



# Asymmetric Gray Matter Volume Changes Associated with Epilepsy Duration and Seizure Frequency in Temporal-Lobe-Epilepsy Patients with Favorable Surgical Outcome

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**Background and Purpose** This study aimed to estimate the changes in gray matter volume (GMV) and their hemispheric difference in patients with mesial temporal lobe epilepsy (MTLE) using a voxel-based morphometry (VBM) methodology, and to determine whether GMV changes are correlated with clinical features.

**Methods** VBM analysis of brain MRI using statistical parametric mapping 8 (SPM8) was performed for 30 left MTLE (LMTLE) and 30 right MTLE (RMTLE) patients and 30 age- and sex-matched healthy controls. We also analyzed the correlations between GMV changes and clinical features of MTLE patients.

**Results** In SPM8-based analyses, MTLE patients showed significant GMV reductions in the hippocampus ipsilateral to the epileptic focus, bilateral thalamus, and contralateral putamen in LMTLE patients. The GMV reductions were more extensive in the ipsilateral hippocampus, thalamus, caudate, putamen, uncus, insula, inferior temporal gyrus, middle occipital gyrus, cerebellum, and paracentral lobule in RMTLE patients. These patients also exhibited notable reductions of GMV in the contralateral hippocampus, thalamus, caudate, putamen, and inferior frontal gyrus. We observed that GMV reduction was positively correlated with several clinical features (epilepsy duration and seizure frequency in RMTLE, and history of febrile seizure in LMTLE) and negatively correlated with seizure onset age in both the RMTLE and LMTLE groups.

**Conclusions** Our study revealed GMV decreases in the hippocampus and extrahippocampal regions. Furthermore, the GMV reduction was more extensive in the RMTLE group than in the LMTLE group, since it included the contralateral hemisphere in the former. This difference in the GMV reduction patterns between LMTLE and RMTLE may be related to a longer epilepsy duration and higher seizure frequency in the latter.

**Key Words** mesial temporal lobe epilepsy, gray matter volume, voxel-based morphometry, hippocampal sclerosis, magnetic resonance imaging.

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## INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) is the most common type of refractory partial epilepsy, and is commonly associated with hippocampal sclerosis (HS).<sup>1,2</sup> Voxel-based morphometry (VBM) has emerged from recent developments in neuroimaging analysis techniques to become a popular technique for whole-brain magnetic resonance imaging (MRI) that allows focal differences between patients and matched healthy controls to be investigated.<sup>3</sup>

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Previous VBM studies have consistently demonstrated decreases in the gray matter volume (GMV) or gray matter concentration in the mesiotemporal structures ipsilateral to the epileptic focus, as well as the bilateral extratemporal regions, in unilateral MTLE patients.<sup>3-7</sup> Gray matter abnormalities have been reported most frequently in the hippocampus,<sup>5,8-11</sup> followed by the thalamus, parietal lobe, and cingulate gyrus. Changes have also been described in the parahippocampal gyrus, middle temporal gyrus, superior temporal gyrus, inferior temporal gyrus, fusiform gyrus, temporal pole, entorhinal cortex, amygdala, and perirhinal cortex.<sup>3-7,9,10,12-16</sup>

However, some of these studies have yielded discrepant results, presumably due to the different methodologies employed. For example, studies have differed with regard to the types of VBM methods applied (e.g., standard vs. optimized VBM), VBM-related parameters (the smoothing kernel, nuisance variables, and normalization scheme), template choice [statistical parametric mapping (SPM) templates vs. user-created templates], sample size (patients and controls), and characteristics of study subjects.

In the current VBM study, we aimed to identify the distribution of focal GMV reductions and hemispheric differences in unilateral MTLE patients who had undergone epilepsy surgery, had histological HS, and who showed a good post-surgical outcome for more than 2 years using SPM8 plus a Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL)<sup>17</sup> algorithm and a new segmentation toolbox.

We compared the brain GMV between MTLE patients and controls. Furthermore, we sought to determine the clinical implications of GMV changes by investigating their relationship with clinical features of the patients.

## METHODS

### Subjects and clinical information

This study included 30 left MTLE patients [LMTLE; age  $34.2 \pm 11.1$  years (mean  $\pm$  SD), age range 11–56 years, 16 females and 14 males] and 30 right MTLE patients (RMTLE; age  $36.9 \pm 9.5$  years, age range 19–57 years of age, 13 females and 17 males). The MTLE patients were enrolled based on the following inclusion criteria: 1) unilateral HS with no other lesion on brain MRI, 2) ictal electroencephalography (EEG) pattern arising from the ipsilateral temporal lobe to HS, 3) an anterior temporal lobectomy with amygdalohippocampectomy, and 4) seizure-free outcome after the surgery. All patients underwent a comprehensive presurgical evaluation including a combination of seizure semiology, ictal and interictal EEG results, neuropsychology, and neuroimaging findings. They underwent surgery (anterior temporal lobec-

tomy with amygdalohippocampectomy) and showed a good surgical outcome (Engle Class I) for at least 2 years postoperatively. In addition, HS was the only lesion in all patients pathologically verified by histological analysis. We excluded patients who had bilateral hippocampal atrophy, normal MRI findings, or multiple pathologies. Thirty age- and sex-matched healthy controls (age  $39.0 \pm 7.9$  years, age range 30–60 years, 15 females and 15 males) with no neurologic or psychiatric disorders were also included. Informed consent was obtained from all participants, and the institutional review board of the Samsung Medical Center approved the study protocol (IRB No. 2011-02-049).

### MRI

All of the included patients underwent high-resolution brain MRI in a 1.5-tesla scanner (GE Medical Systems, Milwaukee, WI, USA) equipped with an eight-channel head coil, yielding T1-weighted three-dimensional spoiled-gradient-recalled (SPGR), T2-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging scans. Coronal SPGR MRI images were obtained with the following parameters: 1.6 mm slice thickness, no gap, 124 slices, repetition time (TR)=30 ms, echo time (TE)=7 ms, flip angle (FA)=45 degrees, number of excitations (NEX)=1, matrix size= $256 \times 192$ , and field of view (FOV)= $22 \times 22$  cm. The voxel dimensions of the SPGR images were  $0.86 \times 0.86 \times 1.6$  mm. Oblique coronal FLAIR MRI was performed with the following settings: 4.0 mm slice thickness, 1.0 mm gap, 32 slices, TR/TE=10,002/127.5 ms, 1 NEX, matrix size= $256 \times 192$ , and FOV= $20 \times 20$  cm. Oblique coronal T2-weighted MRI images were obtained using the following parameters: 3.0 mm slice thickness, 0.3 mm gap, 56 slices, TR/TE=5,300/99 ms, FA=90 degrees, 3 NEX, matrix size= $256 \times 192$ , and FOV= $20 \times 20$  cm.

### Data preprocessing

For all subjects, Digital Imaging and Communications in Medicine format images were transformed into the ANALYZE format specified by the Mayo Clinic using ITK-SNAP freeware (Paul Yushkevich; <http://www.itksnap.org>). A recent VBM approach, including the new segmentation toolbox (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) and DARTEL<sup>17</sup> algorithm in SPM8, was applied to anatomical T1-weighted MRI data to detect GMV differences between unilateral MTLE patients and healthy controls. In the pre-processing stage, all raw images were segmented and spatially normalized using the new segmentation toolbox that is an extension of the default unified method in SPM8,<sup>18</sup> but uses a novel segmentation approach involving an adaptive maximum-a-posterior technique without tissue priori, and additionally uses partial volume estimation with a simplified

mixed model. Furthermore, two denoising methods (spatially adaptive nonlocal-means denoising filter and a classical Markov random-field approach) were applied to the segmentation process. Another important extension to the SPM8 segmentation is integration of the DARTEL normalization in the toolbox, and thus no additional Montreal Neurological Institute (MNI) normalization is necessary. The segmented and normalized images were then modulated and smoothed with a 10-mm full-width-half-maximum isotropic Gaussian kernel to allow for high variability in the intersubject gyral anatomy, while also preserving the total gray matter signal in the normalized tissue images.<sup>19</sup> We further performed manual hippocampal volume (HV) measurements using ANALYZE software (version 10.0, Mayo Clinic) to investigate how changes in GMV were associated with the HV in all patients and healthy controls, according to a previously described anatomical protocol.<sup>20</sup> The entire HV was measured from the anterior head to the posterior tail, including the cornu ammonis, gyrus dentatus, hippocampus, and subiculum. The anterior boundary of the hippocampus was identified as the alveus. The lateral border of the hippocampus was delineated against the entorhinal cortex based on the upper margin of the white matter of the subiculum. The posterior end of the hippocampus was taken as the point at which the tail of the hippocampus disappeared. The rater manually traced the alveus according to the defined hippocampal boundary criteria. In order to calculate the intrarater correlation coefficients (ICCs), the brain images of each subject were manually traced twice. The ICCs were 0.96 and 0.95 for the left and right HVs, respectively.

### Statistical analysis

Prior to statistical analyses, differences in sex, age, and whole-brain volume between patients and control groups were examined using the independent-samples *t*-test, with *p* values of <0.05 being considered indicative of statistical significance. Spatially processed images from the LMTLE and RMTLE

patients and healthy controls were statistically compared on a voxel-by-voxel basis using the general linear model, which can be used to detect increases or decreases in gray matter in specific brain regions. Whole-brain voxel analyses were corrected for multiple comparisons using a topological false discovery rate (FDR) statistical threshold of  $p_{\text{FDR}} < 0.05$  with an extent threshold for clusters with at least 100 contiguous voxels (each voxel had a size of  $1 \times 1 \times 1$  mm). We confirmed a set of MNI stereotaxic coordinates (*x*, *y*, *z*) provided in the SPM results by visual analyses and further converted them into anatomical names using xjView8.4 (Xu Cui, www.alive-learn.net/xjview8), which is compatible with SPM8. For all voxel-wise analyses, we applied analysis of covariance with age and sex as nuisance covariates to minimize the influence of potential confounding factors, and we corrected for the intracranial volume by globally correcting the individual head sizes between the RMTLE, LMTLE, and healthy control groups. No grand-mean scaling and non-sphericity correction were performed or set. Implicit masking was used to restrict the analysis to one tissue type (gray matter). The intracranial volume was manually measured on sagittal T1-weighted MRI images of each subject using ITK-SNAP software. For MTLE patients, the correlations of changes in GMV with the duration of epilepsy, seizure frequency, age at seizure onset, history of febrile seizure, and number of anti-epileptic drugs (AEDs) were assessed by applying an uncorrected probability ( $p_{\text{UNC}}$ ) significance value of <0.001. The extent threshold for the whole brain was set to  $K_E > 100$ .

## RESULTS

### Demographic and clinical characteristics

All patients and healthy controls were right-handed and predominantly middle-aged (mean age 33.4 years). We inspected T1-weighted, T2-weighted, and FLAIR images to exclude subjects with gross structural abnormalities observable in brain MRI scans. The detailed clinical findings for the pa-

**Table 1.** Demographic and clinical information for patients with left mesial temporal lobe epilepsy (LMTLE), patients with right mesial temporal lobe epilepsy (RMTLE), and healthy controls (HC)

Clinical parameter	LMTLE	RMTLE	HC	<i>p</i>
Number of subjects (males/females)	30 (14/16)	30 (17/13)	30 (15/15)	NS
Age, years; mean $\pm$ SD (range)	34.2 $\pm$ 11.1 (11–56)	36.9 $\pm$ 9.5 (19–57)	39.0 $\pm$ 7.9 (30–60)	NS
Duration of epilepsy, years	17.3 $\pm$ 9.1 (6–40)	18.7 $\pm$ 6.2 (8–41)	-	NS
Number of seizures per month	3.0 $\pm$ 3.3 (0.2–18)	3.8 $\pm$ 7.9 (0.2–45)	-	NS
Seizure onset age, years	17.0 $\pm$ 8.6 (3–32)	15.5 $\pm$ 9.2 (2–37)	-	NS
History of febrile seizure	20	15	-	NS
Number of current AEDs	2.7 $\pm$ 0.7 (1–4)	2.8 $\pm$ 0.9 (1–5)	-	NS

Data are mean $\pm$ SD (range) values or *n* values.

AED: antiepileptic drug, NS: not significant in independent-samples *t*-test.

tients with MTLE and control subjects are summarized in Table 1. No significant differences in any of the demographic data (age or sex) were observed between the control, LMTLE, and RMTLE groups. The seizure frequency, average duration of epilepsy, seizure onset age, history of febrile seizure, and number of AEDs did not differ significantly between the LMTLE and RMTLE groups.

### Reduced GMV in MTLE

Relative to healthy controls, patients with LMTLE showed significant GMV reductions in the left hippocampus, left parahippocampal gyrus, bilateral thalamus, and right putamen ( $p_{FDR}<0.05$ ) (Fig. 1, Table 2). In patients with RMTLE, the GMV was significantly decreased in the bilateral hippocampus, right parahippocampal gyrus, right uncus, right insula, right middle temporal gyrus, right inferior temporal gyrus, bilateral thalamus, bilateral putamen, bilateral caudate, left inferior frontal gyrus, right paracentral lobule, right middle occipital gyrus, and right cerebellum ( $p_{FDR}<0.05$ ) (Fig. 2, Table 2). We observed that the whole-brain GMVs in patients with RMTLE were not only negatively correlated with the duration of epilepsy and seizure frequency, but also positively correlated with seizure onset age ( $p_{UNC}<0.001$ ). More-

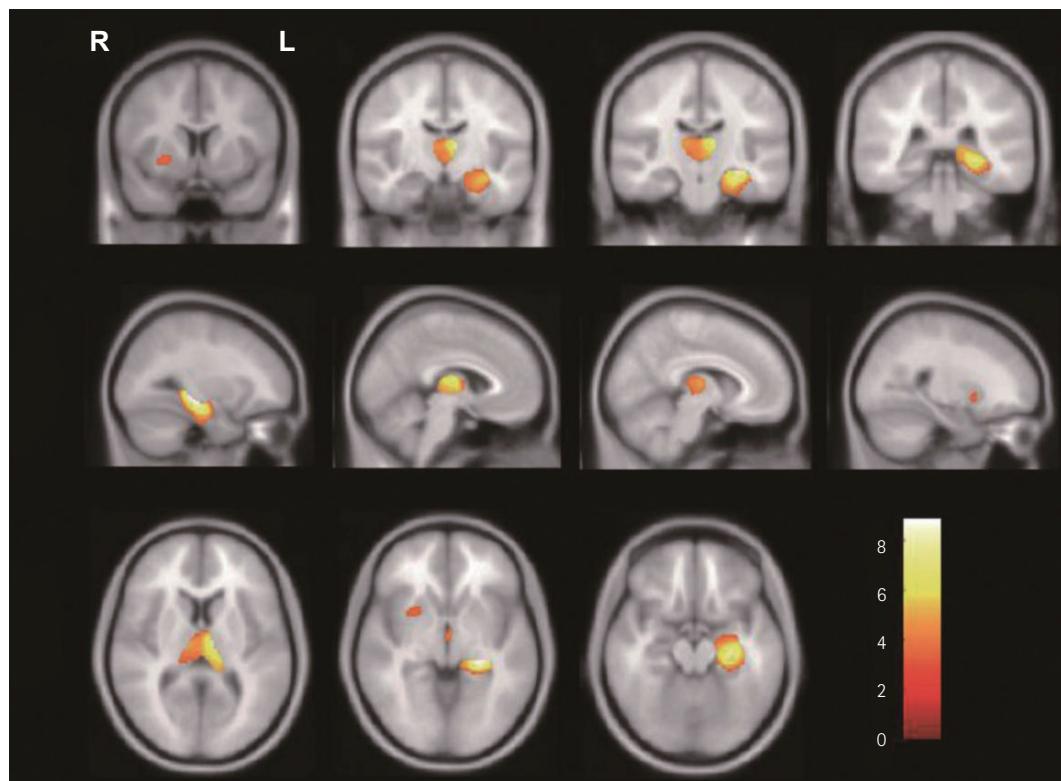
over, the whole-brain GMVs in patients with LMTLE were positively correlated with seizure onset age and negatively correlated with a history of febrile seizure ( $p_{UNC}<0.001$ ) (Fig. 3, Table 3).

## DISCUSSION

We applied VBM analysis to patients with MTLE and observed GMV reductions in the hippocampus and extrahippocampal regions. The main findings of this study were as follows:

1. Patients with LMTLE or RMTLE exhibited a significant GMV reduction in the ipsilateral mesial temporal lobe (including in the hippocampus and the parahippocampal gyrus) on the side of the seizure focus.
2. In patients with RMTLE, widespread reductions of GMV were observed in both cortical and subcortical structures.
3. GMV was negatively correlated with epilepsy duration and seizure frequency in patients with RMTLE, and positively correlated with seizure onset age in both LMTLE and RMTLE groups and with febrile seizure in patients with LMTLE.

Previous VBM studies have drawn conflicting conclusions



**Fig. 1.** Statistical brain map revealing gray matter volume (GMV) reductions in the brains of patients with left mesial temporal lobe epilepsy (LMTLE) compared with controls. Decreased GMV in patients with LMTLE in the ipsilateral (left) hippocampus, bilateral thalamus, and contralateral (right) putamen. These findings were significant at a corrected false discovery rate (FDR) statistical threshold of  $p_{FDR}<0.05$ . The left side of the brain images corresponds to the right hemisphere.

regarding GMV reduction patterns in patients with temporal lobe epilepsy (TLE), and their association with unilateral HS. Some studies found that the loss of gray matter was more extensive in patients with LMTLE than in those with RMTLE.<sup>6,21,22</sup> Another study found that the bilateral frontal lobe and the right cingulate gyrus are more susceptible to injury in patients with left TLE than in those with right TLE, and that these regions are involved in cognitive disorders and impaired executive functions.<sup>23</sup> In contrast, we observed that the GMV reduction was more extensive in patients with RMTLE than in those with LMTLE. A widespread pattern of GMV reduction in RMTLE is consistent with the results obtained in the VBM-MRI study<sup>11</sup> for the ipsilateral/contralateral insula, especially the contralateral thalamus, in RMTLE compared with LMTLE. Those authors concluded that the magnitude and extent of right mesiotemporal connectivity to the extrahippocampal structures—especially to the contralateral thalamus—are greater in RMTLE than in LMTLE. Another study also found that the GMV reductions in the contralateral

hippocampus ( $p=0.065$ ) and thalamus ( $p=0.052$ ) were more pronounced in RMTLE, even though distinct patterns of structural and metabolic changes within both hippocampal and thalamic regions were observed in two subgroups.<sup>24</sup> That study did not explain these differences based on the clinical factors of patients in each group, such as epilepsy duration, seizure frequency, age at seizure onset, or interictal EEG pattern, instead explaining these differences by noting that significant correlations between neuroanatomical and functional changes were found only in the RMTLE patients.

Some VBM studies have noted that the degree of atrophy and regional distribution differ between LMTLE and RMTLE groups. Some studies have revealed a more widespread hemispheric GMV reduction in LMTLE<sup>6,9,22</sup> or an identical pattern of GMV decrease in LMTLE and RMTLE patients.<sup>5</sup> These discrepancies among the studies—in terms of variations in GMV decreases—probably reflect variations in methodology, such as the absence of customized templates,<sup>5</sup> the types of correlations compared between patients and

**Table 2.** Brain regions with significant gray matter volume reduction in patients with unilateral mesial temporal lobe epilepsy (MTLE) compared with control subjects

Location	Side	Peak level				MNI coordinates (mm)		
		T	K <sub>E</sub>	Z <sub>E</sub>	P <sub>FDR</sub>	x	y	z
<b>LMTLE patients</b>								
Hippocampus	L	8.83	5,251	7.00	<0.001	-27	-30	-6
Parahippocampal gyrus	L	8.83	1,548	7.00	<0.001	-24	-32	-8
Thalamus	L	7.65	512	6.34	<0.001	-9	-15	11
	R	5.19	153	4.69	<0.001	11	-15	11
Putamen	R	3.51	128	3.33	0.030	27	9	-5
<b>RMTLE patients</b>								
Inferior frontal gyrus	L	3.55	132	3.37	0.016	-50	30	-3
Paracentral lobule	R	3.38	140	3.23	0.023	26	-33	-6
Hippocampus	L	4.99	443	4.53	<0.001	-18	-30	-6
	R	11.20	10,095	Inf.	<0.001	30	-18	-18
Parahippocampal gyrus	R	11.20	2,946	Inf.	<0.001	28	-37	-8
Uncus	R	11.20	254	Inf.	<0.001	8	11	4
Insula	R	11.20	1,935	Inf.	<0.001	38	-2	3
Superior temporal gyrus	R	3.35	127	3.19	0.024	52	10	-12
Middle temporal gyrus	R	3.35	121	3.19	0.024	59	4	-14
Inferior temporal gyrus	R	3.35	145	3.19	0.024	60	-4	-20
Thalamus	L	4.79	174	4.38	0.001	-6	-21	9
	R	4.99	685	4.53	0.046	3	-15	9
Putamen	L	3.41	180	3.24	0.022	42	-59	11
	R	5.29	513	4.76	0.049	-28	-33	-17
Caudate	L	4.03	447	3.77	0.005	-15	20	0
	R	4.75	463	4.35	0.001	17	18	0
Middle occipital gyrus	R	4.22	239	3.92	0.003	33	-75	21
Cerebellum	R	3.67	156	3.46	0.012	9	-71	-54

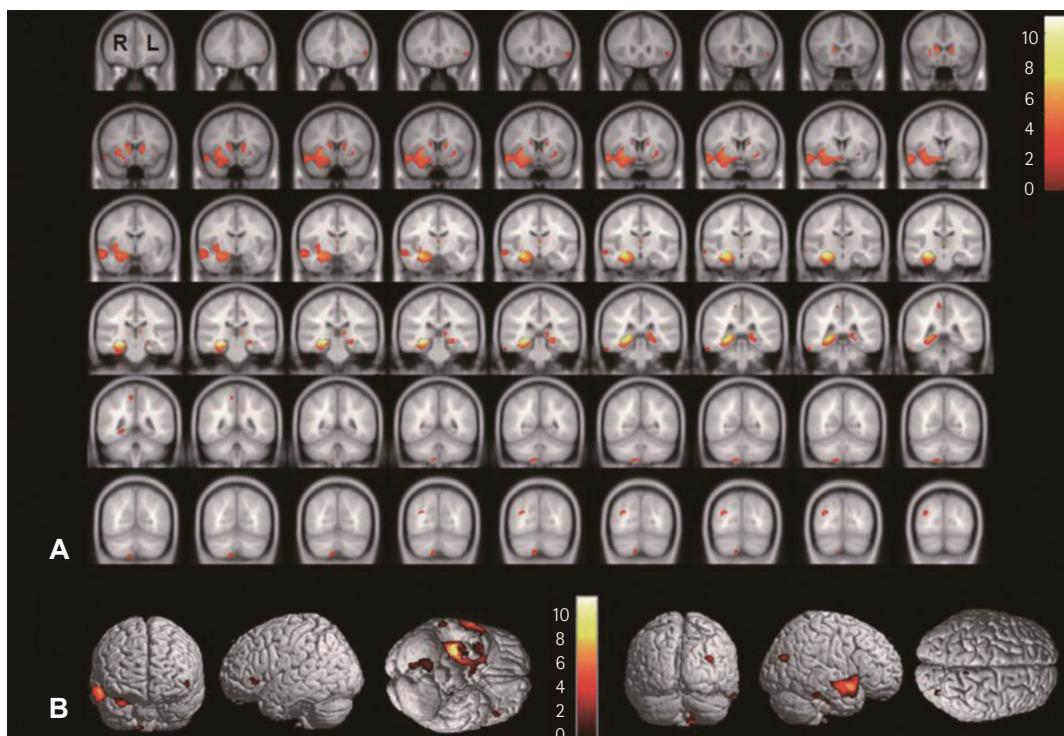
FDR: false discovery rate, Inf: infinity (z-score >7.0), K<sub>E</sub>: cluster extent threshold (=100 voxels), L: left, MNI: Montreal Neurological Institute, R: right, T: test statistics, ZE: z-score (the number of standard deviations away from the mean).

controls,<sup>6</sup> the cortical thickness measurements, or the *t*-test applied to the adjusted local GMV in the present study. Some results were based on only small samples.<sup>22</sup> It is significant that all of our patients had been seizure-free for 24 h, given that seizures very close to the time of scanning might influence the VBM analysis.

The extensive GMV reduction observed in RMTLE in this study is supported by the following findings: first, the GMV reduction was negatively correlated with several clinical factors, including epilepsy duration and seizure frequency, in the RMTLE group, but not in the LMTLE group. Although the correlations detailed in Table 3 (at the level of a cluster extent threshold of  $K_E \geq 100$ ) do not cover all of the regions in which the RMTLE and LMTLE patients differed, we identified that, at borderline significance, GMV reductions in the middle frontal gyrus [ $K_E=91$ , coordinates=(39,48,12),  $p_{FDR}=0.020$ ] and temporal subgyral [ $K_E=55$ , coordinates=(47,-4,-18),  $p_{FDR}=0.027$ ] areas were negatively correlated with the duration of epilepsy and seizure frequency, respectively. Second, the average ipsilateral and contralateral HVs were slightly smaller in patients with RMTLE than in patients with LMTLE (ipsilateral: RMTLE=1898±559 mm<sup>3</sup>, LMTLE=1973±462 mm<sup>3</sup>,  $p=0.32$ ; contralateral: RMTLE= 3110±453 mm<sup>3</sup>, LMTLE=3287±449

mm<sup>3</sup>,  $p=0.094$ ). Moreover, HVs in RMTLE were negatively correlated with the epilepsy duration ( $p=0.004$ ,  $r=-0.505$ ). This conclusion is supported by a recent study<sup>25</sup> that examined patterns of changes in GMV and white-matter connectivity in TLE patients with or without HS. That study found that the damage to the white matter was more extensive in TLE patients with HS than in those without HS, despite widespread extrahippocampal GMV reduction being observed in both groups. Those authors suggested that the positive correlation between ipsilateral HV loss and fractional anisotropy (FA) reduction of the corpus callosum and ipsilateral cingulum in the group of patients with TLE and HS supports the hypothesis that neuronal dysfunction and white-matter abnormality are due to the excitotoxic effects of spreading epileptogenic activity in the hippocampus, and in extrahippocampal brain regions that are directly or indirectly connected to it.

We observed GMV reductions in the subcortical region and bilateral thalamus in both MTLE groups, with the GMV reduction being greater in the ipsilateral thalamus than in the contralateral thalamus. These results are consistent with those of previous studies.<sup>12,26</sup> The thalamus has been widely considered to be part of a mesial temporal-limbic network, and to exhibit widespread reciprocal connections with sub-



**Fig. 2.** Statistical brain map revealing GMV reductions in the brains of patients with right mesial temporal lobe epilepsy (RMTLE) compared with control subjects. A: Decreased GMV in patients with RMTLE in the bilateral hippocampus, right parahippocampal gyrus, right uncus, right insula, bilateral thalamus, bilateral putamen, bilateral caudate, right inferior temporal gyrus, right superior/middle/inferior temporal gyrus, right middle occipital gyrus, right cerebellum, and left inferior frontal gyrus. These findings were significant at  $p_{FDR}<0.05$ . B: Brain regions with decreased GMV are shown on a rendered three-dimensional brain surface. The left side of the brain images corresponds to the right hemisphere. GMV: gray matter volume.

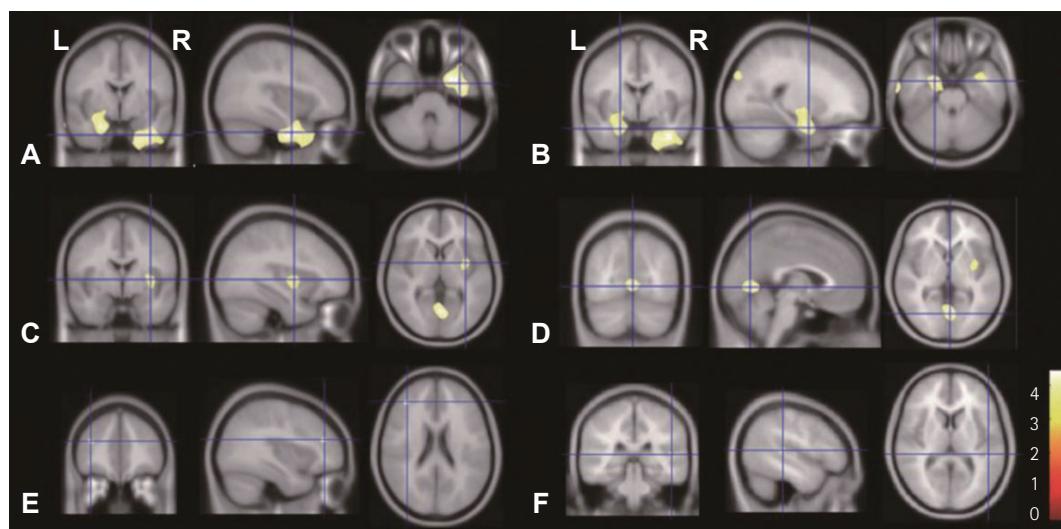
cortical structures and other cortical regions. The thalamus might play an important role in determining the extent of seizure propagation to other brain regions.<sup>13,17,20-24,26,27</sup> The findings of other studies also support the idea that structural abnormalities in the thalamus influence the pathogenesis of TLE seizures.<sup>13,28,29</sup> These studies have suggested that the ipsilateral thalamic GMV reduction could be associated with HS, and that contralateral thalamic atrophy could be caused by

the secondary generalization of seizure activities via the interhemispheric pathway. Similarly, we found in the present study that the GMV reductions in the caudate and putamen were greater in the RMTLE group than in the LMTLE group. These results are similar to those obtained in previous VBM studies.<sup>9</sup> We hypothesize that the atrophic pattern of basal ganglia could be influenced by clinical factors including the degree of HS, epilepsy duration, seizure onset age, and sei-

**Table 3.** Brain regions with significant correlations between GMV and clinical parameters in patients with unilateral MTLE

Group	Location	Peak level			MNI coordinates (mm)			
		T	Z <sub>E</sub>	P <sub>UNC</sub>	x	y	z	
<b>RMTLE</b>								
Duration of epilepsy (-)	Middle frontal gyrus	R	4.03	3.55	<0.001	29	-1	59
	Precentral gyrus	R	3.62	3.25	0.001	48	15	9
	Parietal lobe (subgyral)	L	3.49	3.16	0.001	-32	-45	49
Seizure frequency (-)	Temporal lobe (subgyral)	R	3.77	3.36	<0.001	46	-33	-5
Seizure onset age (+)	Superior frontal gyrus	L	3.69	3.30	<0.001	-9	-7	67
	Middle temporal gyrus	R	4.16	3.64	<0.001	37	-2	-35
	Parahippocampal gyrus	L	3.99	3.52	<0.001	-23	-2	-27
	Medial globus pallidus	L	3.85	3.42	<0.001	-17	-7	-6
	Cuneus	L	3.84	3.41	<0.001	-23	-88	33
<b>LMTLE</b>								
Seizure onset age (+)	Occipital lobe	R	4.18	3.65	<0.001	2	-71	0
	Extranuclear	R	3.82	3.40	<0.001	34	-2	3
	Insula	L	3.56	3.20	0.001	-35	2	-5
Febrile seizure (-)	Middle frontal gyrus	L	3.77	3.36	<0.001	-38	41	21
	Superior temporal gyrus	R	3.47	3.14	0.001	48	-33	9

+: positive correlation, -: negative correlation, GMV: gray matter volume, L: left, MNI: Montreal neurological institute, MTLE: mesial temporal lobe epilepsy, T: test statistics, R: right, UNC: uncorrected, ZE: z-score (the number of standard deviations away from the mean).



**Fig. 3.** Brain regions exhibiting significant correlations between changes in GMV and clinical parameters. A and B: Seizure onset age was positively correlated with the GMVs of the right middle temporal gyrus (A) and left parahippocampal gyrus (B) in patients with RMTLE. C and D: In LMTLE patients, seizure onset age was positively correlated with GMV changes in the right extranuclear (C) and right occipital (D) lobes. E and F: Febrile seizures were negatively correlated with GMV changes in the left middle frontal gyrus (E) and right superior temporal gyrus (F) in patients with LMTLE. These findings were significant at an uncorrected  $p$  value of  $<0.001$ . GMV: gray matter volume, LMTLE: left mesial temporal lobe epilepsy, RMTLE: right mesial temporal lobe epilepsy.

ture frequency in patients with MTLE.<sup>30-32</sup>

GMV reduction in the left uncus was previously reported in patients with left TLE.<sup>33</sup> Those authors suggested that the uncus damage could be associated with the febrile seizures and status epilepticus being more intense in left TLE than in right TLE. However, we found significant GMV reductions in the right uncus in the RMTLE group. The GMV reduction in the right uncus, which lies anatomically at the anterior and most-medial portion of the parahippocampal gyrus, may be related to the more-frequent seizures propagated from the ipsilateral hippocampus in the patients with RMTLE. We also observed GMV reductions in the bilateral inferior frontal gyrus. This finding may be explained by structural or functional deficits caused by the propagation of epileptic discharges from the temporal epileptic focus to the frontal lobes that have been observed in MTLE (e.g., damage to fronto-subcortical circuits, volume loss, and metabolic changes in the extratemporal regions).<sup>34-36</sup>

In conclusion, our study has revealed the extent and asymmetric pattern of brain GMV reductions in patients with RMTLE and LMTLE using the VBM approach in SPM8 plus the DARTEL algorithm and a novel segmentation toolbox. We detected that the structural abnormalities in the bilateral subcortical and ipsilateral extrahippocampal areas were more extensive in the RMTLE group. Furthermore, we found that the GMV reductions were positively correlated with multiple clinical factors (duration of epilepsy and seizure frequency in RMTLE, and history of febrile seizure in LMTLE) and negatively correlated with seizure onset age in both groups. Our study indicates that the SPM8-based VBM method may be useful for obtaining a deeper understanding of the pathophysiology and epileptic networks involved in MTLE.

#### Conflicts of Interest

The authors have no financial conflicts of interest.

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