Epilepsia, 52(6):1100–1109, 2011
doi: 10.1111/j.1528-1167.2011.03052.x

FULL-LENGTH ORIGINAL RESEARCH

Hyperactivation of parahippocampal region and fusiform gyrus associated with successful encoding in medial temporal lobe epilepsy

*†‡§Eric Guedj, *§¶Gaelle Bettus, #**Emmanuel J. Barbeau, §¶††Catherine Liégeois-Chauvel, *‡§Sylviane Confort-Gouny, §¶††Fabrice Bartolomei, §¶††Patrick Chauvel, *‡§Patrick J. Cozzone, *‡§Jean-Philippe Ranjeva, and *‡§Maxime Guye

*Center for Magnetic Resonance in Biomedicine (CRMBM), UMR CNRS 6612, Marseille, France; †Nuclear Medicine Department, Marseille, France; ‡Medical Imaging Department (PIM), AP-HM, Marseille, France; §Medical School, University of the Mediterranean, Marseille, France; ¶INSERM U751, Epilepsy and Cognition Unit, Marseille, France; #Paul Sabatier, University, Brain and Cognition Research Center (CerCo), Toulouse, France; **CNRS UMR 5549, Toulouse, France; and ††Clinical Neurophysiology Department, Marseille, France

Summary

Purpose: Performance in recognition memory differs among patients with medial temporal lobe epilepsy (MTLE). We aimed to determine if distinct recognition performances (normal vs. impaired) could be related to distinct patterns of brain activation during encoding.

Methods: Event-related functional magnetic resonance imaging (fMRI) activation profiles were obtained during successful encoding of non–material-specific items, in 14 MTLE patients tested for recognition of stimuli afterward. Findings were compared to those of 25 healthy subjects, and voxel-based correlations were assessed between brain activation and performance.

Key Findings: Patients with left and right MTLE showed similar activations and similar performances. As a whole, the group of patients demonstrated altered recognition scores, but three of the seven patients with left MTLE and three of the seven patients with right MTLE exhibited normal performance relative to controls. In comparison to healthy subjects and patients with impaired recognition, patients with normal recognition showed weaker activations in left opercular cortex, but stronger activations in bilateral parahippocampal region/fusiform gyrus (PH/FG). By contrast, patients with impaired performance showed weaker activations in bilateral PH/FG, but stronger activations in a frontal/cingulate and parietal network. Recognition performance was correlated positively to bilateral PH/FG activations, and negatively correlated to bilateral frontal/cingulate activations, in the whole group of patients, as well as in subgroups of patients with either left or right MTLE.

Significance: These results suggest occurrence of effective functional compensation within bilateral PH/FG in MTLE, allowing patients to maintain recognition capability. In contrast, impairment of this perceptive–memory system may lead to alternative activation of an inefficient nonspecific attentional network in patients with altered performance.

KEY WORDS: fMRI, Memory, Recognition, Compensation, Reorganization, Ventral visual stream.

The quality of life of patients with medial temporal lobe epilepsy (MTLE) is negatively influenced by memory impairment. However, despite an apparent homogeneous electroclinical presentation, memory performance appears variable among patients (French et al., 1993; Williamson et al., 1993; Engel, 1996; Helmstaedter et al., 2003; Elger et al., 2004).

Accepted February 2, 2011; Early View publication April 11, 2011.
Address correspondence to Maxime Guye, CRMBM, UMR CNRS 6612, Faculté de Médecine, 27 Boulevard Jean Moulin, 13385 Marseille Cedex 05, France. E-mail: maxime.guye@ap-hm.fr

If left-sided MTLE is commonly associated with verbal memory deficits, patients with right MTLE tend to have impairment on memory tests that involve nonverbal visual material (Elger et al., 2004). This visuoverbal dissociation is nevertheless not constantly supported by neuropsychological assessment. In addition, MTLE should not be considered as a pure model of well-lateralized medial temporal dysfunction, since bilateral functional or morphologic abnormalities have been described in patients with unilateral MTLE (King et al., 1995; Quigg et al., 1997; Woermann et al., 1999; Martin et al., 2001; Guye et al., 2002; Joo et al., 2004). In this way, patients with right MTLE may exhibit retrieval deficit on verbal memory

(Dupont et al., 2002). Moreover, only few differences have been reported at recognition between patients with right and left MTLE on visual and verbal memory tasks (Hermann et al., 1995; Baxendale, 1997; Eliassen et al., 2008).

In addition to the effect of epilepsy lateralization, differences in memory performance may be influenced by other factors, such as presence of morphologic lesion, age at onset, duration of epilepsy, or seizure frequency (Elger et al., 2004). This heterogeneity may induce variability in functional reserve of injured structures, as well as in possible remote compensatory processes (Helmstaedter et al., 2003; Elger et al., 2004). However, whether these mechanisms are effective is still debated (Dupont et al., 2000; Richardson et al., 2003; Powell et al., 2007; Eliassen et al., 2008). For example, Dupont et al. (2000) showed that patients with left MTLE had greater activation of the left frontal dorsolateral region than healthy subjects during both verbal encoding and retrieval tasks. Nevertheless, the memory performance of the seven patients studied remained poor despite this supplementary activation. Similarly, Powell et al. (2007) suggested an ineffective reorganization on the opposite side of hippocampal sclerosis (HS), by testing the correlation between functional magnetic resonance imaging (fMRI) activations and memory performance. In this material-specific encoding study, hyperactivation of undamaged hippocampus correlated negatively with visual performance in seven patients with left TLE, and with verbal performance in seven patients with right TLE. Conversely, greater activation in the damaged hippocampus (i.e., on the side of HS) correlated with better verbal memory performance in patients with left TLE, and with better nonverbal memory in patients with right TLE. Taken as a whole, these findings suggest that material-specific memory function in unilateral TLE is better when it is sustained by activation within the damaged hippocampus, and that reorganization of the contralateral MTL is an inefficient process, incapable of preserving memory function. Conversely, Eliassen et al. (2008) recently argued for effective extratemporal compensatory processes in 11 patients with frontal or temporal lobe epilepsy. Using a verbal recognition fMRI task, patients exhibited, in comparison to healthy subjects, greater activations within insula, cuneus, and anterior cingulate cortex, and equivalent performance to controls.

The general objective of the present study was to better understand differences in recognition memory performance among patients with similar electroclinical features suggestive of unilateral MTLE (Maillard et al., 2004). We aimed to determine if distinct recognition profiles (normal vs. impaired) could be related to distinct activation patterns during successful encoding. We hypothesized that the effectiveness of reorganization processes inside cortical encoding networks accounts for the variability observed among patients for recognition performance.

We designed a ''low effort'' task consisting of a delayed matching to sample task using nameable pictures that subjects had to encode during the fMRI acquisition. This visual task is known to induce bilateral activations of the ventral visual stream and of MTL, including the parahippocampal region (Detre, 2004; Powell et al., 2004; Powell & Duncan, 2005). This low effort encoding task, based on non–material-specific items, could be a favorable condition for potential occurrence of effective compensatory processes, by recruiting additional cerebral resources in patients, usually unsolicited in healthy subjects, but also a favorable condition for potential identification of these processes, by allowing us to isolate a subgroup of patients with a performance equivalent to that of healthy subjects for this easy task. To assess this goal, we aimed at extracting the efficient compensatory mechanisms among the whole reorganized cortical encoding networks observed in MTLE patients relative to controls, by looking at activation levels of cortical areas showing hyperactivation and positive correlations with memory performances.

Methods

Subjects

Fourteen patients with unilateral MTLE (7 patients with left MTLE and 7 patients with right MTLE), and 25 healthy controls were enrolled in this study. In order to limit potential bias, inclusions were limited to right-handed subjects. The 14 patients were selected prospectively after a comprehensive noninvasive presurgical evaluation for drug-resistant epilepsy associated with unilateral HS (11 female; age 36.9 years, SD 13.8). This evaluation included detailed history and neurologic examination, neuropsychological testing, brain MRI, and surface video–electroencephalography (EEG). All patients presented with similar electroclinical features compatible with unilateral MTLE, as defined previously (Maillard et al., 2004). Handedness was studied with a standard Oldfield test (Oldfield, 1971), confirming that all subjects included were right-handed. Interictal and postictal language testing was in addition performed in all patients to evaluate hemispheric dominance for language, as proposed previously (Privitera et al., 1991; Ramirez et al., 2008; Privitera & Kim, 2010). Six patients with questionable findings (Patients 1, 2, 4, 5, 6, and 10; Table 1) were secondarily evaluated with fMRI (Powell & Duncan, 2005; Trebuchon-Da Fonseca et al., 2009), confirming left hemispheric language dominance. Normative evaluation of intelligent scale and memory capacity of patients were assessed using the *Wechsler Adult Intelligent Scale*, third edition (WAIS III) (Wechsler, 2000), and the *Wechsler Memory Scale*, third edition (Wechsler, 2001).

The 25 healthy subjects were free of neurologic disease and cognitive complaints (14 female, age 30.2 years ± 11.1). No abnormal findings were observed on their conventional brain MRI. Patients and healthy subjects were not different for age ($p = 0.110$, *t*-test), or for gender ($p = 0.159$, chi-square test).

Table 1. Characteristics of patients with MTLE

Patient	Age	Gender	Handedness	Epilepsy	MRI visible lesion	Epilepsy onset (year)	Epilepsy duration (year)	Seizure frequency (per month)	Recognition performance	Recognition performance subgroup	WAIS III			WMS III			Ipsilateral hippocampal volume (cm^3)	Contralateral hippocampal volume (cm^3)
											FSIQ	VIQ	PIQ	IMQ	DMQ	WMQ		
1	23	Female	Right	L MTLE	HS	10	13	6	38	Normal	85	77	98	110	109	88	2.793	3.471
2	26	Female	Right	L MTLE	HS	16	10	18	39	Normal	86	87	87	100	90	66	2.454	2.747
3	46	Male	Right	L MTLE	HS	34	12	12	37	Normal	96	91	103	98	101	103	2.803	3.177
4	31	Male	Right	L MTLE	HS	26	5	8	28	Impaired	92	95	90	87	85	85	2.848	2.909
5	49	Female	Right	L MTLE	HS	14	35	8	35	Impaired	90	89	94	105	102	85	2.676	2.828
6	37	Male	Right	L MTLE	HS	13	24	10	33	Impaired	95	88	106	119	121	82	2.686	3.015
7	60	Female	Right	L MTLE	HS	13	47	14	34	Impaired	106	107	91	105	97	97	2.540	2.767
8	19	Female	Right	R MTLE	HS	15	4	4	37	Normal	73	84	64	78	69	79	2.859	3.395
9	24	Female	Right	R MTLE	HS	17	7	2	38	Normal	87	94	80	107	111	105	2.221	2.277
10	38	Female	Right	R MTLE	HS	12	26	12	38	Normal	92	89	98	110	104	79	1.943	2.160
11	18	Female	Right	R MTLE	HS	6	12	12	36	Impaired	51	58	70	86	85	74	2.550	2.879
12	35	Female	Right	R MTLE	HS	22	13	12	34	Impaired	80	78	84	98	84	94	2.686	2.752
13	57	Female	Right	R MTLE	HS	16	41	1.5	33	Impaired	86	86	81	103	96	77	2.696	2.975
14	54	Female	Right	R MTLE	HS	13	41	16	34	Impaired	58	62	55	103	96	77	2.585	2.919

L MTLE, Left medial temporal lobe epilepsy; R MTLE, right medial temporal lobe epilepsy; WAIS III, *Wechsler Adult Intelligent Scale* – Third edition; FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient; WMS III, *Wechsler Memory Scale* – Third edition; IMQ, Immediate Memory Quotient; DMQ, Delayed Memory Quotient; WMQ, Working Memory Quotient.
Hippocampal volumes are ipsilateral and contralateral to the epileptogenic side.

Investigations were approved by the local Committee on Ethics of the Marseille Public Hospital, and informed consent was obtained for each patient and healthy subject.

Conventional MRI

All subjects underwent an MRI examination in the framework of a multimodal MRI protocol, on a 1.5T MR scanner (Magnetom Siemens, Erlangen, Germany). Conventional MRI, acquired in the bihippocampal plane, included T_1-weighted images [TE/TR = 15/700 ms, 23 contiguous slices, 5-mm slice thickness, field of view (FOV) 240 mm, matrix 256], T_2-weighted images (TE/TR = 112/7,308 ms, FOV 240 mm, matrix 256, 23 contiguous slices, 5-mm slice thickness), T_1-weighted inversion recovery images (TE/TR = 60/8,000 ms, TI = 350 ms, FOV = 240 mm, matrix 512, 5-mm slice thickness), and fluid-attenuated inversion recovery (FLAIR) images (TE/TR = 110/8,000 ms, TI = 2,500 ms, FOV = 240 mm, matrix 256, 5-mm slice thickness). Brain MRIs were visually interpreted by the same experienced neuroradiologist specialized in epilepsy. In addition, left and right hippocampal volumes were determined (King et al., 1995). Hippocampal cross-sectional areas were outlined manually and measured by the same operator on contiguous MR slices acquired in the bihippocampal plane, using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). The sum of the hippocampal cross-sectional areas multiplied by slice thickness gave total hippocampal volume.

Memory paradigm and fMRI acquisition

Subjects performed a visual encoding task, based on non–material-specific item, during the fMRI scanning, and were tested for recognition of stimuli afterward. We hypothesized that differences in recognition performance could be explained by variations in activation during encoding, since MTL structures are known to be both crucial for encoding processes (Diana et al., 2007) and impaired in patients with MTLE (Powell et al., 2007).

Event-related fMRI was performed using single-shot gradient-echo echo-planar imaging (GE-EPI) sequence (TE 60 ms, TR = 3 s, 30 contiguous slices, 4-mm thickness, matrix 64, FOV = 256 mm). During scanning, subjects were asked to memorize 40 readily named pictures randomly sorted (10 animals, 10 vegetables, 10 tools, and 10 transportation means), delivered every 15 s for 2.5 s, constituting the encoding phase. A fixation cross was displayed for implicit baseline (rest condition), before and after presentation of each item. Stimuli were visually displayed on a screen located inside the scanner room through a video projector and a PC equipped with E-Prime software (v1.1 Psychology Software Tools Inc., Pittsburgh, PA, U.S.A.).

Forty-five minutes later, recognition performance was evaluated. Subjects were asked to identify whether they had or had not already seen the displayed items among a set of 80 pictures: the 40 previously delivered (i.e., the targets),

and 40 new pictures from the same four previous categories (i.e., the distractors). Stimuli were sorted randomly across categories (animal, vegetable, tool, and transportation mean) and conditions (target and distractor). We verified, before the experiment, that the 80 pictures could be easily named with a similar name across healthy subjects.

Data processing

fMRI activations of encoding phase were studied against implicit baseline (i.e., the fixation cross), using an event-related design, in comparison to data obtained in the control group of 25 healthy subjects. Because we aimed to specifically determine brain areas involved during successful encoding, only encoding-related responses to pictures thereafter correctly recognized (i.e., the hits) were kept for analyses.

Brain scans were processed using SPM5 software (Wellcome Department of Cognitive Neurology, University College, London, UK). Images were converted from DICOM to Analyze format using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html) and then transferred to SPM5. After slice timing correction, images were realigned, spatially normalized onto the Montreal Neurological Institute atlas (MNI) (16 nonlinear registration $7 \times 6 \times 7$ basis functions), and finally smoothed using a 12-mm gaussian kernel to blur individual variations in gyral anatomy and to increase signal-to-noise ratio.

A two-level random-effect analysis was employed. At the first level, trial-specific responses were modeled for each subject by convolving a delta function that indicated each event onset with the canonical hemodynamic response function (HRF) to create regressors of interest: one for the pictures to remember and one for the implicit baseline (i.e., the fixation cross). Each subject's movement parameters were included as confounds. Parameter estimates pertaining to the height of the HRF for each regressor of interest were calculated for each voxel. A statistical parametric map of brain activation was computed for each subject, representing the contrast: ''hits'' minus ''fixation cross.'' These images of individual profiles of successful encoding were exploited in the following analyses using a second-level random effect procedure. At this second level, one-sample *t*-tests were performed to examine effects within groups, and two-sample *t*-tests performed to examine between-group effects, with age as confounding variable.

Two questions were asked: (1) Did the lateralization of MTLE impact on brain activations obtained during successful encoding, and (2) Did these activations differ between patients with normal and impaired recognition? The whole group of patients was thus subdivided: (1) according to epilepsy lateralization (subgroups of patients with left or right MTLE, whatever the recognition memory performance), and (2) according to recognition memory performance (subgroups of patients with normal or impaired recognition memory performance, whatever the epilepsy lateralization). The performance, based on hits, was considered abnormal if it fell below the fifth percentile of the control group, and was normal otherwise. Relationship between recognition memory performance and brain activation was in also assessed using regression analysis at the second level, in the whole group of patients, and in subgroups of patients with left and right MTLE, with age as confounding variable.

All significant brain voxels were reported at a threshold of p-value <0.005, and a cluster of >18 voxels (Eliassen et al., 2008). This uncorrected voxel threshold was adopted, as reported previously (Powell et al., 2007; Eliassen et al., 2008), in particular because of the low signal-to-noise ratio in MTL (Ojemann et al., 1997; Strange et al., 2002; Powell et al., 2005).

MNI coordinates were transformed to Talairach coordinates with a nonlinear transformation, and anatomic localization of most significant voxels was identified using Talairach Daemon (http://ric.uthscsa.edu/projects/talairachdaemon.html). The parahippocampal region was referred to as encompassing the pre- and parasubiculum, the entorhinal cortex, the perirhinal cortex, and the postrhinal cortex (Witter & Wouterloud, 2002).

Clinical differences between groups were evaluated at a threshold of significant p-value <0.05 using chi-square test (for qualitative data), Mann-Whitney test (for comparison of quantitative data between patients' subgroups, n = 14), and *t*-test (for comparison of quantitative data between patients and healthy subjects, n > 30). Interactions between clinical/volumetric characteristics and fMRI activation values extracted from significant clusters were studied using analysis of covariance (ANCOVA), at a threshold of significant p-value <0.05.

Results

Clinical characteristics, recognition performance, and hippocampal volumetry

Characteristics of patients are described at individual level in Table 1. Performance in recognition was significantly worse for patients with MTLE than for healthy subjects (respectively, 35.3 ± 2.8 and 38.6 ± 1.3 recognized images, $p < 0.001$, *t*-test). Hippocampal atrophy was found bilaterally (i.e., ipsilateral and contralateral to the epileptogenic side, $p < 0.001$, *t*-test in comparison to volumes of left and right hippocampus of healthy subjects; no significant difference was found between volumes of left and right hippocampus in healthy subjects), but more severe ipsilaterally to epileptogenic side ($p = 0.024$, *t*-test in comparison to contralateral hippocampal volumes in patients). No significant correlation was found between recognition performance or Wechsler Scale scores and hippocampal volumes (either left or right, and either ipsilateral or contralateral to epileptogenic side).

Subgroups of patients with left and right MTLE did not differ according to age, gender, epilepsy onset, epilepsy

duration, seizures frequency, quotients of the *Wechsler Memory Scale*, performance in recognition, and volumetry of ipsilateral and contralateral hippocampus (related to epileptogenic side) (Mann-Whitney and chi-square tests). Patients with right MTLE showed lesser full scale and performance intelligence quotients of the *Wechsler Adult Intelligent Scale* than patients with left MTLE ($p = 0.025$ and 0.011, respectively, Mann-Whitney test).

At the individual level, three of the seven patients with left MTLE and three of the seven patients with right MTLE had normal recognition performance, with at least 37 of 40 recognized images (above the fifth percentile of the control group of healthy subjects).

Subgroups of patients with normal and impaired recognition memory were not different for age, gender, epilepsy lateralization (left vs. right), epilepsy onset, epilepsy duration, seizures frequency, *Wechsler Adult Intelligent* and *Memory Scales,* and volumetry of ipsilateral and contralateral hippocampus (related to epileptogenic side) (Mann-Whitney and chi-square tests).

fMRI activation profiles obtained during encoding

Activation in healthy controls

Significant MTL activations were found during encoding bilaterally within fusiform gyrus and perirhinal cortex in healthy subjects.

Activations were also found within left superior temporal gyrus, left inferior and middle frontal gyri, bilateral premotor and precentral cortices, bilateral anterior cingulate cortex, bilateral superior parietal cortex, and left inferior parietal cortex (Fig. 1 and Table S1).

Activation in patients with left and right MTLE

No significant differences in activation patterns were found during encoding between left and right MTLE patients whether relative to healthy subjects or directly compared ($p < 0.005$, uncorrected). At a less-restrictive statistical threshold ($p < 0.01$, uncorrected), differences were found in patients, in comparison to healthy subjects, (1) with stronger activations within right perirhinal cortex, right inferior frontal gyrus, and left inferior parietal; and with (2) weaker activation within left inferior frontal gyrus. No significant differences were found between left and right MTLE patients at this threshold.

Activations in patients with normal and impaired recognition performance

We then focused on patients with normal recognition performance. They showed during encoding, in comparison to healthy subjects: (1) weaker activations within left inferior and middle frontal gyri and left superior temporal gyrus; and (2) stronger activations within bilateral perirhinal cortex, bilateral fusiform gyrus, and left occipital cortex (within cuneus, inferior occipital gyrus, and lingual gyrus) (Fig. 2 and Table S1).

By contrast, patients with impaired recognition performance showed during encoding, in comparison to healthy subjects: (1) weaker activations within bilateral perirhinal cortex and left fusiform gyrus; and (2) stronger activations within bilateral cingulate cortex, right inferior and middle frontal gyri, right precentral gyrus, right precuneus, and left paracentral lobule (Fig. 2 and Table S1).

Findings were confirmed by direct comparison of patients' subgroups. Relative to patients with impaired recognition, those with normal performance showed stronger activations within bilateral perirhinal and entorhinal cortices, bilateral fusiform gyrus, and right lingual gyrus (Fig. 3 and Table S1).

In comparison with patients with normal recognition, those with impaired performance showed stronger activations within right middle and superior temporal gyri, right inferior frontal gyrus, and bilaterally within cingulate cortex, precuneus, and inferior parietal cortex (Fig. 3 and Table S1).

No interaction was found between intergroup activation values, extracted from clusters obtained by comparing patients with normal and impaired recognition performance, and age, epilepsy onset, epilepsy duration, seizures frequency, or corresponding hippocampal volumes (ANCOVA). These activation values were not different between patients with left and right MTLE (Mann-Whitney test).

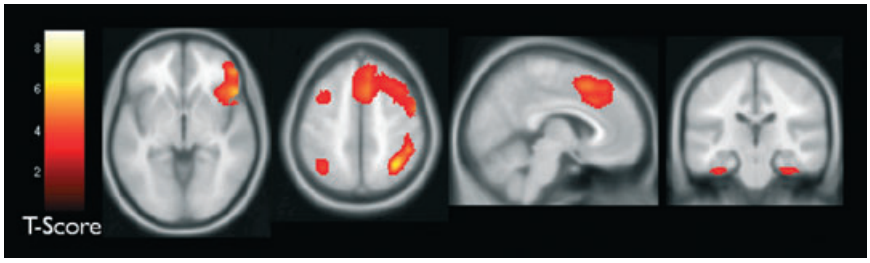

Figure 1.
Anatomic localization of activation profiles obtained in healthy subjects during the encoding task (p-voxel <0.005, uncorrected; radiologic convention: left hemisphere is on the right side).

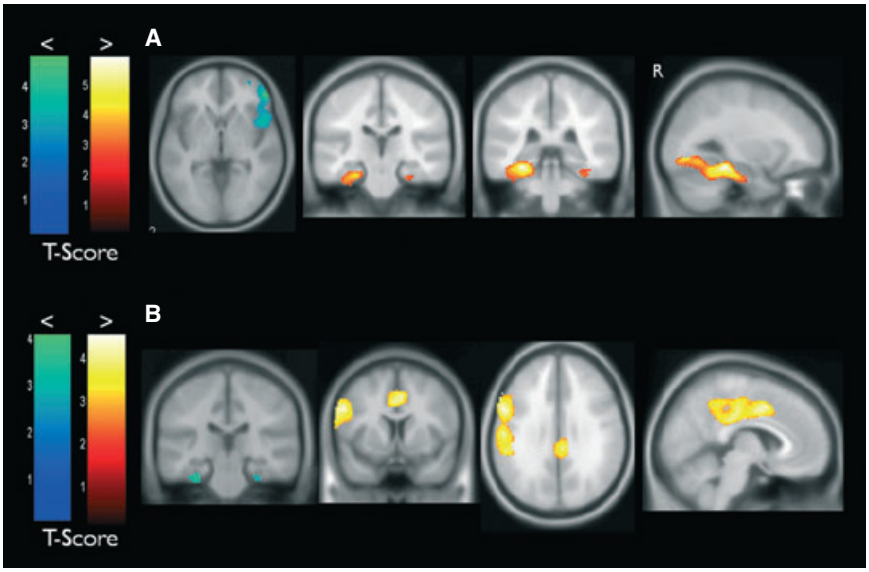

Figure 2.
Anatomic localization of activation profiles obtained during the encoding task in MTLE patients with normal (**A**) and impaired (**B**) recognition memory performance, in comparison to healthy subjects (p-voxel <0.005, uncorrected; radiologic convention: right hemisphere [R] is on the left side; yellow-red = stronger activations in patients than in healthy subjects [>]; blue = weaker activation in patients than in healthy subjects [<]).
Epilepsia © ILAE

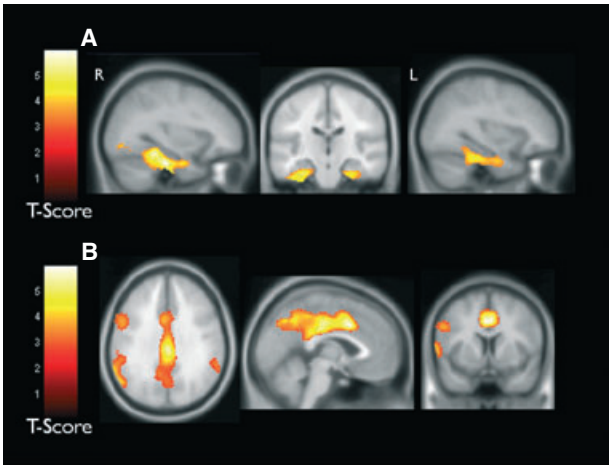

Figure 3.
Comparison of activation profiles obtained during the encoding task in MTLE patients with normal and impaired recognition memory performance (p-voxel <0.005, uncorrected; radiologic convention: left hemisphere [L] is on the right side; right hemisphere [R] is on the left side). (**A**) Stronger activations in patients with normal recognition than in those with impaired performance. (**B**) Stronger activations in patients with impaired recognition than in those with normal performance.
Epilepsia © ILAE

Activation correlated to recognition performance in patients

In the whole group of patients, recognition memory performance was correlated: (1) positively with activations of bilateral perirhinal cortex, left entorhinal cortex, bilateral fusiform gyrus, left subcallosal gyrus, left lingual and inferior occipital gyri and left caudate head; and (2) negatively with activations of bilateral cingulate cortex, bilateral superior frontal gyrus, bilateral middle frontal gyrus, left inferior frontal gyrus, right precentral gyrus, right superior temporal gyrus, and left precuneus (Fig. 4 and Table S1).

Activation of these clusters was not correlated with age, epilepsy onset, epilepsy duration, seizures frequency, and volumes of corresponding hippocampus (Spearman rank test).

These correlations between recognition performance and brain activations were confirmed in subgroups of either left or right MTLE (Figs. S1 and S2 and Table S1).

Positive correlation was also found between ipsilateral and contralateral PH/FG activations in the whole group of patients ($\rho = 0.9560$, $p < 0.001$; Spearman rank test), as well as in subgroups of patients with either left or right MTLE, and with either normal or impaired recognition memory performance ($p < 0.05$; Spearman rank test).

Discussion

The study shows that distinct profiles of recognition performance are sustained at encoding by distinct profiles of activation, especially involving bilateral crucial structures at the interface of the ventral visual stream and medial temporal memory structures. To our knowledge, this is the first demonstration of stronger fMRI activations of memory networks within MTL, in MTLE patients with HS and normal task performance, in comparison to healthy subjects. As previously reported in patients with mild cognitive impairment (Dickerson et al., 2004; Hämäläinen et al., 2007), PH/FG appears to play a decisive role in these possible compensatory processes, arguing for MTL functional reserve among diseases affecting MTL structures.

Methodologically, several limitations should be mentioned. First, if the number of healthy subjects seems

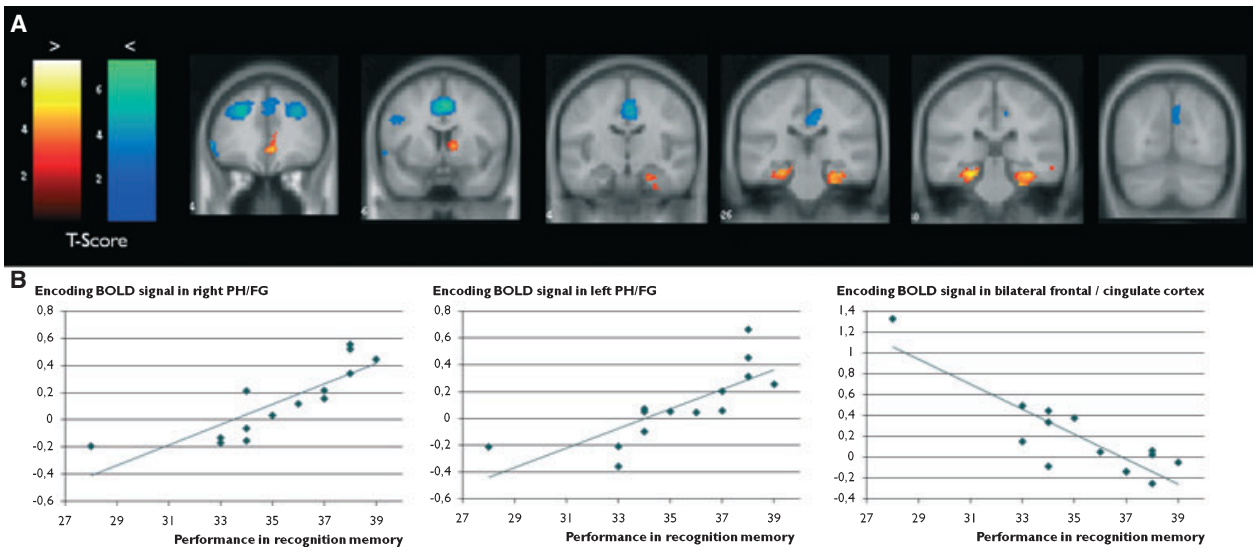

Figure 4.
Encoding activations correlated to recognition memory performance in MTLE patients. (**A**) Anatomic localization. (**B**) Distribution of values (p-voxel <0.005, uncorrected; radiologic convention: left hemisphere is on the right side; yellow-red = positive correlation [>]; blue = negative correlation [<]).
Epilepsia © ILAE

appropriate, we acknowledge that the results are derived from a small-sized sample of 14 patients. This number of patients included is, however, concordant with the few previous studies having evaluated efficiency of compensatory networks for memory functions in patients with TLE using fMRI (Dupont et al., 2000; Powell et al., 2007; Eliassen et al., 2008). Difficulties in recruitment in such studies are partly explained by the need to include homogenous patients with strictly similar morphologic and electroclinical features. Voxel-based findings have been thereafter obtained by comparing patients with normal recognition to healthy subjects, and to patients with impaired performance. No statistical difference was found between patients with normal and impaired recognition performance for all confounding factors tested [i.e., age, gender, epilepsy lateralization, epilepsy onset, epilepsy duration, seizures frequency, *Wechsler Adult Intelligent and Memory Scales,* and volumetry of ipsilateral and contralateral hippocampus (related to epileptogenic side)]. Nevertheless, in order to account for possible influence of unidentified factors inherent to any between-group analysis, we secondarily studied the voxel-based correlation between recognition memory performance and brain activation in the whole group of patients, and as previously methodologically shown in a small sample of seven patients (Powell et al., 2007), separately in subgroups of either left or right MTLE. We used the fifth percentile of recognition performance in the control group to define the cutoff for being a patient with a normal or impaired memory performance. Due to the low effort encoding memory task used, patients with impaired performance still have recognition rates between 33 and 36 out of 40 (37–39/40 for patients with normal performance), and only one patient had a recognition rate of 28. Therefore, correlations reported in the whole group of patients and in the subgroup of patients with left MTLE could have been driven by this one low performer. Findings obtained in these two analyses were concordant with those performed within the subgroup of patients with right MTLE, which did not include a potential outlier. Moreover, the correlations obtained from the extracted cluster were still significant if the one patient with a recognition rate of 28 was removed ($p < 0.0477$, $\rho = 0.886$, Spearman rank test), except for the posterior cingulate cluster reported in the subgroup of patients with left MTLE, for which only a trend was found ($p = 0.064$, $\rho = -0.829$, Spearman rank test). These preliminary findings will need to be confirmed in a larger series, including patients with recognition performance more clearly delineating patients with normal performance from patients with impaired performance. This larger study may, in addition, allow investigation of low and high performers in a subgroup of patients with left or right TLE separately, in order to better understand the influence of epilepsy side on reorganization.

By limiting the statistical analysis to thereafter correctly recognized items, we identified specific regions where activations are related to successful memory encoding. Profile of activations was first obtained in healthy subjects, with regions consistent with the literature (Stern et al., 1996; Gabrieli et al., 1997; Pihlajamäki et al., 2003). In particular and as expected, MTL activations were bilateral, suggesting that non–material-specific items were registered both visually and semantically. These activations involved the

fusiform gyrus, the parahippocampal region, especially the perirhinal cortex, but not the hippocampus. For some authors, this apparent discrepancy between MTL structures could be explained by methodologic limitations, the relative high static susceptibility of hippocampus resulting in decreased sensitivity blood oxygen level dependent (BOLD) detection (Detre, 2004). On the other hand, strong interactions have been described between the fusiform gyrus and medial limbic cortices, in particular with the perirhinal cortex, which shares many common anatomic and physiologic characteristics with the fusiform gyrus (Lavenex et al., 2002, 2004; Eichenbaum et al., 2007; Murray et al., 2007). During encoding, representation of distinct items is formed in the anterior MTL, which could be considered as the highest level of a perceptive-memory system, hierarchically organized as a continuum through the ventral-visual-perirhinal stream, as proposed by Bussey and Saksida (2007); (Felleman & Van Essen, 1991; Nakamura & Kubota, 1996; Barbeau et al., 2008; Maillard et al., 2011).

No significant difference in activations was found during encoding between patients with left and right MTLE, corroborating their similar performance at recognition (Hermann et al., 1995; Baxendale, 1997; Eliassen et al., 2008). Memory performance was, however, nonhomogeneous among patients. Whereas recognition was significantly decreased in the whole group of 14 patients, 6 of them (43%) exhibited normal performance. The other eight patients were impaired, despite similar electroclinical features. The main originality of our study is thereby the direct comparison of activation profiles of two subgroups of patients only discriminated by their recognition performance. Independently of epilepsy lateralization and as previously methodologically proposed at recognition (Eliassen et al., 2008), profiles of activation were studied at encoding by pooling patients into two new subgroups according to performance, each subgroup including the same number of patients with either left or right MTLE.

Patients with normal recognition demonstrated weaker frontal activations than healthy subjects. Such functional remote effects have been largely described in temporal lobe epilepsy, in particular within the frontal cortex (Jokeit et al., 1997). On the opposite, and perhaps more surprisingly, patients with impaired performance showed stronger activations, within frontal/cingulate and parietal cortices, in comparison both to healthy subjects and to patients with normal recognition. These distinct fMRI profiles in patients with normal and impaired performance certainly explained the few differences in activations found when comparing patients, as a whole, to healthy subjects. Dupont et al. (2000) similarly reported greater frontal activations, during verbal encoding and retrieval tasks, in left MTLE patients with impaired performance. In our study, activation of this probable attentional network (Chun & Turk-Browne, 2007) was correlated negatively with recognition performance in the whole group of patients, as well as in each subgroup of either left or right MTLE. These findings suggest nonspecific recruitment of inefficient attentional capacities, in patients with impaired performance. On the other hand, patients with normal performance showed stronger activation than healthy subjects in PH/FG. Activation of this same region was, on the contrary, weaker in patients with impaired recognition performance than in healthy subjects. Positive correlation between recognition performance and bilateral PH/FG activations was in addition demonstrated in the whole group of patients, as well as in both subgroups of either left or right MTLE. Taken as a whole, these findings suggest that non–material-specific recognition performance is sustained, during the encoding phase, by the functional reserve of crucial structures from the ventral-visual-perirhinal stream (Bussey & Saksida, 2007). We hypothesize that impairment of this perceptive-memory system leads to alternative activations of an inefficient attentional network in patients with decreased performance.

In contrast, Powell et al. (2007) suggested previously that contralateral MTL reorganization was incapable of preserving material-specific memory function: Verbal and visual performances were negatively correlated, respectively, with right and left undamaged hippocampus, in left and right MTLE with HS. This important discrepancy, despite a similar neuroimaging approach (fMRI voxel-based correlation between encoding activations and memory performance in seven left and seven right MTLE patients with HS), could be explained by the distinct memory paradigm used. We made the assumption that a low effortful encoding task, based on non–material-specific items, would be a more favorable condition. Our findings suggest that effective functional compensation occurs in a subset of MTLE patients through a highly automatic system (Eddy et al., 2007), with nevertheless, its own probable limits for memory tasks of highest level.

In addition, a strong positive correlation was shown between ipsilateral and contralateral PH/FG activations, suggesting a global unbalanced involvement of ventral-visual-perirhinal stream. Therefore, the weaker activation of the HS side was not associated with greater contralateral activations. Qualitative changes in PH/FG activations (increase or decrease) were similar in both hemisphere (ipsilaterally and contralaterally to HS). On the one hand, dysfunction and atrophy of the contralateral temporal lobe has been previously described in unilateral MTLE within connected areas (King et al., 1995; Woermann et al., 1999; Guye et al., 2002; Joo et al., 2004). In particular, bilateral hippocampal atrophy was found in our study, prevailing on the epileptogenic side, as previously shown in unilateral MTLE (King et al., 1995). Conversely, we recently reported contralateral increases in functional connectivity at rest in patients with MTLE, suggesting compensatory processes (Bettus et al., 2009). On the other hand, ipsilateral decreased activations can obviously be explained by alterations secondary to epileptic processes. By contrast,

ipsilateral hyperactivation of PH/FG may appear more surprising. We hypothesize that these structures, relatively spared by epileptic networks in some patients, may underlie synaptic compensation. Indeed, beyond the definition of MTLE as a homogeneous syndrome, depth-recordings demonstrate that different MTL networks may be involved within the epileptogenic zone (Bartolomei et al., 2004, 2005; Bertram, 2009). In particular, two distinct subtypes of MTLE have been described depending on the preferential involvement of either hippocampus or entorhinal cortex (Bartolomei et al., 2004, 2005). In this way, neuroradiologic studies have confirmed that patients with MTLE may show atrophy of hippocampus with or without involvement of the parahippocampal region (Bernasconi et al., 2000; Salmenpera et al., 2000; Bernasconi et al., 2001; Jutila et al., 2001; Bernasconi et al., 2003). Further studies, including depth-recording, will be necessary to confirm that distinct organizations of epileptogenic networks within the MTL, could be responsible for distinct functional involvement of MTL structures inside memory compensatory networks.

Conclusions

The study shows that distinct profiles of recognition performance are sustained at encoding by distinct profiles of activation, especially involving bilateral crucial structures at the interface of ventral visual stream and medial temporal structures. Stronger activations of memory networks were found, in comparison to healthy subjects, within the PH/FG, in MTLE patients with normal task performance. These bilateral activations correlated positively with recognition score in the whole group of patients, as well as in subgroups with either left or right MTLE, suggest an effective functional compensation. On the other hand, impairment of this perceptive–memory system may lead to alternative fronto-cingulate activations of an inefficient attentional network in patients with impaired performance.

Acknowledgments

This work was supported by CNRS and ANR (Agence Nationale pour la Recherche).

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Barbeau EJ, Taylor MJ, Regis J, Marquis P, Chauvel P, Liegeois-Chauvel C. (2008) Spatio temporal dynamics of face recognition. *Cereb Cortex* 18:997–1009.

Bartolomei F, Wendling F, Regis J, Gavaret M, Guye M, Chauvel P. (2004) Pre-ictal synchronicity in limbic networks of mesial temporal lobe epilepsy. *Epilepsy Res* 61:89–104.

Bartolomei F, Khalil M, Wendling F, Sontheimer A, Régis J, Ranjeva JP, Guye M, Chauvel P. (2005) Entorhinal cortex involvement in human mesial temporal lobe epilepsy: an electrophysiologic and volumetric study. *Epilepsia* 46:677–687.

Baxendale SA. (1997) The role of the hippocampus in recognition memory. *Neuropsychologia* 35:591–598.

Bernasconi N, Bernasconi A, Caramanos Z, Andermann F, Dubeau F, Arnold DL. (2000) Morphometric MRI analysis of the parahippocampal region in temporal lobe epilepsy. *Ann N Y Acad Sci* 911: 495–500.

Bernasconi N, Bernasconi A, Caramanos Z, Dubeau F, Richardson J, Andermann F, Arnold DL. (2001) Entorhinal cortex atrophy in epilepsy patients exhibiting normal hippocampal volumes. *Neurology* 56:1335–1339.

Bernasconi N, Bernasconi A, Caramanos Z, Antel SB, Andermann F, Arnold DL. (2003) Mesial temporal damage in temporal lobe epilepsy: a volumetric MRI study of the hippocampus, amygdala and parahippocampal region. *Brain* 126:462–469.

Bertram EH. (2009) Temporal lobe epilepsy: where do the seizures really begin? *Epilepsy Behav* 14:32–37.

Bettus G, Guedj E, Joyeux F, Confort-Gouny S, Soulier E, Laguitton V, Cozzone PJ, Chauvel P, Ranjeva JP, Bartolomei F, Guye M. (2009) Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. *Hum Brain Mapp* 30:1580–1591.

Bussey TJ, Saksida LM. (2007) Memory, perception, and the ventral visual-perirhinal-hippocampal stream: thinking outside of the boxes. *Hippocampus* 17:898–908.

Chun MM, Turk-Browne NB. (2007) Interactions between attention and memory. *Curr Opin Neurobiol* 17:177–184.

Detre JA. (2004) fMRI: applications in epilepsy. *Epilepsia* 45:26–31.

Diana RA, Yonelinas AP, Ranganath C. (2007) Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends Cogn Sci* 11:379–386.

Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN, Dale AM, Stern CE, Blacker D, Albert MS, Sperling RA. (2004) Medial temporal lobe function and structure in mild cognitive impairment. *Ann Neurol* 56:27–35.

Dupont S, Van de Moortele PF, Samson S, Hasboun D, Poline JB, Adam C, Lehéricy S, Le Bihan D, Samson Y, Baulac M. (2000) Episodic memory in left temporal lobe epilepsy: a functional MRI study. *Brain* 123:1722–1732.

Dupont S, Samson Y, Van de Moortele PF, Samson S, Poline JB, Hasboun D, Le Bihan D, Baulac M. (2002) Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 73:478–485.

Eddy MD, Schnyer D, Schmid A, Holcomb PJ. (2007) Spatial dynamics of masked picture repetition effects. *Neuroimage* 34:1723–1732.

Eichenbaum H, Yonelinas AP, Ranganath C. (2007) The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 30:123–152.

Elger CE, Helmstaedter C, Kurthen M. (2004) Chronic epilepsy and cognition. *Lancet Neurol* 3:663–672.

Eliassen JC, Holland SK, Szaflarski JP. (2008) Compensatory brain activation for recognition memory in patients with medication-resistant epilepsy. *Epilepsy Behav* 13:463–469.

Engel J Jr. (1996) Introduction to temporal lobe epilepsy. *Epilepsy Res* 26:141–150.

Felleman DJ, Van Essen DC. (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex* 1:1–47.

French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, Spencer DD. (1993) Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Ann Neurol* 34:774–780.

Gabrieli JD, Brewer JB, Desmond JE, Glover GH. (1997) Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science* 276:264–266.

Guye M, Le Fur Y, Confort-Gouny S, Ranjeva JP, Bartolomei F, Régis J, Raybaud CA, Chauvel P, Cozzone PJ. (2002) Metabolic and electrophysiological alterations in subtypes of temporal lobe epilepsy: a combined proton magnetic resonance spectroscopic imaging and depth electrodes study. *Epilepsia* 43:1197–1209.

Hämäläinen A, Pihlajamäki M, Tanila H, Hänninen T, Niskanen E, Tervo S, Karjalainen PA, Vanninen RL, Soininen H. (2007) Increased fMRI

responses during encoding in mild cognitive impairment. *Neurobiol Aging* 28:1889–1903.
Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. (2003) Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Ann Neurol* 54:425–432.
Hermann BP, Connell B, Barr WB, Wyler AR. (1995) The utility of the Warrington Recognition Memory Test for temporal lobe epilepsy: pre and postoperative results. *J Epilepsy* 8:139–145.
Jokeit H, Seitz RJ, Markowitsch HJ, Neumann N, Witte OW, Ebner A. (1997) Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain* 120:2283–2294.
Joo EY, Lee EK, Tae WS, Hong SB. (2004) Unitemporal vs bitemporal hypometabolism in mesial temporal lobe epilepsy. *Arch Neurol* 61:1074–1078.
Jutila L, Ylinen A, Partanen K, Alafuzoff I, Mervaala E, Partanen J, Vapalahti M, Vainio P, Pitkänen A. (2001) MR volumetry of the entorhinal, perirhinal, and temporopolar cortices in drug-refractory temporal lobe epilepsy. *AJNR Am J Neuroradiol* 22:1490–1501.
King D, Spencer SS, McCarthy G, Luby M, Spencer DD. (1995) Bilateral hippocampal atrophy in medial temporal lobe epilepsy. *Epilepsia* 36:905–910.
Lavenex P, Suzuki WA, Amaral DG. (2002) Perirhinal and parahippocampal cortices of the macaque monkey: projections to the neocortex. *J Comp Neurol* 447:394–420.
Lavenex P, Suzuki WA, Amaral DG. (2004) Perirhinal and parahippocampal cortices of the macaque monkey: intrinsic projections and interconnections. *J Comp Neurol* 472:371–394.
Maillard L, Vignal JP, Gavaret M, Guye M, Biraben A, McGonigal A, Chauvel P, Bartolomei F. (2004) Semiologic and electrophysiologic correlations in temporal lobe seizure subtypes. *Epilepsia* 45:1590–1599.
Maillard L, Barbeau EJ, Baumann C, Koessler L, Bénar C, Chauvel P, Liégeois-Chauvel C. (2011) From perception to recognition memory: time course and lateralization of neural substrates of word and abstract picture processing. *J Cogn Neurosci* 23:782–800.
Martin RC, Sawrie SM, Knowlton RC, Bilir E, Gilliam FG, Faught E, Morawetz RB, Kuzniecky R. (2001) Bilateral hippocampal atrophy: consequences to verbal memory following temporal lobectomy. *Neurology* 57:597–604.
Murray EA, Bussey TJ, Saksida LM. (2007) Visual perception and memory: a new view of medial temporal lobe function in primates and rodents. *Annu Rev Neurosci* 30:99–122.
Nakamura K, Kubota K. (1996) The primate temporal pole: its putative role in object recognition and memory. *Behav Brain Res* 77:53–77.
Ojemann JG, Akbudak E, Snyder AZ, McKinstry RC, Raichle ME, Conturo TE. (1997) Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. *Neuroimage* 6:156–167.
Oldfield RC. (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97–113.
Pihlajamäki M, Tanila H, Hänninen T, Könönen M, Mikkonen M, Jalkanen V, Partanen K, Aronen HJ, Soininen H. (2003) Encoding of novel picture pairs activates the perirhinal cortex: an fMRI study. *Hippocampus* 13:67–80.
Powell HW, Duncan JS. (2005) Functional magnetic resonance imaging for assessment of language and memory in clinical practice. *Curr Opin Neurol* 18:161–166.
Powell HW, Koepp MJ, Richardson MP, Symms MR, Thompson PJ, Duncan JS. (2004) The application of functional MRI of memory in temporal lobe epilepsy: a clinical review. *Epilepsia* 45:855–863.
Powell HW, Koepp MJ, Symms MR, Boulby PA, Salek-Haddadi A, Thompson PJ, Duncan JS, Richardson MP. (2005) Material-specific lateralization of memory encoding in the medial temporal lobe: blocked versus event-related design. *Neuroimage* 27:231–239.
Powell HW, Richardson MP, Symms MR, Boulby PA, Thompson PJ, Duncan JS, Koepp MJ. (2007) Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. *Epilepsia* 48:1512–1525.
Privitera M, Kim KK. (2010) Postictal language function. *Epilepsy Behav* 19:140–145.
Privitera MD, Morris GL, Gilliam F. (1991) Postictal language assessment and lateralization of complex partial seizures. *Ann Neurol* 30:391–396.
Quigg M, Bertram EH, Jackson T, Laws E. (1997) Volumetric magnetic resonance imaging evidence of bilateral hippocampal atrophy in mesial temporal lobe epilepsy. *Epilepsia* 38:588–594.
Ramirez MJ, Schefft BK, Howe SR, Hwa-Shain Y, Privitera MD. (2008) Interictal and postictal language testing accurately lateralizes language dominant temporal lobe complex partial seizures. *Epilepsia* 49:22–32.
Richardson MP, Strange BA, Duncan JS, Dolan RJ. (2003) Preserved verbal memory function in left medial temporal pathology involves reorganisation of function to right medial temporal lobe. *Neuroimage* 20:S112–S119.
Salmenpera T, Kalviainen R, Partanen K, Pitkanen A. (2000) Quantitative MRI volumetry of the entorhinal cortex in temporal lobe epilepsy. *Seizure* 9:208–215.
Stern CE, Corkin S, González RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR. (1996) The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proc Natl Acad Sci U S A* 93:8660–8665.
Strange BA, Otten LJ, Josephs O, Rugg MD, Dolan RJ. (2002) Dissociable human perirhinal, hippocampal, and parahippocampal roles during verbal encoding. *J Neurosci* 22:523–528.
Trebuchon-Da Fonseca A, Guedj E, Alario FX, Laguitton V, Mundler O, Chauvel P, Liegeois-Chauvel C. (2009) Brain regions underlying word finding difficulties in temporal lobe epilepsy. *Brain* 132:2772–2784.
Wechsler D. (2000) *Echelle d'Intelligence de Wechsler pour Adulte III (WAIS-III)*. Les éditions du Centre de Psychologie appliquée, Paris.
Wechsler D. (2001) *Echelle clinique de mémoire de Wechsler MEM-III (WMS-III)*. Les éditions du Centre de Psychologie appliquée, Paris.
Williamson PD, French JA, Thadani VM, Kim JH, Novelly RA, Spencer SS, Spencer DD, Mattson RH. (1993) Characteristics of medial temporal lobe epilepsy: II. Interictal and ictal scalp electroencephalography, neuropsychological testing, neuroimaging, surgical results and pathology. *Ann Neurol* 34:781–787.
Witter M, Wouterloud F. (2002) *The parahippocampal region: organization and role in cognitive function*. Oxford University Press, Oxford.
Woermann FG, McLean MA, Bartlett PA, Parker GJ, Barker GJ, Duncan JS. (1999) Short echo time single-voxel 1H magnetic resonance spectroscopy in magnetic resonance imaging-negative temporal lobe epilepsy: different biochemical profile compared with hippocampal sclerosis. *Ann Neurol* 45:369–376.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Anatomic localization of encoding activations correlated to recognition memory performance in patients with left MTLE.

Figure S2. Anatomic localization of encoding activations correlated to recognition memory performance in patients with right MTLE.

Table S1. Talairach coordinates of significant fMRI activations during encoding task (p-voxel <0.005, uncorrected).

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.