of seizure semiology, prolonged interictal and ictal video-electroencephalograph (EEG) monitoring of spontaneous seizures by using scalp IFO/EFO (internal/external foramen ovale), or intracranial electrodes, MRI, and neuropsychological assessment. Surgical candidates also typically undergo a Wada Test and interictal fluorodeoxyglucose-positron emission tomography (FDG-PET). For this investigation, only patients with unilateral temporal lobe onset of spontaneous seizures were included. Patients

**TABLE 1.** Demographic and clinical seizure characteristics

Characteristics	Controls (n = 66)	Left TLE (n = 15)	Right TLE (n = 19)
Age (yr)	33.3 (12.5)	29.9 (12.0)	38.8 (13.3)
Education (yr)	13.6 (2.4)	11.9 (2.3)	13.2 (2.3)
Gender (M/F)	29/37	4/11	7/12
Duration	—	18.7 (11.9)	23.1 (13.8)
Onset age (yr)	—	11.2 (10.1)	15.8 (9.0)
IPI (Y/N)	—	6/9	8/11
Febrile seizure	—	4	2
Encephalitis/Meningitis	—	2	6

TLE, temporal lobe epilepsy; IPI, initial precipitating incident.

with independent left and right temporal lobe onset were excluded.

All TLE patients were between 14 and 60 years of age, showed no evidence of gross MRI abnormalities [e.g., arteriovenous malformation (AVM), neoplasm] other than hippocampal sclerosis on clinical reading, and had no other diagnosed neurologic disorder. Healthy controls were either friends or family members of the TLE patients. They were also between the ages of 14 and 60 years, with no current substance abuse, medical, or acute psychiatric condition, no history of loss of consciousness > 5 min, and no history of developmental learning disorder.

TLE patients were typically interviewed in the presence of a family member regarding details of their epilepsy history and clinical course. Available medical records concerning previous epilepsy-related hospitalizations and records from physicians who had treated the patients' epilepsy were reviewed and abstracted, blinded to the MRI and neuropsychological findings. We recorded information concerning significant medical events that occurred before the onset of TLE: initial precipitating incidents (IPIs) including febrile seizures, meningitis or encephalitis, closed head injury, and perinatal event. A listing of recorded IPIs for the TLE groups is provided in Table 1 along with the demographic and clinical seizure characteristics of the left and right TLE groups and healthy controls. No significant group effect for age was noted [ $F(2, 97) = 2.28, p = 0.10$ ]. Education level did differ between groups [ $F(2, 97) = 3.45, p < 0.05$ ]; Neumann-Keuls post hoc *t* tests indicated that the left TLE group was less educated than both the controls and the right TLE group, who did not differ from one another ( $p > 0.10$ ). The distribution of male and female subjects was similar across the three groups. The left and right TLE groups were similar in their age at recurrent seizure onset, duration of epilepsy, and history of IPIs (all *p* values > 0.10).

### Magnetic resonance imaging

Images were obtained on a 1.5-Tesla GE Signa MRI scanner. Sequences acquired for each subject included (a)  $T_1$ -weighted, three-dimensional spoiled grass (SPGR) acquired with the following parameters: TE = 5, TR = 24,

flip angle = 40, NEX = 2, FOV = 26, slice thickness = 1.5 mm, slice plane = coronal, matrix = 256 × 192; (b) proton density (PD); and (c) T<sub>2</sub>-weighted images acquired with the following parameters: TE = 36 ms (for PD) or 96 ms (for T<sub>2</sub>), TR = 3,000 ms, NEX = 1, FOV = 26, slice thickness = 3.0 mm, slice plane = coronal, matrix = 256 × 192, and an echo train length = 8.

MRIs were acquired at the University of Wisconsin and transferred to the Image Processing Laboratory of the Mental Health Clinical Research Center at the University of Iowa, where they were processed using a semiautomated software package [i.e., Brain Research: Analysis of Images, Networks, and Systems (BRAINS)] (30,31). Neuroimaging analyses were conducted blinded to group status and clinical and sociodemographic characteristics of the subjects. MRI regions of interest for this investigation included supratentorial hemispheric cerebrum tissue volume decomposed into segmented gray and white matter volumes, lobar (frontal, temporal, parietal, and occipital) segmented gray and white tissue volumes, and hippocampus.

The T<sub>1</sub>-weighted images were spatially normalized so that the anteroposterior axis of the brain was realigned parallel to the anterior and posterior commissure (ACPC) line, and the interhemispheric fissure was aligned on the other two axes. A 6-point linear transformation was used to warp the standard Talairach atlas space onto the resampled image. Images from the three pulse sequences were then co-registered by using a local adaptation of automated image registration software (32). After alignment of the image sets, the PD and T<sub>2</sub> images were resampled into 1-mm cubic voxels. Segmentation of the image set was achieved by using a tissue-classification program. Sample tissue plugs were generated over a large extent of the brain and subsequently used as input for discriminant analysis functions to classify each voxel as gray matter, white matter, CSF, blood, or unclassified (30). The brains were then delineated from the skull by using a neural network application that had been trained on a set of manual traces (33). Manual inspection and correction of the output of the neural network tracing was conducted. A stereotaxic method based on the Talairach atlas yields measures of left and right frontal, temporal, parietal, and occipital lobes. The BRAINS software and procedures have been shown to be of high interrater reliability, intrarater reliability, and scan-rescan reproducibility, particularly for the MRI indices that are the focus of this study (30,31,33,34).

A neural network application (33) was used to trace the hippocampus by using guidelines established and psychometrically validated by the University of Iowa (35) with manual correction of the traces by a qualified technician. These tracings included the pes or head of the hippocampus, the body, and the tail. Within the hippocampus, the subiculum, Ammon's horn, and dentate gyrus were in-

cluded. The white matter structures of the alveus, fimbria, and the fornix were excluded. Within the sagittal orientation, the alveus and the uncus marked the anterior border. Posteriorly, the tail of the hippocampus ended at the atrium of the lateral ventricle. Ventrally, the white matter of the parahippocampal gyrus defined the border. Dorsally, the temporal horn of the lateral ventricle served as the border, except in the tail of the hippocampus, where the pulvinar of the thalamus was the border.

### Statistical analyses

All brain volume indices under examination were adjusted for height, gender, and age by using multiple regression analyses based on the control subjects (n = 65). The regression equations were then applied to TLE subject volumes, and the predicted variance removed from their observed brain volumes. The result is a residual score that removes variance due to body size and age. Z-score transformations of adjusted volumes were computed based on control subject mean adjusted volumes. The results to be reported were similar when volumes of interest were adjusted for total intracranial volume or age, gender, and height.

We initially present findings comparing the right and left TLE groups with controls by using multivariate analysis of variance (MANOVA) followed by univariate ANOVA. Post hoc comparisons of group main effects were conducted with Bonferroni correction for multiple comparisons. After the similarity in findings for the two TLE groups is established, findings are presented for the TLE groups together compared with controls, in that the larger sample size provides more statistical power. To permit formal statistical comparison of ipsilateral and contralateral regions, controls were assigned "ipsilateral" and "contralateral" volume values by calculating an average of the relevant left and right hemisphere regions.

Clinical seizure predictors of MR volumes included neurodevelopmental factors [presence/absence of a history of an IPI, age at recurrent seizure onset], and markers of chronicity/severity of epilepsy (epilepsy duration), and estimated lifetime number of generalized seizures]. The relation of IPI history to MRI volumes was examined with group comparisons with *t* tests. Positive IPI history included complex febrile seizures (n = 6) and infectious events (n = 8). Pearson product zero-order correlations were used to examine the relation of age at onset, epilepsy duration, and estimated lifetime generalized seizure frequency with the MRI volumes of interest. Because of the inherent difficulty frequently encountered in establishing, on a retrospective basis, a reliable count of the lifetime number of generalized seizures, an ordinal scale was used to quantify estimated lifetime generalized seizures (1, none; 2, 1–10 seizures; 3, 11–50; 4, 50–99; 5, 100+).

**TABLE 2.** Absolute values of brain volumes

Region	Controls (n = 65)	Left TLE (n = 15)	Right TLE (n = 19)
Left hippocampus	1.92 (0.32)	1.50 (0.38)	1.81 (0.34)
Right hippocampus	1.86 (0.29)	1.71 (0.25)	1.40 (0.33)
Left cerebral gray	331.87 (36.71)	328.86 (34.24)	310.04 (35.12)
Right cerebral gray	341.06 (38.58)	341.47 (37.61)	315.94 (33.92)
Left cerebral white	228.79 (32.53)	202.06 (28.65)	207.13 (24.53)
Right cerebral white	229.93 (32.91)	207.76 (29.40)	202.46 (22.49)

TLE, temporal lobe epilepsy.

## RESULTS

### MRI volume comparisons between groups (controls, left TLE, right TLE)

A one-way MANOVA was conducted to determine group differences (controls, left TLE, right TLE) for hippocampus, cerebral white matter, and cerebral gray matter in the left and right hemispheres. A significant overall main effect of group was obtained [ $F(12, 184) = 7.78$ ;  $p < 0.001$ ]. One-way ANOVA indicated significant group volume differences for left hippocampus [ $F(2, 98) = 7.32$ ;  $p < 0.001$ ], right hippocampus [ $F(2, 98) = 15.2$ ;  $p < 0.001$ ], left cerebral white [ $F(2, 98) = 6.46$ ;  $p < 0.002$ ], and right cerebral white matter [ $F(2, 98) = 9.95$ ;  $p < 0.001$ ]. In contrast, no significant group differences were found for left cerebral gray [ $F(2, 98) = 0.97$ ;  $p > 0.10$ ] or right cerebral gray volume [ $F(2, 98) = 1.37$ ;  $p > 0.10$ ]. Findings for the specific group contrasts across the volumetric indices are detailed separately for the left and right TLE groups later. Table 2 provides a summary of the absolute values for these volume indices.

#### Left TLE versus controls

As shown in Fig. 1A, the left TLE group had significantly reduced ipsilateral hippocampal volume, [ $t(78) = 3.83$ ;  $p < 0.001$ ] and reduced volume of ipsilateral hemisphere white matter [ $t(78) = 2.80$ ;  $p < 0.02$ ] compared with controls. In addition, they showed a similar trend for contralateral hemisphere white matter volume [ $t(78) = 2.25$ ;  $p = 0.08$ ]. In contrast, the left TLE group did not differ significantly from controls in either ipsilateral gray matter volume [ $t(78) = 0.03$ ;  $p > 0.10$ ], contralateral gray matter volume [ $t(78) = 0.05$ ;  $p > 0.10$ ], or contralateral hemisphere hippocampal volume [ $t(78) = 0.47$ ;  $p > 0.10$ ].

#### Right TLE versus controls

As shown in Fig. 2A, white matter volume was significantly reduced in the right TLE group in both the ipsilateral hemisphere [ $t(82) = 3.55$ ;  $p = 0.002$ ] and the contralateral hemisphere [ $t(82) = 2.79$ ;  $p < 0.02$ ] compared with controls. They also exhibited significantly smaller ipsilateral hippocampal volume than controls [ $t(82) = 5.80$ ;  $p < 0.001$ ], but did not differ in contralateral hippocampal volume [ $t(82) = 0.94$ ;  $p > 0.10$ ]. Similar to the left

TLE group, no significant reductions were noted in volumes of ipsilateral gray matter [ $t(82) = 1.60$ ;  $p > 0.10$ ] or contralateral gray matter [ $t(82) = 1.38$ ;  $p > 0.10$ ].

#### Lobar white matter volumes

A MANOVA was conducted to examine the distribution of white matter volume differences in the TLE groups and controls across the lobar regions. A significant main effect of group was obtained [ $F(16, 182) = 3.70$ ;  $p < 0.001$ ]. One-way ANOVAs indicated a significant group effect for left frontal white matter [ $F(2, 98) = 3.78$ ;  $p < 0.05$ ]; left temporal lobe white matter [ $F(2, 98) = 7.86$ ;  $p < 0.001$ ]; left parietal lobe white matter [ $F(2, 98) = 6.95$ ;  $p = 0.002$ ]; left occipital lobe white matter [ $F(2, 98) = 3.69$ ;  $p < 0.05$ ]; right frontal lobe white matter [ $F(2, 98) = 6.79$ ;  $p = 0.002$ ]; right temporal lobe volume [ $F(2, 98) = 11.21$ ;  $p < 0.001$ ]; and right parietal lobe volume [ $F(2, 98) = 6.48$ ;  $p = 0.002$ ]. Only right occipital lobe volumes failed to show a significant group effect [ $F(2, 98) = 1.06$ ;  $p > 0.10$ ].

Follow-up post hoc tests indicated diffuse ipsilateral and contralateral white matter volume loss for both the left and right TLE groups compared with controls. As illustrated in Fig. 1B, the left TLE group showed reduced ipsilateral hemisphere white matter volume compared with controls in the temporal lobe [ $t(78) = 3.73$ ;  $p < 0.001$ ], parietal lobe [ $t(78) = 2.98$ ;  $p = 0.01$ ], and occipital lobe [ $t(78) = 2.51$ ;  $p < 0.05$ ]. In addition, the left TLE group exhibited significant contralateral hemisphere white matter volume loss in the temporal lobe [ $t(78) = 3.00$ ;  $p < 0.01$ ], with a similar trend in the parietal lobe [ $t(78) = 2.13$ ;  $p = 0.10$ ].

As shown in Fig. 2B, the right TLE group showed significant ipsilateral white matter volume loss in the temporal lobe [ $t(82) = 4.21$ ;  $p < 0.001$ ] and extratemporal lobe regions, including the ipsilateral frontal lobe [ $t(82) = 3.54$ ;  $p = 0.002$ ] and parietal lobe [ $t(82) = 3.29$ ;  $p = 0.004$ ]. The right TLE group also showed evidence of contralateral hemisphere white matter volume loss in the frontal lobe [ $t(82) = 2.49$ ;  $p < 0.05$ ], temporal lobe [ $t(82) = 2.11$ ;  $p < 0.05$ ], and parietal lobe [ $t(82) = 2.82$ ;  $p < 0.02$ ].

#### Lobar gray matter volumes

A MANOVA conducted to examine the distribution of gray matter volume differences observed that the

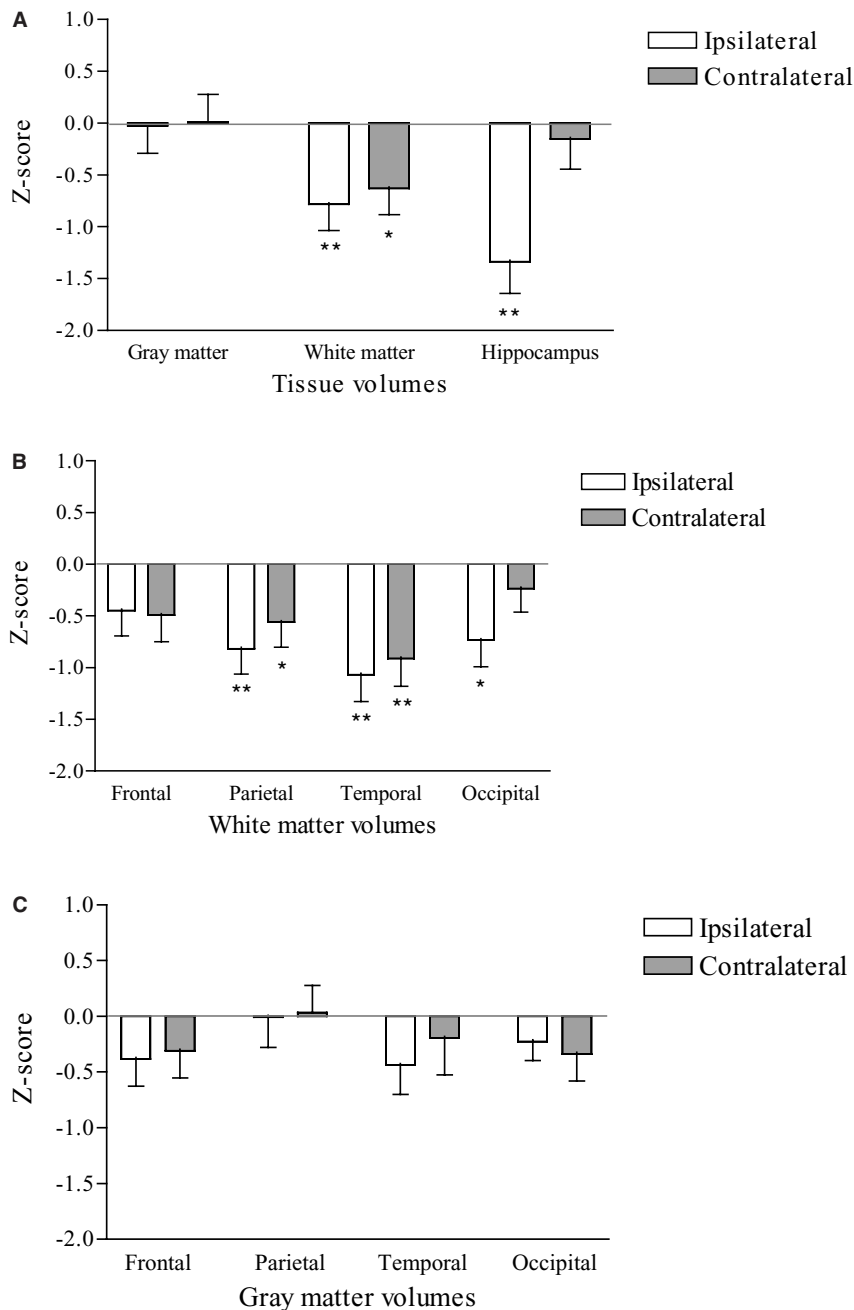


FIG. 1. Volumetric findings for the left temporal lobe epilepsy group.

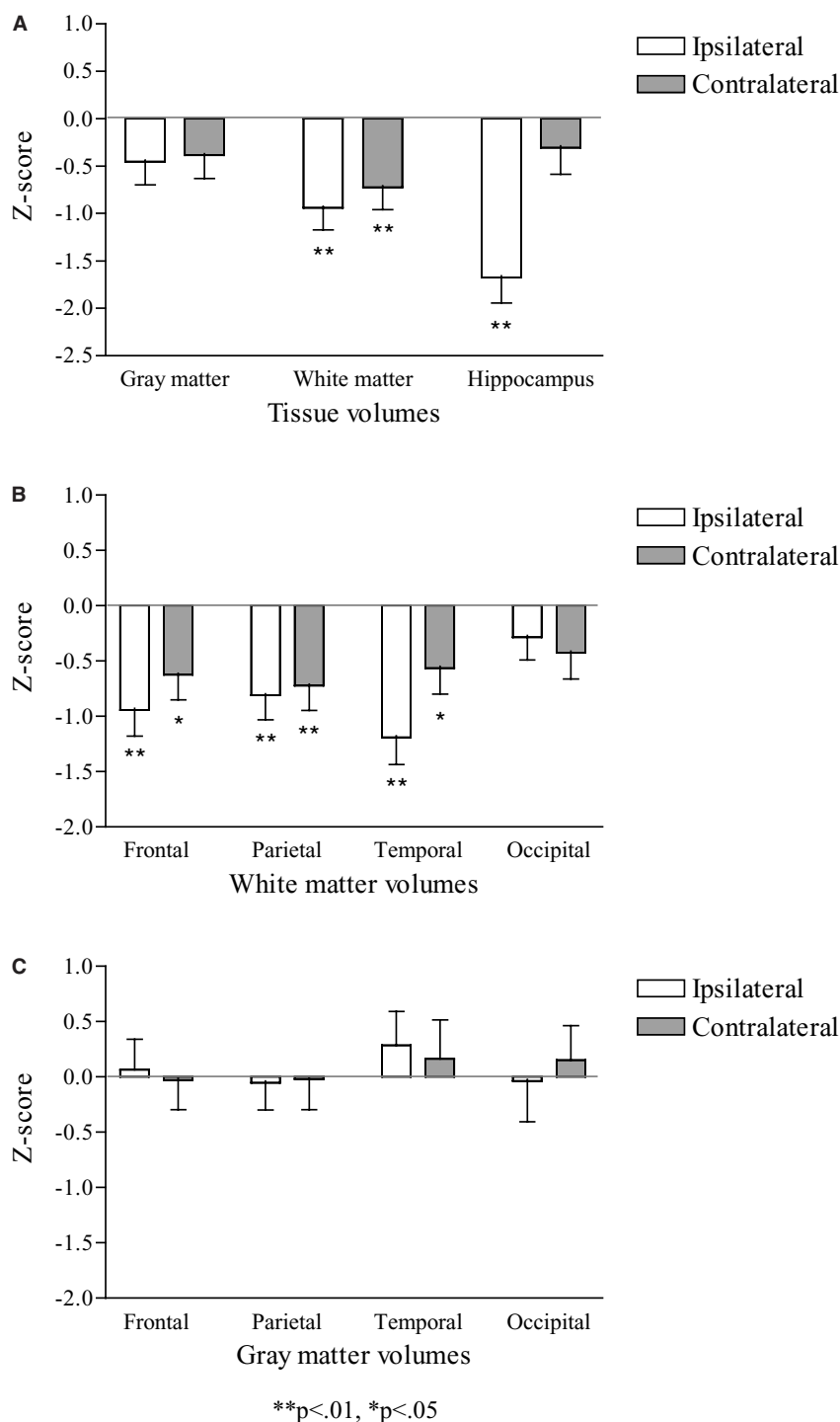
\*\*\*p<.001, \*\*p<.01, \*p<.05

TLE groups across the cortical lobar regions produced a nonsignificant main effect of group [ $F(16, 182) = 1.17$ ;  $p > 0.10$ ].

**Combined ipsilateral and contralateral MRI volumes in TLE versus controls**

Figure 3A–C illustrates the findings comparing the combined left and right TLE groups with controls for ipsilateral versus contralateral hemisphere white and gray tissue volume and hippocampus (top panel), ipsilateral and contralateral lobar white tissue volumes (middle panel),

and ipsilateral and contralateral lobar gray tissue volume (bottom panel). Consistent with the specific group contrasts detailed earlier but with more statistical power, the combined TLE groups show significant volume reduction in ipsilateral hippocampus [ $t(97) = 7.35$ ;  $p < 0.001$ ], but not contralateral hippocampus [ $t(97) = 1.35$ ;  $p = 0.19$ ]. Significant volume differences were also found in both ipsilateral [ $t(97) = 4.86$ ;  $p < 0.001$ ] and contralateral white tissue volume [ $t(97) = 3.98$ ;  $p < 0.001$ ], but not for ipsilateral [ $t(97) = 1.27$ ;  $p = 0.21$ ] and contralateral gray tissue volumes [ $t(97) = 0.99$ ;  $p = 0.33$ ]. At the lobar level



**FIG. 2.** Volumetric findings for the right temporal lobe epilepsy group.

for white matter tissue volumes, significant ipsilateral [ $t(97) = 3.76$ ;  $p < 0.001$ ] and contralateral [ $t(97) = 3.09$ ;  $p < 0.005$ ] volume reduction was seen in the frontal region, ipsilateral [ $t(97) = 5.00$ ;  $p < 0.001$ ], and contralateral temporal region [ $t(97) = 3.26$ ;  $p < 0.002$ ], and ipsilateral [ $t(97) = 4.11$ ;  $p < 0.001$ ] and contralateral parietal lobe region [ $t(97) = 3.39$ ;  $p < 0.001$ ]. A significant reduction appeared in the ipsilateral occipital lobe [ $t(97) = 2.39$ ;  $p < 0.05$ ] but not in the contralateral occipital region

[ $t(97) = 1.54$ ;  $p = 0.13$ ]. In contrast, no statistically significant differences were noted between the TLE group and controls across all lobar regions for gray matter tissue volume (all  $p$  values  $> 0.05$ ).

**Presence/absence of significant hippocampus volume loss**

The TLE groups were divided on the basis of the presence/absence of significant ipsilateral hippocampus

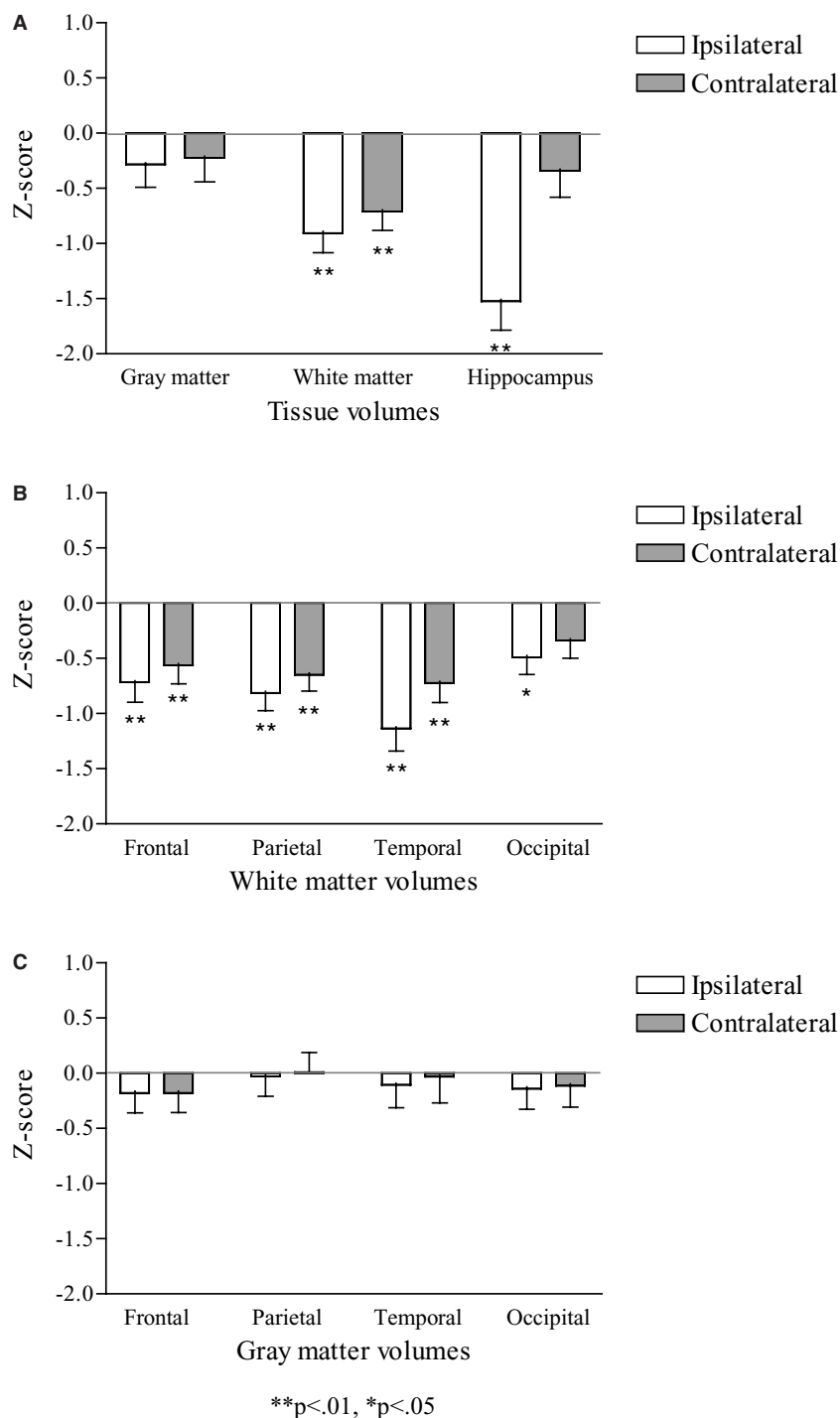


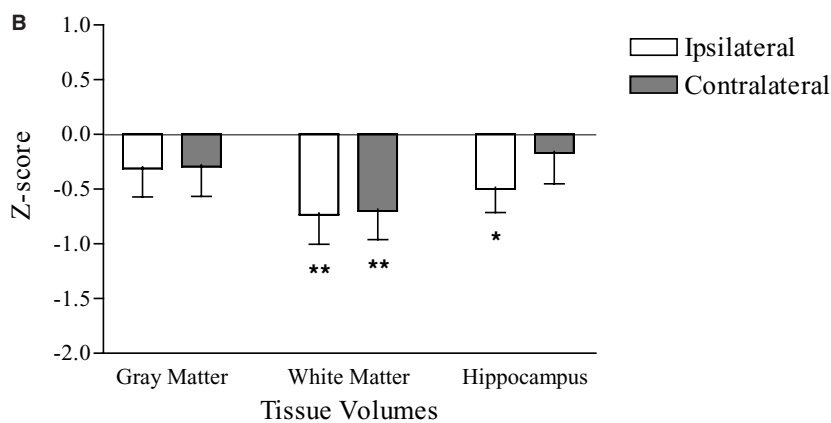
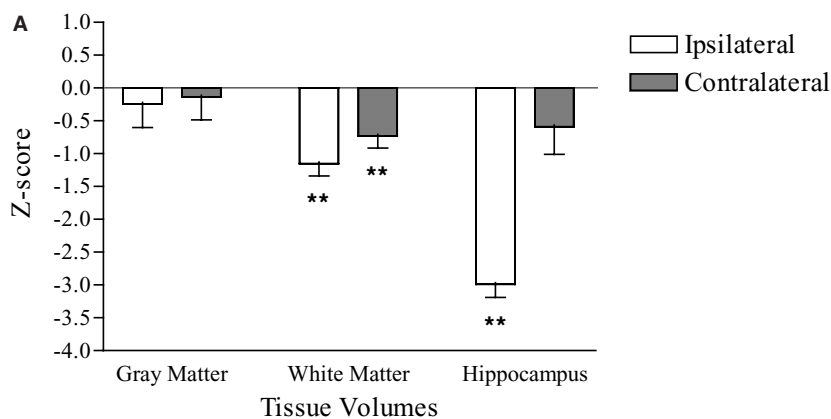
FIG. 3. Volumetric findings for combined right and left temporal lobe epilepsy groups.

volume loss, based on a 2-SD cutoff from the mean of the control group. This produced a group of 14 patients with significant hippocampus volume loss and 20 patients without significant hippocampus volume loss. As shown in Fig. 4, the pattern of findings described earlier is similar for both groups. Significant ipsilateral [ $F(2, 98) = 18.99$ ;  $p < 0.001$ ] and contralateral [ $F(2, 98) = 11.43$ ;  $p < 0.001$ ] reductions in cerebral white matter volume are apparent for both groups compared with controls. In contrast, no

significant group differences were found in either ipsilateral or contralateral gray matter volumes.

**Clinical seizure characteristics and volumetric abnormalities**

Analyses examining the relation between ipsilateral and contralateral MRI volumes and clinical seizure correlates were conducted for the combined left and right TLE groups to increase the sample size ( $n = 34$ )



**FIG. 4.** Volumes for subjects with hippocampal sclerosis (A), and subjects without hippocampal sclerosis (B).

\*\*p<.01, \*p<.05

and statistical power. The findings reported for the combined groups are similar when both groups were examined separately.

**Effects of chronicity and severity of epilepsy**

As shown in Table 3, increasing duration of epilepsy was significantly correlated with smaller ipsilateral hippocampal volume ( $r = -0.63$ ;  $p < 0.001$ ), and a larger asymmetry between the ipsilateral and contralateral hippocampal volumes ( $r = -0.62$ ;  $p < 0.001$ ), and cerebral white matter volumes ( $r = -0.57$ ;  $p < 0.001$ ) (i.e., ipsilateral volume smaller than contralateral volume). The duration relation was similar for both left and right TLE groups, and for those with a positive IPI history as well as those without a positive IPI history. In contrast, duration of epilepsy was not significantly correlated with gray matter volumes in the ipsilateral hemisphere, contralateral hemisphere, or gray matter volume asymmetry (all  $p$  values  $>0.05$ ).

The number of estimated lifetime generalized seizures was significantly related to ipsilateral hippocampus volume ( $r = -0.54$ ;  $p < 0.01$ ) and degree of white matter volume asymmetry ( $r = -0.39$ ;  $p < 0.05$ ). A higher number of lifetime generalized seizures was associated with smaller ipsilateral hippocampus volume and increas-

ing asymmetry in ipsilateral compared with contralateral white matter volume. Once again, no significant relation was evident between lifetime generalized seizures and indices of gray matter volume.

**TABLE 3.** Bivariate correlations of magnetic resonance imaging volumes with epilepsy duration, age at onset and number of lifetime generalized seizures

Region	Duration	Age at seizure onset	Generalized seizures <sup>a</sup>
<b>Ipsilateral region</b>			
Hippocampus	-0.63 <sup>b</sup>	0.35 <sup>c</sup>	-0.54 <sup>d</sup>
White matter	-0.23	0.27	-0.06
Gray matter	0.18	0.05	-0.08
<b>Contralateral region</b>			
Hippocampus	0.13	-0.01	-0.37
White matter	-0.05	0.09	-0.03
Gray matter	0.23	0.04	-0.01
<b>Volume asymmetry</b>			
Hippocampus	-0.62 <sup>d</sup>	0.25	-0.25
White matter	-0.57 <sup>d</sup>	0.62 <sup>d</sup>	-0.39 <sup>c</sup>
Gray matter	0.02	0.09	-0.15

<sup>a</sup>n = 25; nine subjects missing.  
<sup>b</sup>p < 0.001 level.  
<sup>c</sup>p < 0.05 level.  
<sup>d</sup>p < 0.01 level.

### Effects of neurodevelopmental factors

Comparisons between TLE subjects with and without a history of an IPI revealed a trend for a smaller ipsilateral hippocampus volume for the positive IPI history group [ $t(32) = 1.88$ ;  $p = 0.07$ ]. However, no significant group differences were seen for contralateral hippocampus volume, ipsilateral or contralateral white and gray matter volumes, or for indices of asymmetry in hippocampus or gray and white matter volumes (all  $p$  values  $>0.10$ ). Age at recurrent seizure onset was significantly correlated with ipsilateral hippocampus volume ( $r = 0.35$ ;  $p < 0.05$ ) and asymmetry of white matter volumes ( $r = 0.62$ ;  $p < 0.001$ ). Earlier age at onset is associated with decreased ipsilateral hippocampal volume and greater reduction in ipsilateral white matter relative to contralateral white matter volume.

## DISCUSSION

Two major sets of findings emerged from this study. First, examination of whole brain volumes provides further evidence that volumetric abnormalities among patients with chronic unilateral TLE extend beyond the affected ipsilateral hippocampus and temporal lobe. Specifically, chronic unilateral TLE patients showed the expected reduction in ipsilateral hippocampal volume, but also evident was significant volumetric reduction in cerebral white matter both ipsilateral and contralateral to the side of seizure onset compared with that in controls. Affected regions included both ipsilateral and contralateral temporal, frontal, and parietal lobes. In contrast, contralateral hippocampus was not significantly different between the TLE group and controls, and ipsilateral and contralateral cerebral gray matter volumes were reduced, but not significantly different from controls. This pattern of findings was seen in both the left and right TLE groups, reflecting symmetry of findings across the lateralized groups. These findings both confirm and extend a limited number of previous reports of whole brain volumetric abnormalities in unilateral TLE (17,19,21–24).

Second, clinical markers of neurodevelopmental insult as well as chronicity of epilepsy exhibited distinct patterns of relations across the MRI volume indices. Duration of epilepsy was associated with reduced ipsilateral hippocampus volume and ipsilateral white matter volume. Age at recurrent seizures was associated with ipsilateral hippocampus volume and white matter volume asymmetry. In contrast, neither age at onset nor duration of epilepsy was significantly correlated with contralateral hippocampus or cortical gray matter volumes.

### Hippocampal volume abnormalities in TLE

The presence of significant ipsilateral hippocampal volume abnormality in patients with unilateral chronic TLE was expected. The significant asymmetry in hippocampal volumes (ipsilateral volume  $<$  contralateral volume)

observed in both the left and right TLE groups is the characteristic MRI signature associated with unilateral TLE. We did not find evidence of significant contralateral hippocampus volume loss in either the left- or the right-TLE groups, which is consistent with the bulk of the MRI volumetric literature examining hippocampal volumes in chronic unilateral TLE (4,27,36).

Consistent with previous reports, we found evidence indicating that both neurodevelopmental factors (i.e., positive IPI history and early age at seizure onset) as well as chronicity-related factors (i.e., increasing duration and number of lifetime generalized seizures) affected ipsilateral but not contralateral hippocampal volumes (28,37,38). The impact of duration of epilepsy on ipsilateral hippocampal volume was evident in both the left and right TLE groups and was observed irrespective of the presence or absence of an IPI. This finding is consistent with results from cross-sectional studies (12,28), case study reports (39), and two recent longitudinal studies that indicate that ipsilateral but not contralateral hippocampus is more likely to show evidence of progressive volume loss (38,40).

### Temporal and extratemporal gray and white matter volumes

White matter abnormalities (e.g., loss of gray–white differentiation, diffuse glial cell proliferation, neuronal heterotopias) in the resected temporal lobes of TLE patients have been previously described (15,41). The current findings indicate that white matter volume loss in TLE may not be limited to the temporal lobe, but may be diffuse and bilateral. Although the identification of significant bilateral white matter brain volume abnormality in patients with unilateral TLE has not been the focus of previous MRI reports, it has been previously noted (21). Furthermore, recent investigations using voxel-based morphometry have demonstrated the presence of extratemporal white matter volume reduction (10), and progressive loss in white matter brain volume (diffusely) has also been noted in a heterogeneous sample of patients with chronic epilepsy (42). We also found evidence for bilateral white matter reductions regardless of the presence or absence of significant ipsilateral hippocampal volume reduction, a finding that is consistent with the results of a recent study examining temporal lobe white matter  $T_2$  relaxation increases in patients with and without evidence of unilateral hippocampal atrophy (43).

We previously suggested that white matter volume abnormality in TLE may reflect a neurodevelopmental vulnerability associated with an early insult to the developing brain, which affects the subsequent normal development of white matter connectivity (44). This hypothesis is consistent with findings reported on the effects of electroconvulsive-induced seizures in rats at different developmental stages (10,42) and recent findings of

significant MRI volume reduction and MRI diffusion abnormalities in the corpus callosum of chronic TLE patients with an early age at recurrent seizure onset (45,46). We have also called attention to the potential significance of white matter volume abnormalities in TLE in contributing to the widespread cognitive disturbances frequently evident among patients with unilateral TLE (24).

In the current study, age at seizure onset and duration of epilepsy were significantly related to both hippocampal and white matter volume asymmetry, but not to gray matter volume asymmetry. Thus, greater reduction of white matter volume and hippocampus in the ipsilateral hemisphere compared with the contralateral hemisphere was evident with earlier age at seizure onset and longer epilepsy duration. In addition, hippocampal volume asymmetry was significantly correlated with white matter volume asymmetry ( $r = 0.53$ ;  $p < 0.001$ ), suggestive of a common responsible process. In contrast, neither hippocampus volume asymmetry nor white matter volume asymmetry was significantly correlated with gray matter volume asymmetry ( $r$  values = 0.22 and 0.30, respectively;  $p$  values  $>0.05$ ). Consistent with this notion, both the ipsilateral hippocampus and ipsilateral white matter showed a similar pattern of relations with clinical seizure variables consistent with a “two-hit” model (28). In contrast, cortical gray matter volume was not significantly correlated with any of the clinical seizure variables examined and also was relatively independent of the integrity of hippocampus and white matter volumes.

The relative absence of temporal lobe and extratemporal lobe gray matter volume abnormalities (other than ipsilateral hippocampus) in the current study sample deserves mention. Several reports have identified volume loss in specific gray matter structures such as the amygdala, thalamus, and basal ganglia (10,11,13). However, these studies tend to focus on a single or limited region of interest without a broader investigation of whole brain morphometry. In this regard, the current study TLE sample does exhibit 4% overall reduction in total gray matter volume compared with controls. Although this volume reduction is not statistically significant, it is evident that gray matter volume is affected, albeit not to the same extent as white matter brain volume. MRI volume analysis based at the cortical lobar level may not adequately capture the volumetric reductions observed in specific gray matter structures that may be more substantially affected in TLE.

We have included a wide age range in the study sample (14–60 years), and this may affect the results of tissue segmentation, particularly among the younger subjects whose brains may not yet be fully myelinated. We do note that a similar number of subjects at the younger age (14–20 years) range are in both groups, so the potential influence of age is presumably similar for both the controls and the TLE sample. Education also was significantly lower

for the left TLE group compared with both the right TLE group and controls. It is unlikely, however, that the current findings are related to education level. First, a similar pattern of ipsilateral and contralateral volumetric abnormalities was evident for the right TLE group despite an education level similar to that of controls. In addition, the association of education with MRI indices was not significant.

In summary, the current study findings highlight the presence of MRI-identified extratemporal lobe volume abnormalities in unilateral TLE, which is particularly pronounced for white matter and is evident in a diffuse and bilateral fashion. Findings also suggest a similar responsible etiologic mechanism characterized by a combination of neurodevelopmental and chronicity factors for both hippocampus and white matter volume abnormalities. The potential implications of extrahippocampal abnormalities in TLE for surgery outcome (22) and cognitive status (24) have been noted, and warrant additional examination as a factor underlying the clinical and behavioral heterogeneity evident among TLE patients. However, we underscore the cross-sectional nature of the current study; studies using a longitudinal design are needed to clarify further the nature, course, and interrelation of MRI volume abnormalities in TLE.

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