

MRI-based high-dimensional hippocampal mapping in mesial temporal lobe epilepsy

R. Edward Hogan,¹ Lei Wang,² Mary E. Bertrand,¹ L. James Willmore,¹ Richard D. Bucholz,³ A. Sami Nassif⁴ and John G. Csernansky²

Departments of ¹Neurology, ³Surgery and ⁴Radiology, Saint Louis University and ²Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA

Correspondence to: R. Edward Hogan, MD, Saint Louis University, 1221 S. Grand, 1st floor, Epilepsy Offices, St Louis, MO 63104, USA
E-mail: hoganr2@slu.edu

Summary

MRI-based evaluation of the hippocampus is important in the assessment and treatment of patients with mesial temporal lobe epilepsy (MTLE). Using MRI-based large-deformation high-dimensional mapping (HDM-LD), which allows structural evaluation of regions of the hippocampus, we document the HDM-LD-defined pattern of hippocampal deformation in MTLE patients compared with matched controls. In 30 subjects with MTLE and confirmed medial temporal lobe sclerosis (MTS), we performed measurements of intracranial area, brain parenchymal volume and deformation-based hippocampal segmentations, and then grouped patients into right and left MTS groups (resulting in 15 subjects in each group). Using HDM-LD techniques, we compared the right and left MTS groups with a group of 15 matched controls. Analysis included both the MTS and contralateral hippocampi, and covariance for changes in brain parenchymal volume.

Final results were interpreted using a segmentation showing normal hippocampal surface subfield anatomy. Comparing the MTS groups with controls, after covarying with brain parenchymal volume, the MTS hippocampi showed significant volume loss ($P < 0.0001$), contralateral hippocampi showed no significant volume loss. HDM-LD techniques showed significant shape changes, with marked inward deviation in the Sommer sector of the MTS hippocampi. In the contralateral hippocampi, the inferior surface of the hippocampal body showed inward deformation in the medial aspect of the subiculum, with minimal involvement of the Sommer sector. HDM-LD shows involvement of subregions of the hippocampus which are consistent with MTS histopathology. Contralateral hippocampi show different HDM-LD changes, suggesting that the underlying disease process in the contralateral hippocampi is different from MTS.

Keywords: temporal lobe epilepsy; hippocampus; mesial temporal sclerosis; MRI; epilepsy surgery

Abbreviations: ANOVA = analysis of variance; HDM-LD = large-deformation high-dimensional mapping; MTLE = mesial temporal lobe epilepsy; MTS = medial temporal lobe sclerosis; TLE = temporal lobe epilepsy

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Introduction

Mesial temporal lobe epilepsy (MTLE) is a common type of refractory epilepsy that is amenable to treatment with surgery (Wiebe *et al.*, 2001). In most epilepsy surgery series, the most common associated pathological lesion in patients with MTLE is mesial temporal sclerosis (MTS) (Lencz *et al.*, 1992; Kim *et al.*, 1995; Arruda *et al.*, 1996). MRI-based hippocampal volumetric measurements are useful in the assessment of patients with MTLE. In the clinical setting

of a seizure history compatible with MTLE, significant asymmetry of hippocampal volumes is predictive of MTS (Lencz *et al.*, 1992; Cascino, 1995a) and of favourable outcome after epilepsy surgery (Jack *et al.*, 1992; Cascino, 1995b; Kim *et al.*, 1995; Arruda *et al.*, 1996; Holmes *et al.*, 1997). Most prior studies used manual segmentation of the hippocampus from MR images to determine hippocampal volumes (Watson *et al.*, 1997).

Post-acquisition automated image processing allows a more objective and sensitive interpretation of three-dimensional shape and volume of neuroanatomical structures. In the emerging field of computational anatomy, general pattern theory (Wang *et al.*, 2001) and other mathematical principles provide an analytical framework and tools for studying structures, such as the hippocampus, using large-deformation high-dimensional mapping (HDM-LD) (Wang *et al.*, 2001). HDM-LD has been shown previously to generate highly reproducible results in patients with MTLE and pathologically verified MTS (Hogan *et al.*, 2000).

In a previous study, we demonstrated changes in hippocampal surface anatomy in patients with MTS (Hogan *et al.*, 2003). However, these initial results of intrasubject comparison of hippocampi were affected by bilateral involvement of the hippocampi in MTS, as well as normal right–left volume differences (Csernansky *et al.*, 2000) and spatial asymmetries of the right and left hippocampi (Wang *et al.*, 2001). The aim of the present study was to characterize the HDM-LD pattern of hippocampal change in patients with MTLE compared with matched controls, to account for bilateral hippocampal changes in MTS, and normal right–left asymmetries, and determine if there is a typical pattern of hippocampal HDM-LD-defined change in MTS.

Since some patients with MTS show no abnormalities of hippocampal volume (Jackson *et al.*, 1994), a potential application of HDM-LD in epilepsy is in the evaluation of patients with temporal lobe epilepsy and normal hippocampal volume. HDM-LD may also have research applications in investigating the pathophysiology of MTLE. Documenting a specific HDM-LD-defined change in MTS in clinically well-confirmed cases would be prerequisite for application of the technique in patients with TLE and normal MRI findings using conventional techniques.

Material and methods

Subject selection

Subjects were identified retrospectively from consecutive cases from the epilepsy surgery series at Saint Louis University over the period from 1997 to 2002, as outlined in our Institutional Review Board protocol. Retrospective review of cases during this time yielded 43 cases of temporal lobectomy for epilepsy surgery. These cases were then further reviewed to select cases with post-surgical pathological confirmation of MTS, as well as asymmetry of MRI-based hippocampal volume loss (>10% hippocampal asymmetry) concordant with the side of pathologically documented MTS. Only subjects fulfilling both criteria for pathology and MRI-based hippocampal volume loss were included in the study. A neuropathologist both macroscopically and microscopically assessed all specimens and identified substantial neuronal loss in hippocampal subregions of CA4 and the Sommer sector (CA1 and adjacent subiculum), with relative sparing of CA2 neurons. After selection on this basis, clinical records of all cases were reviewed to confirm a clinical history of focal seizures consistent with MTLE, including seizures with arrested activity, impairment of consciousness, automatisms and postictal confusion. Duration of epilepsy at the time of MR scanning was noted. All patients underwent video EEG

telemetry monitoring to confirm the semiology and EEG localization of their seizures (Risner, 1989).

The volunteers for normal control MR studies had no history of CNS disease, significant head trauma or alcohol abuse.

MR scanning was performed with a 1.5 Tesla Signa scanner (General Electric, Milwaukee, WI, USA). For epilepsy subjects, whole-brain acquisitions were obtained in the course of their clinical evaluation in the coronal plane with a fast spoiled grass technique, with one of two protocols: (i) TR = 14, TE = 3, flip angle = 30°, voxel dimensions 0.859 × 0.859 × 1.5 mm, field of view 22 × 22 cm, matrix size 256 × 256; (ii) TR = 8.8, TE = 1.8, flip angle = 30°, voxel dimensions 0.742 × 0.742 × 1.5 mm, field of view 38 × 38 cm, matrix size 512 × 512. At Saint Louis University Hospital, epilepsy protocol MR studies were changed to a higher matrix size to improve resolution of images; hence the two different MR protocols above. All normal control subjects had MR studies using protocol 2. All studies, for both epilepsy subjects and controls, were performed on the same MRI scanner.

In the subjects with epilepsy, MR studies were grouped according to the side of MTS. Average age and intracranial area were determined for all subject groups. Fifteen subjects were included in the left and the right MTS groups. There were also 15 subjects in the control group. Age, sex and duration of epilepsy of the right and left MTS groups are recorded.

A single investigator (REH) performed intracranial and brain parenchymal volume measurements. The techniques for determining intracranial area and brain parenchymal volume differed, as described below.

To determine intracranial area, images were integrated into Analyze AVW 4.0 (Rochester, MN, USA). Measurement of the intracranial area in the mid-sagittal plane was performed as described by Free and colleagues (Free *et al.*, 1995), tracing along the inner limit of the subcutaneous fat over the convexity, along the margins of the cerebral hemispheres at the base of the brain, and including the brainstem to the foramen magnum.

Brain parenchymal volumes were determined with Analyze AVW 4.0, using a technique described previously (Hohne and Hanson 1992; Hogan *et al.*, 1996).

Comparisons of mean age, intracranial area and brain volume

Average age, brain volume and intracranial area were determined for all three groups. Statistical comparisons of average age, brain volume and intracranial area were performed using the unpaired *t* test with a two-tailed *P* value. To assess age as a covariate in volume comparisons, brain size and age were used as covariates separately in the volume analysis of variance (ANOVA), and the Spearman non-parametric correlation was calculated between hippocampal volumes and age.

HDM-LD segmentation of the hippocampus

The hippocampus was semi-automatically segmented as previously described (Hogan *et al.*, 2000) using a provisory template MR scan (a healthy subject not otherwise included in this study) in which the template hippocampus had been outlined manually.

To quantify hippocampal volume and shape differences between left MTS, right MTS and the control group, a surface with triangulated points was superimposed onto the hippocampus segmentation in the template and then carried along each deformation of the template to the subjects. The triangulation was obtained using the marching cubes algorithm (Claudio and Roberto, 1994), the surface points being the vertices of the triangulated graph. Methods for the representation and construction of such a smooth surface have been described previously

(Joshi *et al.*, 1997). Left and right hippocampal surfaces for each subject were obtained by carrying the template surface along the deformation of the template scan to each hemisphere of the subject scan. Hippocampal volume was calculated as the volumes enclosed by the transformed surfaces.

Hippocampal volume comparison

MTS hippocampi and contralateral hippocampi (for both the right and left MTS groups, independently) were first compared with the control group, with brain parenchyma volumes as a covariate. In order to assess the degree of hippocampal involvement compared with total brain parenchymal involvement, the ratios of average hippocampal volumes between the MTS group and control group in the MTS and contralateral sides were separately compared with the ratio of average brain parenchyma volumes between the MTS group and the control group. For analysis of right–left hippocampal asymmetries, a repeated-measures ANOVA was used with group as the main effect and hemisphere as repeated factors. Group \times hemisphere interaction was used to test for volume asymmetry differences.

Hippocampal shape comparison

For simultaneous left and right hippocampal shape comparison, all subject surfaces were first registered to the template surfaces with a six-parameter rigid-motion transformation (three for translation and three for rotation). Statistical analyses were performed on the registered surfaces as follows: (i) an overall mean surface was computed for the entire population of registered subject surfaces; (ii) vector fields describing hippocampal shape variation within this population were characterized by the covariance matrix of the vector fields; and (iii) the dimensionality of the covariance matrix was reduced by computing a complete orthonormal set of eigenvectors via singular value decomposition (Joshi *et al.*, 1997).

The asymmetry in the volumes of the hippocampus was studied by quantifying the group \times hemisphere interaction in the above repeated-measures ANOVA of hippocampal volumes. The asymmetry in the shape of the hippocampus was studied by forming an asymmetry vector field based on flipping the right-side hippocampal surface across the mid-sagittal plane to the left side in each subject. The asymmetry vector field was then characterized by its covariance structure, the dimensionality of which was again reduced by computing a complete orthonormal set of eigenvectors via singular value decomposition (Wang *et al.*, 2001). The methodology of this type of analysis has been described previously (Wang *et al.*, 2001).

Results

Imaging protocols

In the right MTS group, six subjects underwent protocol 1 for their MR scans and nine subjects underwent protocol 2. In the left MTS group, seven subjects underwent protocol 1 for their MR scans and eight subjects underwent protocol 2.

Clinical data of epilepsy subjects

The right TLE group included seven women and eight men with an average duration of epilepsy of 28.4 years. The left TLE group included eight women and seven men with an average duration of epilepsy of 25.3 years.

Comparisons of mean age, intracranial area and brain volume

The mean \pm SD age (P value compared with controls), in years, for the control group was 35.7 ± 10.4 , for the right MTS group it was 35.7 ± 8.7 ($P = 0.999$), and for the left MTS groups it was 34.7 ± 8.6 ($P = 0.754$). The mean \pm SD intracranial area (P value compared with controls), in cm^2 , for the control group was 188.1 ± 9.9 , for the right MTS group it was 192.8 ± 11.9 ($P = 0.2497$), and for the left MTS group it was 185.0 ± 7.7 ($P = 0.3871$). The mean \pm SD brain volume (P value compared with controls), in cm^3 , for the control group was 1341 ± 95.6 , for the right MTS group it was 1249 ± 131 ($P = 0.0365$), and for the left MTS group it was 1198 ± 104 ($P = 0.005$).

Age as a covariate in volume comparisons

When age was used as a covariate in the volume comparisons, the results of the analyses did not change. Moreover, there was no overall correlation between hippocampal volumes and age (left, $r = 0.14$, $P = 0.37$; right, $r = 0.4$, $P = 0.80$). For the control group, correlation between hippocampal volumes and age was non-existent (left, $r = 0.04$, $P = 0.90$; right, $r = -0.07$, $P = 0.80$). In the left MTS group, the healthy right-side hippocampal volume had no correlation with age ($r = 0.10$, $P = 0.72$), and the diseased left side showed a slight trend towards correlation with age ($r = 0.37$, $P = 0.17$). In the right MTS group, the healthy left-side hippocampal volume had no correlation with age ($r = 0.12$, $P = 0.67$), and neither did the diseased right side ($r = 0.12$, $P = 0.67$).

Bilateral hippocampal volume comparison

The mean \pm SD, in mm^3 , hippocampal volume for the control group was 3185 ± 413 on the right and 2803 ± 330 on the left, for the right MTS group it was 1953 ± 403 on the right and 2567 ± 362 on the left, and for the left MTS group it was 2765 ± 467 on the right and 1555 ± 215 on the left. Group volume data are presented in Table 1. Figure 1 shows the distribution of hippocampal volumes for the right MTS, left MTS and control groups. Our control subjects showed a greater volume in the right hippocampus, consistent with past studies (Csernansky *et al.*, 2000). Repeated-measures ANOVA yielded a strong overall difference among the three groups [$F(2,42) = 26.1$, $P < 0.0001$], and between-group contrasts were also highly significant (left MTS versus control, $F = 43.8$, $P < 0.0001$; right MTS versus control, $F = 34.0$, $P < 0.0001$). Highly significant overall group \times hemisphere interaction ($F = 147.7$, $P < 0.0001$) as well as between-group group \times hemisphere interactions (left MTS versus control, $F = 60.7$, $P < 0.0001$; right MTS versus control, $F = 87.9$, $P < 0.0001$) indicated highly significant group differences in hippocampal volume asymmetry.

Comparison of hippocampal volume changes with brain parenchymal volume changes

In the left MTS group, after covarying with brain parenchyma volume, the difference between the diseased (left) side

Table 1 Mean hippocampal and brain parenchyma volumes in all groups

	Left MTS		Right MTS		Control	
	Left	Right	Left	Right	Left	Right
Hippocampus						
Volume (cm ³), mean ± SD	1.555 ^a ± 215	2.765 ^b ± 467	2.567 ± 362	1.953 ± 403	2.803 ± 330	3.185 ± 413
Ratio to control	0.56	0.87	0.92	0.61	–	–
Brain parenchyma						
Volume (cm ³)	1198 ^c		1249 ^d		1341	
Ratio to control	0.89		0.93		–	

In the left and right MTS groups, the difference between the contralateral hippocampal volume and that of the control group became non-significant after covarying with brain parenchyma volume. This suggests that the process that affected the contralateral side of the brain was similar in magnitude to the process that affected the whole brain.

^a $P < 0.0001$, univariate comparison with controls; remained $P < 0.0001$ after covarying with brain parenchyma volume.

^b $P < 0.05$, univariate comparison with controls; became non-significant after covarying with brain parenchyma volume.

^c $P < 0.01$, univariate comparison with controls.

^d $P < 0.05$, univariate comparison with controls.

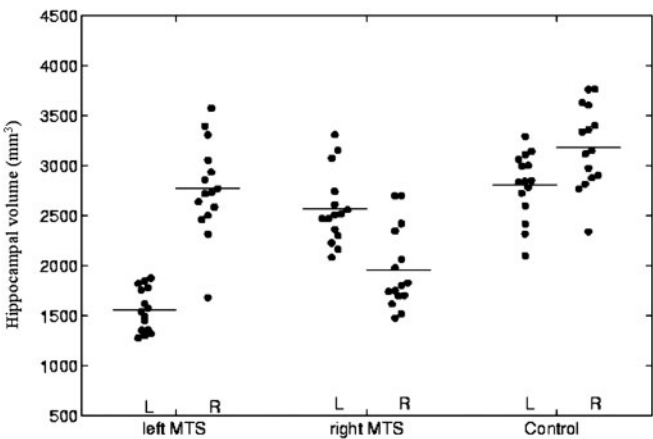


Fig. 1 Hippocampal volume comparisons.

hippocampal volume and that of the control group remained highly significant ($P < 0.0001$), and the ratio of the mean hippocampal volume between the two groups (mean left hipp_{left MTS}/mean left hipp_{control} = 0.56) was smaller than the ratio of mean brain parenchyma volumes (mean brain_{left MTS}/mean brain_{control} = 0.89). However, the difference between the contralateral (right) side hippocampal volume and that of the control group became non-significant after covarying with brain parenchyma volume, while the ratio of the mean hippocampal volumes (mean right hipp_{left MTS}/mean right hipp_{control} = 0.87) between the two groups was similar to the ratio of mean brain parenchyma volume (0.89). This suggests that the process that affected the contralateral side of the brain was part of the process that affected the whole brain. Similar observations can be made in the diseased side of the right MTS group, the contralateral side being the left.

Bilateral hippocampal shape comparison

Figures 2 and 3 show the statistical significances of deformations for the left and right MTS groups, respectively, compared with controls, projected on the mean surfaces of the control group. Colours represent regions of deformity by statistical significance as follows: inward in purple ($P < 0.01$) and turquoise ($0.01 = P < 0.05$), outward in red ($P < 0.01$) and yellow ($0.01 = P < 0.05$), and non-significant deformations ($P > 0.05$) are shown in green.

Figures 2 and 3 show the regions of statistically significant change in the right MTS and left MTS groups, respectively. There were wide regions of inward deviation in the MTS hippocampus regardless of which side was affected by MTS (i.e. right or left). Comparing the pattern of these changes with the pattern of projections of the known cornu ammonis subfields onto the hippocampal surface (Fig. 4), regions of significant inward deviation associated with MTS appear to correlate with anatomical localization of the CA1 hippocampal subfield and the subiculum. The hippocampi contralateral to MTS in both the right and left MTS groups also showed significant regional inward deformations, but the pattern of these changes was notably different compared with the pattern of changes associated with MTS. In the contralateral hippocampi, the hippocampal head showed a region of inward deformation over the medial hippocampal head on its superior surface, extending towards the intralimbic gyrus in the right MTS group, and extending to include the intralimbic gyrus in the left MTS group. This region correlates with the junction of CA1 and the subiculum in the hippocampal head. In the hippocampal body, the inferior surface of the contralateral hippocampus in both the right and left MTS groups showed inward deformation in the medial aspect of the subiculum, with minimal involvement at the junction of CA1 and the subiculum, again representing a notable difference from the MTS hippocampi. Finally,

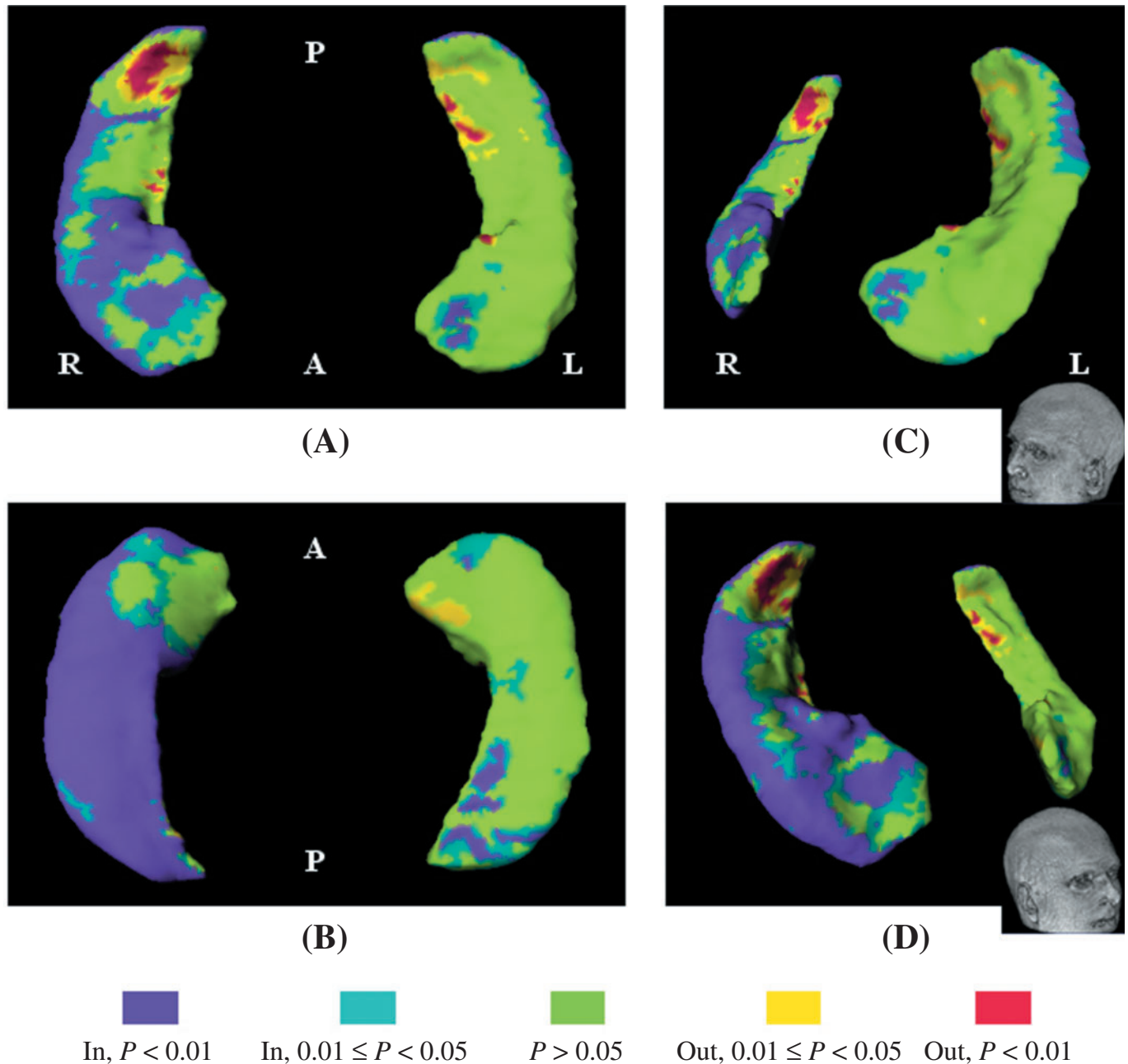


Fig. 2 Bilateral hippocampal deformity: right MTS versus controls (bottom row: colour scales). Statistical significance of the deformations, using Wilcoxon's signed rank test: inward in purple ($P < 0.01$) and turquoise ($0.01 \leq P < 0.05$), outward in red ($P < 0.01$) and yellow ($0.01 \leq P < 0.05$); non-significant deformations ($P > 0.05$) are shown in green. (A) View from above. (B) View from below. (C) View from a perspective slightly above and to the left of a midline plane, showing the top side. (D) View from a perspective slightly above and to the right of a midline plane, showing the top side. Right (R), left (L), anterior (A) and posterior (P) are marked on the images. Pictures of the head in C and D serve to orient the viewer to the direction of rotation of the hippocampal surface projections.

there was significant inward deviation in the lateral aspect of the posterior half of the hippocampal body in the contralateral hippocampi of both the right and left MTS groups, also correlating with the CA1 region.

Perhaps surprisingly, there were two general regions of significant outward deviation in Figs 2 and 3. On the superior surface of the junction of the hippocampal body and tail, there

is a region of outward deviation in both hippocampi of the right and left MTS groups. These generally correlate to a region where multiple hippocampal subfields project to the surface. In the contralateral hippocampi in both the right and left MTS groups, the inferior surface of the uncinate gyrus also showed a region of significant outward deviation, in the region of the subiculum.

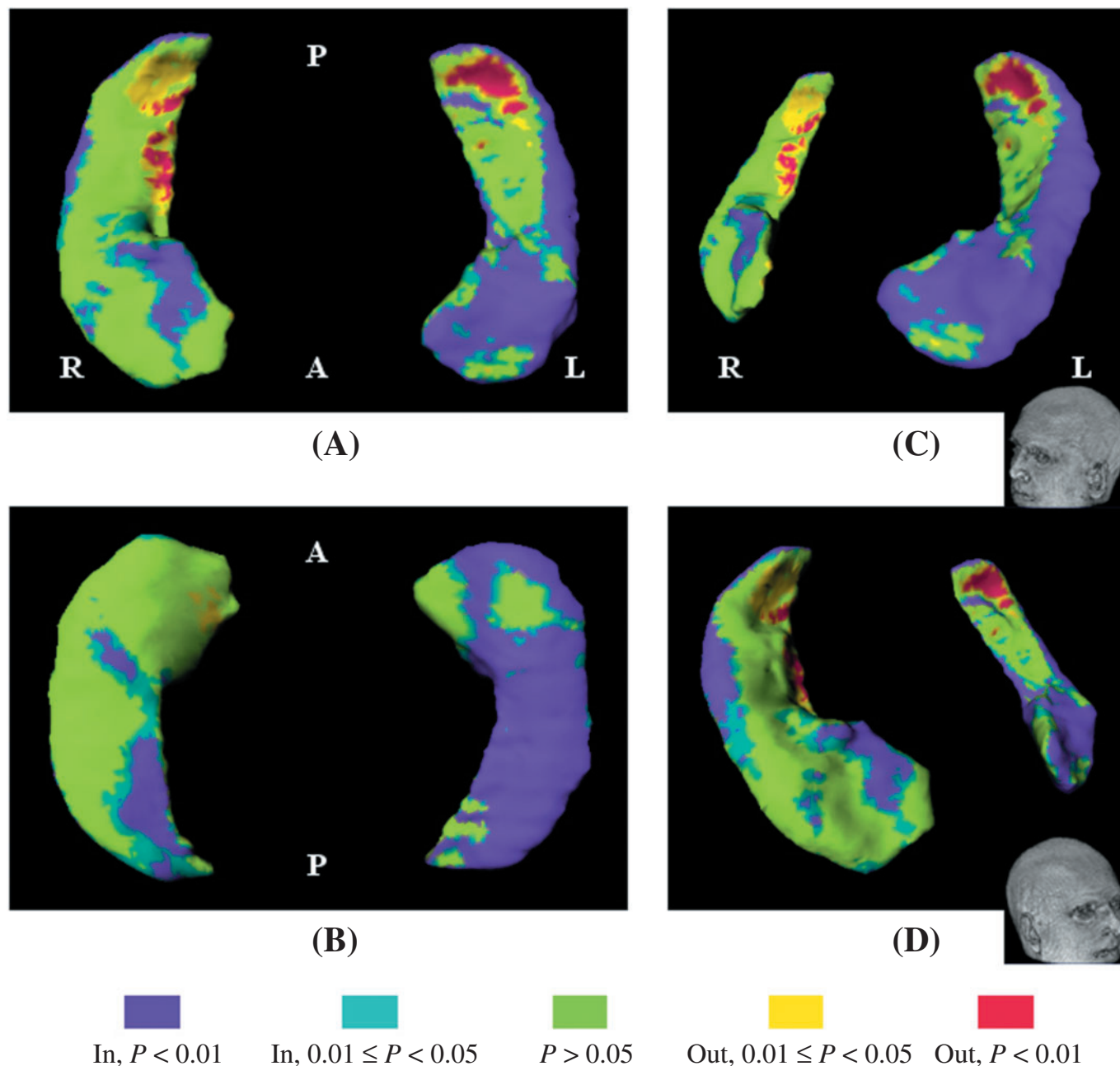
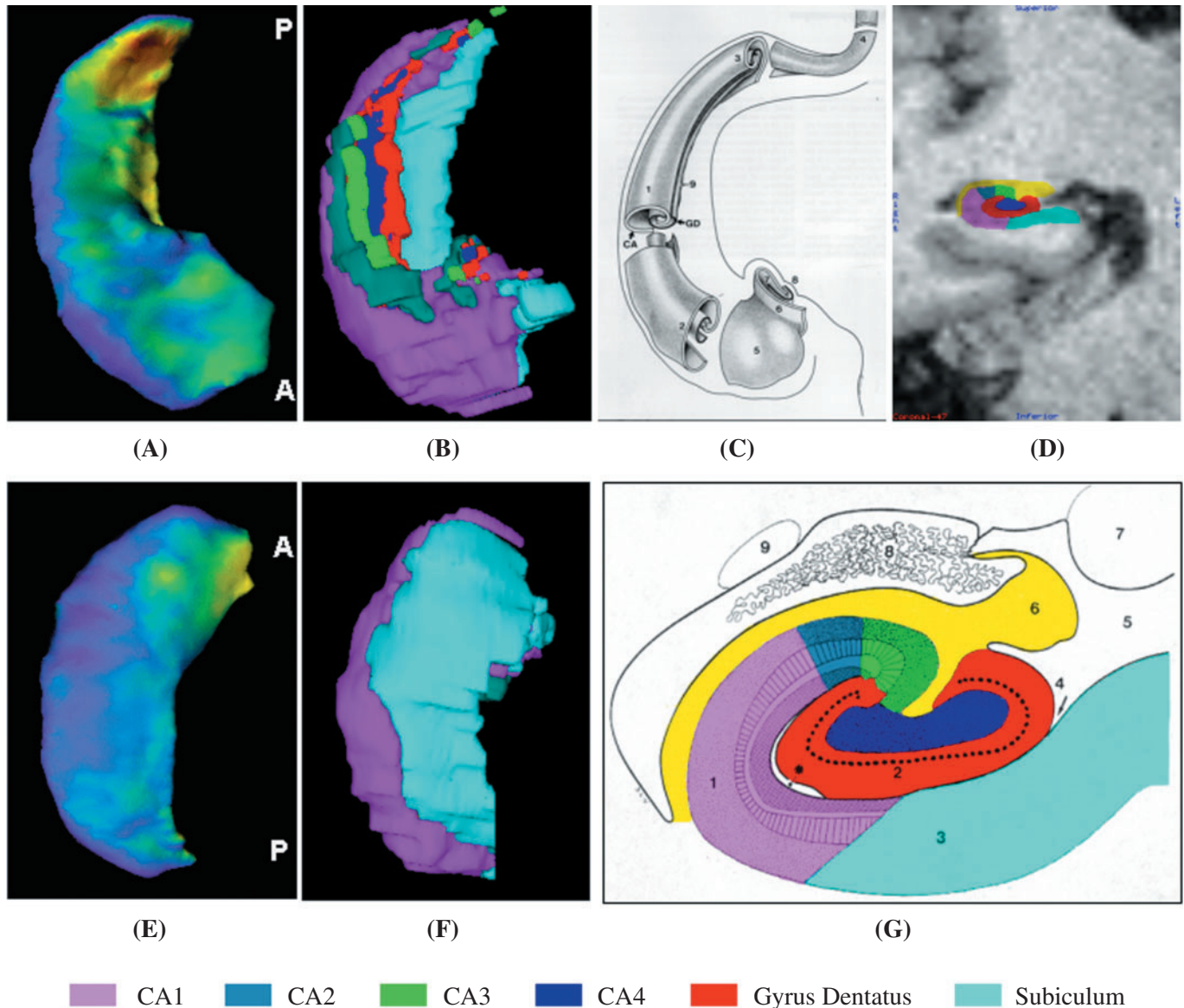


Fig. 3 Bilateral hippocampal deformity: left MTS versus controls. (bottom row: colour scales). Statistical significance of the deformations, using Wilcoxon's signed rank test: inward in purple ($P < 0.01$) and turquoise ($0.01 \leq P < 0.05$), outward in red ($P < 0.01$) and yellow ($0.01 \leq P < 0.05$); non-significant deformations ($P > 0.05$) are shown in green. (A) View from above. (B) View from below. (C) View from a perspective slightly above and to the left of a midline plane, showing the top side. (D) View from a perspective slightly above and to the right of a midline plane, showing the top side. Right (R), left (L), anterior (A) and posterior (P) are marked on the images. Pictures of the head in C and D serve to orient the viewer to the direction of rotation of the hippocampal surface projections.

Inspection of Figs 2 and 3 shows remarkably symmetrical involvement of the MTS hippocampi in the right and left MTS groups, perhaps best represented by the inferior surface views in Figs 2B and 3B.

A flame scale surface representation of the differences of the right hippocampus of the right MTS cases, compared with the controls, is shown in Fig. 4A and E. To provide a

comparative illustration of the underlying hippocampal subfields, we included segmentation from a normal subject's MRI, segmented to show normal subfield anatomy. The subfield segmentation, from a previous study (Posener *et al.*, 2003), is reproduced in Fig. 4B and F. Panels C, D and G in Fig. 4 illustrate the anatomical relationships of the hippocampal subfields.



Legends refer to panels B, D, F, G only. For legends of panels A and E, please refer to Fig. 3.

Fig. 4 Hippocampus subfields atlas. (A and E) Hippocampal deformation map for the right MTS group versus controls, with the right hippocampus, shown here, viewed from above (A) and below (E). The flames scale showed continuous deformation from -2 mm (cooler colours) to $+2$ mm (warmer colours). The anterior hippocampus is marked 'A' and the posterior hippocampus 'P' in panels A and E. (C) 3D orientation of hippocampal subfields, showing the cornu ammonis (CA) and gyrus dentatus (GD) interlocking laminae. Reproduced with permission from Duvernoy (1998). (G) Coronal section of hippocampal body. Reproduced with permission from Duvernoy (1998). The authors have coloured in the subfields; see legends above. (D) Coronal section of hippocampal body from the template MR scan, section 55. The manual delineation of the subfields (Posener *et al.*, 2003) has been overlaid, using the same colours as those used in panel G, omitting the alveus/fimbria. (B and F) Composite model of the template hippocampus subfields, showing the right hippocampus; see legends in the bottom row. Panels B and F: copyright 2003, The American Psychiatric Association; <http://ajp.psychiatryonline.org>. Reprinted by permission.

Discussion

Technical issues are important for the validation of HDM-LD as a segmentation tool for the hippocampus (Jack *et al.*, 1995). We have documented previously the validity of our deformation-based technique in patients with MTS, showing a 92.8% overlap in sequential deformation-based hippocampal

segmentations (Hogan *et al.*, 2000). Using general pattern matching, anatomical structures can be segmented using global shape models. By representing the typical structures by the construction of templates and their variability by the definition of transformations applied to the templates, MRIs of the hippocampus may be segmented semi-automatically (Christensen

et al., 1993; Miller *et al.*, 1993; Joshi *et al.*, 1995), which improves the reliability and precision of hippocampal segmentations (Hogan *et al.*, 2000).

Because the scans were collected in the patients for clinical as well as research purposes, and because upgrades in scanning software were made for the clinical scanning protocols, two different MR protocols were used to collect the scans in the epilepsy subjects. We previously demonstrated the validity of our HDM-LD technique (Hogan *et al.*, 2000) using the earlier of these protocols, which had the lower resolution (as described in Material and methods). By changing to the later, higher-resolution protocol, improvements in the precision of our measurements would be expected with no systematic bias. However, possible volumetric measurement differences in the protocols could still exist, and the inclusion of subjects with different MR protocols in the epilepsy subject groups and only one MR protocol for the control subject group could introduce inaccuracies into our results. Past investigators have outlined the difficulties of validating MR-based volumetric measurement techniques in the context of ongoing technical improvements in MR acquisition (Jack *et al.*, 1995). While this is a possible weakness, the magnitude of the hippocampal changes in the epilepsy groups compared with controls, as well as the marked similarity in results in the right and left TLE groups (each compared separately with the control group), suggest that differences in the MR protocols did not affect the outcome of the study significantly.

In this study of groups of patients with right and left TLE and normal controls, it was important to match the three groups for intracranial volume and age. Prior investigators have reported a linear correlation between hippocampal volume and intracranial volume (Free *et al.*, 1995; Jack *et al.*, 1995). Free and colleagues demonstrated the validity of estimating the intracranial volume from the area of a mid-sagittal MR section (Free *et al.*, 1995). We therefore used the mid-sagittal area measurement to estimate intracranial volume. Our results show non-significant differences in intracranial area, but significant differences in brain parenchymal volume, in both the right and the left MTS groups, compared with controls. Therefore, the groups were adequately matched for intracranial area. The significant decrease in brain parenchymal volume is consistent with results from other studies of patients with chronic, intractable temporal lobe epilepsy, who have shown widespread brain parenchymal volume loss compared with controls (Marsh *et al.*, 1997; Briellmann *et al.*, 1998). Because of the possibility of age-related hippocampal volume loss (Sullivan *et al.*, 1995; Jack *et al.*, 1998), we compared the mean age of the right and left MTS groups with that of the control group, and evaluated age as a covariate in volume comparisons. Results showed no significant differences between the groups with respect to age.

We selected patients with well-localized epileptic seizures, who underwent epilepsy surgery and had neuropathological confirmation of MTS. Study of this well-defined group enables documentation of typical changes in hippocampal structure associated with MTS. Establishing typical hippocampal

changes in MTS is essential for the further study of the use of HDM-LD to detect subtle hippocampal changes that may not be detected by other methods, such as hippocampal volumetry and T2-weighted signal changes (Jackson and Van Paesschen, 2002). For HDM-LD-based intrasubject comparison of right and left hippocampi (intrasubject comparison being the common method of investigation using hippocampal volumes in TLE) (Watson *et al.*, 1997), delineation of shape changes in the hippocampus contralateral to MTS is also important. To account for contralateral hippocampal changes using hippocampal volumes, past investigators used groups of control subjects to establish normal ratios of hippocampal volumes to intracranial or brain parenchymal volume (Jack *et al.*, 1995a). In a similar manner, documenting shape changes in the contralateral hippocampi compared with controls may enable more accurate algorithms for intrasubject comparison of hippocampal shape in patients with TLE.

In a previous study, we demonstrated changes in hippocampal surface anatomy in patients with MTS (Hogan *et al.*, 2003). In this previous study, we used HDM-LD to quantify the difference between the hippocampi and coregistered the mean transformation of the hippocampus with MTS to the contralateral hippocampus, considering groups of patients with left MTS and right MTS separately. Both the right and left MTS groups showed similar shape changes, with maximal inward deformation in the medial and lateral hippocampal head, and the hippocampal tail. However, there was more extensive involvement in the lateral hippocampal body in the right MTS group compared with the left. These initial results, from our previous study, may have been affected by bilateral involvement of the hippocampi in MTS, as well as normal right-left volume differences (Csernansky *et al.*, 2000) and spatial asymmetries of the right and left hippocampi (Wang *et al.*, 2001). In the present study, we used HDM-LD to more directly compare patients with MTS with controls and eliminate difficulties caused by bilateral involvement of MTS and normal hippocampal asymmetries.

Our hippocampal volume results confirm previous findings, showing significant volume loss in both the MTS and contralateral hippocampi (Jack *et al.*, 1995b; King *et al.*, 1995; Barr *et al.*, 1997; Quigg *et al.*, 1997) (Table 1). To further evaluate the relationship of hippocampal volume loss with total brain parenchymal volume loss, we statistically covaried results of hippocampal volume loss with brain parenchymal volume loss. After covariance, MTS hippocampal volumes continued to show significant change, while contralateral hippocampal volume changes became non-significant. The findings indicate that contralateral hippocampal volume changes occur in proportion to total brain parenchymal changes, possibly as part of a global brain disease process underlying chronic epilepsy.

Pathologically, MTS preferentially involves CA4, and Sommer sector (Bratz, 1899; Babb *et al.*, 1984; Armstrong 1993; Thom *et al.*, 2002). Figure 4 illustrates the surface representations of MTS changes compared with normal hippocampal subfield surface anatomy. There is a clear correlation between the most involved regions in the MTS hippocampi

(represented in purple) and the Sommer sector. Several aspects of the results support the accuracy of HDM-LD in depicting the changes in hippocampal shape associated with MTS. First, our results show that there are specific regions of volume loss within the hippocampus in patients with epilepsy and MTS that correlated with the well-established histopathological pattern of MTS (Thom *et al.*, 2002). Secondly, even though we statistically considered the right and left MTS groups separately, after accounting for normal variations in the volume and shape of the right and left hippocampi, the results of shape changes of the MTS hippocampi in the right and left MTS groups were nearly identical. Since some patients with MTS show no abnormalities in hippocampal volumes (Jackson *et al.*, 1994), a potential application HDM-LD in epilepsy is in the evaluation of patients with TLE and normal hippocampal volumes. HDM-LD shows specific hippocampal surface regional changes in MTS, which would theoretically be involved, to a lesser degree, in patients with MTS and normal hippocampal volumes.

The underlying pathophysiology of MTS remains uncertain (Jackson and Van Paesschen, 2002). Therefore, correlation of HDM-LD measurements of the hippocampus with other clinical factors associated with MTS, such as febrile seizures, duration of epilepsy, cognitive function and the outcome after epilepsy surgery, may yield important findings, which will help us understand the disease process underlying MTS and intractable temporal lobe epilepsy. Documentation of hippocampal changes over time, in relation to ongoing epileptic seizures, is also a topic of longstanding interest. Most studies correlating seizure duration with severity of MTS and hippocampal volume loss have been retrospective and offer conflicting results (Watson *et al.*, 1997; Briellmann *et al.*, 2002). However, some recent prospective studies have examined the issue of seizure-induced hippocampal volume loss. Briellmann and colleagues followed 24 patients with mild temporal lobe epilepsy over a period of 3.5 ± 0.7 years and reported one case that developed MTS (Briellmann *et al.*, 2002). They reported a significant relationship between the incidence of generalized tonic-clonic seizures and hippocampal volume loss ipsilateral to the side of seizure onset. In another recent prospective study, following patients with new onset epilepsy over a 3.5-year period, there was no significant change in hippocampal volumes compared with controls (also followed over a 3.5-year period) (Liu *et al.*, 2002a). Only one patient in the study had MTS associated with their seizures. In a follow-up study by the same research group (Liu *et al.*, 2003) looking at neocortical changes in groups of patients with new-onset and chronic active epilepsy, there were 13 patients with MTS. There was significant neocortical volume loss in the MTS group compared with controls, six patients showing generalized volume loss. While the study did not detect hippocampal volume loss, the method used may have been insensitive in the detection of hippocampal changes (Liu *et al.*, 2003). Differences in results of recent prospective studies examining the issue of seizure-induced progressive hippocampal atrophy may be due to the technical or methodological design of the investigations (Liu *et al.*, 2002b). More precise measures of

hippocampal volume change, using HDM-LD, may play a role in clarifying this issue.

Another interesting aspect of HDM-LD hippocampal changes in MTLE is comparison of differences with other disease states. Our findings of accentuated volume changes differ, either in pattern or degree, from hippocampal shape changes in schizophrenia, Alzheimer's disease and depression. Patients with schizophrenia show minimal volume loss in the lateral hippocampal head and subiculum (Csernansky *et al.*, 1998). In very mild dementia of Alzheimer's type, subjects show inward deformities in the head of the hippocampus and along the lateral surface of the hippocampal body with substantial overall hippocampal volume loss (Csernansky *et al.*, 2000). While there is similarity in the pattern of HDM-LD hippocampal changes in mild dementia of Alzheimer's type and MTS, the relative degree of volume loss is greater in MTS. Finally, patients with depression show a shape deformation of the subiculum without any measurable volume loss (Posener *et al.*, 2003). Therefore hippocampal HDM-LD changes may illustrate changes due to different pathophysiological mechanisms of disease. In the light of HDM-LD findings in other disease states, the differences in MTS and contralateral hippocampi in the present study are suggestive that there are different underlying pathophysiological mechanisms in the MTS and contralateral hippocampi.

In summary, HDM-LD mapping of hippocampal surface structure in patients with MTLE and MTS, in comparison with controls, indicated that MTS is associated with deformities of specific subregions of the hippocampus. Hippocampi contralateral to MTS hippocampi also show deformity, but with a different pattern, and volume changes that were proportional to overall brain parenchymal volume loss.

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