

## Effects of Illness Duration on Memory Processing of Patients with Temporal Lobe Epilepsy

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**Summary:** *Purpose:* To examine the effects of illness duration on the neural processing of memory in patients with temporal lobe epilepsy (TLE) by using functional MRI.

*Methods:* Twenty-three TLE patients (16 left, seven right) performed a complex visual scene-encoding task during functional MRI. Region-of-interest (ROI) analyses were used to quantify functional activation in the mesial temporal and frontal lobes. The patients' verbal and visual memory performances were evaluated by standardized neuropsychological tests. Analyses included group comparison and correlations of duration of epilepsy with functional activation and memory performance.

*Results:* Compared with normal controls, TLE patients demonstrated reduced activation bilaterally in the mesial temporal lobe ( $p = 0.003$ ), and the reduction was more pronounced

on the ipsilateral side of the seizure focus. Moreover, a longer duration of illness was associated with fewer voxels activated in both the left ( $p = 0.038$ ) and right ( $p = 0.017$ ) mesial temporal lobe. Furthermore, the duration of illness was found to be significantly and negatively correlated with both verbal ( $p = 0.020$ ) and visual ( $p = 0.000$ ) memory functioning.

*Conclusions:* TLE seems to affect the memory processes in the mesial temporal lobes progressively (i.e., the longer the duration of illness, the lower the brain activation). In turn, the reduction of brain activation negatively affects memory functioning. Finally, the reduction is not limited to the side of seizure but also is observed in the contralateral hemisphere. **Key**

**Words:** Functional MRI—Temporal lobe epilepsy—Memory processing—Duration.

It is well known that the mesial part of the temporal lobes is essential for memory, particularly for the conscious recollection of recently occurring facts and events (1–3). Based on animal studies, damage to the mesial temporal lobe may result in different severities of amnesia, depending on the extent and the location of the lesion (3, 4). By using functional MRI (fMRI), the effects of pathologic involvement in the mesial temporal lobe on memory processing have been explored in patients with temporal lobe epilepsy (TLE) (5–8). Compared with normal subjects who demonstrated bilateral symmetric activation in the mesial temporal lobe (8–11), asymmetric activation in the mesial temporal lobe is usually observed in TLE patients, who demonstrate either a decrease of activation in the mesial temporal lobe ipsilateral to the seizure focus (10–13), or greater activation in the mesial temporal lobe contralateral to the seizure focus (14). Specifically, Bellgowan et al. (12) found that left-TLE patients demonstrated a decrease in activation in the left mesial tempo-

ral lobe compared with patients with right TLE during verbal encoding tasks. In another study based on a task using covertly recalling routes within the subject's hometown (10), TLE patients had significantly reduced activation in the mesial temporal lobe ipsilateral to the side of seizure onset (that is, left-TLE patients had less activation in the left mesial temporal lobe, whereas right-TLE patients demonstrated less activation in the right mesial temporal lobe).

Although the pathologic involvement in the left and right mesial temporal lobes is found to result in a reduction of activation in the mesial temporal lobe, the factors relating to the reduced activation in the remain unclear. Given that empirical evidence on this issue has not been available, we speculated that the duration of illness may be a significant factor in the activation patterns in patients with TLE. This hypothesis was made based on previous studies of epilepsy patients, in which duration of illness has been found to be a significant factor affecting the structure, metabolism, and function of the mesial temporal lobe. Specifically, the duration of illness was found to be associated with smaller hippocampal volume (15–17) and lower glucose metabolism (15,18) in the mesial temporal lobe ipsilateral to the seizure focus. It also was found to be associated with lower IQ (19,20), worse

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performance on memory tasks, and poorer language function (15,20). One recent study further revealed that duration of illness was the most important predictor for long-term surgical outcome for patients having TLE with hippocampal sclerosis (21). Therefore duration of illness is believed to have deleterious and progressive effects on memory processing, affecting brain activation in the mesial temporal lobe. One purpose of the present study was to evaluate the impact of the duration of illness on the neural processing of memory in TLE patients by using *fMRI*, and we hypothesized that duration of illness will likely be associated with the hemodynamic activation in the mesial temporal lobe (that is, lower levels of brain activation is found for patients with longer duration of illness). Moreover, we also studied whether frequency of seizures and hippocampal volume will affect the functional activation in the mesial temporal lobe.

Apart from examining the pattern of brain activation in memory processing in TLE patients, many studies have used *fMRI* to examine memory lateralization and compared the findings with results from the intracarotid amobarbital procedure (IAP) (8, 10, 11, 13). Although good agreement is found between the memory lateralization revealed by the *fMRI* and the IAP, relatively few studies have looked at the association between the functional activation and their level of memory impairment (10). If the functional activation patterns in the TLE patients are associated with their memory performance in the neuropsychological tests, the results from the *fMRI* will have its additional clinical value in preoperative evaluation of memory performance. Therefore in the present study, we also explored the association between memory performance as measured by standardized neuropsychological tests with (a) the functional activation and (b) the duration of illness. We speculated that the memory performance of TLE patients is associated with functional activation in the mesial temporal lobe and is affected by their duration of illness.

## METHODS

### Participants

Twenty-three right-handed preoperative patients with TLE (16 left, seven right), who were candidates for surgical treatment of refractory TLE, were recruited from the Prince of Wales Hospital, Hong Kong. The presurgical evaluation of the epilepsy patients included *fMRI*, video-EEG monitoring, comprehensive neuropsychological assessment, routine brain MRI, and the intracarotid amobarbital test (IAT, also known as Wada test). Information on the neurologic history for each patient with TLE is presented in Table 1. At the time of investigation, all patients were receiving one or a combination of antiepileptic drugs (AEDs), including valproic acid (VPA), carbamazepine (CBZ), topiramate (TPM), phenytoin (PHT), lamotrigine (LTG), gabapentin (GBP), and levetiracetam (LEV). They

reported of absence of a seizure at least 1 day before and during *fMRI* and neuropsychological assessment.

The normal control group consisted of 23 healthy, right-handed individuals with no previous history of neurologic or psychiatric disorder. Normal participants and the TLE patients did not differ in age [ $t(44) = 1.261$ ;  $p > 0.01$ ], level of education [ $t(44) = 2.216$ ;  $p > 0.01$ ], or sex [ $\chi^2(1) = 0.789$ ;  $p > 0.01$ ]. Demographic information is summarized in Table 2.

All participated voluntarily and gave informed consent according to institutional guidelines. The study was ethically approved by the Clinical Research Ethics Committee of The Chinese University of Hong Kong.

### *fMRI* activation paradigm

A block design with three epoch cycles was used. Each cycle consisted of a 20-s novel picture-encoding task (22) and a 20-s visual fixation task. The stimuli were presented through a notebook computer by using E-prime (Psychological Software Tools, Pittsburgh, PA, U.S.A.) and projected on a screen placed in front of the scanner bed. The participants viewed the stimuli through a reflective mirror fixed on the head coil. They were instructed to memorize the pictures for a recognition test after the scan. The control stimulus was a cross placed in the center of the screen. It was displayed continuously for 20 s in each epoch, and participants were instructed to remain silent and visually to fixate on it.

After the scanning session, normal controls and patients were tested to evaluate their performance in encoding the visual information. Subjects were presented with a sequence of 20 pictures, consisting of 10 targets and 10 distractors, and were asked to decide whether they had seen each picture during scanning. A discrimination score (range, 0 to 100%) in the recognition task was calculated for each participant by using the equation

$$[(\text{Correct hits} - \text{False alarms})/10] \times 100\%$$

Scores  $>0$  represented above-chance performance.

### *fMRI* data acquisition

MR imaging was performed with a 1.5-T MRI scanner (Gyrosan ACS-NT, Philips Medical Systems, Eindhoven, the Netherlands) with a circularly polarized head coil. Before the *fMRI* activation tasks, 3D Fast Field Echo  $T_1$ -weighted (axial) high-resolution structural images covering the whole brain were acquired by using a  $T_1$ -weighted gradient echo [repetition time (TR), 30 ms; echo time (TE), 5 ms; flip angle (FA), 40 degrees; slice thickness, 2 mm; acquisition matrix,  $256 \times 256$ ]. This anatomic scan was later coregistered with the functional images. Sixteen contiguous coronal  $T_1$ -weighted structural images (slice thickness, 7 mm) mapping with the functional data were then reconstructed from these high-resolution images for measuring the cross-sectional areas of the hippocampal volume in the left and right mesial temporal lobes. The areas were outlined manually by using the IMAGEJ

TABLE 1. Clinical information on TLE patients

Patient	Gender	Age (yr)	Age at onset (yr)	Duration of epilepsy (yr)	EEG	MRI
<b>LTLE</b>						
1	F	26	16	10	BF	Low-grade glioma in LT
2	F	40	10	30	LT	L mts
3	F	26	10	16	LT	L mts
4	F	17	11	6	LT	L mts
5	M	31	17	14	LT	L mts
6	F	23	13	10	LT	Cyst in LT
7	F	52	50	2	N	Low-grade glioma in LT
8	F	26	4	22	LT	L mts
9	F	27	23	4	LT	L mts
10	F	14	12	2	LT	L mts
11	F	31	12	19	LT	L mts
12	F	16	12	4	LT	L mts
13	M	23	19	4	RT	Cavernous hemangioma in LT
14	M	33	18	15	LT	L mts
15	M	33	13	20	LT	Low-grade glioma in LT
16	M	23	14	9	BT	L mts
<b>RTLE</b>						
1	F	29	10	19	RT	R mts
2	F	29	16	13	RT	Small cyst in the R hippo
3	M	30	20	10	RT	Cyst in RT
4	F	23	14	9	RT	Lesion in the R middle T. N hippo
5	M	14	12	2	RT	Astrocytoma in R anterior hippo
6	M	28	6	22	RT	R mts
7	M	31	15	16	RT	N hippo

TLE, temporal lobe epilepsy; DNET, dysembryoplastic neuroepithelial tumor; MRI, magnetic resonance imaging; EEG, electroencephalogram; IAT, intracarotid amobarbital test; L, left; R, right; T, temporal lobe; mts, mesial temporal sclerosis; hippo, hippocampus; N, normal; B, bilateral; F, frontal.

computer software (Version 1.34) (NIH, Bethesda, MD, U.S.A.) by a well-trained technician who was blind to the patient data. The number of pixels identified was spatially calibrated into area measured in terms of square millimeters. The sum of the hippocampal cross-sectional areas was multiplied by slice thickness, resulting in hippocampal volume.

The functional images were obtained by using a gradient-echo, echo-planar imaging sequence [TE, 40 ms; TR, 2000 ms; FA, 90 degrees; acquisition matrix, 128 × 128; field of view, 220 × 220 mm]. During each functional scan, a brain volume composed of 16 contiguous 7-mm-thick coronal images covering the whole brain and perpendicular to the anterior–posterior commissure lines

TABLE 2. Demographic information on normal controls and epilepsy groups

Variables	Normal controls (n = 23)	Temporal lobe epilepsy (n = 23)
	Mean (SD)	Mean (SD)
Age (yr)	30.48 (9.33)	27.17 (8.41)
Education (yr)	12.91 (2.68)	11.09 (2.91)
Gender (Male/Female)	12/11	9/14
Duration of epilepsy (yr)	N.A.	12.09 (7.66)
Age at onset (yr)	N.A.	15.04 (8.76)
Frequency of seizures (mo)	N.A.	8.31 (11.15)

N.A., not applicable.

was obtained. Each functional scan consisted of 60 sequential echo-planar volumes, producing a total of 960 images for each participant.

### fMRI data analysis

Data analyses were performed with the fMRI software package BrainVoyager 2000 version 4.9.6 (<http://www.brainvoyager.com>, Brain Innovation, Maastricht, Holland). Before statistical analysis, motion corrections were performed by aligning the time series of functional images for each slice to minimize the signal variations due to small movements of the participants during image acquisition. Gaussian filtering was applied in the spatial (FWHM, 4 mm) domains, while linear trend removal and 0.016-Hz temporal high-pass filtering also were performed on the data. The complete functional dataset for each participant was then transformed into Talairach space. The individual brain image was aligned by rotation in the anterior commissure (AC) – posterior commissure (PC) plane, and coordinates of each brain were transformed to the coordinates of the Talairach brain (23). Realigned images were then coregistered to the high-resolution structural images.

Data were analyzed on both the group and the individual levels. On the group level, the activation pattern for normal controls was first obtained. A multiple-subject general linear model (GLM) was applied to compute the pooled activation maps, based on the boxcar model with

the hemodynamic response (24). The signal values during the experimental and control stimuli were the effects of interest to be explored. A three-dimensional statistical map was generated for each condition by corresponding each voxel with the  $F$  value for the specified set of predictors and calculated by the least-mean-square solution of the GLM. The effect was considered significant only when the  $t$  value for group analysis was  $>5$  at  $p < 0.01$  (corrected for whole-brain multiple comparisons by using the Bonferroni method), and that the threshold of the activated regions consisted of  $\geq 600$  voxels. Clusters not reaching this statistical threshold were not displayed. Talairach-transformed group data were finally displayed on a volume-rendered brain of an individual from the cohort. Regions of interest (ROIs) were first identified in the normal control as areas having a significant activation in the group analysis. ROIs in the mesial temporal lobe mainly included the hippocampus, parahippocampal (BA 35 and 36), and fusiform gyri (BA 20 and BA 36); ROIs in the frontal lobe included the middle frontal gyrus (BA 6, 8, and 9), superior frontal gyrus (BA 6), and precentral gyrus (BA 6 and 9). Similar group analysis was done for the patient group.

On the individual level, the functional images were coregistered with each individual's own brain image in the identification of ROIs. The data were also analyzed by using independent  $t$  tests between the stimulation and fixation sessions with an uncorrected threshold of  $p < 0.00001$ , corresponding to a  $t$  value  $>4$ . The total number of activated voxels in the ROIs in the mesial temporal and frontal lobes for each individual were counted for subsequent group comparison by statistical analysis.

Apart from post hoc region-based analysis, voxel-based comparison between normal controls and two patient groups also was performed to obtain contrast results between normal controls and patient groups. A fixed-effect multistudy GLM between groups (normal vs. left TLE; normal vs. right TLE) with BrainVoyager was used, and the cluster was considered to be significantly activated when the  $t$  value was  $>5$  with corrected  $p < 0.01$ .

### Behavioral performance

Outside the scanner, we evaluated the verbal and visual memory performance of each patient individually. Verbal memory was assessed by using the Hong Kong List Learning Test (HKLLT) (25–27), which is a clinically validated verbal memory test for the Chinese population. Participants were presented with a list of 16 two-character Chinese words during three learning trials. They were asked to recall the items after each learning trial and after delays of 10 and 30 min. Visual memory was evaluated by the Rey-Osterrieth Complex Figure Test (Rey-O) (28,29). Participants were asked to copy a complicated figure as accurately as they could and to draw the figure after 30 min. The total number of words recalled in the 30-min

delay trial of the HKLLT (maximum score, 16) (25) or figure recalled in the Rey-O (maximum score, 36) (30) was used as the verbal and visual memory scores.

We also followed the standard procedure for the Wada test (31, 32), and with a forced-choice instruction paradigm, the patients had to decide whether any given item had been presented after injection of amobarbital. Totally, eight targets and 16 distractors for discrimination were used. A discrimination Wada memory score for recognition performance of the hemisphere contralateral to the injection side with the formula

$$\frac{(\text{True Positive} - \text{False Positive})}{8} \times 100$$

was computed for each patient.

## RESULTS

### Activation pattern for normal controls and TLE patients

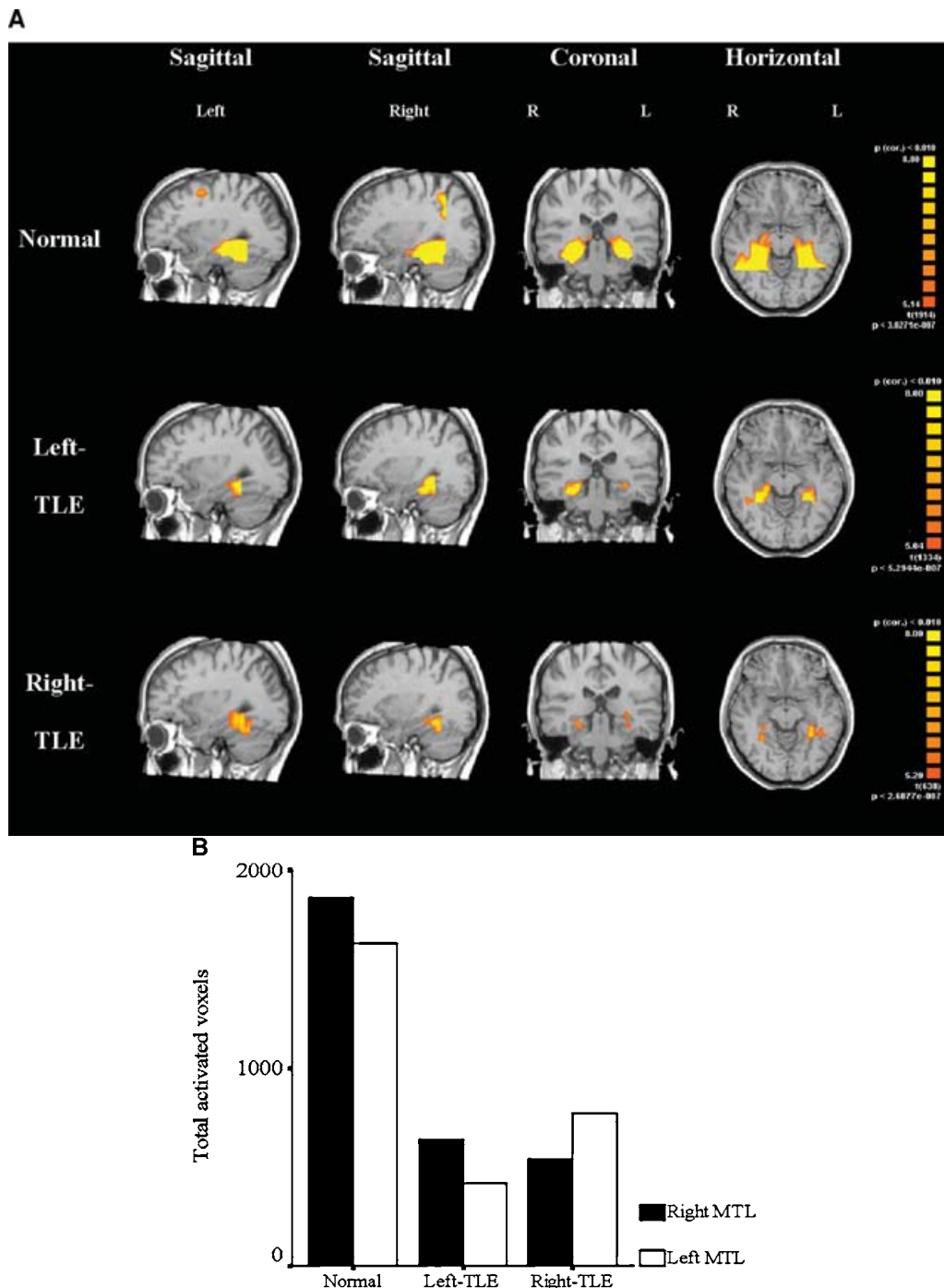
Figure 1A shows the group activation in the mesial temporal lobe during complex visual scene encoding for normal controls and left- and right-TLE patients. The three groups demonstrated different patterns of mesial temporal lobe activation. For the normal controls, extensive bilateral symmetric activation was found in the mesial temporal lobe, mainly over the posterior hippocampal formation and parahippocampal and fusiform gyri. Compared with normal controls, TLE patients demonstrated significantly less activation, in terms of smaller numbers of activated voxels, in the mesial temporal lobe [ $F(2, 43) = 6.486$ ;  $p = 0.003$ ; Fig. 1B]. Post hoc analysis revealed that reduced activation was observed in both the left and right mesial temporal lobes for left-TLE patients (left,  $p = 0.012$ ; right,  $p = 0.003$ ) but was more obvious in the right mesial temporal lobe for right-TLE patients ( $p = 0.023$ ). In sum, TLE patients demonstrated significantly less activation in the mesial temporal lobe, and the reduction was more obvious ipsilateral to the side of seizure.

Consistent findings were obtained in the voxel-based between-group analyses. Both left-TLE and right-TLE patients demonstrated less activation than the normal controls in the hippocampus and parahippocampal (BA 35 and 36) and fusiform (BA 20 and 36) gyri in both left and right mesial temporal lobes. Conversely, the left-TLE and right-TLE groups did not show greater activation than the normal controls in any regions of the brain, as shown in the voxel-based analysis.

Activation also was observed in the frontal lobe for the normal controls and both groups of TLE patients, and the three groups did not differ in the number of activated voxels in either hemisphere [left,  $F(2, 43) = 3.543$ ;  $p > 0.01$ ; right,  $F(2, 43) = 2.830$ ;  $p > 0.01$ ].

### Picture-recognition performance after scanning

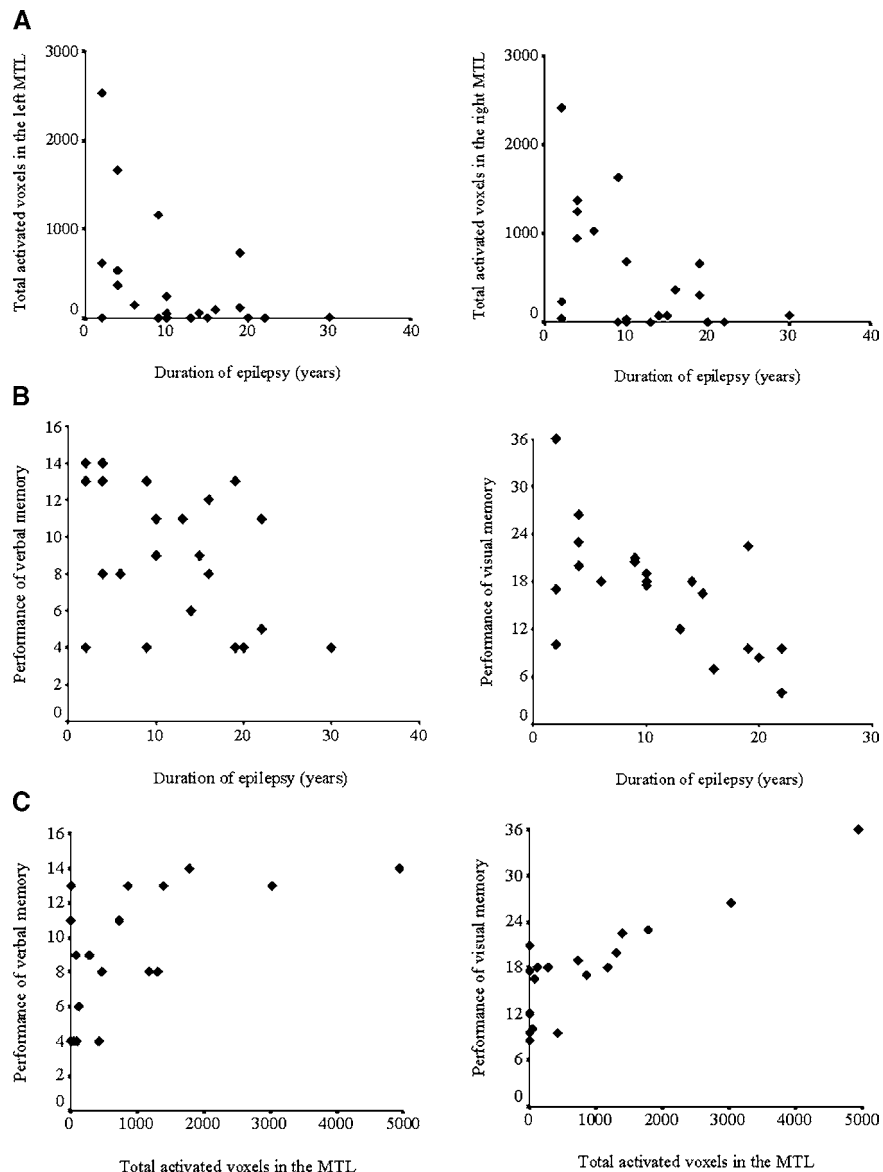
Performance on the recognition test administered after scanning showed that the normal controls (mean, 40.87%; SD, 23.14%) and patients (mean, 21.90%; SD, 26.57%)



**FIG. 1. A:** Group activation patterns during complex scene-encoding memory task with corrected  $p < 0.01$ . **B:** Total activated voxels in the left and right mesial temporal lobe (MTL) for normal controls and patients with either left or right temporal lobe epilepsy (TLE).

performed above chance in the picture-discriminating task, and their discrimination scores were significantly different from zero [normal,  $t(22) = 8.469$ ;  $p = 0.000$ ; patients,  $t(20) = 3.777$ ;  $p = 0.001$ ]. Although the difference did not reach statistical significance between patient and normal groups [ $t(42) = 2.53$ ;  $p > 0.01$ ], the patients seemed to do less well than the normal controls in discriminating the pictures, so they might be less effective

in encoding pictures during scanning, affecting the functional activation. Therefore further analysis was made on the correlation between their discrimination scores and the activated voxels in the mesial temporal lobe to see whether the decreased brain activation in the mesial temporal lobe for the TLE patients was due to their efficiency in encoding. The correlation did not reach significance level for normal controls [ $r(23) = -0.025$ ;  $p = 0.910$ ],



**FIG. 2.** Correlation between duration of epilepsy, total activated voxels in the mesial temporal lobe (MTL), and memory performance. **A:** Longer duration of epilepsy had fewer activated voxels in both left and right MTL. **B:** Longer duration of epilepsy had poor verbal and visual memory performance, as measured by the 30-min delayed recall of the Hong Kong List Learning Test and Rey-Osterrieth Complex Figure Test, respectively. **C:** Patients with better verbal and visual memory performance tended to have more activated voxels in the MTL.

whole patient groups [ $r(21) = 0.018$ ;  $p = 0.940$ ], and separate patient groups (left-TLE,  $r(15) = 0.174$ ;  $p = 0.534$ ; right-TLE,  $r(6) = -0.189$ ;  $p = 0.720$ ). Statistical analyses were also made between the discrimination score and brain activation in specific ROIs in the left and right mesial temporal lobes (that is, the hippocampus and parahippocampal and fusiform gyri). Similar nonsignificant correlation was found ( $p > 0.05$ ), suggesting that although the patients did not discriminate the pictures as well as the normal controls, the decreased activated voxels in the TLE patients did not seem to be associated with their efficiency.

To examine the factors relating to the reduction of activated voxels in the mesial temporal lobe for the patients,

correlation analyses were performed on the duration of illness, frequency of seizures, patients' memory performance, and the amount of activation in the mesial temporal lobe.

#### Effects of duration of illness on the activation in the mesial temporal lobe and memory performance in the TLE patients

A negative linear correlation was found between the duration of illness and the total number of voxels activated in the mesial temporal lobe among the TLE patients [ $r(21) = -0.501$ ;  $p = 0.021$ ] (i.e., patients with longer duration of illness were found to have less overall activation in the mesial temporal lobe). The correlation was significant

for the functional activation in both the left [ $r(21) = -0.456$ ;  $p = 0.038$ ] and right mesial temporal lobes [ $r(21) = -0.513$ ;  $p = 0.017$ ] (Fig. 2A). In addition, the duration of illness was negatively correlated with the memory performance on the HKLLT [ $r(23) = -0.418$ ;  $p = 0.047$ ] and Rey-O [ $r(21) = -0.633$ ;  $p = 0.002$ ] (Fig. 2B). Therefore temporal lobe epilepsy seemed to have an ongoing and deleterious effect on the mesial temporal lobes, which in turn adversely affected the memory performance of the patients.

Because the decreased activation may be related to hippocampal volume, stepwise linear regression analysis using duration of illness and hippocampal volume as independent variables was done. The overall activation in the mesial temporal lobe was significantly predicted by the duration of illness [ $F(1, 19) = 6.370$ ;  $p = 0.021$ ;  $R^2 = 0.251$ ], whereas the hippocampal volume was not selected by the regression as a significant factor in the model. To rule out whether hippocampal volume is strongly correlated with illness duration, resulting in the absence of its additional independent predictive value, correlation analysis was made between the duration of illness and hippocampal volume in the left and right mesial temporal lobes. The results did not reach statistically significant level [left,  $r(21) = 0.090$ ;  $p = 0.699$ ; right,  $r(21) = 0.037$ ;  $p = 0.874$ ]. No significant correlation was found between the frequency of seizures [ $r(21) = -0.199$ ;  $p = 0.388$ ] and functional activation in the mesial temporal lobe.

#### Relation between brain activation in the mesial temporal lobe and memory performance

Figure 2C shows that the total number of activated voxels in the mesial temporal lobe is positively correlated with patients' performance on the HKLLT [ $r(20) = 0.517$ ;  $p = 0.020$ ] and Rey-O [ $r(18) = 0.857$ ;  $p = 0.000$ ]. Patients with better memory performance tended to have relatively greater activation in the mesial temporal lobes. Further analyses revealed that verbal and visual memory performance was not specifically correlated with activation in the left and right mesial temporal lobes, respectively. Instead, verbal memory performance on the HKLLT was positively correlated with activation in both mesial temporal lobes [left,  $r(20) = 0.53$ ;  $p = 0.016$ ; right,  $r(20) = 0.468$ ;  $p = 0.038$ ]. A similar pattern was observed on the visual memory performance on the Rey-O [left,  $r(18) = 0.829$ ;  $p = 0.000$ ; right,  $r(18) = 0.826$ ;  $p = 0.000$ ].

For the performance from the Wada test, the number of activated voxels in the right mesial temporal lobe was positively correlated with right hemisphere Wada memory performance [mean, 66.48%; SD, 37.87%;  $r(22) = 0.565$ ;  $p = 0.006$ ], but the number of activated voxels in the left mesial temporal lobe and left hemisphere Wada memory performance was not correlated [mean, 85.12%; SD, 17.06%;  $r(21) = 0.331$ ;  $p = 0.142$ ].

No significant correlation was found between the total number of voxels activated in the frontal lobe and verbal [left frontal,  $r(22) = 0.054$ ;  $p > 0.05$ ; right frontal,  $r(22) = 0.166$ ;  $p > 0.05$ ], as well as visual [left frontal,  $r(19) = 0.222$ ;  $p > 0.05$ ; right frontal,  $r(19) = 0.231$ ;  $p > 0.05$ ], memory performance.

## DISCUSSION

The present study demonstrated that while bilateral symmetrical activation over the mesial temporal lobes, including the posterior hippocampal formation and the parahippocampal and fusiform gyri, was found in normal controls during a complex visual scene-encoding task, TLE patients demonstrated significantly reduced and asymmetric activation over the mesial temporal lobes. The reduction was bilateral and was specific to the mesial temporal lobe, with decreased activation more obvious ipsilateral to the side of seizure focus. This reduction was observed in both left- and right-TLE patients. These results were consistent with previous studies (9,33), which reported that bilateral reduction in activation in the mesial temporal lobe was observed for both left- and right-TLE patients, and support the idea that unilateral pathologic involvement in the mesial temporal lobe may result in bilateral functional reduction of memory processing and is not limited to the temporal lobe ipsilateral to the seizure focus.

In the present study, we also found that functional activation in the mesial temporal lobes was negatively associated with the duration of TLE (i.e., patients with longer duration of illness had less activation in the mesial temporal lobes than did patients with shorter duration of illness). This association was significant in both the left and right mesial temporal lobes. Therefore the impact of the duration of illness on brain activation during memory-encoding tasks, similar to the effects of pathologic involvement, is not limited to the mesial temporal lobe ipsilateral to the seizure focus but also is contralateral to the seizure focus. In addition, we found that verbal and visual memory performance was positively correlated with functional activation in the mesial temporal lobe and negatively correlated with the duration of illness of TLE. Therefore although the pathologic involvement in TLE patients was unilateral, both verbal and visual memory performances were influenced by the epilepsy. These findings suggested that longer duration of epilepsy may affect memory processing and memory performance on both sides of the mesial temporal lobes.

In accordance with findings from positron emission tomography (PET), structural, and behavioral studies (15–20), our results from fMRI provided further support that epilepsy is a progressive brain disorder, resulting in both structural and functional abnormality of the mesial temporal lobes. Together with a global functional decline, the

activation patterns observed in TLE patients are likely to reflect a dysfunction rather than a reorganization of memory processing, and impair the memory functioning of the patients persistently and progressively. Although the impact of the duration of illness of TLE may be a result of the cumulative adverse effects of electrophysiologic and metabolic disturbances associated with epilepsy, which may not be reversed or lessened by medication, duration of illness also was recently found to be the most important predictor for long-term surgical outcome for patients having TLE with hippocampal sclerosis (21). Therefore the effects of the duration of TLE on memory processing and surgical outcome cannot be overlooked. Specifically, because the longer duration of illness was associated with greater functional and structural impairment as well as a higher risk of non-seizure-free surgical outcome, early surgical operation may be considered for patients who do not benefit from medication in controlling seizure.

Some previous studies (12–14) suggested that despite the pathologic involvement in the mesial temporal lobes, some TLE patients have relatively intact memory performance and suggested that a functional reorganization of memory processing may cause the relatively intact memory performance of the TLE patients. Greater activation in the mesial temporal lobe contralateral to the seizure focus has been reported in left-TLE patients during verbal encoding and in right-TLE patients during nonverbal encoding (13), whereas Richardson et al. (14) reported relatively preserved verbal memory functioning in left-TLE patients who demonstrated greater activation in the right hippocampus and parahippocampal gyrus than did normal controls. However, we did not find greater activation contralateral to the seizure focus in our TLE patients compared with normal controls. Instead, the overall activation over the contralateral hemisphere was lower in TLE patients than in normal controls. In comparing different sites of activation, we also did not find increased signal changes in any particular brain region. One possible reason for this inconsistency may be the use of different stimuli during *fMRI*. Whereas we used a complex visual scene-encoding task, Dupont et al. (13) and Richardson et al. (14) used verbal memory tasks through encoding or retrieval. It is known that different memory tasks will have different activation patterns in normal controls [i.e., although complex visual scenes are encoded through both visuospatial and verbal strategies, thus resulting in bilateral activation over the mesial temporal lobes (22), preferential activation of the left mesial temporal lobe is found in verbal episodic memory encoding (34)]. Because of the difference in the neural processing involved in the different memory tasks, it is possible that a difference in the functional activation may be caused by the pathologic involvement in the mesial temporal lobes across the different tasks. Compensatory strategies, such as using the temporal lobe contralateral to the seizure focus, may be possible for memory tasks

involving one temporal lobe. However, for memory tasks that tend to involve both temporal lobes, such as complex visual scene-encoding tasks, compensatory strategies may be more difficult to observe.

Because the present study was a cross-sectional study on the effects of the duration of illness on memory processing and memory performance in TLE patients, an association but not a causal relation can be drawn at this stage. Therefore to establish a causation effect, longitudinal studies on TLE patients are necessary. In addition, although a reorganization of memory processing was not observed through *fMRI* in the present study, we have seen that this possibility cannot be ruled out. It is, therefore, worthwhile to find out whether any difference exists in the functional activation between TLE patients with intact memory performance and those with impaired memory performance, so as to shed light on the issue of reorganization of memory processing in TLE patients. Finally, the present study showed that the negative impact of duration of illness on the functional activation in the mesial temporal lobe was independent of the frequency of seizures and hippocampal volume. Although a previous study suggested that the hippocampal volume is a strong predictor of functional activity in the mesial temporal lobe (35), our study did not find consistent results. One possible explanation for this inconsistency may be the relatively heterogeneous lesions types (e.g., mesial temporal sclerosis, cysts in the temporal lobe) in our TLE patients, which was another limitation of the present study. As shown in Table 1, some of them had normal hippocampus (right-TLE patients 4 and 7) in spite of having TLE for years. Therefore illness duration may induce the functional but not structural abnormality in some patients. To explore the potential impact of hippocampal volume on the functional activation in the mesial temporal lobe, further study recruiting a more homogeneous patient group can be considered. Some other potential factors, such as long-term effects of a specific type or different combination of AEDs or a history of generalized tonic-clonic seizures, have not been addressed and may deserve investigation in further studies.

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