Hippocampal Sclerosis in Temporal Lobe Epilepsy: Findings at 7 T¹

Thomas R. Henry, MD
Marie Chupin, PhD
Stéphane Lehericy, MD, PhD
John P. Strupp, MSEE
Michael A. Sikora, BS
Zhiyi Y. Sha, MD, PhD
Kâmil Uğurbil, PhD
Pierre-François Van de Moortele, MD, PhD

Purpose:

To determine if ultrahigh-field-strength magnetic resonance (MR) imaging can be used to detect subregional hippocampal alterations.

Materials and Methods:

Subjects provided written consent to participate in this prospective institutional review board–approved HIPAA-compliant study. T1- and T2-weighted 7-T brain MR images were acquired in 11 healthy subjects and eight patients with temporal lobe epilepsy (TLE). In all subjects, images were qualitatively examined for evidence of hippocampal atrophy, signal change, and malrotation with the Bernasconi definition, and digitations of the hippocampal heads were counted (agreement was measured with the κ statistic). Data were analyzed quantitatively with manual subregional hippocampal body segmentation. Subregional data in individual subjects with TLE were compared with data in control subjects to detect deviation from the control range for volume measures on each side and with asymmetry indexes.

Results:

All eight patients with TLE had hippocampal abnormalities on the epileptogenic side. Subregional analysis revealed selective lateral Ammon horn atrophy in six patients and diffuse Ammon horn and dentate gyrus atrophy in one patient. Paucity of hippocampal digitations occurred on the epileptogenic side in all patients with TLE and also on the contralateral side in three patients (interrater κ value, 0.80). Hippocampal malrotation was observed in three patients with TLE and four control subjects.

Conclusion:

Ultrahigh-field-strength MR imaging permitted detection of selectively greater Ammon horn atrophy in patients with TLE and hippocampal sclerosis. Paucity of digitations is a deformity of the hippocampal head that was detected independent of hippocampal atrophy in patients with mesial TLE.

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¹From the Department of Neurology, University of Minnesota, 420 Delaware St SE, MMC 295, Minneapolis, MN 55455 (T.R.H., Z.Y.S.); Center for Research, Institute of the Brain and Spinal Cord, Université Pierre et Marie Curie, Paris, France (M.C., S.L.); Center for Neuroimaging Research and Department of Neuroradiology, Hôpital Pitié-Salpêtrière, Paris, France (S.L.); and Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, Minn (J.P.S., M.A.S., K.U., P.F.V.d.M.). Received September 2, 2010; revision requested October 11; revision received April 7, 2011; accepted April 14; final version accepted May 5. Supported by the Keck Foundation, with institutional support from the University of Minnesota.

Address correspondence to T.R.H. (e-mail: trhenry@umn.edu).

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Focal hippocampal dysfunction initiates electrophysiologic seizures and impairs interictal cognition in patients with mesial temporal lobe epilepsy (TLE) (1). The lesion most commonly reported in surgical and autopsy series of mesial TLE is hippocampal sclerosis (HS), although temporal lobe encephalomalacia, neoplasia, vascular malformations, and developmental malformations often occur in patients with TLE (2–4). Ammon horn sclerosis—defined as loss of pyramidal neurons predominantly in the cornu ammonis (CA) 1 region, with sprouting of mossy fibers of dentate granule cells and often with lesser CA3 and dentate hilar neuronal loss—is encountered more frequently than is end-folium sclerosis, which is defined as neuronal loss in CA4 and the adjacent hilus of the dentate gyrus. This latter lesion may represent a lesion observed after convulsive status epilepticus in various forms of epilepsy. Ammon horn sclerosis and end-folium sclerosis coexist as total HS in patients with severe TLE (2,5).

An *in vivo* technique that defined subregional distributions of hippocampal atrophy and other fine details of the hippocampus could be used to study a

larger population of patients with epilepsy than that studied at autopsy. In addition, this technique could ideally be used to examine the hippocampi bilaterally, unlike the unilateral hippocampal tissue examination of surgical specimens, and it could be performed serially within subjects, perhaps to better determine the pathophysiology of hippocampal dysfunction in patients with TLE. Finally, this technique could enable us to better select patients with TLE who should or should not undergo surgery for their epilepsy.

Brain magnetic resonance (MR) imaging often depicts HS (6–8). In patients with HS evident in surgically resected specimens, preoperative clinical MR imaging has revealed hippocampal atrophy, T2 increases, and other hippocampal signal alterations; loss of internal architecture of the hippocampus; and other alterations of the hippocampus and extrahippocampal structures (6,9). Hippocampal atrophy has been quantified with manual and automated volumetric techniques (10–15). In patients with HS, intrahippocampal gray-white matter contrast on 1.5- and 3-T MR images may be insufficient to enable us to detect the continuous band of intrahippocampal white matter bordering the vestigial hippocampal sulcus (16); however, this white matter band is continuous at microscopy of sclerotic hippocampal specimens. This MR observation has been referred to as the partial loss of hippocampal striation (16). Other groups have reported malrotation of the hippocampus in patients with HS (17–19).

Cerebral MR imaging at 1.5 T or 3 T does not yield reliable images of the major intrahippocampal structures because of submillimetric dimensions and

limited MR contrast in these tissues. Ultrahigh-field-strength (7 T and higher) MR systems offer a greatly increased signal-to-noise ratio, allowing for increased spatial resolution (20) and increased tissue contrast (21) compared with 1.5- and 3-T fields. Technical advances permit high-spatial-resolution hippocampal and whole-brain T1- and T2-weighted MR imaging at 7 T (22,23). Internal hippocampal structures have been defined with 7-T MR imaging in healthy young adults (24), but hippocampal atrophy is likely to render these substructures more difficult to define. This prospective investigation addressed the hypothesis that the increased spatial and contrast resolution of ultrahigh-field-strength MR imaging compared with those of standard clinical MR imaging would depict subregional distributions of hippocampal atrophy and might enable detection of associated hippocampal malformations.

Advances in Knowledge

- Intrahippocampal structures can be detected with 7-T MR imaging in healthy subjects and those with hippocampal sclerosis, permitting subregional hippocampal volumetry.
- In sclerotic hippocampi, 7-T MR imaging can be used to distinguish atrophy predominantly affecting the Ammon horn from that affecting the dentate gyrus.
- Deformity of the hippocampal head consisting of paucity of interdigitations can be detected in the presence or absence of hippocampal atrophy with 7-T MR imaging.
- Internal structures of malrotated hippocampal bodies were visible with 7-T MR imaging.

Implication for Patient Care

- 7-T MR imaging may improve the performance of structural imaging in patients with medically refractory TLE over that achieved with current clinical imaging, with further development and validation, so as to increase safety and efficacy of presurgical epilepsy evaluations.

Materials and Methods

Patients with epilepsy and healthy adults provided written consent to participate in this institutional review board–approved

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Abbreviations:

AI = asymmetry index
CA = cornu ammonis
HS = hippocampal sclerosis
TLE = temporal lobe epilepsy

Author contributions:

Guarantors of integrity of entire study, T.R.H., K.U., P.F.V.d.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, T.R.H., M.C., S.L., M.A.S., P.F.V.d.M.; clinical studies, T.R.H., M.A.S., Z.Y.S., P.F.V.d.M.; statistical analysis, T.R.H., M.C., M.A.S., P.F.V.d.M.; and manuscript editing, T.R.H., M.C., S.L., M.A.S., Z.Y.S., K.U., P.F.V.d.M.

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Potential conflicts of interest are listed at the end of this article.

study, which complied with Health Insurance Portability and Accountability Act regulations. Image analyses were performed without awareness of subject identity or the results of other analyses by using methods that will be presented later in this article. Whole hippocampus volumetric methods and results are presented in Appendixes E1 and E2, Figures E1 and E2, and Tables E1–E3 (online).

Subject Selection

We recruited 11 adult patients with TLE (five men, six women) and 13 healthy adult volunteers (eight men, five women) for 7-T MR imaging, which was performed between April 2009 and January 2010. Each subject was 18–64 years old, was not pregnant, had never undergone intracranial surgery, had no contraindication to MR imaging, and reported no claustrophobia or any other reason for intolerance of MR imaging. Healthy subjects had no neurologic, psychiatric, or medical conditions. Patients with epilepsy were consecutively recruited among clinic patients by two authors (T.R.H., Z.Y.S.; >20 and 8 years, respectively, of clinical neurophysiology and epileptology experience) on the basis of the following clinical and MR imaging characteristics: Mesial TLE was diagnosed with ictal video electroencephalographic recordings showing unilateral temporal lobe ictal onset patterns (25), reported ictal semiology characteristic of mesial TLE (26), and absence of reported insults uncharacteristic of mesial TLE. Each patient with TLE had undergone prior clinical 1.5- or 3-T MR imaging, which revealed unilateral hippocampal atrophy or T2 signal increases and enabled us to exclude encephalomalacia, tumor, and vascular malformation (reviewed by S.L., >10 years of neuroradiologic MR imaging experience).

MR Acquisition

MR image acquisition was performed with a 7-T magnet (MagneX, Oxford, England) operated from a console (Siemens, Erlangen, Germany) and a 16-channel head coil. The MR protocol included acquisition of (a) scout images for positioning and B₀ shimming, (b) whole-

brain T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient-echo images ($0.8 \times 0.8 \times 0.8$ -mm resolution) and nonprepared three-dimensional images to correct T1-weighted images for intensity field bias (23), and (c) T2-weighted fast spin-echo images ($0.25 \times 0.25 \times 1.2$ -mm resolution) in 54 contiguous oblique coronal sections (perpendicular to hippocampal axis) covering both hippocampi entirely. The 27 odd and 27 even sections of T2-weighted MR images were acquired in two separate sets (each sequence was repeated three times to enable us to calculate the average), with a contiguous 54-section T2-weighted data set acquired at lower spatial resolution to coregister and calculate the average for odd and even sections. Details are provided in Appendix E1 (online).

MR Qualitative Analysis

A neuroradiologist (S.L.) qualitatively scored all T1- and high-spatial-resolution T2-weighted MR images for the following items: presence of hyperintense signal on T2-weighted images and morphology of the head (flat vs normal) and body (size). Hippocampal atrophy and abnormal signal intensity were rated as follows: A score of 0 indicated absence of atrophy or signal intensity change; a score of 1, possible presence of atrophy or signal intensity change but no diagnosis could be made with confidence; a score of 2, probable presence of atrophy or signal intensity change; and a score of 3, definite presence of atrophy or signal intensity change. The following items were rated on high-spatial-resolution T2-weighted MR images: (a) Ammon horn white matter (partial loss of hippocampal striation sign) (S.L.); (b) presence or absence of hippocampal malrotation (M.C., 10 years of experience with hippocampal MR image analysis) according to eight criteria based on relative positions (shape and length of the hippocampus, collateral sulcus, parahippocampal gyrus, and subiculum; five of them were detected in the head, body, and tail of the hippocampus and the remaining three were detected only in the body, as described by Bernasconi [17]); and (c) hippocampal head

digitations (27,28) (S.L., T.R.H.). Findings made with previously published and clinically established methods of describing the hippocampus were further evaluated for variability by having the investigator repeat the interpretation of each study more than 6 months after the initial evaluation, with comparison of the two data sets.

The number of digitations of the hippocampal head was counted on coronal T2-weighted images obtained in each control subject and patient with epilepsy by using a method that, to our knowledge, has not been described previously. A fully convoluted digitation was considered one in which the superior surface had a continuously convex (not flat) contour and in which a virtual line connecting the deepest extents of the alveus on each side of the digitation contacted the internally located dark stripe of the hippocampal striation (Fig 1). In some individuals, the lateral portion of the hippocampal head featured a wide and flat superior surface; this was not considered a fully convoluted digitation because of flattening of the crest. The medial (uncinate) portion of the hippocampal head was not considered a digitation, as the superior surface of this part of the hippocampus did not fold back in a convex fashion. This was consistent with earlier anatomic studies, in which authors defined hippocampal digitations so as to exclude the area of the hippocampus at the uncus (28). The data presented herein are the digitations counted during one viewing by two investigators (S.L., T.R.H.) working independently. When the digitation counts did not agree, a third investigator (P.F.V.d.M., 10 years of experience in MR image analysis) independently counted digitations, thereby producing a majority to constitute the final digitation number.

MR Quantitative Analysis

Manual segmentation of hippocampal body subregions was performed (M.C.) on high-spatial-resolution coronal T2-weighted MR images. The hippocampal head and tail were not segmented according to subregion because the more complex shape of these structures posed

Figure 1: Coronal T2-weighted MR images of, *A, B*, head of hippocampus in a control subject (31-year-old man) and, *C, D*, body of hippocampus in a patient with TLE (patient 5, 32-year-old man). On these and other coronal images, the subject's right side is on the left side of the image. In *B*, anatomic correlates of the hippocampal digitation counting method are superimposed on the same 7-T images shown in *A*. Note the most superior points of hippocampal striation (*) and the most inferior inflections of alveus (yellow lines). *C*, A 7-T MR image is located near, *D*, a 1.5-T fast spin-echo (repetition time msec/echo time msec, 6650/113; section thickness, 2 mm; 1×1 -mm in-plane pixel size) MR image. Both *C* and *D* were obtained in the same patient. Each patient with TLE underwent 1.5- or 3-T MR imaging for clinical purposes; images were used only to select subjects for this study. *E, F*, Semischematic images show, *E*, head of right hippocampus (modified from *A*) and, *F*, body of left hippocampus (modified from *C*) and indicate likely anatomic correlates of corresponding MR images. 1 = CA1, 2 = CA2, 3 = CA3, 4 = CA4, CA = cornu ammonis, DG = dentate gyrus, S = subiculum, U = uncus.

difficulties in labeling procedures. Two subregions were manually segmented based on anatomy described by Duvernoy (27): The first subregion was the Ammon horn, more precisely the CA1, CA2, and CA3 fields, termed CA1-3. The second was the hilum, including CA4 and the dentate gyrus (Fig 2).

Limits of the hippocampal body were defined on coronal sections, with reference to sagittal sections. The most anterior section was the first section without the uncus (Fig 2a). The most posterior section of the body was the most anterior section with a more transversely oriented hippocampal main axis

(Fig 2b). Quantitative analysis methods are further described in Appendix E1 (online).

Subregional data in individual subjects with TLE were compared with the range of values in the control group for all volume measures. We also calculated an asymmetry index (AI) for each volume measure with the following equation $AI = (R - L) / [(R + L) / 2]$, where R represents right-sided data and L represents left-sided data. Individual patients' AIs were compared with the range of AIs in the control group for that type of volume measure. Reproducibility of subregional volume measurements was evaluated by repeating the same measurements for five healthy control subjects chosen at random, with the same investigator (M.C.) performing segmentation of these hippocampi without knowledge of the previous segmentation more than 12 months after the first segmentation procedure was performed. Error was measured by computing a relative index (RI) with the following equation: $RI = (V_2 - V_1) / [(V_2 + V_1) / 2]$, where V_1 and V_2 represent the first and second volumes, respectively.

Statistical Analysis

The reproducibility of our method of counting hippocampal digitations was evaluated by having two investigators (S.L., T.R.H.) independently count digitations in data in each healthy subject and patient with epilepsy on a second occasion more than 6 months after the initial interpretation. We compared variability in reporting paucity (no or one digitation) with multiplicity (two or more digitations) as intra- and interrater κ statistics for each hippocampus.

Results

Subjects and Imaging Performance

No adverse events occurred in healthy subjects or patients with epilepsy during 7-T MR data acquisition. Images in two control subjects and three patients were excluded because of head movement and degraded image quality sufficient to prevent accurate analysis of hippocampal subregions. The mean age of the remaining 11 control subjects was

26 years. The mean age of the remaining eight patients with TLE was 28 years. The clinical characteristics of the patients are summarized in Table 1.

Qualitative Visual Assessment

In control subjects, the internal structure was visible in all sections of the head, body, and tail of the hippocampus (Fig 3). In each patient (Table 2), the abnormal hippocampus had at least one of the following signs: atrophy ($n = 7$), T2-weighted hyperintense signal ($n = 6$), and flattening of the head ($n = 6$). In each subject, hippocampal striation and additional detailed anatomic features were clearly apparent. In each control subject, it was possible to delineate continuous hippocampal striation. This white matter band appeared to be less distinguished from surrounding gray matter in all sclerotic hippocampi. Thus, the partial loss of hippocampal striation was observed in the hippocampus on the side of ictal onset in all but two patients (patients 1 and 7) and in none of the control subjects. Definite hippocampal malrotations were observed in three patients; they were seen twice in patients with ipsilateral onset and once in a patient with contralateral to ictal onset (Fig 4). Malrotations were observed in four control subjects: They were observed bilaterally in subject 1 and on the left side in subjects 6, 10, and 11. The determination of malrotation showed no variation between the first and second observations in 18 of 19 subjects; however, one healthy control subject (subject 4) was rated as having bilateral hippocampal malrotation at the second viewing but not at the first. Ratings of hippocampal size, signal, shape, and striation did not vary between the first and second viewings.

Each patient had either no or one hippocampal digitation on the side of ictal onset (Table 2). Three patients also had either no or one contralateral hippocampal digitation. Several patients had definite hippocampal atrophy. Interestingly, one patient (patient 1) had bilateral nondigitated hippocampal heads but only mild hippocampal atrophy on the epileptogenic side and contralateral normal hippocampal volume

Figure 2

Figure 2: Manual segmentation of two subregions of body of hippocampus on T2-weighted 7-T MR images in subject 2 (24-year-old man). (a, b) Most posterior coronal section in (a) head and (b) body of hippocampus, as the image on the left of these pairs. Red cross marks the same point on the paired coronal and sagittal images, and on sagittal section (as the image on the right of these pairs) indicates level of coronal section (front is on left side of sagittal image). (c) Limits of CA1–CA3 (dark blue) and CA4 and dentate gyrus (light blue) regions on coronal section in middle of body (with no colored subregions on left image and colored subregions on middle image, both showing the same image plane), as indicated on the sagittal section (right image). (d) Three-dimensional rendering of two subregions in body of hippocampus, displayed separately (left, with CA1–CA3 in dark blue, and middle, with CA4 and dentate gyrus in light blue) and together (right).

(Fig 4, A). All healthy subjects had two or three bilateral digitations of the hippocampal head; however, one of these

22 hippocampal heads had one digitation, consistent with reports of post-mortem studies in cadavers without

Figure 3

Figure 3: Coronal T2-weighted 7-T MR images through the, *A*, *B*, head, *C*, body, and, *D*, tail of hippocampus in four control subjects (31-year-old man, 24-year-old woman, 19-year-old woman, and 22-year-old man, respectively) show internal structure of hippocampus. Hippocampal striation (arrows) was visible in all.

brain disease (28). Within and between the two observers who each independently counted hippocampal digitations twice, this method was used to generate 25 instances of complete agreement on all four readings among 38 hippocampi in healthy subjects and patients with epilepsy. There were four instances of intraobserver disagreement and nine instances of interobserver

disagreement (complete data are given in Appendix E1 [online]). When disagreements occurred, the number of digitations reported never varied by more than one (usually one digitation vs two digitations or two vs three digitations). In determining paucity versus multiplicity of digitations in the 38 hippocampal

Figure 4

Figure 4: Coronal T2-weighted 7-T MR images through, *A*, head and, *B–D*, body of hippocampus in three patients. *A*, Patient 1 (30-year-old woman). Absence of hippocampal digitations bilaterally and slightly increased signal intensity in head of right hippocampus. Hippocampal striation was barely visible in head of right hippocampus (arrows). *B*, Body of left hippocampus in patient 1 (arrow) had an unusual malrotated vertical shape. *C*, Patient 3 (22-year-old man). Hippocampal atrophy and increased signal intensity predominating in CA4 and dentate gyrus region in body of left hippocampus (arrow). *D*, Patient 8 (29-year-old woman) had hippocampal atrophy and increased signal intensity predominating in CA1–3 region in body of the left hippocampus (arrow). This patient also had globular hippocampal shape.

heads, κ values were 0.93 for intrarater agreement in both raters and 0.80 for interrater agreement.

Quantitative Evaluation

Subregional segmentation of the hippocampal body on T2-weighted images proved feasible in all control subjects and

Table 1

Clinical Characteristics of Patients

Patient No./Age (y)/Sex	Epilepsy Predisposing Factors	Age at Seizure Onset (y)	Electroencephalographic Ictal Onset	Clinical MR Imaging Finding	Seizure Type
1/30/F	Febrile convulsions of infancy, family history of epilepsy	28	R temporal	R MTS	A, C, G
2/25/M	Gestational or perinatal injury	13	R temporal	R MTS	A, C, G, SE
3/22/M	Febrile convulsions of infancy	5	L temporal	L MTS	A, C, G
4/20/F	None	14	L temporal	L MTS	A, C
5/32/M	Central nervous system infection	28	R temporal	R MTS	A, C
6/49/F	None	11	L temporal	L MTS	A, C, G
7/20/F	None	17	L temporal	L MTS	A, C, G
8/29/F	Gestational or perinatal injury and family history of epilepsy	23	L temporal	L MTS	A, C

Note.—A = aura, C = complex partial, G = generalized tonic-clonic, L = left, MTS = mesial temporal sclerosis, R = right, SE = generalized convulsive status epilepticus.

Table 2

Visual Assessment of Hippocampi in Patients with TLE

Patient No. and Side	Ictal Onset Side	Head				Body				MR
		Shape	Signal Intensity	Hippocampal Striation	No. of Digitations	Size	Signal	Hippocampal Striation		
1										
Right	Y	Flat	2	Flat, partial	0	1	0	N	...	...
Left	N	...	...	Less flat, partial	0	...	...	...	...	Y
2										
Right	Y	Flat	2	Flat, partial	0	3	3	Blurred	...	...
Left	N	...	...	Less flat, partial	1	...	...	Blurred but less	...	...
3										
Right	N	...	...	...	1	...	...	...	...	...
Left	Y	Flat	2	Less visible, flat, partial, blurred	0	3	3	Visible, thinner	...	...
4										
Right	N	...	...	Reduced visibility	3	...	...	...	...	...
Left	Y	Normal	2	Reduced visibility	1	0	1	Less visible	...	...
5										
Right	Y	Flat	2	Not visible	0	3	2	Less visible	...	...
Left	N	...	...	...	2	...	...	...	...	...
6										
Right	N	...	...	...	3	...	...	...	...	...
Left	Y	Flat	1	Thin, blurred	0	3	1	Blurred	Y	...
7										
Right	N	...	...	...	2	...	...	...	...	...
Left	Y	Partially flat	0	...	1	0	1	Normal	...	...
8										
Right	N	...	...	Visible, interrupted	2	...	...	...	...	...
Left	Y	Flat	2	Not visible	0	3	3	Visible, thinner	Y	...

Note.—Atrophy and T2-weighted signal intensity ratings: 0 = normal, 1 = possibly present (mild), 2 = probably present (moderate), 3 = definitely present (severe). MR = hippocampal malrotation, N = no, NA = not applicable, Y = yes.

patients. Examples of resulting structures in control subjects and patients with malrotations and those without are shown (Fig 5). The mean subregional hippocampal volumes in control subjects and patients are displayed in Table 3. As expected, the average volume of the CA1–CA3 region appeared smaller for sclerotic hippocampi. Surprisingly, CA4 and the dentate gyrus were slightly larger on the contralateral side in patients. We observed two hippocampal subregions, one consisting predominantly of the lateral Ammon horn and the other consisting predominantly of dentate gyrus with CA4, that were slightly smaller on the left side of healthy subjects than on the right. This permitted us to compare the ratio of lateral Ammon horn (CA1–CA3) to dentate CA4 in healthy subjects with that in patients with TLE.

Patient subregional measurements with respect to the control population are shown in Figure 6. The values in healthy control subjects were, on average, slightly smaller on the left side than on the right side for both CA1–CA3 volume and CA4 and dentate gyrus volume. Mean AI for CA1–CA3 of the entire hippocampal body was 0.12 (range, –0.04 to 0.47); mean AI for volume per section of CA1–CA3 was 0.06 (range, –0.20 to 0.34); mean AI for CA4 and dentate gyrus of the entire body was 0.06 (range, –0.06 to 0.22); mean AI for volume per section of CA4 and dentate gyrus was 0.00 (range, –0.24 to 0.18); and mean ratio of AIs for CA1–CA3 to CA4 and dentate gyrus of the entire body was 0.06 (range, –0.08 to 0.34). The volume of the CA1–CA3 subregion was less than the mean volume in control subjects on both sides in all patients but patient 1. The average volume per section was more sensitive than the entire volume. Interestingly, the ratio of CA1–CA3 to CA4 and the dentate gyrus was less than the mean ratio in control subjects in all patients on both sides of the hippocampus. Furthermore, in six of eight patients, the ratio of CA1–CA3 to CA4 and dentate gyrus on the side of ictal onset was less than the range in the control group for that side (Fig 6e). Volumetric asymmetry of the hippocampal CA1–CA3 subregions was observed in

Table 3

Volume of Hippocampal Body Subregions on T2-weighted MR Images

Volume (mm ³)	Control Group		Patient Group	
	Right	Left	Ictal Onset Side	Contralateral Side
CA1–CA3				
Whole body	238 ± 88	207 ± 50	130 ± 61	194 ± 33
Volume per section	21 ± 4	20 ± 3	11 ± 4	19 ± 1
CA4 and dentate gyrus				
Whole body	172 ± 46	162 ± 45	166 ± 47	180 ± 17
Volume per section	16 ± 3	15 ± 3	15 ± 4	18 ± 2

Note.—Data are means ± standard deviations.

Figure 5

Figure 5: Manually segmented volumes of the two subregions of body of hippocampus (CA1–3 [dark blue] and CA4 and dentate gyrus [light blue]) in four control subjects (*h2*, *h3*, *h1*, and *h10*) and four patients with epilepsy (*t3*, *t5*, *t6*, and *t8*) in the slightly oblique coronal view, with the left side of the brain on right side of the image. Images in subjects 1 and 10 show unilateral malrotation of the hippocampus. Image in patient 3 shows left HS, image in patient 5 shows right HS, and images in patients 6 and 8 show left HS with malrotation of hippocampus.

five patients with TLE and HS. Patient 3 had substantial volume reduction compared with values in control subjects for both CA1–CA3 and CA4 and dentate gyrus and a lower asymmetry index for the ratio than for both volumes

separately. The distribution of atrophy in five patients was consistent with Ammon horn sclerosis, while the distribution of atrophy in patient 3 was consistent with combined end-folium and Ammon horn sclerosis. The sclerosis was not detected

Figure 6

Figure 6: (a–e) Graphs of hippocampal subregional volumetric data. DG = dentate gyrus. Paired graphs for each measurement show data by side in the left graph, and AI data in the right graph. Healthy subjects' values are pooled in a single column to the left of each graph, with each patient's data displayed separately. Horizontal lines facilitate comparison of values in patients with TLE with the range of values in the control group. For data by side, the lowest value in the control group is indicated by a color-coded dotted line for side, except in **c** and **d**, in which one line appears because right and left sides had the same lowest values in the control group; for AI data, a pair of solid horizontal lines indicates highest and lowest values in control group.

in patients 1 or 7 with subregional volumetry of the hippocampal body. Reproducibility results are given in Appendix E2 (online). Briefly, results were better for measurements based on the volume per section than for measurements based on the entire body (relative index values averaged for both right- and left-sided CA1–CA3 and both right- and left-sided CA4 and dentate gyrus in five subjects: 12% for entire body, 5% for volume per section). This was expected because of the limited number of sections (about 10), which makes an error in even one section become an error of about 10% for the complete volume. Volumes for the second segmentation were larger than those for the first segmentation, with two exceptions (out of 40). This can be explained by the fact that most borders are made of partial volumes between two or more structures and the fact that the threshold is subjective. Finally, errors were larger for CA4 and the dentate gyrus than for the CA1–CA3 region (relative index values for the volume per section averaged for the five subjects for both right- and left-sided CA1–3, 3%; relative index values for the volume per section averaged for the five subjects for both right- and left-sided CA4 and dentate gyrus, 6%). Overall, variability between these two sets of segmentations was lower than that between the healthy control subjects for each type of measurement.

In summary, high-spatial-resolution high-contrast 7-T MR imaging revealed three findings that clinical MR imaging in patients with mesial TLE did not. First, most of the patients in whom clinical

MR imaging revealed only atrophy over the entire hippocampal formation had atrophy specific to the main portion of the Ammon horn, with little or no atrophy in the dentate gyrus. Second, absence or paucity of hippocampal head digitations was observed on the epileptogenic side in all of the patients with TLE and in only one of the healthy control subjects on only one side. Third, the internal structure of malrotated hippocampi was clearly visible, unlike in previous 1.5-T studies (17).

Discussion

Our findings suggest that absence or paucity of digitations of the hippocampal head may represent a specific hippocampal deformity in patients with mesial TLE. This deformity occurred most often in atrophic hippocampi on the side of electroencephalographic ictal onset, but it also occurred on 7-T MR images in nonatrophic hippocampi contralateral to ictal onset. Patients with moderate or severe hippocampal atrophy have been reported to have loss of these digitations at clinical MR imaging (9). These lower-spatial-resolution and lower-contrast-resolution studies may enable us to detect reduced digitations on the basis of atrophy-related enlargement of the adjacent ventricle so that the superior hippocampal surface has high contrast against a widened cerebrospinal fluid space. At 7 T, we consistently detected the thin white matter layer of the alveus, situated between the gray matter masses of the hippocampus and amygdala, to accurately define the hippocampal surface, including its gyral pattern, even in the absence of moderate or severe hippocampal atrophy with enlarged cerebrospinal fluid spaces. Normal gyral morphology of the hippocampal head may be absent or reduced in many patients with mesial TLE and to some extent may be independent of hippocampal atrophy. Tissue examination would be necessary to determine if this hippocampal deformity represents a malformation of hippocampal development with microstructural dysplasia.

Others have questioned whether subtle dysplasias may be associated with

HS. Isolated hippocampal tectonic malformations are detected microscopically within small portions of sclerotic hippocampi in patients with surgically treated TLE (29). Isolated hippocampal dysplasias have rarely been reported in studies of mesial TLE with tissue correlation to clinical MR imaging (30,31). In syndromes other than TLE, clinical MR imaging can depict hippocampal hypertrophy and other large hippocampal malformations in association with extrahippocampal malformations of cortical development (17,32–34). An isolated hippocampal malformation, malrotation of the hippocampal body, has been reported at MR imaging not only in patients with mesial TLE but also in healthy subjects without epilepsy (18,19). Here, 7-T MR images clearly showed major internal structures of the hippocampus and enabled detailed evaluation of normal and abnormal hippocampal folding and rotation. Ultrahigh-field-strength MR imaging may prove to be the preferred technique with which to study large affected and control groups and define benign and abnormal hippocampal malformations in relationship to specific neurologic syndromes.

The limitations of the current study are largely related to the relatively small number of subjects imaged and to the incomplete development of 7-T brain imaging techniques. Our method for counting digitations of the hippocampal head was associated with concordant interpretations across independent observers, but it has not been compared with an independent measure of these convolutions. Our intrahippocampal volumetric technique has not yet been validated for reproducibility and relationships with tissue findings. Larger groups of healthy control subjects, patients with mesial TLE, patients with epilepsy but not TLE, and patients with nonepileptic brain disease must be studied to determine the specificity of our findings for mesial TLE. Observations regarding apparent hippocampal deformity on 7-T images in patients with mesial TLE should be confirmed with histopathologic examination of tissue specimens at subsequent epilepsy surgery. Cadaveric imaging should be performed to confirm

relationships between submillimetric hippocampal surface and intrahippocampal features of 7-T images and histologic results. Avoiding head motion enough to benefit from the higher spatial resolution was a challenge in several subjects in this study. New strategies will be needed to permit routine acquisition of images with submillimetric spatial resolution, particularly in patients with brain disease. We did not have available software designed for automated hippocampal segmentation and surface morphometry at 7-T-generated spatial and contrast resolution, such as that which is available for 1.5- and 3-T studies (35). The greater complexity of intrahippocampal substructures in the head and tail of the hippocampus limited our current subregional segmentation approach to the hippocampal body. If 7-T MR imaging is developed to depict subtle hippocampal alterations reliably and these alterations are shown to accurately define anatomic abnormalities, considerable additional effort will be required to clarify their relationships with epileptogenesis and to establish any useful role in presurgical evaluation of epilepsy. Our *in vivo* findings strongly support future efforts in the study of larger groups with improved acquisition and image analysis protocols specifically adapted to the information provided by 7-T MR imaging.

Brain imaging with 7-T MR probably can be used to fully define a wide range of macroscopically visible findings in patients with hippocampal sclerosis, including atrophy of hippocampal subregions and deformities of the hippocampal head and body. Future applications of 7-T MR imaging in presurgical evaluations may benefit the numerous individuals with refractory mesial TLE who have normal or nonspecifically abnormal brain imaging findings at clinical MR imaging (6–8). Increased spatial and contrast resolution at 7 T might enable unilateral detection of mild HS in patients currently considered to have MR-negative TLE, leading to efficacious ablative surgery. Alternatively, improved detection of bilateral HS in patients who currently have only unilateral hippocampal abnormalities detected with clinical MR imaging might enable us to avoid intracranial

monitoring procedures whose results ultimately do not support therapeutic resection (36).

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