Brain Plasticity for Verbal and Visual Memories in Patients with Mesial Temporal Lobe Epilepsy and Hippocampal Sclerosis: An fMRI Study

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Abstract: We aimed to identify the brain areas involved in verbal and visual memory processing in normal controls and patients with unilateral mesial temporal lobe epilepsy (MTLE) associated with unilateral hippocampal sclerosis (HS) by means of functional magnetic resonance imaging (fMRI). The sample comprised nine normal controls, eight patients with right MTLE, and nine patients with left MTLE. All subjects underwent fMRI with verbal and visual memory paradigms, consisting of encoding and immediate recall of 17 abstract words and 17 abstract drawings. A complex network including parietal, temporal, and frontal cortices seems to be involved in verbal memory encoding and retrieval in normal controls. Although similar areas of activation were identified in both patient groups, the extension of such activations was larger in the left-HS group. Patients with left HS also tended to exhibit more bilateral or right lateralized encoding related activations. This finding suggests a functional reorganization of verbal memory processing areas in these patients due to the failure of left MTL system. As regards visual memory encoding and retrieval, our findings support the hypothesis of a more diffuse and bilateral representation of this cognitive function in the brain. Compared to normal controls, encoding in the left-HS group recruited more widespread cortical areas, which were even more widespread in the right-HS group probably to compensate for their right mesial temporal dysfunction. In contrast, the right-HS group exhibited fewer activated areas during immediate recall than the other two groups, probably related to their greater difficulty in dealing with visual memory content. *Hum Brain Mapp 34:186–199, 2013.*   © 2011 **Wiley Periodicals, Inc.**

Key words: cognitive functions; neuropsychological evaluation; hippocampal atrophy; functional reorganization

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INTRODUCTION

Neuropsychological evaluation of patients with refractory mesial temporal lobe epilepsy (MTLE) associated with hippocampal atrophy (HA) and other MRI signs of hippocampal sclerosis (HS) usually reveal a mild-to-moderate memory deficit [Engel et al., 1997; French et al., 1993]. According to the classic material-specific model of memory, lesions in the hippocampus of the left temporal lobe (dominant for language) may implicate in verbal memory deficits [Meyer and Yates, 1955; Milner, 1972; Novelly et al., 1984] and those of the right temporal lobe, in visual memory deficits [Jones-Gotman, 1987; Kimura, 1963; Milner et al., 1962]. However, more recent studies in epilepsy surgery have shown that the relationship between lateralized hippocampal pathology and memory dysfunction is more evident in left MTLE than in right MTLE [Alessio et al., 2004a,b; Hermann et al., 1997; Jones-Gotman, 1996; Lencz et al., 1992; Saling et al., 1993; Trenerry et al., 1995]. Evidences have suggested that the most important predictor factor for postoperative memory decline is the functional capacity of the ipsilateral mesial temporal lobe (MTL; hippocampal adequacy model) rather than the functional reserve of the contralateral MTL (hippocampal reserve model) to sustain memory performance [Powell et al., 2007; Rabin et al., 2004]. However, MRI findings associated with neuropsychological data are not always sufficient to determine the risk of language and/or memory impairment following mesial temporal resection. Application of more invasive procedures, such as intracranial monitoring with depth electrodes (SEEG) and intracarotid sodium amytal test (IAT or Wada test), may be considered necessary [Dinner, 1991; Golby et al., 2002; Lineweaver et al., 2006; Rausch and Langfitt, 1991].

Even though considered the gold standard, the IAT has a series of limitations, including its invasiveness, poor spatial resolution, insufficient time for detailed evaluation of language and memory functions and limited ability to distinguish verbal versus visual memory deficits [Dade and Jones-Gotman, 1997; Gotman et al., 1992; Loring et al., 1990; Lukban et al., 1994; Rausch, 2002]. Because of these limitations of IAT, some researchers have aimed to explore alternative methods, such as fMRI [Aldenkamp et al., 2003; Golby et al., 2002; Rausch, 2002].

Although the role of fMRI in the lateralization of hemispheric dominance for language is relatively well-established, such an application has so far not been proved reliable in the lateralization of verbal and visual memories [Jokeit et al., 2001]. fMRI evaluation of memory is more difficult than fMRI evaluation of other cognitive functions due to some neuropsychological and technical issues [Alessio et al., 2004b; Detre et al., 1998; Jones-Gotman, 1996; Powell et al., 2004, 2005 Strange, 2002; Richardson et al., 2003].

Keeping all the above factors in mind, the purposes of this study were: (1) to identify the brain areas involved in verbal and visual memory processing in normal controls and patients with unilateral MTLE associated with ipsilateral HS, by means of fMRI; and (2) to assess the sensitivity and potential clinical role of memory tests applied during fMRI experiments in lateralizing and localizing verbal and visual memory functions, during two distinct stages of memory processing, namely: encoding and retrieval.

PATIENTS AND METHODS

Ascertainment of Subjects

In this study we included patients with diagnosis of refractory MTLE followed at our epilepsy clinic. We also included a control group, which were submitted to the same protocols. All individuals signed a written consent, approved by the ethics committee of UNICAMP Medical School.

The clinical criterion was a history of simple partial and/or complex partial seizures with characteristics of MTL origin, such as: rising epigastric sensation, fear, experiential phenomena, and autonomic signs and symptoms. As a complement of this clinical criterion, no suggestion of any other partial epilepsy syndrome could be present. The EEG criterion was the presence of interictal epileptiform discharges over mid-inferomesial temporal regions and no clear-cut epileptiform abnormalities elsewhere.

The selected 26 individuals were divided into three groups, as follows: control group, composed of nine normal controls with no history of epilepsy or any other neurological and/or psychiatric pathology, and at ages and education level similar to the patient groups; right-HS group, composed of eight patients who fulfilled clinical-EEG criteria for right MTLE and who had right HA and other signs of unilateral right HS on MRI; and finally, left-HS group, composed of nine patients who also had clinical and EEG diagnosis of left MTLE and had left HA and other signs of unilateral left HS on MRI. All patients had normal hippocampal volumes contralateral to the EEG lateralization, determined by MRI volumetric analysis according to a previously defined protocol [Bonilha et al., 2004]. Other MRI signs of HS, including hyperintense T2 signal were evaluated clinically by one of the authors with experience in neuroimaging investigation in epilepsies (F.C.).

Neuropsychological Evaluation

Both patient groups were submitted to an extensive neuropsychological evaluation, which included: (1) vocabulary and block design subtests of the Wechsler adult intelligence scale-revised (WAIS-R) to estimate IQ; (2) the Edinburgh handedness inventory and dichotic listening test to determine hemispheric dominance for language and, by inference, to lateralize verbal and visual memories; (3) the logical memory and verbal paired associates of the Wechsler memory scale-revised (WMS-R) to investigate verbal
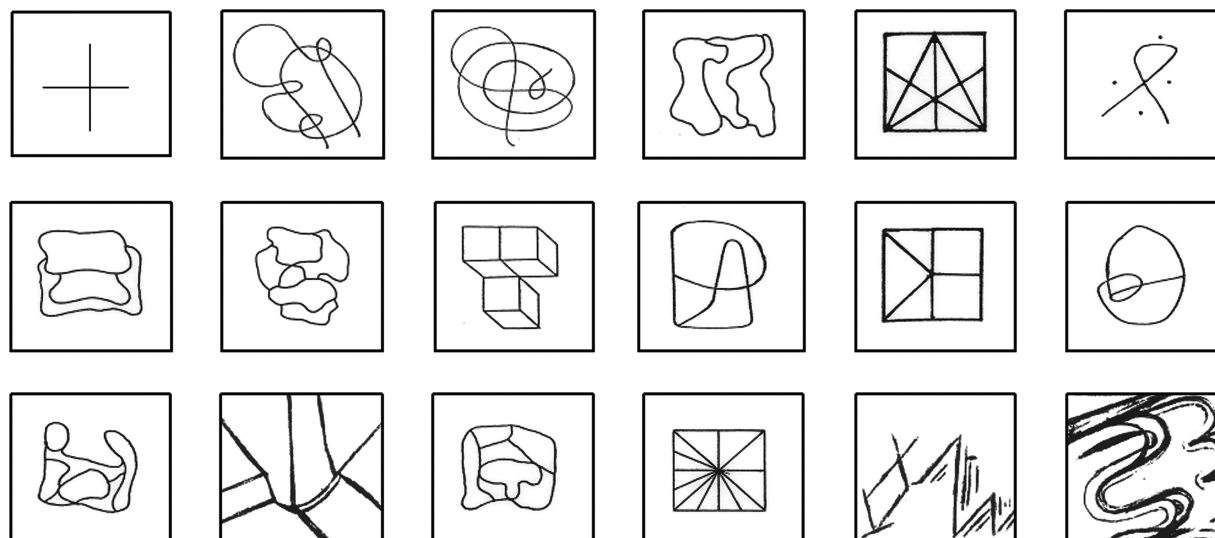
Figure 1.
The cross and the 17 abstract drawings.

memory; and (4) the figural memory, visual reproduction, and visual paired associates of the WMS-R to investigate visual memory. To control other cognitive functions that could somehow influence memory tasks, they were also submitted to tests for language (verbal fluency test and Boston naming test/BNT), and attention [Strub and Black Vigilance Test; Fromm-Auch and Yeudall, 1983; Kaplan et al., 1983; Oldfield, 1971; Spreen and Strauss, 1998; Strub and Black, 1993; Wechsler, 1981, 1987]. These tests were adapted for our population by means of few stimuli substitutions. However, the procedures were kept the same as the originals. The results of each test were compared with results for normal controls matched by age and educational level. We did not use the same fMRI control group for neuropsychological data.

Verbal and Visual Memory Tests During fMRI

Verbal memory evaluation during fMRI consisted of encoding and immediate recall of 17 abstract and emotionally neutral words [the equivalent Portuguese translations for HONOR, OPINION, PROBLEM, DUTY, INTEREST, PATIENCE, SOUL, LAW, OPTION, HAZARD, SYMPATHY, PRIDE, DECISION, CRITERIA, SYSTEM, LIFE, METHOD, as proposed by Jones-Gotman et al., 1997] presented in four blocks alternating with a non-word string (ARLTIP) presented in five blocks. Likewise, visual memory evaluation consisted of encoding and immediate recall of 17 abstract drawings presented in four blocks alternating with a fixation point ("+") presented in five blocks [Damasceno et al., 2005; Jones-Gotman et al., 1997; see Fig. 1].

Individuals were instructed to focus their attention on the non-word/fixation point for 34 s during the baseline condition, and to try to memorize the 17 words/drawings in 34 s during the experimental condition. At the end of this encoding period, they rested for 120 s and, soon afterward, they attempted to recall silently all words/drawings during 60 s (see Fig. 2). After this immediate recall period, the individuals were requested to try to recognize, by pressing a push-button, the 17 memorized words/drawings among another 17 new abstract words/drawings.

fMRI Acquisition and Data Analysis

Before getting into the MR scanner, all subjects received complete instructions about the verbal and visual memory tests they were supposed to perform inside the machine.

Images were acquired in a bottom/up interleaved mode, using a 2T Elscint Prestige (Haifa, Israel) MR scanner with an EPI protocol (TR = 2 s, TE = 45 ms, voxel size = $3 \times 3 \times 6$ mm^3). Two hundred and ninety cerebral volumes with 20 slices each were obtained in the run.

The functional images acquired were then (1) reconstructed and temporally reorganized, (2) transformed from DICOM-2D into ANALYSE-3D format by using the MRIcro software, and finally (3) slice timed, realigned, normalized (MNI standard template), smoothed (6 mm/FWHM) and analyzed by using the SPM2 software package (http://www.fil.ion.ucl.ac.uk/spm/). The imaging preprocessing was carried out individually for each subject and run, while the data analysis was performed putting together all subjects of the same group (control group, right-HS group and left-HS group).

We attempted to maximize the signal-to-noise ratio before acquiring the EPI images by following a semi-automatic shimming procedure to homogenize the magnetic
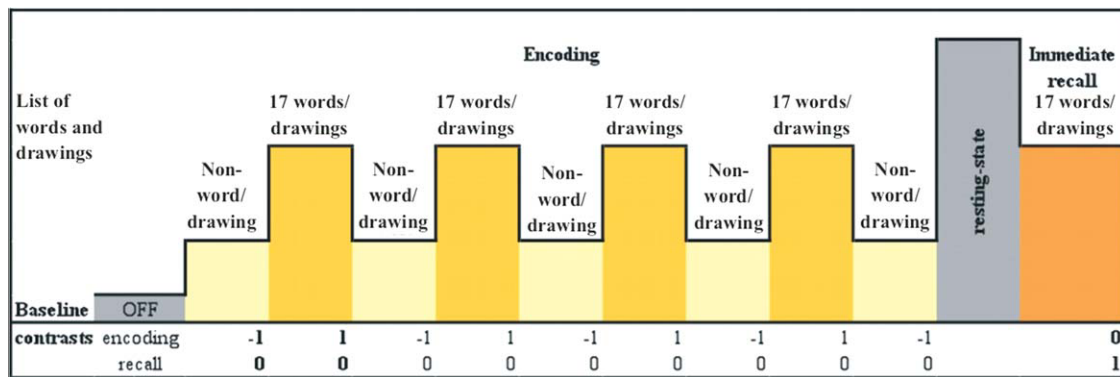
Figure 2.
Verbal and visual memory paradigms. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

field strength in the brain region to the sub-ppm level. In order to reduce the chance for ghost artifacts, we have made use of an algorithm proposed by Buonocore and Gao [1997] during the image reconstruction stage.

For data analysis, the following parameters were adopted: gama function with window length of 32 and order 1, whereas model interaction, parametric modulation, other regressors, removal of global effects, high-pass filter and correction for serial correlations were left aside. Three T-test contrasts were created in order to identify cerebral areas related to verbal memory encoding (word blocks—*minus*—nonword blocks) and immediate recall (words recall). The same procedure was adopted for visual memory encoding and immediate recall (see Fig. 2). In other words, the first two contrasts designed were word blocks and nonword blocks and the third one, immediate recall. In order to identify the cerebral areas activated during encoding stage, we assigned the value "1" to the word blocks and the value "-1" to the nonword blocks, while no value was assigned to the baseline condition (OFF). We also assigned the value "0" to the immediate recall block because in doing so it was left aside of this analysis. Then, the program performed not only the subtraction of word blocks—*minus*—nonword blocks but also compared this result to the baseline condition result. Soon afterwards, to identify the cerebral regions activated during immediate recall stage, we assigned the value "1" to the immediate recall block and no value to the baseline condition. Once again, the value "0" was assigned to the word and nonword blocks, which were left aside of this second analysis.

Finally, for the results visualization a threshold of $P <$ 0.001, uncorrected for multiple comparisons, and clusters of 125/0 voxels were used for the encoding/retrieval phase.

RESULTS

The three groups had similar age and educational level (Table I). The two patient groups were similar in age of

seizure onset, duration of epilepsy, seizure frequency, and number of antiepileptic drugs used, as well as in the results of the Edinburgh handedness inventory, dichotic listening test, Boston naming test, verbal fluency test, Strub&Black vigilance test, visual memory tests, and fMRI recognition tests. The only difference between them was that patients with left HS had lower IQ ($F = 9.656$; $P = 0.008$) and worse performance on tests of general memory ($F = 15.387$; $P = 0.002$), verbal memory ($F = 14.510$; $P = 0.002$), and delayed recall ($F = 6.345$; $P = 0.025$) than patients with right HS (Table II).

As already mentioned, three contrasts were designed during the SPM2 analysis aiming to visualize the results for encoding [-1 1 0] and immediate recall [0 0 1] stages. The differences between cerebral areas activated during encoding and immediate recall of verbal versus visual memories are shown in Table III.

Verbal Memory Test

The data analysis of the encoding stage revealed activations of: (1) bilateral occipital cortices in the three groups; (2) right parietal cortex in control group, and bilateral parietal cortices in right-HS and left-HS groups; (3) left superior temporal cortex in control group, bilateral superior temporal cortices in right-HS group, and right superior temporal cortex in left-HS group; (4) bilateral middle frontal cortices in control and left-HS groups, and left middle frontal cortex in right-HS group (see Fig. 3); and (5) bilateral>left ventro-lateral frontal cortices in right-HS group and bilateral>right ventro-lateral frontal cortices in left-HS group, while there was no such activation in control group (see Fig. 4).

The data analysis of immediate recall showed activations of: (1) left occipital cortex in control and right-HS groups, and bilateral occipital cortices in left-HS group; (2) left parietal cortex in the three groups; (3) right superior temporal cortex in control and left-HS groups, whereas no

TABLE I. Demografic and fMRI data of subjects

Subjects	Age (years)	Education (years)	fMRI verbal memory (correct answers)	fMRI visual memory (correct answers)	Edinburgh handedness inventory
Controls					
1	38	4	7	13	right
2	23	16	17	14	right
3	19	11	12	8	right
4	29	15	10	8	right
5	31	11	10	16	right
6	50	7	12	11	right
7	40	15	17	17	right
8	35	5	12	8	right
9	31	11	16	12	right
Right-HS group					
1	34	11	12	12	right
2	32	11	5	NA	right
3	43	11	13	11	right
4	49	11	14	14	left
5	50	16	14	15	right
6	41	13	15	11	right
7	38	8	12	13	right
8	35	8	17	16	right
Left-HS group					
1	48	15	15	14	right
2	42	4	7	11	right
3	24	11	14	11	right
4	34	11	8	13	right
5	47	8	11	13	left
6	33	11	8	9	right
7	42	7	0	NA	right
8	20	4	15	14	Right
9	31	5	11	12	Right
F and	1.5	1.574	1.402	0.508	0.536
P values	0.244	0.229	0.266	0.609	0.592

NA, not available.

such activation was detected in right-HS group; (4) bilateral>right infero-medial temporal cortices in control group and right infero-medial temporal cortex in right-HS group, and absence of such activation in left-HS group (see Fig. 5); (5) right ventro-lateral frontal cortex in right-HS and left-HS groups, while no such activation was identified in control group (see Fig. 6); and (6) right prefrontal cortex in control and right-HS groups, and bilateral prefrontal cortices in left-HS group.

Visual Memory Test

The data analysis of the encoding stage revealed activations of: (1) bilateral occipital and parietal cortices in the three groups, (2) right frontal cortex in control group, and bilateral superior and inferior frontal and prefrontal cortices in right-HS and left-HS groups (see Fig. 7); and (3) bilateral inferior temporal cortices in right-HS group (see Fig. 8), while there was no such activation in control and left-HS groups.

The data analysis of immediate recall showed activations of: (1) bilateral cerebellum in the three groups; (2) right occipital cortex in control group, and left occipital cortex in left-HS and right-HS groups; (3) bilateral parietal cortices in control group, and left parietal cortices in left-HS and right-HS groups; (4) right prefrontal cortex in control group and bilateral prefrontal cortex in left-HS group (see Fig. 9), whereas no such activation was detected in right-HS; (5) bilateral inferior temporal cortices in control group, and right inferior temporal cortex in left-HS and right-HS groups; (6) right mid-temporal cortex in control and left-HS groups, while there was no such activation in right-HS; and (7) bilateral hippocampal cortices in control group (see Fig. 10).

DISCUSSION

As already well-established in the literature, neuropsychological evaluation of patients with refractory MTLE

TABLE II. MRI, clinical, and neuropsychological data of patients

Patients	MRI	Side of TL spikes on EEG	Age at seizure onset (years)	Duration of epilepsy (years)	Seizure frequency (P/month)	AEDs	Dichotic listening test	WAIS-R estimated IQ	Boston naming test (z score)	Verbal fluency test (z score)	Vigilance test (errors)	WMS-R general memory (z score)	WMS-R verbal memory (z score)	WMS-R visual memory (z score)	WMS-R delayed recall (z score)
Right-HS group															
1	RHA	right	4	30	20	CBZ; CLN	left	100	0.12	-0.63	0	1.23	1.53	-0,05	1,95
2	RHA	right	8	24	12	CBZ; CLB	NA	97	-4.8	-0.63	0	0.4	0.68	-0,37	-0,24
3	RHA	right	7	36	2	PNT; CLB	left	86	-3.39	-0.19	0	-0.55	-0.54	-0,76	-1,02
4	RHA	right	0	49	14	CBZ; CLB	left	100	-2.13	-0.85	1	0.46	-0.02	1,68	-0,45
5	RHA	right	19	31	2	LMT; CLB	left	115	-0.11	0.02	0	2.38	2.96	0,46	3,16
6	RHA	right	6	34	12	CBZ; CLB	left	100	1.32	0.46	1	0.9	0.77	0,63	0,48
7	RHA	right	4	34	30	CBZ	left	92	-1.11	NA	0	-0.04	0.07	-0,11	-1
8	RHA	right	4	31	4	CBZ; CLB	left	97	-0.58	-0.85	0	1.29	1.07	1,04	1,88
Left-HS group															
1	LHA	left	1	47	2	OXC; CLB	NA	94	-1.26	-0.85	0	-0.76	-1.19	0.78	-0.77
2	LHA	left	20	22	40	CBZ; CLB	left	80	-501	-1.02	1	-0.23	-0.22	-0.24	-1.3
3	LHA	left	2	22	6	CBZ; TPM	left	88	-4.49	-0.85	0	-1.25	-1.12	-0.5	-0.24
4	LHA	left	4	29	1	CBZ; PNT; CLB	left	94	-2.69	-0.19	0	-0.83	-1.55	0.59	-0.65
5	LHA	left	3	44	5	CBZ; CLB	left	89	-1.27	0.46	0	-0.04	-0.22	0.27	-0.03
6	LHA	left	7	26	2	LMT; TPM; CLB	left	89	-1	1.34	0	-0.04	-0.09	0.01	-0.59
7	LHA	left	2	40	4	CBZ; CLB	left	80	-7.97	-1.64	0	-1.83	-2.3	0.01	-1.73
8	LHA	left	2	18	11	CBZ	left	NA	NA	NA	NA	NA	NA	NA	NA
9	LHA	left	**4**	**27**	**4**	**CBZ**	left	86	-4.45	NA	0	-1.51	-1.12	-1.53	-3.15
F and			0.287	0.482	0.461	0.204		9.656	3.855	0.001	0.368	15.387	14.51	1.061	6.345
P values			0.600	0.498	0.508	0.658		**0.008**	0.07	0.979	0.554	**0.002**	**0.002**	0.32	**0.025**

TL, temporal lobe; **RHA,** right hippocampal atrophy; **LHA,** left hippocampal atrophy; **AEDs,** antiepileptic drugs; **CBZ,** carbamazepine; **CLB,** clobazam; **PNT,** phenytoin; **LMT,** lamotrigine; **TPM,** topiramate; **CLN,** clonazepam; **NA,** not available.

TABLE III. Comparison of verbal and visual memories activation areas

Activation areas	Encoding of verbal memory									Immediate recall of verbal memory								
	Control group			Right-HS group			Left-HS group			Control group			Right-HS group			Left-HS group		
	R	L	B	R	L	B	R	L	B	R	L	B	R	L	B	R	L	B
Superior temporal cortex		*				*	*			*						*		
Infero-medial temporal cortex												*	*					
Middle frontal cortex			*		*				*									
Ventro-lateral frontal cortex						*			*					*		*		
Parietal cortex	*					*	*				*			*			*	
Occipital cortex			*			*	*				*			*				*
	Encoding of visual memory									Immediate recall of visual memory								
Inferior temporal cortex						*						*	*			*		
Mid-temporal cortex											*					*		
Hippocampal cortex											*							
Superior and inferior frontal cortex	*					*	*											
Prefrontal cortex	*					*	*			*								*
Parietal cortex			*			*	*					*		*			*	
Occipital cortex			*			*	*			*				*			*	
Cerebellum												*			*			*

R, right; L, left; B, bilateral; * presence of activation.

associated with HA usually reveals a mild-to-moderate memory deficit [Engel et al., 1997; French et al., 1993]. According to our previous studies [Alessio et al., 2004a,b], patients with refractory MTLE have more memory deficits than those with drug-responsive MTLE, regardless of the presence and degree of HA on MRI. On the other hand, individuals with HA on MRI exhibit more memory impairment than individuals with normal MRI, regardless of the presence and frequency of seizures. However, the interaction of refractory seizures and HA is related to the worst memory performance [Alessio et al., 2004a,b].

Verbal Memory

A matter of less agreement in the literature concerns the classic material-specific model of memory. More recent studies in epilepsy surgery have shown that the
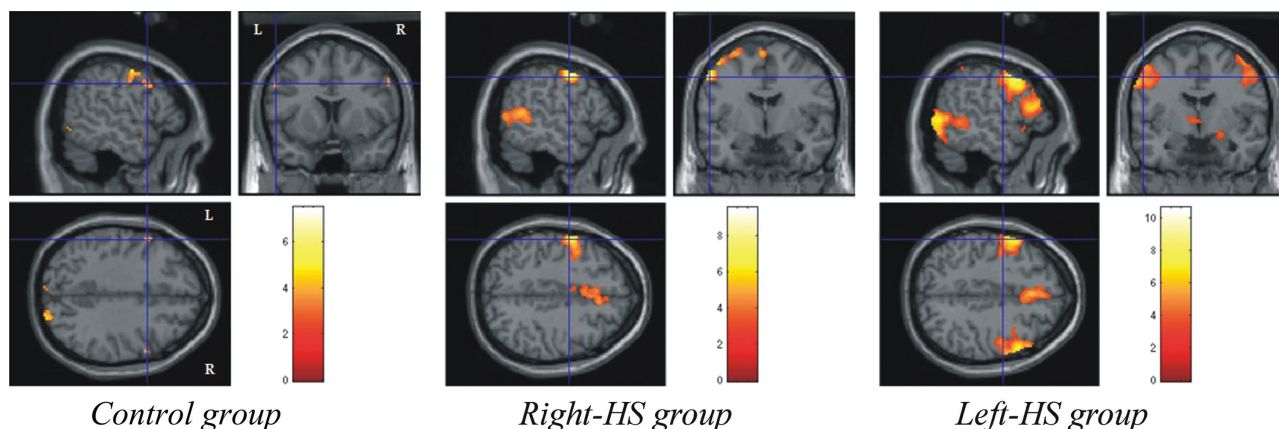

Control group   *Right-HS group*   *Left-HS group*

Figure 3.
Encoding activations of bilateral middle frontal cortices in control and Left-HS groups, and left middle frontal cortex in Right-HS group.
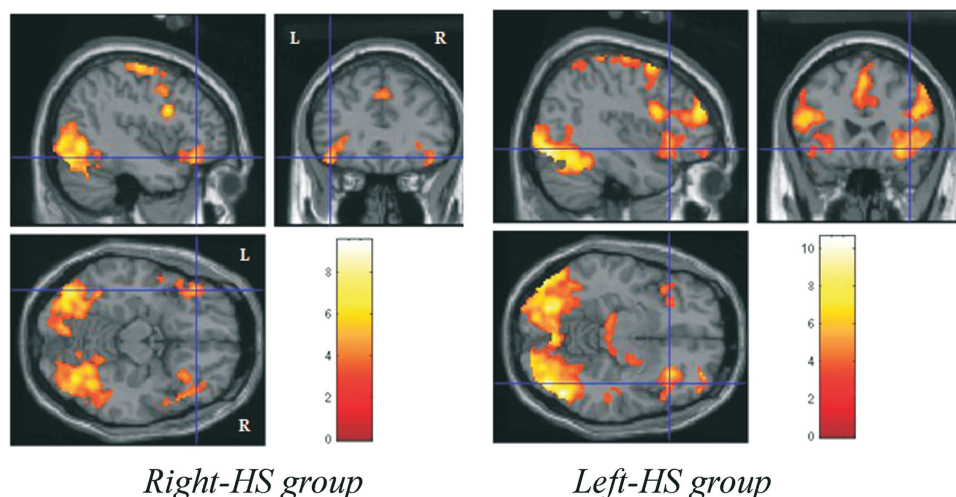
Right-HS group   Left-HS group

Figure 4.
Encoding activations of bilateral > left ventro-lateral frontal cortices in Right-HS group and bilateral > right ventro-lateral frontal cortices in Left-HS group.

relationship between lateralized hippocampal pathology and memory dysfunction is more evident in left MTLE for verbal memory deficits than in right MTLE for visual memory [Alessio et al., 2004a,b]. However, it is not well established what kind of verbal memory process (encoding, consolidation, or retrieval) is related to which cortical brain regions in these patients, and this issue is particularly important when selecting candidates for resection of mesial temporal lobe structures.

Hence, one of the purposes of this study was to identify and compare the cerebral areas involved in verbal memory processing in normal controls and in patients with refrac-

tory MTLE by means of fMRI. More specifically, we tried to localize and lateralize verbal memory function, during two distinct stages of memory processing: encoding and retrieval.

The first important result of this study is the fact that the two patient groups were similar as regards several variables which can influence verbal memory performance, such as age of seizure onset, duration of epilepsy, seizure frequency, and number of antiepileptic drugs used, as well as vigilance, language and visual memory functions. Nevertheless, patients with left HS had worse performance on verbal memory, general memory and delayed recall
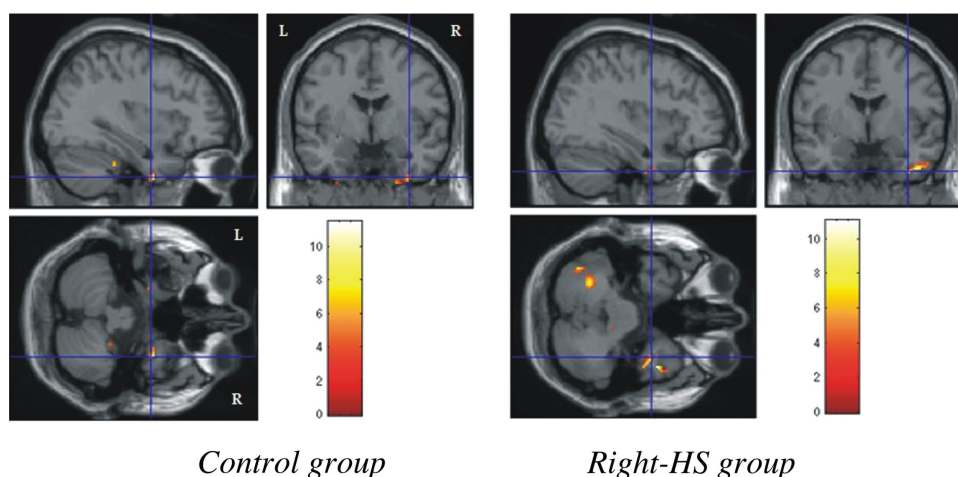

Control group   Right-HS group

Figure 5.
Immediate recall activations of bilateral > right infero-medial temporal cortices in control group and right infero-medial temporal cortex in Right HS group.
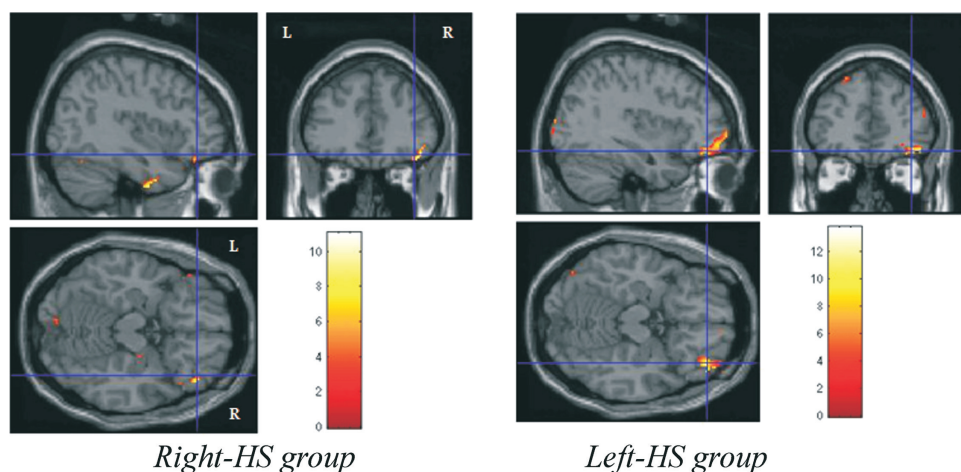
Figure 6.
Immediate recall activations of right ventro lateral frontal cortex in Right HS and left HS groups.

than patients with right HS. Moreover, they also had lower IQ, which may have contributed to their inferior memory performance.

In addition, although the three groups were similar in age, educational level, handedness, and hemispheric dominance for language, they exhibited different patterns of activations not only in the encoding stage, but also in the retrieval stage of verbal memory processing.

With regard to the encoding stage, patients with left HS showed more widespread areas of activations than patients with right HS, and even more than normal controls. Although this pattern had been observed in the occipital (Brodmann areas [BA]: 17/18), parietal (BA: 7) and temporal regions (BA: 21/22), it seemed to be mostly remarkable in the middle and ventro-lateral frontal regions

(BA: 6/8 and 44/45, respectively). These findings are in accordance with previous fMRI studies that have demonstrated a larger involvement of frontal cerebral areas in verbal memory processing in patients with left MTLE [Dupont et al., 2000; Golby et al., 2001].

Patients with left HS also tended to exhibit more bilateral or right lateralized encoding related activations (Figs. 3 and 4). This functional reorganization and, consequently, cortical reallocation of verbal memory encoding in more widespread bilateral fronto-parietal, and right temporal areas in patients with left MTLE may indicate a compensatory strategy for the dysfunction of left MTL system [Dupont et al., 2000]. A less evident functional reorganization of verbal memory encoding was also detected in the bilateral parietal, bilateral>left ventro-lateral frontal, left
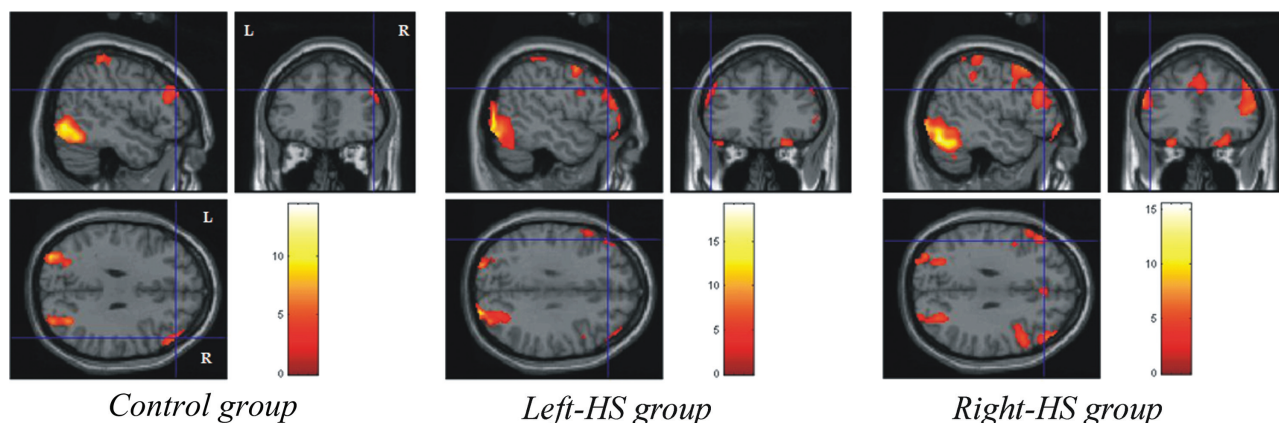

Figure 7.
Encoding activations of right frontal cortex in control group, and bilateral superior and inferior frontal and prefrontal cortices in Right HS and left HS groups.
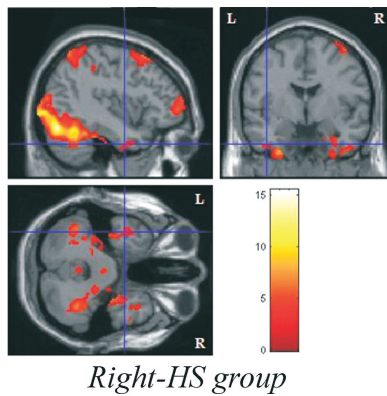
Right-HS group

Figure 8.
Encoding activations of bilateral inferior temporal cortices in Right HS group.

middle frontal, and bilateral superior temporal cortices in patients with right HS, as compared to normal controls. We could also hypothesize that this functional rearrangement can be secondary to the failure of right MTL system.

Another interpretation of our regional activation data during verbal encoding is that the block designed visual presentation of the abstracts words could also activate the semantic working memory processing of these words, whose meanings (concepts) are accessed almost automatically. Indeed, a "semantic working memory system" responsible for retrieving, maintaining, monitoring and manipulating semantic representations and composed particularly by the left anterior-inferior prefrontal cortex and the polar region of the left temporal lobe, has been proposed by Gabrieli et al. [1998], Wagner [1999], and Martin and Chao [2001]. Additional evidence for the relevance of the left lateral prefrontal cortex for semantic processing of

abstract words has been yielded afterward by other authors [Fiebach and Friederici, 2004; Goldberg et al., 2007]. In an event-related fMRI study of normal readers Fiebach and Friederici [2004] found that different semantic classes of nouns are processed in distinct cortical regions within the left hemisphere, with concrete nouns activating preferentially the left basal temporal cortex, and abstract nouns the left inferior frontal cortex. In patients with left MTLE and HS, on the contrary, similar studies have shown a shift of activations to homologous regions in the right hemisphere during the processing of abstract words as compared to concrete words and non-words [Edwards et al., 2005; Koylu et al., 2006]. Our group of left MTLE and HS patients showed similar shifted distribution of activations: right temporal, right or bilateral inferolateral frontal, bilateral middle frontal and bilateral parietal. Thus, this widespread contralateral and ipsilateral cortical activation may be interpreted as resulting not only from the episodic encoding but also from the semantic working memory processing of the words presented.

With respect to the retrieval stage, patients with MTLE associated with left HS continued to show more widespread areas of activations than patients with right HS and normal controls. Once more, this pattern was more evident in the frontal region. However, it is important to emphasize that the activation areas observed in the retrieval stage were smaller than those detected in the encoding stage in the three groups.

In the retrieval period, as opposed to the encoding stage, not only patients with left HS, but also patients with right HS and normal controls tended to exhibit more bilateral and right-sided activations (Figs. 5 and 6).

This prevalence of right hemisphere activations during the retrieval stage is in agreement with the hemispheric encoding/retrieval asymmetry (HERA) model, which predicts prefrontal activation during encoding of new
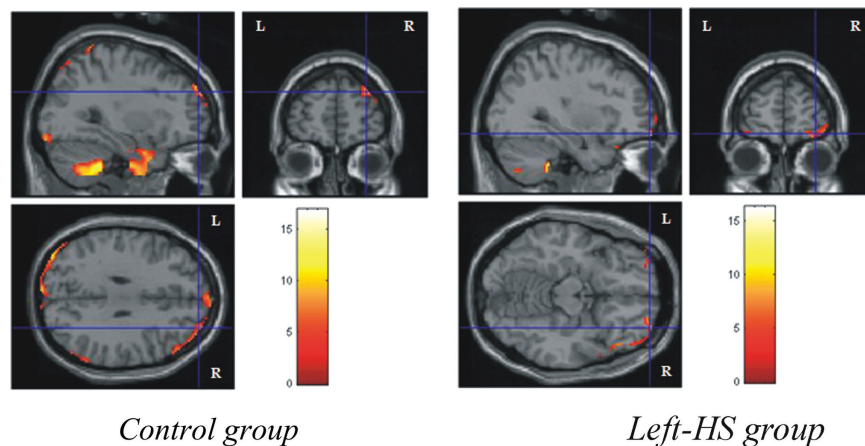

Control group   *Left-HS group*

Figure 9.
Immediate recall activations of right prefrontal cortex in control group and bilateral prefrontal cortices left HS group.
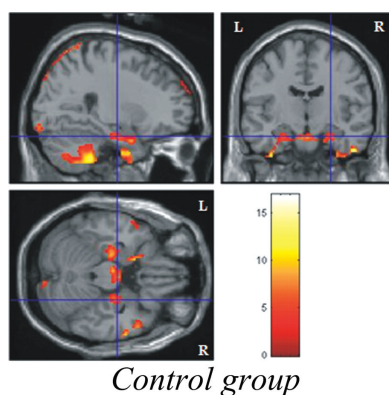
Control group

Figure 10.
Immediate recall activations of bilateral hippocampal cortices in control group.

information mainly in the left hemisphere, whereas retrieval of previously learned information is accompanied by increased activity in right prefrontal areas [Dupont et al., 2000; Kapur et al., 1994; Kennepohl et al., 2007; Powell et al., 2004; Tulving et al., 1994]. Although it concerns only to the material-independent lateralization of certain memory tasks in frontal lobes, some authors have recommended that it be extended to temporal lobe regions [Kennepohl et al., 2007]. During retrieval, our group of left MTLE patients showed bilateral prefrontal activation with right frontal ventrolateral predominance, which indicates a reduction of the functional hemispheric asymmetry in this task, similarly to that observed with normal aging (the so called HAROLD, Hemispheric Asymmetry Reduction in Older adults), [Cabeza, 2002]. In patients with left MTLE, the increased (bilateral) prefrontal activation not only may be compensatory, but also may represent a decrease in the level of functional differentiation of the task-relevant neural systems, as proposed by Chen et al. [2002] for the HAROLD model. It remains unexplained why our group of patients with right MTLE presented ipsilateral activation (right prefrontal, frontal ventrolateral, and temporal inferomedial), thus preserving the prevalence of right hemisphere activations during retrieval. It is possible that their long epilepsy duration with early development of right HS has led to intrahemispheric reorganization of cognitive functions.

Visual Memory

Our previous studies did not show a significant correlation between the degrees of right HA and visual memory deficits in patients with right MTLE [Alessio et al., 2004a,b, 2006; Bonilha et al., 2007]. Two hypotheses have been raised to explain this lack of correlation: (1) the visual memory may have a more diffuse and bilateral representation in the brain [Helmstaedter and Kurthen, 2001;

Jones-Gotman, 1996], and/or (2) the visual memory tests employed may not be robust enough to identify nondominant hippocampal dysfunction [Jones-Gotman, 1996]. We believe in a combination of these two hypotheses, because: (1) we found visual memory deficits in MTLE patients with bilateral HA and rarely in those with right unilateral HA, and (2) we observed that some patients made use of verbal strategies in order to memorize a visual content [Alessio et al., 2004a].

Hence, another purpose of this study was to identify and compare the cerebral areas involved in visual memory processing in normal controls and patients with refractory MTLE by means of fMRI.

With regard to the encoding stage, patients with right MTLE showed more widespread and bilateral areas of activations than patients with left MTLE, and even more than normal controls. Moreover, while normal controls tended to exhibit asymmetrical (bilateral>right) activated regions, patients with right HS tended to show more symmetrical and bilateral activated regions probably to compensate for the failure of their right MTL system (Figs. 7 and 8).

These findings are in agreement with the hypothesis of a more diffuse and bilateral representation of visual memory in the brain. Not only MTL structures, but also temporoparietal and prefrontal areas seem to be involved with the functional neuroanatomy of visual memory, as follows: (1) posterior parietal cortex provides a bridge from perception to recognition, it is related to attention and spatial awareness, and it takes part in spatial memory; and (2) dorsolateral prefrontal cortex is associated with attention, working memory and executive functions that are also critical for memory processes [Burgess et al., 2001; Desgranges et al., 1998].

However, in contrast to some authors [Detre et al., 1998; Stern et al., 1996; Szaflarski et al., 2004] who have found bilateral-symmetrical hippocampal activation in normal controls and bilateral-asymmetrical hippocampal activation in MTLE patients, we did not find hippocampal activations in the three groups during encoding stage of a visual content. This discrepancy could be explained by (1) differences in the fMRI task design; and/or (2) lack of MTL activation in our study owing to those technical limitations mentioned before, such as geometric distortions, signal loss artifacts, and partial volume effects [Figueiredo et al., 2008; Powell et al., 2004, 2005, 2007]. For different reasons some other functional studies have also failed to demonstrate hippocampal activation either during encoding or retrieval stages [Cabeza and Nyberg, 2000; Schacter and Wagner, 1999].

With respect to the retrieval stage, the activation patterns found in the three groups were exactly the opposite of those detected in the encoding stage. Compared to patients with right MTLE, left MTLE patients retrieval produced more diffuse activation, which was even more diffuse in normal controls (Figs. 9 and 10). It is important to note that in the retrieval stage we were able to detect

bilateral symmetrical hippocampal activation in the control group [Jokeit et al., 2001]. Again, not only MTL structures but also temporal, parietal and prefrontal areas seem to be involved in visual memory processing [Burgess et al., 2001; Engelsen et al., 2006; Fletcher, 1995; Ungerleider et al., 1998].

In addition, patients with right-HS tended to exhibit more left-sided activated areas during retrieval as opposed to patients with left-HS and normal controls, which tended to show more bilateral and right-sided activations. This prevalence of right hemisphere activations during the retrieval stage in normal controls is in agreement with the hemispheric encoding/retrieval asymmetry (HERA) model. Patients with right MTLE, on the contrary, tended to show more left-sided activated areas probably to compensate for the failure of their right MTL system.

Limitations

As already mentioned, fMRI evaluation of memory is more difficult than fMRI evaluation of other cognitive functions, due to some neuropsychological and technical issues [Powell et al., 2004, 2005]. As regards the neuropsychological aspects, we polarized as much as possible the verbal versus the nonverbal (visual) memory contents, by using a list of 17 abstract and emotionally neutral words as opposed to a series of 17 abstract drawings. In spite of this, some of the drawings may have led the patients to use verbal strategies in order to memorize the visual content. In addition, the drawings may have led to a different pattern of activation because they were more complex than the fixation point ("+") of the baseline condition. In addition, the technical aspects could not be so well controlled, because (1) the fMRI acquisitions were made using EPI sequence, which is particularly susceptible to geometric distortions and signal loss, and (2) the BOLD response is naturally lower in the hippocampal regions. All these problems may have contributed to the relative lack of MTL activations, and their solution requires paradigms with even less verbalizable visual-spatial test material and more complex stimulus than a fixation point, as well as fMRI equipments with higher spatial resolution and greater sensitivity.

However, we believe that the restrictive and rigorous statistical analysis that we performed in the present study make our findings quite reliable.

CONCLUSION

A complex network including parietal, temporal and frontal cortices seems to be involved in verbal memory encoding and retrieval in normal controls. The extension of such activations was larger in patients with right and left HS, more so in patients with left HS. Whereas normal controls and patients with right HS tended to exhibit more left-sided activated areas, patients with left HS tended to show more bilateral and right-sided activated regions in the encoding stage. These findings can indicate either a dysfunction or a functional reorganization of verbal memory processing in other cerebral regions, particularly in frontal lobes. In contrast, the three groups presented more right-sided activated areas in the retrieval stage, which is in agreement with the HERA model.

As regards visual memory encoding and retrieval, our findings support the hypothesis of a more diffuse and bilateral representation of this cognitive function in the brain. Compared to normal controls, encoding of visual material in patients with left HS recruited more widespread cortical areas, which were even more widespread in patients with right HS probably to compensate for their right mesial temporal dysfunction. On the other hand, when compared to the right MTLE group, the drawing retrieval task produced more diffuse activation in the left MTLE group and even more diffuse activation in the control group (including also both hippocampi). In spite of their effort in memorizing (encoding) the 17 drawings, patients with right MTLE exhibited fewer activated areas during immediate recall probably related to their greater difficulty in dealing with visual memory content.

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