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Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy

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Volumetric MRI studies based on manual labeling of selected anatomical structures have provided in vivo evidence that brain abnormalities associated with temporal lobe epilepsy (TLE) extend beyond the hippocampus. Voxel-based morphometry (VBM) is a fully automated image analysis technique allowing identification of regional differences in gray matter (GM) and white matter (WM) between groups of subjects without a prior region of interest. The purpose of this study was to determine whole-brain GM and WM changes in TLE and to investigate the relationship between these abnormalities and clinical parameters. We studied 85 patients with pharmacologically intractable TLE and unilateral hippocampal atrophy and 47 age- and sex-matched healthy control subjects. The seizure focus was right sided in 40 patients and left sided in 45. Student's *t* test statistical maps of differences between patients' and controls' GM and WM concentrations were obtained using a general linear model. A further regression against duration of epilepsy, age of onset, presence of febrile convulsions, and secondary generalized seizures was performed with the TLE population. Voxel-based morphometry revealed that GM pathology in TLE extends beyond the hippocampus involving other limbic areas such as the cingulum and the thalamus, as well as extralimbic areas, particularly the frontal lobe. White matter reduction was found only ipsilateral to the seizure focus, including the temporopolar, entorhinal, and perirhinal areas. This pattern of structural changes is suggestive of disconnection involving preferentially frontolimbic pathways in patients with pharmacologically intractable TLE.

Keywords: Gray matter; White matter; Epilepsy

Introduction

In clinical practice, the investigation and treatment of patients with epilepsy have been revolutionized by the advent of MRI, which has been demonstrated to be a reliable and accurate indicator of pathologic findings underlying epilepsy. Techniques such as volumetric acquisition with thin contiguous slices and three-dimensional reformatting have enhanced the ability of MRI to display brain anatomy and to visualize epileptogenic brain lesions in vivo.

In temporal lobe epilepsy (TLE), most MRI studies have focused on the assessment of the hippocampus based on pathological (Babb and Brown, 1987; Falconer et al., 1964; Mouritzen Dam, 1980) and electrophysiological (Quesney, 1986) evidence from early studies for its involvement in the epileptogenic process. More recent MRI studies have shown that structural brain abnormalities associated with TLE extend beyond the hippocampus, involving other mesial and limbic structures such as the entorhinal cortex (Bernasconi et al., 1999, 2003a,b; Salmenpera et al., 2000), the thalamus (DeCarli et al., 1998; Natsume et al., 2003), and the fornix (Baldwin et al., 1994; Kuzniecky et al., 1999). There is also MRI evidence for reduction in the total temporal neocortical gray matter and white matter volumes (Coste et al., 2002; Jutila et al., 2001; Lee et al., 1998; Moran et al., 2001). The effect of mesolimbic pathology on the rest of the brain has not been thoroughly evaluated.

To date, most MRI morphometric studies have been based on manual delineation of single brain structures. This procedure, which is labor intensive, suffers from difficulties related to defining reliable anatomical boundaries and may therefore result in low intra- and interrater reliability. These difficulties explain in part why only a selected number of structures have been evaluated so far. Voxel-based morphometry (VBM) is a fully automated technique allowing identification of regional differences in the amount of gray matter (GM) and white matter (WM) with no a priori region of interest, enabling an objective analysis of the whole brain between groups of subjects (Ashburner and Friston, 2000). This technique has been used to reveal pathological changes in GM and WM in various neurological conditions, including Alzheimer's disease and schizophrenia (Karas et al., 2003; Kubicki et al., 2002). Voxel-based morphometry of the GM in TLE has produced conflicting results. In one study, no GM differences were found between TLE patients and healthy controls (Woermann et al., 1999). In another study, areas of decreased GM were found in the hippocampus ipsilateral to the seizure focus and in extratemporal areas (Keller et al., 2001). VBM has shown subtle differences in frontal lobe GM in relation to aggression in TLE (Woermann

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et al., 2000). None of these studies examined WM changes associated with TLE.

The purpose of this study was to examine whole-brain GM and WM changes in TLE using VBM and investigate the relationship between these changes and clinical parameters such as febrile convulsions, age of onset, duration of epilepsy, and secondary generalized seizures.

Methods

We selected 85 consecutive patients with medically intractable TLE (44 males, mean age ± SD = 35 ± 10 years, range = 16–54) and unilateral hippocampal atrophy as determined by volumetric MRI (see below). Patients were compared to 47 neurologically normal controls (24 males, mean age = 33 ± 12 years, range = 20–66). The patients with right TLE and left TLE and healthy controls did not differ in age [ANOVA; $F(2,125) = 0.88$, $P = 0.4$] or sex distribution (for right TLE: $\chi^2 = 2.6$, $df = 1$, $P = 0.1$; for left TLE: $\chi^2 = 0.42$, $df = 1$, $P = 0.5$). The Ethics Committee of the Montreal Neurological Institute and Hospital approved the study and written informed consent was obtained from all participants.

Lateralization of seizure focus

Seizure type and the site of seizure onset were determined by a comprehensive evaluation including detailed clinical history, neurological examination, review of medical records, and neuropsychological evaluation. The seizure focus was determined by predominantly ipsilateral interictal epileptic abnormalities (70% cutoff) and unequivocal unilateral seizure onset recorded during prolonged video-EEG monitoring in all patients. Based on these criteria, TLE patients were divided into those with a left-sided ($n = 45$) or a right-sided ($n = 40$) seizure focus. The side of the focus was concordant with the side of hippocampal atrophy in all patients.

MRI scanning

MRI volumetric images were acquired on a 1.5-T Gyroscan (Philips Medical System, Eindhoven, The Netherlands) using a T1-fast field echo (TR = 18, TE = 10, one acquisition average pulse sequence, flip angle = 30°, matrix size = 256 × 256, FOV = 256,170 slices, thickness = 1 mm).

Image processing

Each image underwent automated correction for intensity nonuniformity due to radiofrequency inhomogeneity of the MR scanner (Sled et al., 1997) and intensity standardization by normalizing gray-level intensities to a common scale. Images were then automatically registered in a standard, stereotaxic space (Talairach and Tournoux, 1988) to adjust for differences in total brain volume and brain orientation (Collins et al., 1994). Classification of brain tissue into GM, WM, and CSF was performed by means of INSECT (Zijdenbos et al., 1998), an automatic algorithm. Briefly, INSECT relies on an artificial neural network classifier, which labels each voxel based on the MRI signal. Gray matter and WM binary masks were blurred with an isotropic Gaussian kernel of 5 mm FWHM to generate 3D-maps of GM and WM "concentration." Statistical maps of differences in GM and WM between patients and healthy controls were obtained using a general linear model (Worsley et al., 1996). Further regression against duration of epilepsy, age of onset, presence of febrile convulsions, and secondary generalized seizures was performed with the TLE population. Since duration and age of onset are highly correlated, correlation with duration of epilepsy was corrected for age of onset, and correlation with age of onset was corrected for duration of epilepsy. The presence of significant peaks at $P < 0.05$ in 3D regression maps was assessed by a method based on 3D Gaussian random-field theory, which corrects for the multiple comparisons involved in searching across a volume (Worsley et al., 1996).

Volumetric measurement of the hippocampus was performed in all subjects according to our previously published protocols (Bernasconi et al., 2003b) and showed unilateral hippocampal atrophy ipsilateral to the seizure focus in all patients, based on a threshold equal to 2 SD below the mean of normal controls.

Results

Areas of GM reduction in TLE patients compared to healthy controls (see Table 1A)

Areas of decreased GM were observed in the temporolimbic and frontal areas (Figs. 1A and B) (Table 1A).

Gray matter reduction in temporolimbic areas

Patients with left and right TLE had GM reduction ipsilateral to the seizure focus in all segments of the hippocampus (head, body, and tail). In patients with left TLE, GM reduction was also present to a lesser extent in the contralateral hippocampal head and tail. Both TLE groups had bilateral GM reduction in the cingulate cortex. Contralateral GM decrease was present in occipital areas in left TLE patients and in the superior temporal gyrus in right TLE patients. In addition, both groups had bilateral thalamic GM reduction. Left TLE patients had also ipsilateral GM reduction in the insula.

Gray matter reduction in the frontal lobe

There was a reduction of GM in various frontal lobe areas (superior, middle, dorsal and orbitofrontal, and paracentral). This reduction was ipsilateral to the seizure focus in the medial and orbital frontal cortices and bilateral for the dorsal frontal cortex in patients with both left and right TLE. GM reduction in the superior frontal cortex was ipsilateral to the seizure focus in right TLE patients and bilateral in left TLE patients. GM reduction within the paracentral lobule was ipsilateral to the seizure focus in patients with right TLE and contralateral in left TLE patients.

Areas of WM reduction in TLE patients compared to healthy controls (see Table 1B)

Compared to normal controls, patients with left and right TLE showed a diffuse reduction of temporal lobe WM (temporopolar, temporal stem, entorhinal, and perirhinal) ipsilateral to the seizure focus, and decrease WM in the body of corpus callosum. Right TLE patients had additional ipsilateral WM reduction in the postcentral region (Fig. 2) (Table 1B).

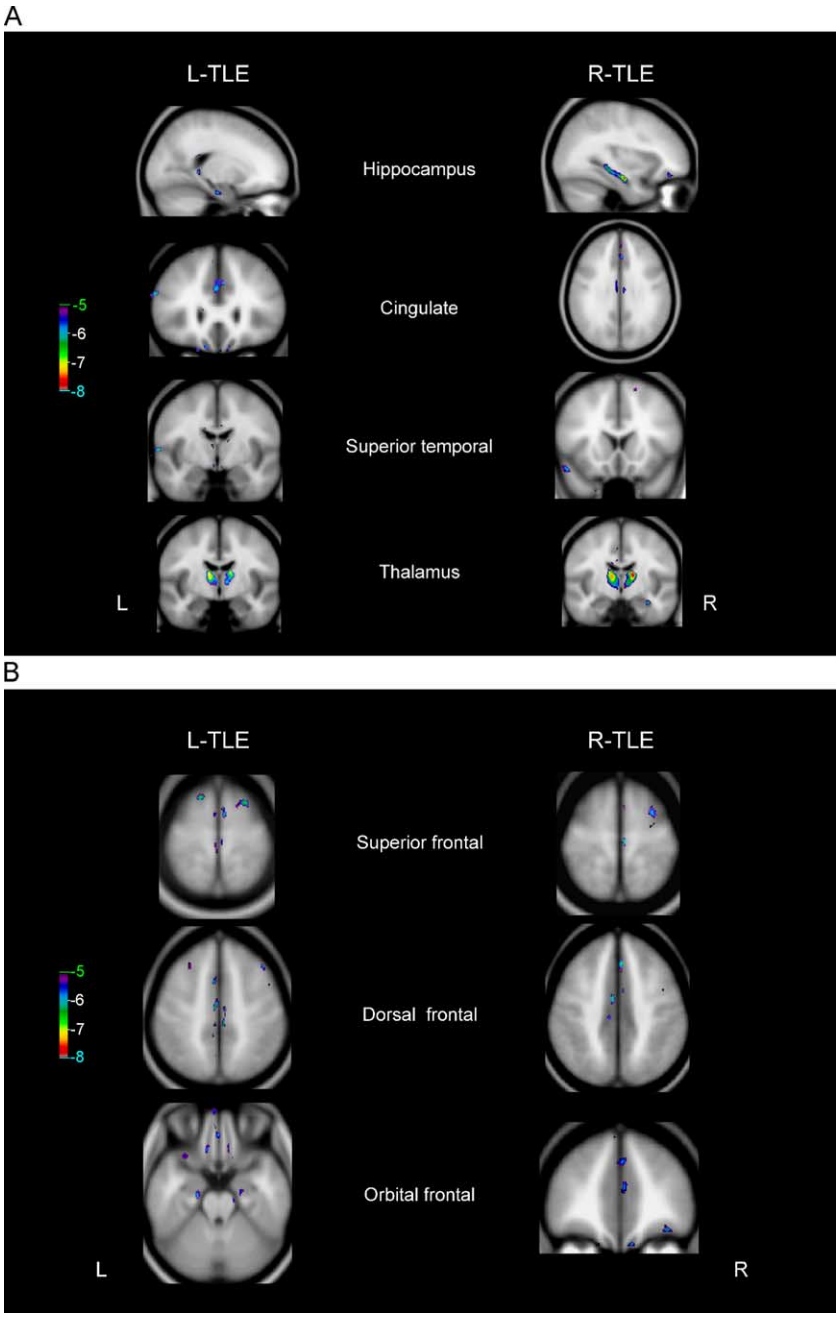

Fig. 1. Statistically significant peaks of gray matter decrease in patients with left and right temporal lobe epilepsy (L-TLE and R-TLE) in temporolimbic (A) and frontal areas (B) superimposed on the ICBM 152 average template of healthy controls for anatomical reference.

In both patient groups, areas of increase in GM were present in the temporopolar area ipsilateral to the seizure focus. In patients with left TLE, GM increase was also present in the entorhinal and perirhinal cortices. All areas of increased GM coincided with those of decreased WM.

Relationship of VBM to clinical parameters

We found no changes in GM or WM in relation to duration of epilepsy. No significant results were found with respect to age of onset, presence of febrile convulsions, and secondary generalized seizures.

Discussion

Voxel-based morphometry showed evidence for both limbic and extralimbic pathology in patients with pharmacologically intractable TLE.

Comparison of VBM and ROI-based segmentation in TLE

The accuracy and sensitivity of VBM analysis depend upon the quality of the underlying preprocessing steps, including tissue segmentation (Ashburner and Friston, 2000; Good et al., 2002). Since tissue classification algorithms commonly used are intensity

Table 1A
Areas of gray matter reduction in temporal lobe epilepsy compared to controls

Anatomical region	BA	*x*	*y*	*z*	*t* statistic*
Left TLE					
Temporolimbic lobe					
Hippo head, L	–	−33	−16	−18	−6.2
Hippo head, R	–	21	−12	−24	−5.6
Hippo body, L	–	−23	−19	−10	−6.2
Hippo tail, L	–	−23	−39	0	−6.1
Hippo tail, R	–	22	−37	1	−6.7
Superior temporal, L	22	−61	−6	5	−6.2
	38	−60	9	−8	−7.4
Cingulate, L	32	−2	30	27	−5.8
Cingulate, R	32	4	40	21	−6.2
	24	6	−14	30	−6.3
Insula, L	–	−37	3	9	−6.1
Frontal lobe					
Superior frontal, L	6	−15	12	67	−6.6
	6	−15	33	56	−6.3
Superior frontal, R	6	22	8	67	−6.6
	6	25	4	65	−6.5
Dorsal frontal, L	6	−5	8	51	−6.3
	6	−3	−12	51	−6.3
	9	−2	42	33	−6.5
	10	−5	67	−6	−6.1
Medial frontal, L	46	−53	29	23	−6.3
Orbital frontal, L	47	−11	24	−23	−5.6
Orbital frontal, R	47	13	18	−22	−5.6
Paracentral lobule, R	5	4	−28	51	−6.2
Occipital lobe					
Lingual, R	17	6	−70	13	−6.8
Subcortical structures					
Thalamus, L	–	−42	−8.4	12	−7.6
Thalamus, R	–	10	−2	11	−7.4
Right TLE					
Temporolimbic lobe					
Hippo head, R	–	32	−11	−20	−7.7
Hippo body, R	–	36	−26	−10	−7.2
Hippo tail, R	–	24	−37	0	−8.8
Superior temporal, L	38	−49	18	−19	−6.2
Cingulate, L	24	−4	−7	43	−5.7
Cingulate, R	23	2	30	30	−6.2
Frontal lobe					
Superior frontal, R	6	−26	−1	64	−5.6
Dorsal frontal, R	6	4	−22	61	−6.8
Medial frontal, R	11	34	40	−15	−6.0
Orbital frontal, R	11	11	23	−23	−5.8
Paracentral lobule, R	5	6	−30	50	−5.9
Subcortical structures					
Thalamus, R	–	14	−14	12	−7.7
Thalamus, L	–	−13	−18	13	−7

BA = Brodmann's area; *x*, *y*, and *z* = Talairach coordinates; L = left; R = right; Hippo = hippocampus.
* *t* statistic > −5.5 ($P < 0.05$ corrected for multiple comparisons).

driven, the presence of lesional tissue may adversely influence their outcome. In particular, pathology may be associated with reduction in GM–WM contrast.

The gold standard for in vivo quantitative assessment of brain atrophy is manual segmentation of selected brain structures. However, for reasons of difficulty in defining accurate anatomical boundaries, labor intensiveness, and wide inter- and intrarater variability, ROI-based morphometry cannot provide comprehensive assessments of the entire brain, and results are difficult to replicate and compare between laboratories. On the other hand, results from the automated and manual methods are not expected to be identical, just as the ROI-based approach would not produce the same results if a different parcellation scheme was adopted (Good et al., 2002).

Fortunately, in TLE there is a large body of literature on MRI quantitative analysis of various temporal and extratemporal brain areas. For reasons cited above, results are not entirely comparable between studies. However, the principal requirement is that ROI- and voxel-based approaches should show the same general trend. In TLE, there is evidence for widespread GM and WM atrophy extending beyond the hippocampus. The majority of the areas of decrease in GM–WM concentration we have found in our VBM study have been previously shown to be atrophic on ROI analysis of volumetric MRI. Manual segmentation of the hippocampus was performed in our patients and showed unilateral atrophy ipsilateral to the seizure focus in all of them. As for other extrahippocampal limbic structures, we have previously reported thalamic atrophy in a subset of patients who were included in the present study (Natsume et al., 2003). Other groups have also reported thalamic atrophy in TLE (DeCarli et al., 1998; Dreifuss et al., 2001).

Extensive GM and WM atrophy has been reported in the temporal lobe of patients with intractable TLE and unilateral hippocampal atrophy (Breier et al., 1996; Coste et al., 2002; Hermann et al., 2003; Lee et al., 1998; Marsh et al., 1997; Moran et al., 2001). Although different portions of the frontal lobe have not been systematically studied, there are MRI reports of GM and WM loss across this lobe (Hermann et al., 2003; Marsh et al., 1997; Sisodiya et al., 1997). A previous MRI morphometric study showed significant regional thinning of the anterior and mid portion of corpus callosum in patients with intractable TLE that are comparable to our present findings (Lee, 1998).

The findings of the abovementioned ROI-based studies showing GM and WM atrophy support the fact that GM and WM decrease in our VBM analysis most likely represent volume reduction.

To date, in TLE, pathology-induced GM–WM contrast changes are known to occur only in the temporal lobe. Indeed, an increase in T2-weighted intensity and blurring of the GM–WM interface on T1-weighted images have been described in the temporopolar region as part of the spectrum of MRI features found in patients with TLE (Choi et al., 1999; Coste et al., 2002; Meiners et al., 1994; Mitchell et al., 1999, 2003). The blurring of the GM–WM interface can results in an overestimation of the GM obtained by automatic segmentation. Indeed in previous VBM studies, areas of increase in GM were reported within the temporal lobe (Keller et al., 2001; Woermann et al., 1999). In these studies (Keller et al., 2001; Woermann et al., 1999), the WM was not assessed. By performing voxelwise analysis of both GM and WM, we were able to observe that areas of increased GM coincided with those of decreased WM.

In our VBM analysis, even if decrease in GM concentration was secondary to intensity differences between the healthy subjects and patients, we would expect this intensity difference to be responsible for all areas of GM decrease we have observed since our patients present all with the same disease. Furthermore, there is no evidence in TLE for intensity changes in areas others that the temporal pole and the hippocampus.

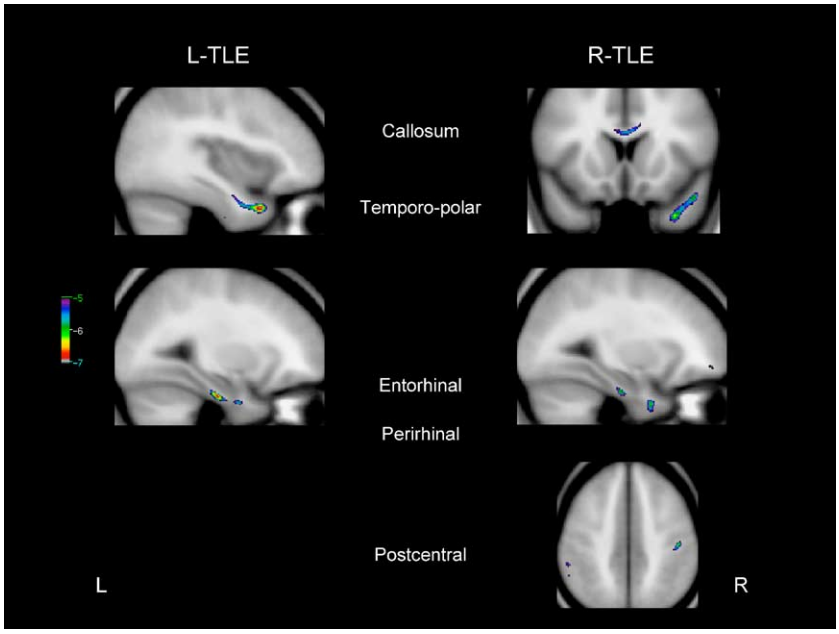

Fig. 2. Statistically significant peaks of white matter decrease in patients with left and right temporal lobe epilepsy (L-TLE and R-TLE) superimposed on the ICBM 152 average template of healthy controls for anatomical reference.

Comparison with previous VBM studies

Voxel-based morphometry in TLE has been limited to few studies (Keller et al., 2001; Woermann et al., 1999) and has shown conflicting results. In the first attempt, this technique was unable to identify any pathology (Woermann et al., 1999) when comparing TLE patients to healthy controls. Limitations of this study included a small sample size and the choice of a blurring kernel of 14 mm used to smoothen the imaging data, which might have been larger than the expected spatial extent of the pathology. In a more recent study based on a larger cohort of TLE patients with hippocampal atrophy, areas of GM reduction were found in temporal and extratemporal regions (Keller et al., 2001). Although our findings are generally in agreement with this study, we were able to show a larger number of areas of decreased GM in the frontal lobe. Contrary to Keller et al. (2001), who found a different distribution of hippocampal GM decrease depending on the lateralization of the seizure focus, we found an identical pattern of GM decrease in both patients with left and right TLE. This is in agreement with our previous volumetric studies (Bernasconi et al., 2003b).

Table 1B
Areas of white matter reduction in temporal lobe epilepsy compared to controls

Anatomical region	BA	*x*	*y*	*z*	*t* statistic*
Left TLE					
Temporal lobe					
Temporopolar, L	38	−38	13	−32	−6.9
Entorhinal, L	28	−27	−18	−28	−7.0
Perirhinal, L	35	−24	−27	−19	−6.2
Callosum, body	–	1	27	8	−6.2
Right TLE					
Temporal lobe					
Temporopolar, R	38	39	6	−27	−7.0
Entorhinal, R	28	29	−16	−27	−6.3
Perirhinal, R	38	31	7	−36	−5.7
Callosum, body	–	1	17	18	−5.6
Parietal lobe					
Postcentral gyrus, R	3	45	−21	47	−6.3

BA = Brodmann's area; *x*, *y*, and *z* = Talairach coordinates; L = left; R = right; Hippo = hippocampus.
* *t* statistic > −5.5 ($P < 0.05$ corrected for multiple comparisons).

Pathophysiological and clinical considerations

In our study, pathological changes in the temporolimbic structures included GM reduction in the hippocampus, cingulate, and thalamus and WM reduction in the temporopolar, entorhinal, and perirhinal areas. Extralimbic pathology was located mainly in the frontal lobe and was characterized by GM reduction in various prefrontal areas.

The preponderance of GM decrease in the temporolimbic and prefrontal areas may reflect loss of white matter projections from the primary epileptogenic areas in the mesial temporal lobe to the frontal lobe. Anterograde and retrograde tracer studies in primates have demonstrated the existence of extensive reciprocal connections between the prefrontal cortex, the mesial temporal lobe, and the thalamus. These connections are known as the frontolimbic network (Cavada et al., 2000; Scannell et al., 1999; Van Hoesen et al., 1975; Young, 1993), which is crucial in cognitive functions such as memory, attention, and emotional behavior (Fuster, 2002; Milner et al., 1985; Squire and Zola-Morgan, 1988). Dysfunction or disconnection of these cortical areas could therefore explain the memory deficit and the spectrum of cognitive impairment observed in patients with TLE (Helmstaedter et al., 2003; Trimble, 1988).

Voxel-based morphometry in our TLE patients showed WM decrease in the temporopolar, entorhinal, and perirhinal areas. No WM abnormalities were found in the frontal lobe. White matter tracts originating from the temporopolar, entorhinal, and perirhinal

cortices form the arcuate fasciculus, an association bundle containing the efferent projections of these cortices and the hippocampus to the frontal lobe (Petrides and Pandya, 1988). It is possible that white matter fibers forming the portion of the arcuate fasciculus adjacent to the primary epileptogenic areas may undergo a more pronounced atrophy secondary to hippocampal and parahippocampal cell loss. White matter abnormalities in the frontal lobe could remain undetected by VBM due to a more subtle degenerative process involving the distal portions of the frontolimbic pathways.

It is known that mesial temporal seizures propagate preferentially to the frontal lobe, in particular to the prefrontal areas (Lieb et al., 1991) and to the cingulate area (Wieser et al., 1993). Therefore, prefrontal and cingulate GM decrease in our patients could be related to a direct effect of seizures themselves in addition to disconnection of frontolimbic pathways.

We found no relationship between VBM and any of the clinical parameters we examined. This could be due to the small sample size in each group or the subtle nature of the changes. Alternatively, our statistical analysis based on peak thresholds might have been too conservative compared to cluster statistics (Worsley et al., 1996). In a previous VBM study based on cluster statistics (Keller et al., 2002), a negative relationship was found between GM reduction in extrahippocampal areas and epilepsy duration, although there was no relationship between hippocampal GM and epilepsy duration.

In conclusion, we have shown that VBM is able to identify diffuse GM and WM abnormalities that extend beyond the known epileptogenic areas, particularly in the frontal lobes. The pattern of GM and WM decrease in TLE may be due to a combined effect of the electrical discharges during seizures and secondary damage due to disconnection. The pertinence of these widespread changes in individual cases with respect to clinical parameters, such as outcome after surgery, remains to be evaluated.

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