Hippocampal and thalamic atrophy in mild temporal lobe epilepsy

A VBM study

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ABSTRACT

Background: Patients with temporal lobe epilepsy (TLE) often have mild drug-responsive epilepsy which is frequently associated with MRI detectable mesial temporal sclerosis (MTS), indicating that MTS is not necessarily related to seizure severity. To better define the anatomic substrates associated with TLE, we applied voxel-based morphometry (VBM) analysis to patients with mild TLE.

Methods: Optimized VBM was applied to the MRI brain images of 95 consecutive unrelated patients who were diagnosed with mild TLE and to 37 healthy controls. We complemented the investigation by calculating the gray matter volume of regions of interest (ROIs) in the bilateral hippocampus. Standard MRI scans revealed evidence of MTS (pTLE) in 34 patients, and no evidence of MTS in the remaining 61 (nTLE).

Results: The VBM analysis provided evidence of a reduction in gray matter volume in the hippocampus and thalami. The gray matter volume reduction in the thalamic and hippocampal networks was significantly more severe in patients with pTLE than in the nTLE or the control groups (at a threshold of FWE-corrected $p < 0.05$). Patients with nTLE showed the same gray matter abnormalities at an uncorrected statistical threshold ($p < 0.001$) compared to normal controls. ROI analysis confirmed the ipsilateral hippocampal atrophy that was detected in routine MRI scans.

Conclusions: The structural abnormalities seen in patients with mild temporal lobe epilepsy (TLE) demonstrate that a temporo-limbic pathway, which includes the thalamus, plays a major role in the pathogenesis of TLE. It is likely that other factors, especially genetic ones, play a major role in the causation and severity of TLE. ***Neurology*® 2008;71:1094–1101**

GLOSSARY

ANCOVA = analysis of covariance; **ANOVA** = analysis of variance; **FC** = febrile convulsion; **FWE** = family-wise error; **GM** = gray matter; **Hf** = hippocampus; **MTLE** = mesial TLE; **MTS** = mesial temporal sclerosis; **nTLE** = patients with TLE without mesial temporal sclerosis; **pTLE** = patients with TLE with mesial temporal sclerosis; **ROI** = region of interest; **TIV** = total intracranial volume; **TLE** = temporal lobe epilepsy; **VBM** = voxel-based morphometry; **WM** = white matter.

Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy in adults,[1-3] and mesial temporal sclerosis (MTS) represents the most common underlying pathologic abnormality, as demonstrated at autopsy and postresection studies.[4,5] Since the early 1990s, it has become accepted that MTS may be evidenced in conventional MRI investigations as hippocampal atrophy and abnormal signal characteristics.[6,7] Pathologic studies of mesial TLE (MTLE) also illustrated that damage and volume losses are not confined to the hippocampus (Hf) but also involve the amygdala and parahippocampal regions, and often extend to extratemporal cortical regions and subcortical structures as well.[5] The damage to regions outside the Hf and amygdala are subtle and complex, and they are consequently not easily detectable with standard MRI techniques.[8]

Quantitative MRI measures are more sensitive in detecting Hf and extrahippocampal pathology and have shown significant volume loss outside the temporal lobe in MTLE.[9,10] Previ-

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ous studies of MTLE have concentrated on manual quantitative analysis and visual inspection, but such analyses are operator dependent.[10,11] Automated unbiased voxel-based methods seem to be more rigorous image analysis procedures of the whole brain in an operator-independent environment as they obviate effects of a priori assumptions and correct carefully for potential technical artifacts.[12] Voxel-based morphometry (VBM) has been implemented in various studies of TLE and illustrated that pathology in TLE extends beyond the mesiotemporal structures such as the frontal regions, cingulum, and thalamus.[13-15] All these VBM studies, however, have been performed in refractory MTLE, so it remains unclear if such abnormalities represent the consequence of ensuing repeated seizures or reflect the extension of the epileptogenic network into the extratemporal structures.

Epidemiologic studies[16,17] in recent years show growing evidence that many patients with MTLE have mild courses and enter remission, with or without medication. Since 1998, our group has focused on studying patients with mild drug-responsive TLE.[18,19] We showed recently that nearly 40% of our patients with mild TLE have MRI detectable MTS.[20] Afterwards, other studies further supported our observation.[21] In this way, such findings indicated that MTS is not necessarily related to seizure severity and that the relationship between mild TLE and severe pharmacoresistant TLE seems to be far more complex, and these conditions might lie on a biologic continuum.[22-24]

This population of patients with mild TLE offers an excellent opportunity to better determine the biologic substrates underlying TLE and the extent to which these are the same as refractory TLE. Thus, the aim of this study was to perform VBM analysis on patients with mild TLE and on a normal control group.

METHODS

Patients. Demographic features of our population are summarized in table 1. Data and evaluation procedures on our patients with TLE have been reported in greater detail elsewhere.[18-20] The study group consisted of 95 consecutive unrelated patients (51 women, mean age 36.6 ± 15.8 years; range 10 to 75) who were diagnosed with TLE and 37 healthy controls (25 women, mean age 37.3 ± 10.6 years). The mean age at seizure onset was 21.4 ± 21.4 years, and the mean duration of epilepsy was 15.1 ± 15.2 years.

All patients and controls were matched for age and sex and gave informed consent to participate in this study. All patients had been seizure free for at least 2 months before the scanning. In each patient, the diagnosis of TLE was made on the basis of a range of clinical seizure semiology, typical temporal auras,[25] EEG and MRI criteria[6,7] that are considered to be reliable indicators of TLE.[25] It is possible that some patients could have an independent bitemporal onset. Any suggestion of seizure onset outside the mesial temporal structures, by semiology or EEG findings, was an exclusion criterion. The diagnosis of TLE was mainly based on typical temporal auras or interictal EEG discharges with a maximum over the temporal lobes.[25] Lateralization was based on lateralized epileptiform discharges, with or without lateralized seizure features. In each patient with MRI features of MTS, EEG discharges were classified as concordant or discordant to the MRI presence of MTS. In all patients, MRI did not

Table 1 Demographic and EEG features of patients with temporal lobe epilepsy (TLE) and controls

	pTLE	nTLE	Controls	p Level (t or χ^2)
No.	34	61	37	
Sex (%)	19 female (56%)	32 female (53%)	12 female (56%)	0.07
Age, y	36.26 ± 15.25	36.75 ± 16.09	37.32 ± 10.61	0.9
Age at onset, y	19.82 ± 15.47	22.39 ± 13.63	—	0.39
Duration, y	16.47 ± 12.48	14.36 ± 12.60	—	0.41
Family history of FC/epilepsy, n (%)	14 (42%)	14 (23%)	—	0.048
Antecedent FCs, n (%)	9 (27%)	5 (8%)	—	0.035
EEG focus			—	
Right	17	16	—	0.52
Left	12	18	—	
Bilateral	2	9	—	
Normal	3	13	—	

pTLE = patients with TLE with mesial temporal sclerosis; nTLE = patients with TLE without mesial temporal sclerosis; FC = febrile convulsion.

detect any mass lesion such as tumor, cortical dysgenesis, vascular lesion, malformation, or post-traumatic scars. MRI allowed the diagnosis of MTS based on a characteristic pattern of abnormalities.[6,7]

All patients had a mild epileptic history. They were seizure-free or had either occasional auras or not more than two disabling seizures per year for at least 2 years, with or without appropriate antiepileptic medication. The vast majority (82/95, 87.2%) of our patients received monotherapy, at subtherapeutic doses, and the most utilized drugs were carbamazepine or oxcarbazepine. Neurologic examinations were unremarkable in all patients. None of our patients had mental retardation.

Magnetic resonance imaging. Brain MR imaging was performed according to our routine protocol by a 1.5-T unit (Signa NV/I; GE Medical Systems, Milwaukee, WI).[20] A neuroradiologist, who was blinded to the study, detected neither abnormal nor unusual findings in any of the screened images.

Voxel-based morphometry. VBM analysis was performed by an optimized protocol[26] using the SPM2 software (www.fil.ion.ucl.ac.uk). Briefly, a customized GM template is generated and subsequently used to normalize all of the structural images in native space to the stereotaxic MNI space. First, to create the customized GM template, all images (patients and controls) were first spatially normalized (16-parameter affine) using the standard MNI template in SPM2. Then each normalized image was segmented into gray and white matter (GM, WM) and CSF. The segmented GM images were averaged and smoothed (isotropic kernel, FWHM = 8 mm) to obtain the customized GM template. Next, each original MR image in native space was segmented into GM, WM, and CSF and then the GM images were spatially normalized to the customized GM template in MNI space. The deformation parameters obtained from this step were then applied to the corresponding original images in native space. The normalized anatomic T1 images were segmented again into the three tissue classes. Finally, all GM images were modulated[12] and smoothed with a 10-mm FWHM Gaussian kernel.

Statistical analysis. The normalized, segmented, modulated, and smoothed GM volume maps were statistically analyzed using the general linear model based on random Gaussian field theory.[27] Statistical analysis consisted of an analysis of covariance (ANCOVA) with total intracranial volume (TIV, derived from the sum of GM, WM, and CSF), age, and sex as the covariates-of-no-interest. Specific statistical analyses were performed to investigate the overall network of regions involved for each TLE subgroup vs healthy controls. For each group we defined linear contrasts to test for differences in gray matter volume among groups. The statistical threshold was set at $p < 0.05$ family-wise error (FWE) correction, 20 contiguous voxels. Although there has been no in vivo evidence of gray matter abnormalities associated with benign temporal lobe epilepsy without MTS (nTLE), the data were also presented by using a less-stringent, uncorrected threshold ($p < 0.001$, cluster threshold = 100 voxels) to detect subtle volume changes in this group. To evaluate any covariation between GM volume reduction and clinical data we performed a correlation analysis using the multiple regression function of SPM2. The duration of epilepsy and the age at onset were treated as covariates-of-interest, with TIV, age, and sex as confounding covariates. Two linear contrasts (1, −1) were made for correlations. We considered as regions of interest (ROI) the identified regions that showed the most significant GM reduction in patients with TLE compared to controls (left and right thalamus and left Hf). Within each of these regions, corrected p values at voxel level (FWE, $p < 0.05$) were assigned using the SPM small volume correction.[28]

Because patients with pTLE presented different distribution of MRI signs, we decided to delineate the different contribution of left and right MRI abnormalities on the VBM pattern of hippocampal atrophy. We defined patients with TLE with mesial temporal sclerosis having MRI signs of the left or right hippocampal abnormalities (pTLE-left no. 19; pTLE-right no. 15). Thus, ROI including both the left and right Hf was drawn. This definition was based on the labels of the Talairach Daemon database (http://ric.uthscsa.edu/projects/talairachdaemon.html) as contained within the in-house software (BrainShow, written in MatLab v.5.3).[29] The resulting ROI image was transformed into a binary mask using *marsbar* tool,[30] which was applied explicitly to compute differences in brain volume between mild TLE patients and controls. To limit the analysis of group differences to these target areas, we repeated the ANCOVA analysis within SPM2 using this defined ROI as mask and TIV, age, and sex as covariates-of-no-interest. A significant level of $p < 0.05$ was established for ROI analyses. The signal change within clusters surviving this threshold was extracted at the peak voxels and was fed into separate statistical analysis. The coordinates of voxels exhibiting the greatest group specific effects were transferred from MNI space to Talairach space using a non-linear transform approach.[30]

For a continuous variable mean, SD and range were reported, and an unpaired t test was used to assess differences among groups. Categorical variables are expressed as frequencies and percentages, and the differences among group distributions were assessed using the χ^2 test. One-way analysis of variance (ANOVA) of the GM values in ROI analysis was performed. Statistical analyses were performed with the Statistical Package for Social Science software (SPSS, version 12.0, Chicago, IL) for Windows. All statistical analyses had a two-tailed alpha level of $p < 0.05$ for defining significance.

RESULTS

Clinical, EEG, and routine MRI findings. Tables 1 and 2 display the results of our population. Thirty-four patients (19 women; 36.3 ± 15.2 years) had evidence for MTS on MRI (pTLE) whereas 61 patients (32 women; 36.7 ± 16.0 years) had normal MRI scan (nTLE). Of these 34 patients with pTLE, 19 had MRI evidence of unilateral left MTS whereas 15 had unilateral right MTS. No abnormalities were found outside the mesial temporal regions.

The interictal EEG was highly concordant to the side of MTS but three patients had normal EEG. In pTLE group, 27 of these 34 (80%) patients had EEG abnormalities concordant with the lateralization of the MRI abnormality. In the remaining, two patients showed EEG abnormalities discordant with the unilateral atrophy (one left) whereas two patients had bilateral abnormalities. Overall, MRI abnormalities strongly correlated (Cohen's kappa coefficient = 0.857; $p < 0.001$) with the interictal epileptiform activity seen on scalp EEG recordings of these patients with pTLE.

There was no difference between pTLE and nTLE in age (36 years vs 36 years), age at onset (20 years vs 22 years), and duration of epilepsy (16 years vs 14 years). Family history of epilepsy or febrile convulsion (FCs)

Table 2 MRI features in patients with pTLE

		MRI (FLAIR and T1 IR)		
Patient, age (y), sex	Age at onset (y)	Hyperintensity + atrophy	Hyperintensity	Atrophy
1, 35, F	3	Left		
2, 52, M	45	Left		
3, 21, M	8			Right
4, 67, M	52			Left
5, 54, F	15			Left
6, 20, F	12		Right	
7, 48, F	12	Right		
8, 30, F	12	Left		
9, 35, M	6	Left		
10, 31, M	27		Left	
11, 46, M	26	Left		
12, 54, F	25			Right
13, 12, M	3			Left
14, 10, F	2	Left		
15, 37, M	5	Left		
16, 29, F	1	Left		
17, 59, F	46		Right	
18, 64, M	64	Left		
19, 27, M	15			Right
20, 39, F	33	Right		
21, 34, M	24		Right	
22, 36, F	23		Left	
23, 27, F	18			Right
24, 47, F	3	Right		
25, 21, F	7	Left		
26, 48, F	43			Left
27, 18, M	17			Right
28, 32, F	25			Left
29, 62, M	20	Left		
30, 30, M	23			Right
31, 17, F	7	Left		
32, 18, F	17			Right
33, 39, F	13	Right		
34, 14, F	4	Right		

pTLE = patients with temporal lobe epilepsy with mesial temporal sclerosis.

was significantly ($p = 0.048$) more frequent in patients with pTLE (14/34, 41%), as compared to patients with nTLE (14/61, 23%). There was also a higher frequency of personal antecedent FCs ($p = 0.035$) in patients with pTLE compared to nTLE. None of our patients had prolonged or complicated FCs, head trauma with loss of consciousness, or cerebral infections prior to seizure onset. We did not observe any demographic differences between right and left pTLE.

VBM results. To exclude overall brain volume difference between groups, global measures of GM were calculated. There were no significant differences in mean global GM volume among the three groups (mean ± SD mL, nTLE = 0.718 ± 0.07; pTLE = 0.703 ± 0.08; controls = 0.72 ± 0.06; $p = 0.56$).

When compared to controls at a threshold of FWE-corrected $p < 0.05$, pTLE patients showed greater GM loss of the bilateral thalamus and left Hf (table 3A, figure 1A). Using this more conservative statistical threshold no significant difference was detected in the comparison between healthy controls and nTLE group. At lower, uncorrected statistical threshold ($p < 0.001$), patients with nTLE showed the same gray matter abnormalities with a decrease in thalamic and marginally in the left Hf compared with controls (figure 1B). A second, larger cluster of GM reduction comprised the bilateral primary motor cortex (table 3). There was no significant thalamic-hippocampal GM difference between nTLE and pTLE group and it became evident only when uncorrected threshold was used (table 3). There were no areas where nTLE and pTLE patients had more gray matter than controls. We also performed a correlation analysis to delineate possible links between GM abnormalities and clinical data. Multiple regression analysis did not show any significant correlation in the TLE groups; neither did the duration of the epilepsy or the age at onset.

When pTLE patients were grouped according to the presence of left and right MRI signs of MTS (pTLE-left [no.19] and pTLE-right [no.15]), a significant decrease in GM volumes was observed in the thalami and left Hf compared to controls (FWE <0.05; data not shown) in either group, showing a complete overlap with GM decrease found in pTLE. At uncorrected threshold ($p < 0.001$) bilateral hippocampal atrophy was detected only in pTLE-right group. Even at an uncorrected threshold, specific cortical GM decrease (bilateral motor cortex) was seen in both pTLE groups.

The mean volume extracted from the ROI positioned at the peak of the left Hf voxel (figure 2) showed significant GM volume reduction in all pTLE-left, pTLE-right, and nTLE patients compared to controls (p level = 0.000002; p level = 0.0002; p level = 0.03). In the ROI analysis of the right Hf only pTLE-right group presented significant GM difference ($p = 0.001$) compared to controls. Furthermore, ROI analysis showed atrophy extending from anterior to middle Hf in pTLE-left, while hippocampal atrophy was more posterior in pTLE-right (figure 2).

DISCUSSION This study provides in vivo evidence of GM abnormalities in patients with drug-responsive TLE and very mild outcome. We

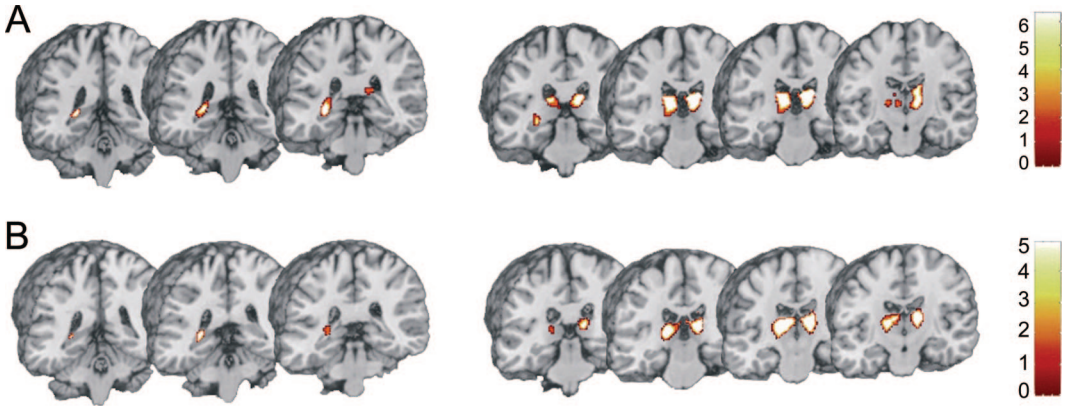
Table 3 Location and Talairach coordinates of significant clusters of grey matter volume loss in temporal lobe epilepsy (TLE) groups

			Talairach coordinates			
	$P_{corrected}$	Cluster (k)	x	y	z	Location
A) Controls > pTLE	0.000	3082	12	−26	14	R thalamus
	0.000	2680	−11	−22	14	L thalamus
	0.001	746	−28	−32	2	L hippocampus
B) Controls > nTLE*	0.014	4093	32	−23	50	R sensorimotor cortex (BA 4)
	0.072	2527	−35	−20	51	L sensorimotor cortex (BA 4)
	0.060	2687	−17	−19	8	L thalamus
	0.081	2417	14	−22	10	R thalamus
	0.963	154	−27	−34	8	L hippocampus
C) nTLE > pTLE*	0.070	2551	8	−13	1	R thalamus
			−8	−8	2	L thalamus
	0.110	2158	−31	−31	−1	L hippocampus

Grey matter (GM) volume loss in pTLE and nTLE groups relative to controls accounting for differences in total intracranial volume, age, and sex. A corrected threshold of $p < 0.05$ (family-wise error) is used to identify the most significant peaks.
*In order to detect subtle GM changes in nTLE group statistical threshold is decreased ($p < 0.001$ uncorrected threshold; cluster threshold = 100 voxels). Coordinates (x, y, z) refer to standard Talairach space (Talairach & Tournoux, 1998). Results are listed by cluster size as indicated by the value k, the number of voxels in a particular cluster.
pTLE = patients with TLE with mesial temporal sclerosis; nTLE = patients with TLE without mesial temporal sclerosis; BA = Brodmann area.

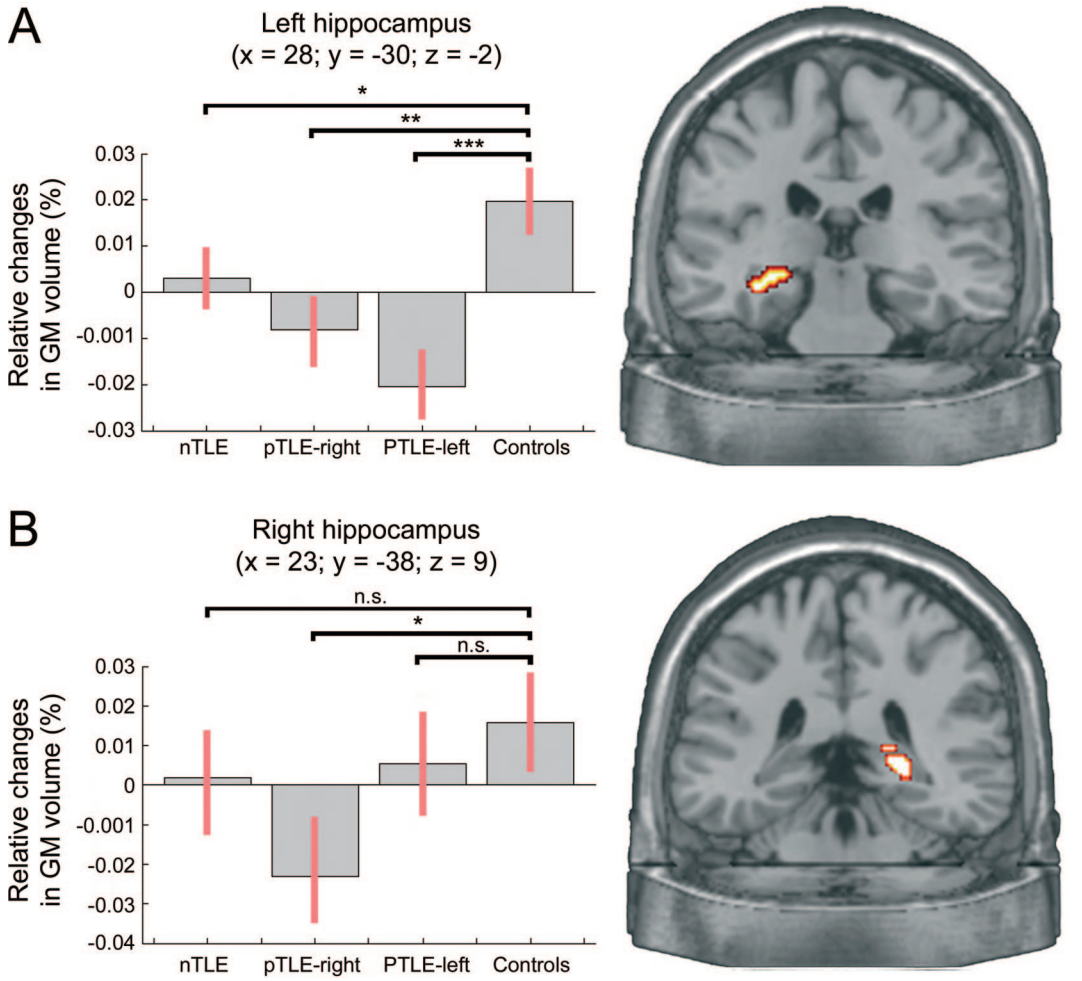
detected a GM volume reduction located in the hippocampus and in the thalami. Like these findings, recent neurophysiologic investigations gave good evidence of the involvement of these structures in the origin and propagation of TLE seizures.[31] Our results are also consistent with previous VBM studies of patients with refractory MTLE indicating a GM reduction in the bilateral thalamic region.[13,15] This was interpreted as a reflection of a damaged network in close connection with the limbic system.[31] Nonetheless, it was unclear if such abnormalities represent the consequence of ensuing repeated seizures or reflect the extension of the epileptogenic network to the extratemporal structures.[10,11,15] Since all our patients with TLE had a very mild epileptic disorder with almost no seizures at long-term follow-up, it is reasonable to hypothesize that the thalamus is primarily caught up in the epileptogenic network underlying the disease. This view is also supported by our observation of no significant correlation between either the duration of the epilepsy or the age at onset and extent of brain damage in these patients with TLE. Overall, these results further

Figure 1 Results of optimized voxel-based morphometry analysis



(A) Gray matter (GM) reduction in bilateral thalamus and left hippocampus displayed by pTLE group with respect to controls. A corrected threshold (family-wise error, $p < 0.05$ corrected for multiple comparisons) is used. At lower, uncorrected statistical threshold ($p < 0.001$, k = 100 voxels) nTLE group shows a GM decrease of the bilateral thalamus and left hippocampus marginally (B). The color bars represent the range of t scores. Images are superimposed on standard MNI template.

Figure 2 Volume of (A) left (peak voxel x, y, z = −28, −30, −2) and (B) right hippocampus (peak voxel x, y, z = 23, −38, 9)



To detect subtle hippocampal morphologic changes within temporal lobe epilepsy (TLE) groups an analysis of variance for comparison of the gray matter (GM) volume extracted from these regions was conducted separately. Significant difference was detected between all TLE groups with respect to controls (*p level = 0.03, **p level = 0.0002, ***p level = 0.000002) within the left hippocampus, whereas only pTLE-right group showed decreased GM volume within right hippocampus (*p = 0.001). The maps are superimposed on standard MNI template. The bar graphs give the mean and SD gray matter volume of voxels showing peak difference in the hippocampal areas. nTLE = patients with TLE without mesial temporal sclerosis; pTLE-right = patients with TLE with mesial temporal sclerosis showing right MRI signs of hippocampal lesions; pTLE-left = patients with TLE with mesial temporal sclerosis showing left MRI signs of hippocampal lesions; NS = not significant.

reinforce the view that a temporo-limbic pathway, which includes the thalamus, plays a major role in the pathogenesis of TLE seizures.[31,32]

Our study also illustrated that the severity and extent of damage seen on brain VBM paralleled the damage detected on routine MRI study. Indeed, patients with routine MRI evidence of MTS had a highly significant reduction (FWE-corrected $p < 0.05$) of the GM volume in the left hippocampus and the thalamus bilaterally. More importantly, even patients with negative MRI showed the same GM abnormalities, albeit at lower threshold, meaning that the absence of visual MTS does not signify a different type of epilepsy and that these apparent variable phenotypes might lie along a biologic continuum. Moreover, our findings further reinforce the belief that MTS is not necessarily related to seizure severity and it is not the only pathology that must be considered in the genesis of temporal lobe seizures.[20,23]

One puzzling result of our VBM study was the lack of significant GM loss in the right hippocampus in patients with MRI evidence of right MTS. One possibility is that the GM volume-related abnormalities in the right hippocampal regions were more subtle and less homogeneous than that detected in the left hippocampus. Asymmetric hippocampal damage, more severe on the left side in patients with MTLE and MTS, has been previously reported, even if the reasons for this peculiar phenomenon remain unclear.[14,15]

In our sample, 13 (65%) pTLE patients out of 20 showing MRI evidence of left MTS had the simultaneous presence of high signal intensity associated with hippocampal atrophy compared to 26,6% of the pTLE-right group. So, since small structures such as the hippocampus show high structural variability, VBM may be insensitive to the detection of subtle changes/atrophy in areas of high variance. Moreover, the nature of GM changes identified with VBM is still poorly understood. Potential structural correlates of the observed morphometric changes include a simple change in cell size, growth, or atrophy of neurons or glia, and changes in the intracortical axonal architecture (synaptogenesis). Hence, the gray matter volume-related abnormalities in hippocampal regions may be due to such different distribution of MRI features of MTS, and we cannot exclude that a high presence of hippocampal hyperintensities could enhance the signal change as detected by VBM. We used ROI analysis to specifically test for the type and extent of atrophy in the hippocampus, especially in patients with routine MRI evidence of unilateral right MTS. The analysis confirmed atrophy of the left hippocampus in all patients and gave evidence of ipsilateral hippocampal damage in the pTLE-right group.

We have confirmed in this study our previous observations that patients with MRI evidence of MTS had more frequent antecedent febrile seizures than patients with normal MRI scans.[20] We have also confirmed an increased risk of epilepsy or febrile seizures in siblings.[20] These differences are consistent with the observation that there exists a familial predisposition to febrile seizures, and that a febrile convulsion will be a major antecedent event, in patients with hippocampal sclerosis.[33,34] Likewise, a common genetic cause for both febrile seizures and TLE has been suggested in pedigrees with febrile seizures and TLE without hippocampal structural abnormalities.[35] Our findings support the view that genetic background, not only in familial TLE,[36] is implicated in the genesis of hippocampal abnormalities in sporadic TLE.[37,38] There is good evidence that TLE, with or without hippocampal sclerosis, may be part of the epileptic phenotype encountered in families carrying mutations of *SCN1A* or *SCN1B* genes.[39,40]

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