Brain (2000), **123,** 1722–1732

Episodic memory in left temporal lobe epilepsy: a functional MRI study

S. Dupont,[1,5] P. F. Van de Moortele,[5] S. Samson,[1] D. Hasboun,[3,4] J. B. Poline,[5] C. Adam,[1,4] S. Lehéricy,[3] D. Le Bihan,[5] Y. Samson[2,5] and M. Baulac,[1,4]

[1]*Unité d'Epileptologie,* [2]*Department of Urgences Cérébro-vasculaires, Clinique Neurologique Paul Castaigne,* [3]*Department of Radiology,* [4]*LENA, CNRS UPR640, Hôpital de la Pitié-Salpêtrière, Paris and* [5]*CEA, SHFJ, Orsay, France*

Correspondence to: Sophie Dupont, MD, CEA-SHFJ, 4 Place du Général Leclerc, 91406 Orsay, France
E-mail: dupont@shfi.cea.fr

Summary

Left medial temporal lobe epilepsy (MTLE) is associated with verbal memory impairment usually related to hippocampal damage. We used functional MRI (fMRI) to investigate the patterns of functional activity in healthy volunteers and MTLE patients engaged in verbal episodic memory tasks to look for evidence of a reallocation of verbal memory in epileptic patients. fMRI data were collected from seven MTLE patients with left-sided hippocampal sclerosis and 10 healthy right-handed control subjects on a 3T scanner. Subjects were instructed to learn a list of 17 words (encoding) and then to recall them (retrieval) on successive trials. Healthy volunteers and patients both exhibited bilateral activation (right higher than left) of the parahippocampal gyrus during the retrieval. This effect was more marked in the control subjects. In contrast to the control subjects, patients exhibited consistent and extensive left prefrontal activations in all the memory tasks. These findings show that verbal memory tasks did not involve the same functional patterns in patients and healthy volunteers. This may be interpreted as a dysfunctional response due to the epilepsy and left hippocampal sclerosis, and could reflect the early onset and progressive course of the disease.

Keywords: functional MRI; temporal lobe epilepsy; episodic memory; dysfunction; hippocampal sclerosis

Abbreviations: BOLD = blood oxygenation level dependent; EPI = echoplanar; fMRI = functional MRI; LTLE = left temporal lobe epilepsy; MTLE = medial temporal lobe epilepsy; SPM = statistical parametric mapping

Introduction

Medial temporal lobe epilepsy (MTLE) is a surgically remediable syndrome with specific clinical presentation and pathophysiological basis, namely hippocampal sclerosis (Engel, 1996). Impairment of verbal memory is associated with left-sided MTLE. This impairment seems to be linked to the dysfunction of the hippocampal region. In the literature there is evidence from both human and animal research that the hippocampal complex and the neocortex play distinct, complementary roles in episodic memory. Patients with lesions confined to the hippocampal structures show impairment of new learning but are able to retrieve memories acquired years before (Scoville and Milner, 1957). Studies have suggested that the temporal neocortex is a crucial site for the storage of knowledge and personal experiences (Kapur *et al*., 1992; Hodges *et al*., 1994). Furthermore, a number of recent functional imaging studies have identified prefrontal and inferior frontal activations during tasks involving episodic memory retrieval (Tulving *et al*., 1994; Fletcher *et al*., 1995; Buckner *et al*., 1996, 1998*a*). The significance and specificity of this prefrontal activation remains debated (Thompson-Schill *et al*., 1997; Buckner *et al*., 1998*b*). In this study we used functional MRI (fMRI) to examine the hippocampal and extrahippocampal activations in healthy volunteers and left-sided MTLE patients engaged in verbal memory tasks. The aim of the experiment was to investigate whether left hippocampal damage altered the pattern of neocortical activations during episodic verbal memory. First, in control subjects, we wanted to assess the contribution of medial temporal structures and the neocortex to verbal memory and the relationships between these structures. Secondly, we sought evidence of a reallocation of verbal memory in MTLE patients in order to gain further insight into the mechanisms by which patients attempt to compensate or not for epilepsy and/or hippocampal sclerosis.

Table 1 *Results of neuropsychological tests in six patients with left MTLE**

	Patient number						Mean ± SD
	1	2	3	4	5	6	
Age at testing (years)	53	21	37	39	52	18	36.7 ± 14.8
Lateralization of language on Wada test	Left	Left	Left	Left	Left	Left	–
VIQ	85	82	75	83	81	81	81.2 ± 3.4
PIQ	79	83	90	106	77	89	87.3 ± 10.5
MQ	82	83	80	91	78	84	83 ± 4.5
Digit span	7	6	4	6	6	7	6 ± 1.1
Immediate recall of story	13	20.5	22	11	5.5	16.5	15.3 ± 5.9
Delayed recall of story	1	16	12	6	1.5	13.5	8.7 ± 6.6
Rey figure (immediate recall)	–†	11	11	11	12	12	11.4 ± 0.5
Rey figure (delayed recall)	–†	6	8	9	8	9	8 ± 1.2
Phonological verbal fluency	26	28	18	32	23	25	25.3 ± 4.7
Semantic verbal fluency	44	50	35	40	38	44	41.8 ± 5.3
Wisconsin card sorting test	3	6	4	6	3	6	4.7 ± 1.5

VIQ = verbal IQ; PIQ = performance IQ; MQ = memory quotient. *Patient 7 did not undergo neuropsychological tests; †missing data.

Subjects and methods

Subjects

The study population included seven patients (four women and three men; mean age 34.4 years, range 18–53 years) with MTLE who were undergoing presurgical evaluation for anterior temporal lobectomy at the Pitié-Salpêtrière Epilepsy Unit. They were matched with a control group consisting of 10 healthy volunteers (eight women and two men; mean age 25.4 years, range 23–30 years). All subjects gave informed written consent in accordance with the Declaration of Helsinki and the study was approved by the ethics committee of the Hôpital de la Pitié-Salpêtrière, Paris. Six patients underwent presurgical evaluation (Adam *et al*., 1996) including medical, neurological and neuropsychological examinations, video-EEG monitoring, brain MRI, [^{18}F]fluorodeoxyglucose (FDG)-PET examinations and an intracarotid amytal test. The seventh patient underwent the same presurgical evaluation, with the exception of the neuropsychological examination and the intracarotid amytal test. The inclusion criteria for our study were the following: right-handed lateralization; surface EEG recordings consistent with left-sided medial temporal lobe seizure onset; neuropsychological examination (Table 1) consistent with a left-sided memory deficit; left hippocampal sclerosis diagnosed on volumetric MRI without any other structural abnormalities; and/or left temporal lobe hypometabolism on interictal FDG-PET.

fMRI procedures

Blood oxygenation level dependent (BOLD) fMRI data were acquired on a 3-T Bruker system equipped with a prototype fast-gradient system and the standard quadrature head coil. Subjects were placed in a supine position in the MRI scanner. Their heads were immobilized with cushions to reduce motion artefact. The stimuli were projected upside down on to a mirror located at the end of the scanner bore. Subjects were equipped with prism glasses that allowed them to see the projection upright in central vision without image distortion. For each subject a series of conventional structural images was first collected to provide detailed anatomical information. Following the acquisition of these sagittal and axial inversion recovery turbo flash T_1-weighted localizer images, gradient echo echoplanar (EPI) fMRI was performed in 22 contiguous 5-mm axial slices (repetition time = 6 s, 64 × 80 matrix, 22 cm^2 field of view) covering the whole brain. The entire session, including both structural and functional sequences, lasted 45 min the first day and 50 min the following day.

Memory tasks procedures

Memory tasks included verbal episodic memory encoding and retrieval tasks. Two sessions were performed on consecutive days, but we only report here the relevant memory tasks performed during the first session. A sequential task-activation paradigm was employed, alternating between an experimental condition and a baseline condition (see Fig. 1). The baseline condition was the same for all the experiments and consisted of the fixation of the letter A. Scanning was performed over a 324-s block. Each block included 5 control and four experimental conditions beginning with the control condition. Two memory experimental blocks were performed the first day. The encoding experimental block consisted of learning a supra-span list of 17 abstract words that has been used to demonstrate verbal episodic memory deficits in epileptic patients (Jones-Gotman *et al*., 1993). In the same block the list of words was presented four times, alternating with baseline condition. The words were displayed at the rate of one word every 2 s. Subjects were instructed to learn the words silently for later recall. At the end of the encoding block, subjects rested for 2 min. During the following retrieval experimental condition, subjects were asked to recall silently the words that they had previously learned. At the end of the session, subjects were tested to establish the efficiency

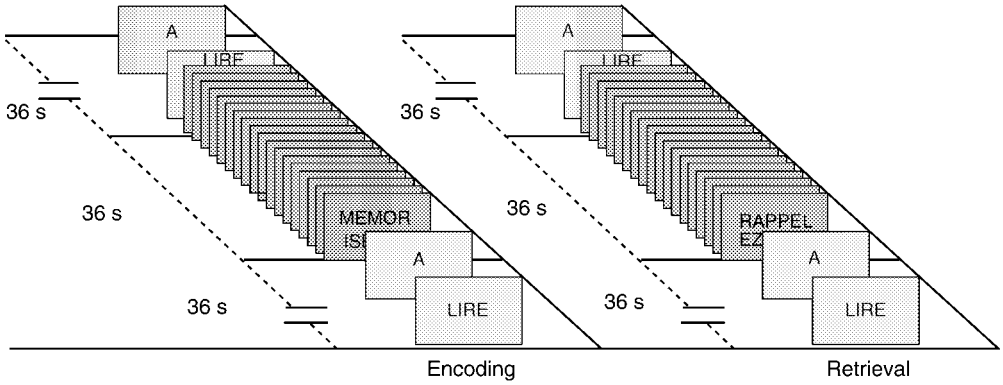

Fig. 1 Experimental conditions.

of the retrieval of the verbal information and were asked to recall out loud the words that they had previously learned.

Image analysis

fMRI data were analysed on SPARC workstations (Sun Microsystems, Mountain View, Calif., USA). Statistical analysis was performed in MATLAB (Mathworks, Natick, Mass., USA) using a statistical parametric mapping (SPM) software package (SPM96) developed by Friston and colleagues (Friston *et al*., 1995).

Statistical analysis

For each subject we performed a stereotaxic reorientation of the images along the bicommissural line. Images were then coregistered and resliced to correct movement and further spatially transformatted to standard stereotaxic coordinates to correct for anatomical variance across subjects. Analysis of the translation and rotation movements across the images was similar for controls and patients. The standard reference space used in SPM96 is based on the Talairach and Tournoux stereotaxic atlas (Talairach and Tournoux, 1988). The resulting images were convolved with a three-dimensional gaussian filter to suppress noise. The data were then analysed statistically on a voxel-by-voxel basis using a two temporal basis functions model. We first performed an individual analysis for each subject and then a multi-subject analysis using a similar method. Since our aim was to investigate the global changes in neocortical activations caused by hippocampal damage, we focused our study on the group analysis and only report here the results of the multi-subject study. For the multi-subject analysis, a given voxel was considered to be significantly activated if, on comparison with a reference task, there was an increase in the haemodynamic response function at $P < 0.0001$, with $P < 0.01$ corrected for multiple comparison. These values correspond to *Z*-scores of 3.72 and above in this study. A region was considered to be activated if a spatially contiguous set of voxels were all independently significant at a level of $P < 0.003$.

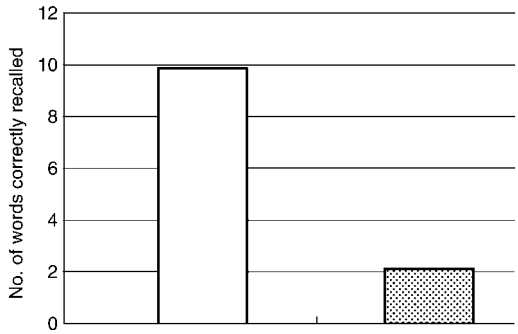

Fig. 2 Memory test performances. Open column = control subject; stippled column = LTLE patients.

Results

Memory test performance

As expected, the retrieval performance of control subjects was uniformly high compared with that of left temporal lobe epilepsy (LTLE) patients, in whom it was significantly impaired. During the retrieval experimental condition, control subjects recalled 10.3 ± 4.4 words (mean ± standard deviation), whereas the LTLE patients recalled only 3.1 ± 2.5 words. The difference between the performances of the two groups was significant $P < 0.0007$ (see Fig. 2).

Within-group comparisons of haemodynamic response

Control subjects (activation minus baseline)

Figure 3 shows the SPM activation maps during the encoding and retrieval tasks for the 10 healthy volunteers. Table 2 indicates the coordinates of the areas of significant activation ($P < 0.0001$, corrected for multiple comparison). During the encoding task, control subjects exhibited significant activation in five cerebral regions: the occipital cortex (Brodmann areas 17 and 18) and the fusiform gyrus bilaterally; the left parietal cortex at the junction between Brodmann areas 40 and 7; the superior temporal cortex (Brodmann area 22 corresponding to Wernicke's area) on the left; and the ventrolateral frontal cortex (Brodmann areas 44 and 45) bilaterally (left greater

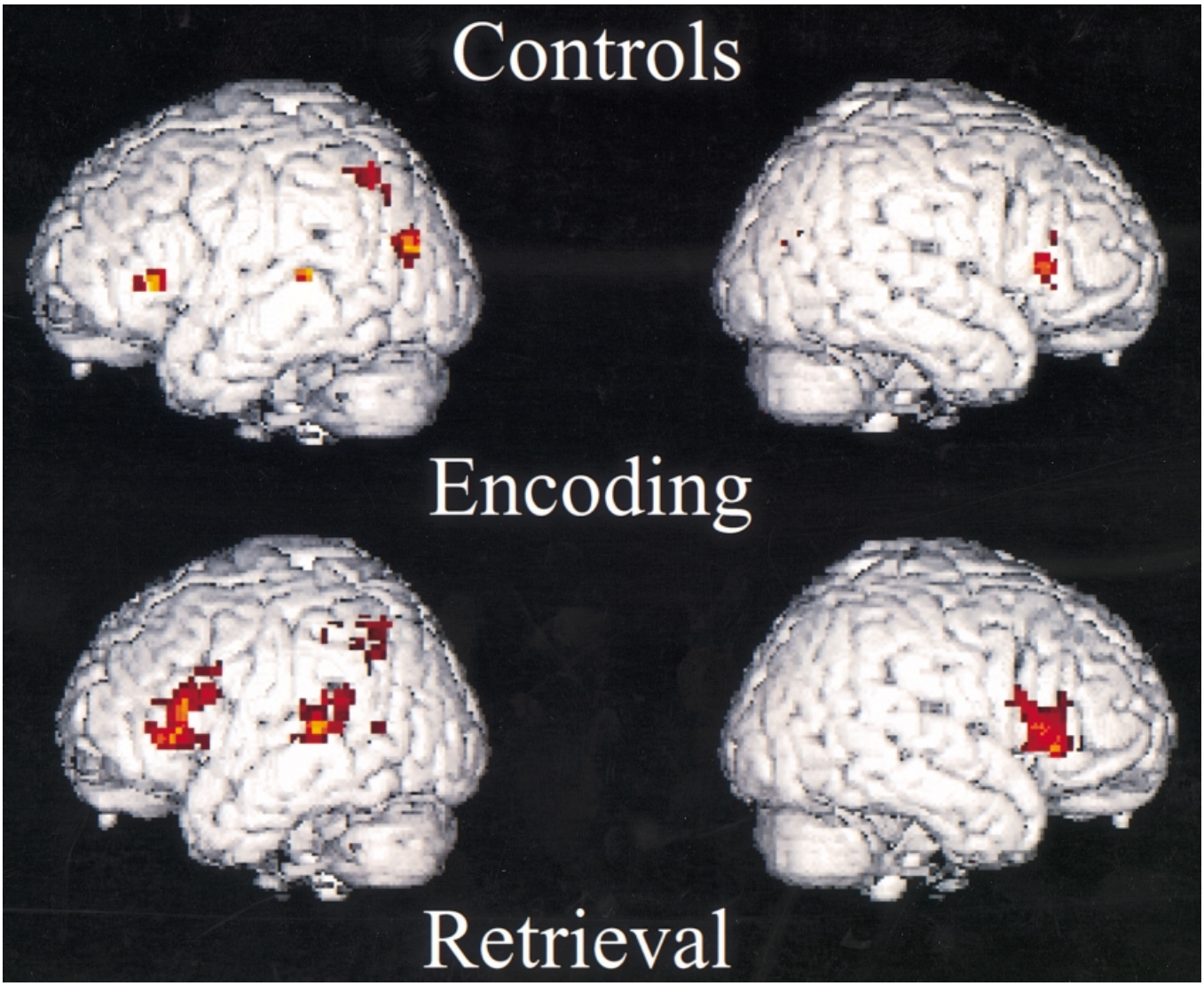

Fig. 3 Statistical parametric maps of mean activation during the encoding and retrieval tasks for 10 control subjects.

than right). A broadly similar activation pattern was observed during the retrieval task with, however, three notable differences. First, there was a slight decrease in occipital activation during the retrieval task, whereas left occipitotemporal activation was present only during this retrieval task. Secondly, there was an apparent increase in the spatial extent of the regions showing significant activation during the encoding task, particularly in the left superior temporal cortex and the left ventrolateral frontal cortex. Thirdly, a significant activation was detected during retrieval in both inferomedial temporal cortices bilaterally and the left frontal medial cingular cortex. The inferomedial temporal cortex activation mainly concerned the parahippocampal gyrus. This parahippocampal activation clearly predominated on the right side (see Fig. 4) in terms of number of activation peaks and *Z*-scores. No hippocampal activation was detected.

LTLE patients

As depicted in Fig. 5 and Table 3, the LTLE patient activation pathway included five cerebral regions: the parietal cortex (Brodmann areas 40 and 7) bilaterally; the left superior temporal cortex, i.e. Wernicke's area; the left ventrolateral frontal cortex, i.e. Broca's area; the medial frontal cortex (Brodmann areas 6 and 8) bilaterally; and the dorsolateral frontal cortex (Brodmann areas 9, 10, and 46) bilaterally (left greater than right). We showed four major differences in epileptic patients compared with controls: a decrease in occipital and occipitotemporal cortical activation; a decrease in left temporal cortex activation; a dramatic increase in frontal cortex activation (see Fig. 6); and a decrease in limbic activation. First, we noted the absence of primary occipital cortex activation during the encoding task compared with the controls. Similary, no activation was detected in the lateral occipitotemporal cortex during the retrieval task,

Table 2 *Activation foci in normal control subjects during the encoding and immediate retrieval tests (stereotaxic coordinates are expressed in millimetres)*

Region	Left hemisphere								Right hemisphere							
	Encoding				Retrieval				Encoding				Retrieval			
	x	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*–score
Occipital cortex	–15	–72	12	4.5	–18	–78	15	5.28	15	–66	12	5.7	.	.	.	.
	–18	–81	15	5.7	–18	–66	21	4.74	18	–75	12	4.3	.	.	.	
	–27	–75	21	7.3	.	.	.	.	21	–84	15	8.1	.	.	.	
Occipitotemporal cortex	.	.	.	.	–42	–60	6	4.77	.	.	.	.	.	.	.	.
(BA 37/41/42)	.	.	.	.	–51	–27	15	4.83	.	.	.	.	.	.	.	.
	.	.	.	.	–45	–24	3	5.1	.	.	.	.	.	.	.	.
Parietal cortex (BA 40/7)	–33	–51	48	6.5	–36	–39	48	5.21	.	.	.	.	.	.	.	.
	–33	–60	45	6.5	–30	–63	48	6.23	.	.	.	.	.	.	.	.
	–30	–66	39	5.2	.	.	.	.	.	.	.	.	.	.	.	.
Superior temporal cortex	.	.	.	.	–66	–33	9	6.04	.	.	.	.	.	.	.	.
(BA 44/45)					–63	–36	18	4.66	.	.	.	.	.	.	.	.
	–57	–36	6	5.6	–57	–42	15	6.78	.	.	.	.	.	.	.	.
	.	.	.	.	–57	–33	6	6.69	.	.	.	.	.	.	.	.
	.	.	.	.	–45	–45	18	8.08	.	.	.	.	.	.	.	.
Ventrolateral frontal cortex	–54	24	6	6.8	–54	24	6	4.8	42	27	9	7.1	54	18	15	6.01
(BA 44/45)	–39	27	3	4.4	–42	18	3	5.87	.	.	.	.	39	27	9	7.72
	.	.	.	.	–42	27	3	6.62	.	.	.	.	.	.	.	.
	.	.	.	.	–48	12	21	7.11	.	.	.	.	.	.	.	.
	.	.	.	.	–45	21	18	6.09	.	.	.	.	.	.	.	.
	.	.	.	.	–42	9	30	5.95	.	.	.	.	.	.	.	.
Inferomedial cortex																
Fusiform gyrus	–6	–63	9	5.0	–30	–54	0	7.18	9	–60	9	5.0	.	.	.	.
Lingual gyrus	.	.	.	.	–12	–57	6	7.77	.	.	.	.	6	–60	3	7.58
	.	.	.	.	.	.	.	.	.	.	.	.	15	–60	0	4.52
Parahippocampal gyrus	.	.	.	.	–12	–48	–6	7.56	.	.	.	.	12	–42	3	5.81
	.	.	.	.	–33	–39	–6	6.73	.	.	.	.	27	–45	–3	7.72
	.	.	.	.	.	.	.	.	.	.	.	.	21	–42	3	6.66
	.	.	.	.	.	.	.	.	.	.	.	.	24	–54	3	7.31
Medial cortex																
Anterior cingulum (BA 32)	.	.	.	.	–21	36	18	4.22	.	.	.	.	.	.	.	.
	.	.	.	.	–15	30	15	4.37	.	.	.	.	.	.	.	.

BA = Brodmann area (Brodmann, 1909). Coordinates are according to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988).

whereas we noted a decrease in the activation of the medial occipitotemporal cortex (i.e. lingual and fusiform gyrus) in terms of size (decrease of the peak number) and significance (decrease in *Z*-scores). Secondly, the left superior temporal cortex, i.e. Wernicke's area, was less activated during the retrieval task. Thirdly, a dramatic activation of the frontal cortex was noted during both the encoding and retrieval tasks. Ventrolateral frontal cortex activation was similar in epileptic patients and control subjects, but a new and extensive activation was noted in LTLE patients in the dorsolateral and medial frontal cortex. Lastly, a medial temporal activation was detected during retrieval but this activation was less significant (lower *Z*-scores) and less extensive than in controls (see Fig. 4). In addition, we detected no anterior cingulate activation during the retrieval task.

Discussion

In this study we examined the patterns of cerebral activity in epileptic patients and controls engaged in verbal episodic memory tasks. The major finding of this study is that LTLE patients and control subjects show different patterns of brain activations during the acquisition and retrieval of verbal episodic information, especially in the frontal cortex.

Memory encoding in normal subjects

During the encoding task, control subjects activated an occipitotemporoparietal network suggesting visual and word processing, with a predominant left-sided lateralization. No specific temporolimbic activation was detected. The ventrolateral frontal cortex was markedly activated,

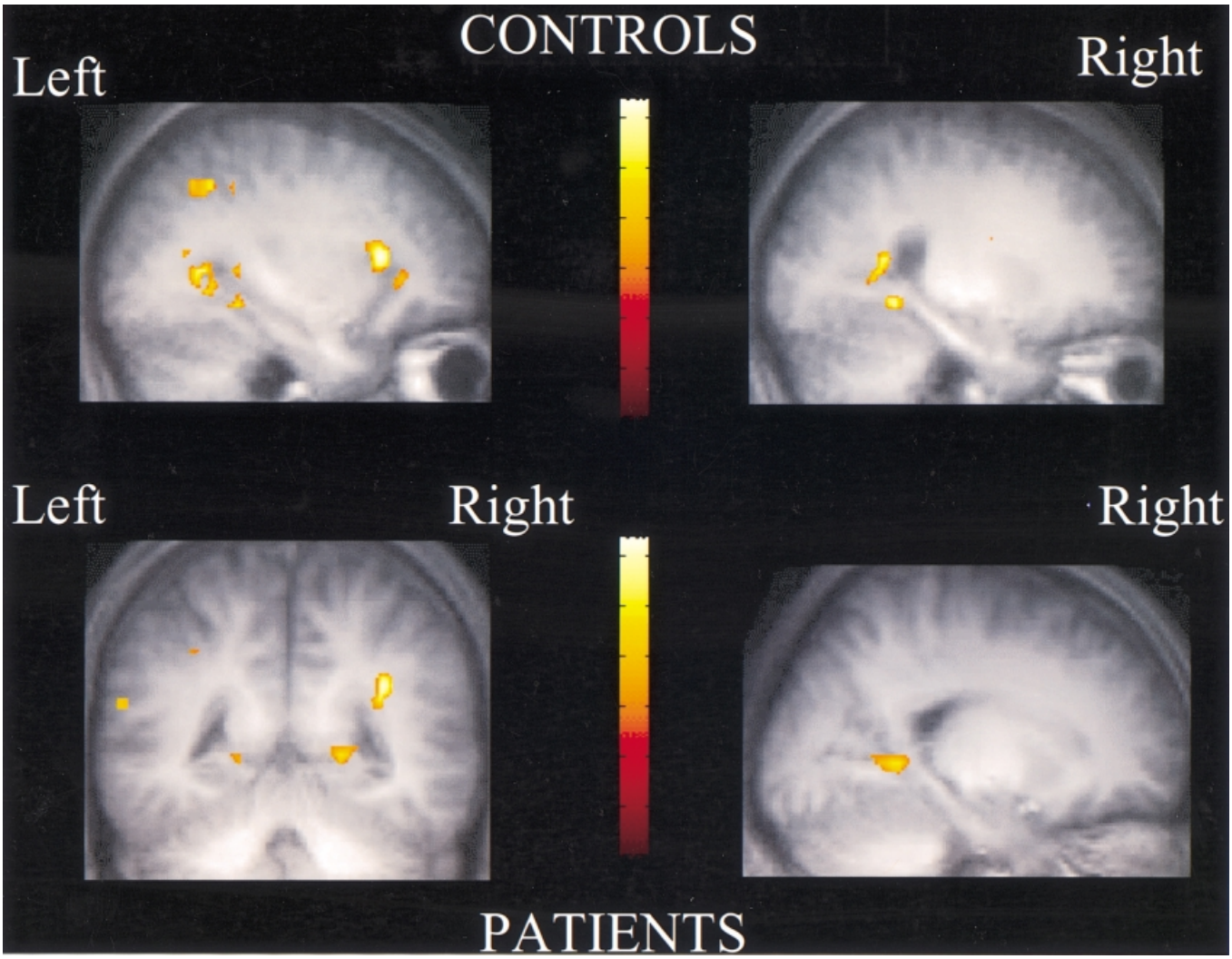

Fig. 4 Mean parahippocampal activations during the retrieval task in control subjects and patients with left MTLE.

predominantly on the left side. Although damage to the human lateral frontal cortex does not usually result in a global memory disorder, recent functional studies have demonstrated the involvement of the lateral frontal cortex in episodic memory (Kapur *et al*., 1994; Tulving *et al*., 1994; Fletcher *et al*., 1995). These functional imaging studies suggest a predominant involvement of the anterior prefrontal cortex (Buckner *et al*., 1995; Grady *et al*., 1995; Haxby *et al*., 1996; Schacter *et al*., 1996), especially the anterior part of Brodmann area 10 (Buckner *et al*., 1996). The consistent observation of prefrontal activation during explicit memory tasks has been conceptualized as the hemispheric encoding/retrieval (HERA) model (Tulving *et al*., 1994). This model proposes that left prefrontal cortical regions are preferentially involved in encoding novel aspects of information into episodic memory, whereas right prefrontal cortical regions are preferentially involved in episodic memory retrieval. This dichotomy does, however, remain the subject of debate and some authors have demonstrated that the left prefrontal cortex could also be involved in retrieval tasks (Thompson-Schill *et al*., 1997), suggesting that left or right prefrontal activations are part of a more general prefrontal system that is required for the selection of responses from memory. In our study the ventrolateral activation of the frontal cortex involved Broca's area. This activation may be related to semantic processing during word encoding and appears to be critical for encoding.

Memory retrieval in normal subjects

The retrieval task was characterized by an increase in the spatial extent of the regions that had been activated during the encoding task, especially the left superior temporal neocortex and the left ventrolateral cortex, as shown in Fig. 5 and Table 3. Another difference with the encoding condition was the parahippocampal activation detected during the retrieval task. This activation clearly predominated on the right side. A right-side lateralization of the medial temporal lobe has already been described during a word retrieval task (Squire *et al*., 1992; Schacter *et al*., 1996). This finding

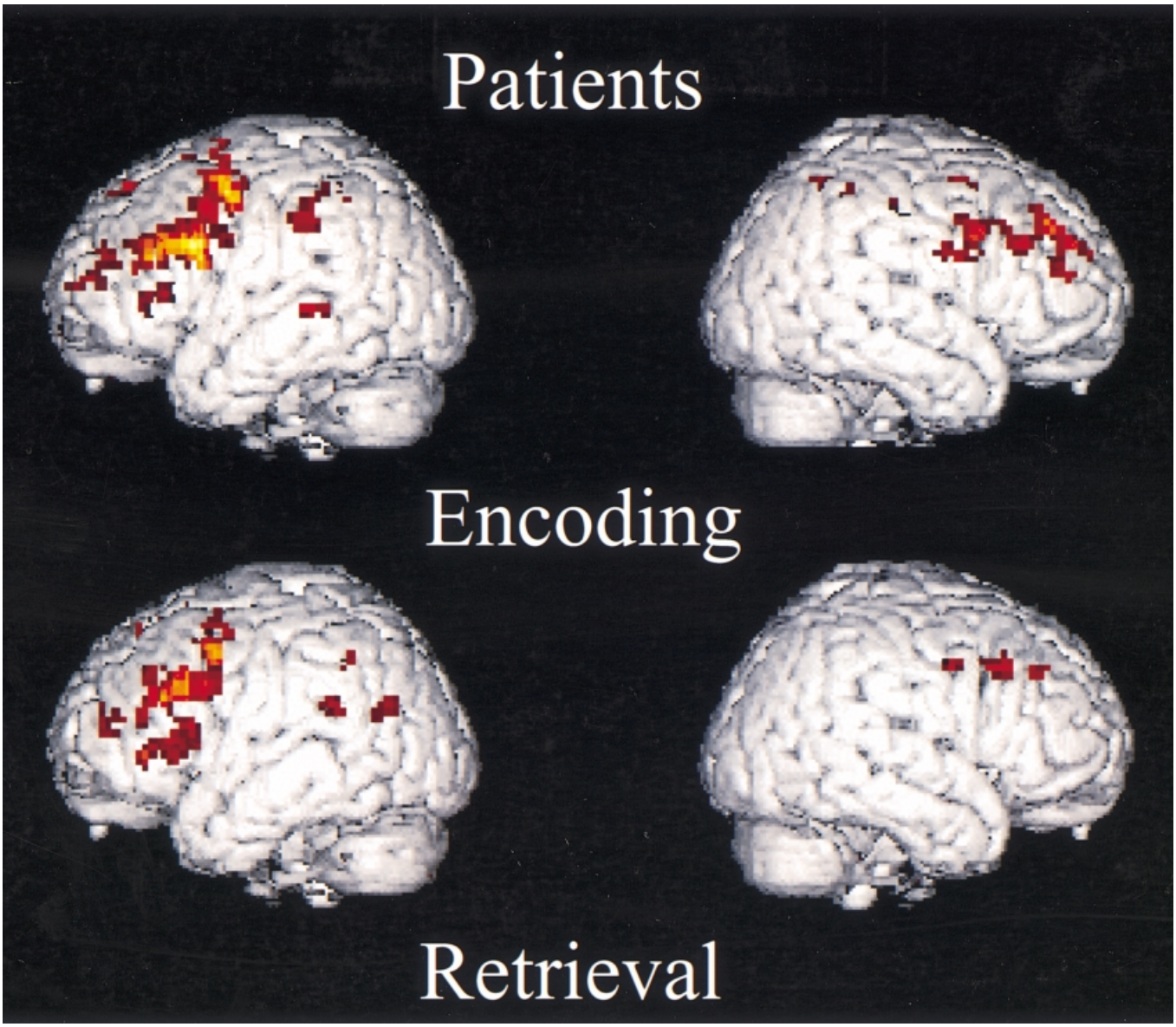

Fig. 5 Statistical parametric maps of mean activation during the encoding and retrieval tasks for patients with left MTLE.

underlines the role played by the parahippocampal formations in retrieval of episodic information. Experimental studies in animals have demonstrated that lesions of perirhinal and parahippocampal cortex, sparing the amygdala and hippocampal formation, can produce severe memory impairment in primates (Zola-Morgan *et al*., 1989; Suzuki *et al*., 1993). Parahippocampal activations have also been found in many functional studies that examined explicit memory (Stern *et al*., 1996; Gabrieli *et al*., 1997). Gabrieli and colleagues have suggested that parahippocampal activation mediates memory processes which discriminate novel from familiar visual stimuli via strong projections from high-level visual areas (Gabrieli *et al*., 1997). However, in apparent contradiction with this hypothesis, we found that the parahippocampal gyrus was activated during the retrieval tasks and not during the encoding task, which could have required discrimination between novel and familiar stimuli.

Differences in memory processing between epileptic patients and controls

In our study the pattern of activations in patients differed from that in controls. LTLE patients exhibited a decreased activation in the parahippocampal and posterior occipitoparietal regions and a dramatic new activation located in the dorsolateral frontal cortex. These differences may reflect either a dysfunction or a reorganization of normal memory processing linked to epilepsy. We could hypothesize that the failure of the left medial temporal lobe system led

Table 3 *Activation foci for patients with left MTLE during the encoding and immediate retrieval tests (stereotaxic coordinates are expressed in mm)*

Region	Left hemisphere								Right hemisphere							
	Encoding				Retrieval				Encoding				Retrieval			
	x	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*-score
Occipital cortex (V1V2)	.	.	.	.	–12	–66	15	6.61	.	.	.	.	.	.	.	.
Parietal cortex (BA 40/7)	–33	–48	48	5.01	–36	–45	42	5.02	36	–42	48	4.63	.	.	.	.
	–45	–33	39	5.77	–45	–66	24	7.18	30	–51	57	4.71	.	.	.	.
	.	.	.	.	.	.	.	.	33	–54	48	5.07	.	.	.	.
Superior temporal cortex	–63	–36	3	5.04	–63	–45	21	5.57	.	.	.	.	.	.	.	.
(BA 22)	–54	–42	3	4.99	–42	–36	15	5.3	.	.	.	.	.	.	.	.
Ventrolateral frontal cortex	–54	27	9	5.85	–57	15	15	6.78	.	.	.	.	.	.	.	.
(BA 44/45)	–36	24	9	6.22	–54	21	3	5.72	.	.	.	.	.	.	.	.
	–36	48	12	4.15	–39	21	9	5.16	.	.	.	.	.	.	.	.
	.	.	.	.	–42	36	0	4.55	.	.	.	.	.	.	.	.
	.	.	.	.	–45	51	12	5.07	.	.	.	.	.	.	.	.
Dorsolateral frontal cortex	–57	0	33	4.28	–57	27	24	4.73	42	30	30	6.9	36	24	36	4.58
(BA 9/10/46)	–57	27	24	5.46	–51	30	30	5.84	27	57	27	4.95	45	21	42	6.63
	–51	30	30	7.22	–48	33	21	5.32	33	51	30	5.43	48	0	39	6.10
	–42	48	24	5.1	–48	45	18	5.03	36	45	21	4.99	.	.	.	.
	–42	54	18	4.18	–39	51	24	3.96	.	.	.	.	.	.	.	.
	–48	21	30	7.05	–48	18	30	6.69	.	.	.	.	.	.	.	.
	–36	42	21	3.92	–42	6	30	6.27	.	.	.	.	.	.	.	.
	–33	60	12	4.47	–51	9	36	4.78	.	.	.	.	.	.	.	.
	.	.	.	.	–45	33	36	5.5	.	.	.	.	.	.	.	.
Inferomedial cortex																
Posterior cingulum	.	.	.	.	.	.	.	.	.	.	.	.	9	–60	6	7.84
(BA 23/30/31)	.	.	.	.	.	.	.	.	.	.	.	.	24	–60	15	7.38
Fusiform gyrus	.	.	.	.	–30	–54	3	4.87	.	.	.	.	.	.	.	.
	.	.	.	.	–21	–54	3	7.01	.	.	.	.	.	.	.	.
Parahippocampal gyrus	.	.	.	.	–18	–45	0	4.74	.	.	.	.	21	–45	3	6.34
	.	.	.	.	.	.	.	.	.	.	.	.	27	–54	3	6.49
Medial cortex (BA 6/8)	–6	9	63	7.97	–9	18	45	5.32	6	3	63	7.38	3	30	51	5.44
	–3	33	48	6.84	–3	6	66	7.57	.	.	.	.	6	18	48	6.86
	–9	21	42	5.99	.	.	.	.	.	.	.	.	.	.	.	.

BA = Brodmann area (Brodmann, 1909). Coordinates are according to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988).

LTLE patients to use a compensatory strategy, resulting in a larger activation of the frontal cortex. This extended activation could then represent a cortical reallocation secondary to a functional reorganization of episodic memory. However, the performance of the patients in this study was poor, suggesting that this reallocation is not efficient. We may therefore postulate that the performance variability between patients and controls results from an activation variability within the brain, leading to the hypothesis that the bad memory performances observed in LTLE patients reflect a cortical dysfunction rather than a reorganization. The abnormal activation of the dorsolateral frontal cortex may reflect an alteration of normal memory strategies dealing with the demands of the task. Numerous reports suggest that the prefrontal cortex is made up of several different anatomical and functional areas with a particular role in conscious awareness and attentional, supervisory and strategic functions (Stuss and Benson, 1986; Squire, 1987). LTLE patients could therefore change their memory strategy to deal with the demands of a difficult task requiring an increased load of selective attention. The activation of the dorsolateral frontal cortex would therefore reflect a dysfunction of cerebral memory processing.

Dysfunction of verbal episodic memory and epilepsy

This dysfunction of verbal episodic memory in epileptic patients may result either from the hippocampal dysfunction or from the epileptogenic process. MTLE associated with hippocampal sclerosis is a pathology that alters the temporal lobe system at an early stage. In most of the patients reported in the literature, an early event of febrile convulsions is noted (French *et al*., 1993) and the epilepsy usually begins in early childhood, around the age of 4–8 years (Adam *et al*., 1996).

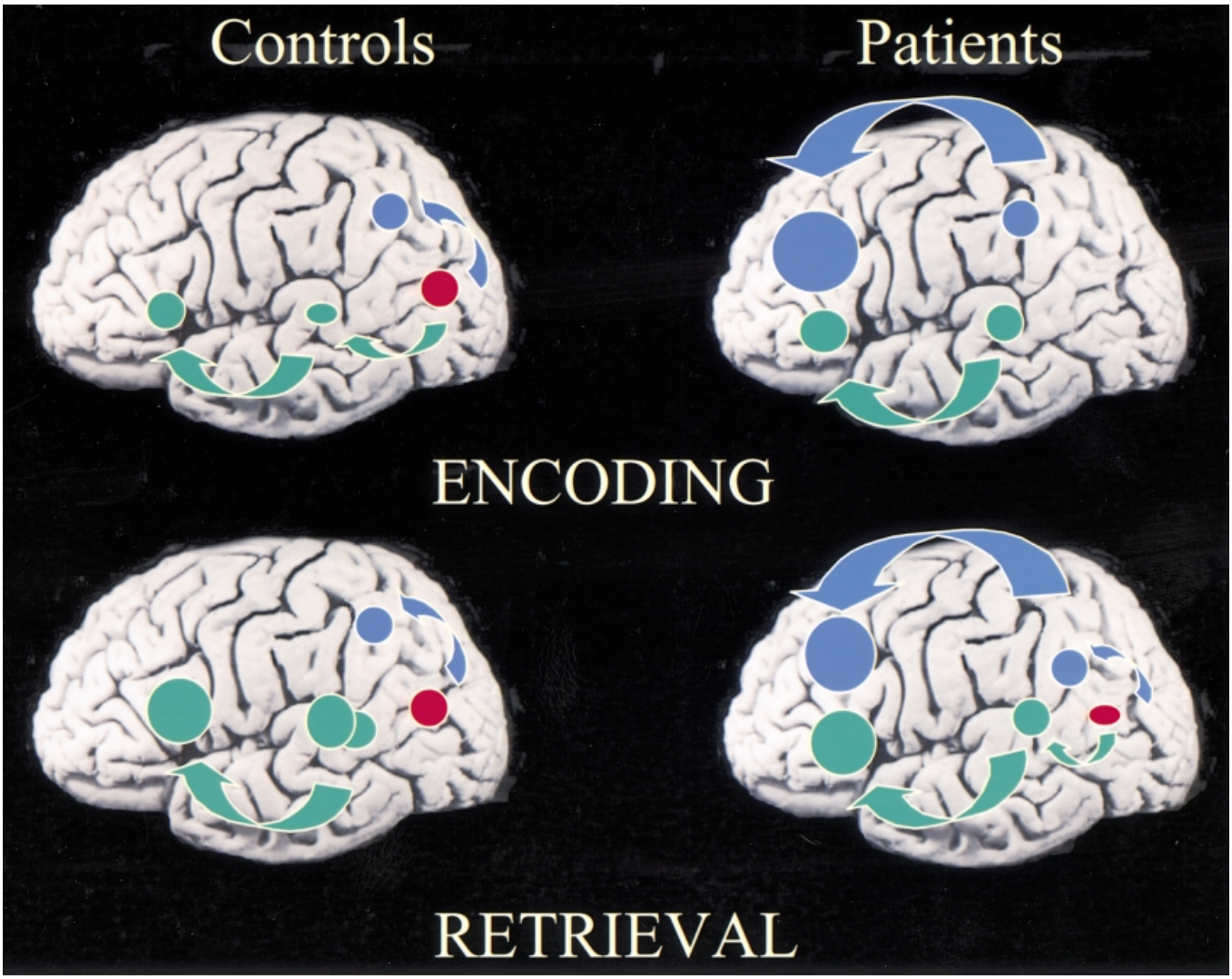

Fig. 6 Activation patterns during the encoding and retrieval tasks in control subjects and patients with left MTLE. To perform this schematic illustration, the 'system of reference' used for normalization in SPM96 [i.e the anterior (CA) and posterior (CP) commissural lines and the vertical line drawn through the anterior commissure (VCA)] was reported on a lateral view of the brain. The stereotaxic coordinates obtained for each regional area of activation were then averaged and are reported on the illustration. The size of each 'spot' of activation reflects the number of stereotaxic coordinates averaged for each region.

Furthermore, some lines of evidence suggest that a subtle pre-existing hippocampal malformation could contribute to the development of subsequent hippocampal sclerosis (Baulac *et al*., 1998; Fernandez *et al*., 1998). These data suggest that MTLE is associated with hippocampal damage or dysfunction at an early stage of development. This hypothesis is also supported by the fact that verbal memory deficit is known to be correlated with several indices of hippocampal integrity such as the MRI measurement of the hippocampal volume (Trenerry *et al*., 1996) or the postoperative histological analysis of the hippocampal pyramidal cell density (Sass *et al*., 1990). On the other hand, MTLE cannot be considered as a model of pure hippocampal dysfunction (Spencer, 1998). The neuropsychological impairment may be attributable to the more diffuse neurobiological consequences associated with an increasing number of years of intractable seizure activity in the temporal lobe and with the propagation of the epileptic discharges into extratemporal regions. Cortico-hippocampal neural networks are modified by the ictal and interictal epileptogenic activity. A decline in memory performances may result from the interference between these epileptic networks and the normal cognitive networks. We can therefore speculate that the specific involvement of the prefrontal region in LTLE patients reflects the interaction between the normal memory networks and the epileptic network.

In conclusion, complex neuroanatomical circuits subserve memory. In healthy subjects, verbal episodic memory is mediated by a specific system of related neocortical and medial temporal brain regions. The parahippocampal formations, temporal neocortex and ventrolateral frontal cortex seem to play a crucial role in this memory system. In

epileptic patients, we have demonstrated a reallocation of these cognitive and cortical resources, which may be caused either by hippocampal dysfunction or by epileptogenesis. This reallocation might be considered alternatively as an alteration of the normal memory strategies, resulting in bad memory performances. A more detailed study of the precise nature of these neural pathways and their neurochemical substrates should lead to a better understanding of their pathophysiology and may well lead to the development of new therapeutic strategies.

References

Adam C, Clemenceau S, Semah F, Hasboun D, Samson S, Aboujaoude N, et al. Variability of presentation in medial temporal lobe epilepsy: a study of 30 operated cases. Acta Neurol Scand 1996; 94: 1–11.

Baulac M, De Grissac N, Hasboun D, Oppenheim C, Adam C, Arzimanoglou A, et al. Hippocampal developmental changes in patients with partial epilepsy: magnetic resonance imaging and clinical aspects. Ann Neurol 1998; 44: 223–33.

Brodmann K. Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig: Barth; 1909.

Buckner RL, Petersen SE, Ojemenn JG, Miezin FM, Squire LR, Raichle ME. Functional anatomical studies of explicit and implicit memory retrieval tasks. J Neurosci 1995; 15: 12–29.

Buckner RL, Raichle ME, Miezin FM, Petersen SE. Functional anatomic studies of memory retrieval for auditory words and visual pictures. J Neurosci 1996; 16: 6219–35.

Buckner RL, Koutstaal W, Schacter DL, Dale AM, Rotte M, Rosen BR. Functional-anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. Neuroimage 1998a; 7: 163–75.

Buckner RL, Koutstaal W, Schacter DL, Wagner AD, Rosen BR. Functional-anatomic study of episodic retrieval using fMRI. I. Retrieval effort versus retrieval success. Neuroimage 1998b; 7: 151–62.

Engel J Jr. Surgery for seizures. [Review]. N Engl J Med 1996; 334: 647–52.

Fernandez G, Effenberger O, Vinz B, Steinlein O, Elger CE, Döhring W, et al. Hippocampal malformation as a cause of familial febrile convulsions and subsequent hippocampal sclerosis. Neurology 1998; 50: 909–17.

Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RS, Dolan RJ. Brain systems for encoding and retrieval of auditory-verbal memory. An in vivo study in humans. Brain 1995; 118: 401–16.

French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, et al. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. Ann Neurol 1993; 34: 774–80.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric mapping in functional imaging: a general linear approach. Hum Brain Mapp 1995; 2: 189–210.

Gabrieli JDE, Brewer JB, Desmond JE, Glover GH. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 1997; 276: 264–6.

Grady CL, McIntosh AR, Horwitz B, Maisog JM, Ungerleider LG, Mentis MJ, et al. Age-related reductions in human recognition memory due to impaired encoding. Science 1995; 269: 218–21.

Haxby JV, Ungerleider LG, Horwitz B, Maisog JM, Rapoport SI, Grady CL. Face encoding and recognition in the human brain. Proc Natl Acad Sci USA 1996; 93: 922–7.

Hodges JR, Patterson K, Tyler LK. Loss of semantic memory: implications for the modulatory of mind. Cogn Neuropsychol 1994; 11: 505–42.

Jones-Gotman M, Smith ML, Zatorre RJ. Neuropsychological testing for localizing and lateralizing the epileptogenic region. In: Engel J Jr, editor. Surgical treatment of the epilepsies. 2nd ed. New York: Raven Press; 1993. p. 245–61.

Kapur N, Ellison D, Smith MP, McLellan DL, Burrows EH. Focal retrograde amnesia following bilateral temporal lobe pathology. Brain 1992; 115: 73–85.

Kapur S, Craik FI, Tulving E, Wilson AA, Houle S, Brown GM. Neuroanatomical correlates of encoding in episodic memory: levels of processing effect. Proc Natl Acad Sci USA 1994; 91: 2008–11.

Sass KJ, Spencer DD, Kim JH, Westerveld M, Novelly RA, Lencz T. Verbal memory impairment correlates with hippocampal pyramidal cell density. Neurology 1990; 40: 1694–7.

Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS. Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. Proc Natl Acad Sci USA 1996; 93: 321–5.

Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 1957; 20: 11–21.

Spencer SS. Substrates of localization-related epilepsies: biologic implications of localizing findings in humans. [Review]. Epilepsia 1998; 39: 114–23.

Squire LR. Memory and brain. New York: Oxford University Press; 1987.

Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. Activation of the hippocampus in normal humans: a functional anatomical study of memory. Proc Natl Acad Sci USA 1992; 89: 1837–41.

Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings P, et al. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci USA 1996; 93: 8660–5.

Stuss DT, Benson DF. The frontal lobes. New York: Raven Press; 1986.

Suzuki WA, Zola-Morgan S, Squire LR, Amaral DG. Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities. J Neurosci 1993; 13: 2430–51.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. Stuttgart: Thieme; 1988.

Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc Natl Acad Sci USA 1997; 94: 14792–7.

Trenerry MR, Jack CR Jr, Cascino GD, Sharbrough FW, So EL. Bilateral magnetic resonance imaging-determined hippocampal atrophy and verbal memory before and after temporal lobectomy. Epilepsia 1996; 37: 526–33.

Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. [Review]. Proc Natl Acad Sci USA 1994; 91: 2016–20.

Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 1989; 9: 4355–70.

Received October 14, 1999. Revised January 2, 2000.
Accepted February 28, 2000