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# Performance in recognition memory is correlated with entorhinal/perirhinal interictal metabolism in temporal lobe epilepsy

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ABSTRACT

In addition to the hippocampus, the entorhinal/perirhinal cortices are often involved in temporal lobe epilepsy (TLE). It has been proposed that these anterior parahippocampal structures play a key role in recognition memory. We studied the voxel-based PET correlation between number of correctly recognized targets in a new recognition memory paradigm and interictal cerebral metabolic rate for glucose, in 15 patients with TLE with hippocampal sclerosis. In comparison to healthy subjects, patients had decreased recognition of targets ($P<0.001$) and ipsilateral hypometabolism (relative to side of hippocampal sclerosis) of the hippocampus, entorhinal/perirhinal cortices, medial temporal pole, and middle temporal gyrus ($P<0.05$, corrected by false discovery rate method). Performance correlated with interictal metabolism of ipsilateral entorhinal/perirhinal cortices ($P<0.005$, Spearman's rank test), but this relationship was not significant in the hippocampus itself ($P>0.18$, Spearman's rank test). These findings highlight the preferential involvement of entorhinal/perirhinal cortices in recognition memory in patients with TLE, and suggest that recognition memory paradigms may be useful in assessing anterior parahippocampal functional status in TLE.


## 1. Introduction

In recent years, there has been increased interest in the role of the anterior parahippocampal structures, such as the entorhinal/perirhinal cortices, in the pathophysiology of temporal lobe epilepsy (TLE). Involvement of these structures in TLE has been demonstrated in patients with and those without hippocampal sclerosis (HS), in neuropathological, MRI volumetric, and electrophysiological studies [1–6]. Our aim in the present study was to gain a clearer understanding of the interictal functional role of the entorhinal/perirhinal cortices in memory impairment in patients with TLE and HS. Beyond the well-known involvement of the hippocampus in memory recall in patients with TLE [7–10], the specific impact of the entorhinal/perirhinal cortices on memory remains debated in TLE. In a PET study of patients with left-sided HS, Weintrob et al. showed that the interictal cerebral metabolic rate for glucose (CMRGlc) of the ipsilateral perirhinal cortex predicted verbal paired associate learning [11]. However, Griffith et al. found such a correlation with the hippocampus, but not with the parahippocampal region [12]. These discrepant results may be explained by the functional specialization of the anterior parahippocampal structures [13–19], which was not taken into account in these two studies [11,12].

These structures indeed appear to be particularly critical for recognition memory. In the nonhuman primate, damage in both the perirhinal and entorhinal cortices severely impaired recognition memory [13]. In humans, isolated damage in the anterior parahippocampal structures that preserved the hippocampus yielded similar impairment [14]. Conversely, isolated damage in the hippocampus that preserved the parahippocampal region did not impair recognition memory [15–17]. In accordance with these studies, influential anatomo-functional models of memory propose that anterior parahippocampal structures are a critical relay for recognition memory, because they play a specific role in this ability, independently of the hippocampus, based on either familiarity or perceptivo-mnesic processes [18,19]. Therefore, if these models hold true, it is possible to formulate the hypothesis that performance in recognition memory tasks in patients with TLE should correlate with the functional status

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of the anterior parahippocampal structures, and not with that of the hippocampus.

Only a few differences have previously been reported in recognition memory performance between patients with left-sided and those with right-sided epilepsy, using either verbal or visual items [20–22]. We therefore designed a new non-material-specific recognition memory task using pictures of objects that could easily be named. We then determined the voxel-based PET correlation between performance in this task and interictal hippocampal and parahippocampal CMRGlc, ipsilateral to the side of epilepsy, in patients with left-sided and those with right-sided TLE. We hypothesized that the involvement of anterior parahippocampal structures in TLE could be indicative of performance in non-material-specific recognition memory tasks, independently of the epileptogenic side.

## 2. Materials and methods

### 2.1. Subjects

#### 2.1.1. Patients

We assessed the performance of a recognition memory task in 25 consecutive patients with unilateral TLE (15 patients with HS, 4 patients with normal brain MRI, 3 patients with cortical dysplasia, and 3 patients with other lesions). They were prospectively enrolled after a comprehensive noninvasive presurgical evaluation for drug-resistant epilepsy. This evaluation included a detailed history and neurological examination, brain MRI, and surface video/EEG monitoring. Normative evaluation of intelligence and memory was assessed using the Wechsler Adult Intelligence Scale III (WAIS-III) [23] and the Wechsler Memory Scale III (WMS-III) [24].

Analyses were first performed in the homogeneous subgroup of patients with HS ($n=15$), as previously suggested [11], and secondarily extended to the entire group of 25 patients with TLE, including distinct etiologies. The 15 patients with unilateral HS (11 females; age $=37.1\pm13.3$ years) presented with similar electroclinical features, compatible with unilateral medial TLE (MTLE), as defined in a previous study [25].

Investigations were approved by the local ethics committee of the Marseille Public Hospitals.

#### 2.1.2. Controls

Twenty-five healthy subjects (14 females, age $=30.2\pm11.1$ years) were also included in this study. These control subjects were free from neurological disease and cognitive complaints and had a normal brain MRI. Patients and healthy subjects did not differ with respect to either age ($P=0.091$, $t$ test) or gender ($P=0.273$, $\chi^2$ test).

Brain PET metabolism findings in patients were compared with normative data previously obtained from a local database (Programme Hospitalier de Recherche Clinique, PHRC 2007/2009), in 32 right-handed controls (18 females; age $=40.0\pm12.0$ years), with scans acquired with the same camera and under the same conditions [26]. These healthy subjects were free from neurological disease and cognitive complaints. They had normal neurological and neuropsychological evaluations and, in particular, normal memory assessment and normal brain MRI. This group of controls did not differ from patients either in age ($P=0.459$, $t$ test) or in gender ($P=0.261$, $\chi^2$test).

### 2.2. Recognition memory task

The 25 patients and the 25 controls performed a recognition memory task based on items that were non-material specific. They were asked to memorize 40 pictures of readily named objects (i.e., targets), visually displayed on a screen (10 animals, 10 vegetables, 10 tools, and 10 means of transportation), shown every 15 seconds for 2.5 seconds. Forty-five minutes later, recognition performance was evaluated using number of targets correctly recognized (i.e., "hits"). Subjects were asked to identify whether they had or had not already seen the displayed items among a set of 80 visual stimuli: the 40 targets, and 40 new pictures from the same four previous categories (i.e., distractors). Stimuli were randomly sorted across categories, and conditions (target and distractor). We verified before the experiment that the 80 pictures could be easily named with a similar name across healthy subjects.

### 2.3. [$^{18}$F]FDG-PET acquisition and processing

Interictal CMRGlc was studied in the 25 patients and the 32 controls with an integrated PET/CT camera (Discovery ST, GE Healthcare, Waukesha, WI, USA). In patients, this exam was performed 2 days after the recognition memory task. For this test, 150 MBq of [$^{18}$F]FDG was injected intravenously into subjects awake and in the resting state, with eyes closed, in a quiet environment. Image acquisition started 30 minutes after injection and ended 15 minutes later. Images were reconstructed using an ordered subset expectation maximization algorithm, with 5 iterations and 32 subsets, and corrected for attenuation using CT transmission scan.

Whole-brain statistical analysis was performed at the voxel level using SPM2 software (Wellcome Department of Cognitive Neurology, University College, London, UK), by flipping the epileptic brain hemisphere to the left side, prior to spatial normalization, as previously done [26,27]. We aimed to identify metabolic correlation with non-material-specific recognition performance within the supposed epileptogenic network, independently of epilepsy lateralization. In this way, ipsilateral and contralateral brain PET metabolism, related to the epileptogenic side, was compared at the voxel level with that of healthy subjects. To maintain the same proportion of reversed brain scans in patients (see below) and controls, 15 of the 32 brain scans performed in healthy subjects were flipped. The PET images were converted from the DICOM to the Analyze format using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html), and then were transferred to SPM2. The data were spatially normalized onto the Montreal Neurological Institute atlas (MNI). The dimensions of the resulting voxel were $2\times2\times2$ mm. The images were then smoothed with a gaussian filter (12 mm FWHM). The resulting PET images were divided by individual [$^{18}$F]FDG uptake of a reference site to control for individual variations in global PET measures [28]. We selected the vermis as a preserved area. The individual vermis value was obtained for each subject using the Anatomical ROIs Analysis toolbox of SPM2, allowing the automatic extraction of the mean value of the labeled region from the Anatomical Automatic Labeling (AAL) atlas (2040 voxels, i.e., 16,320 mm$^3$) [29].

The following intergroup and correlation voxel-based PET analyses were controlled for age. Significant regions of hypometabolism were first sought by comparing the 15 MTLE patients with healthy subjects at the whole-brain level. We secondarily studied the correlation between performance in recognition and brain PET metabolism with an MTL mask from the AAL atlas [29], separately testing metabolic involvement of the hippocampus and the parahippocampal region, ipsilateral and contralateral to HS. In particular, the parahippocampal region consisted of the parahippocampal gyrus and parahippocampal uncus, and included in its anterior part both entorhinal and perirhinal cortices as well as the medial temporal pole [29–31]. These AAL-derived anatomical VOI analyses were performed using the WFU_PickAtlas toolbox with a three-dimensional dilatation of 1 [32].

Lastly, the metabolic cluster of significant correlation with recognition of targets found in the subgroup of 15 patients with MTLE with HS was tested within the entire group of 25 patients with TLE using a nonparametric test (Spearman's rank test).

### 2.4. Statistical analysis

Clinical differences between groups were evaluated at a threshold of $P$ values, $P<0.05$, using the $\chi^2$ test (for qualitative data), Mann–Whitney test (for comparison of quantitative data among patients),

and *t* test (for comparison of quantitative data between patients and healthy subjects).

The SPM maps were thresholded using $P<0.05$ corrected for multiple comparisons with the false discovery rate method (FDR-corrected).

The SPM correlation initially found between number of correctly recognized targets and CMRGlc values was secondarily confirmed using a nonparametric test (Spearman's rank test), at a threshold of $P$ values $<0.05$.

Interactions between epilepsy lateralization, performance in recognition memory, and CMRGlc values extracted from significant clusters of interictal metabolism were finally studied using ANOVA, at a threshold of $P$ values $<0.05$.

## 3. Results

### 3.1. Clinical characteristics and performance in recognition of patients with HS

Characteristics of the 15 patients with HS are described in Table 1. Recognition of targets in the memory task was significantly lower for patients than for healthy subjects ($34.1\pm5.4$ and $38.6\pm1.3$ recognized pictures, respectively; $P<0.001$, *t* test). Subgroups of patients with left and right MTLE did not differ with respect to age, gender, age at epilepsy onset, epilepsy duration, seizure frequency, WMS-III Immediate, Delayed, and Working Memory quotients, and recognition of targets (Mann–Whitney and $\chi^2$ tests). Patients with right-sided MTLE had lower Global and Performance IQs (WAIS-III) than patients with left-sided MTLE ($75.3\pm14.4$ vs $91.9\pm6.7$ for Global IQ, $P=0.037$; $76.0\pm13.1$ vs $94.5\pm6.7$ for Performance IQ, $P=0.009$; Mann–Whitney test).

### 3.2. [$^{18}$F]FDG-PET interictal hypometabolism of patients with hippocampal sclerosis

In comparison to healthy subjects, the subgroup of 15 patients with MTLE showed significant interictal hypometabolism ipsilateral to HS within the hippocampus, perirhinal and entorhinal cortices, medial temporal pole, and middle temporal gyrus (Fig. 1A; Table 2). There was no contralateral hypometabolism (i.e., opposite the side of HS). No metabolic difference was found, ipsilateral or contralateral to HS, between patients with left-sided and those with right-sided MTLE.

**Table 1**
Characteristics of patients with medial temporal lobe epilepsy with hippocampal sclerosis.

| *N* | 15[a] |
|---|---|
| Age (years), mean (SD) | 37.07 (13.31) |
| Gender, female/male | 11/4 |
| Right-handedness | 15 |
| Side of medial temporal lobe epilepsy | |
| Left | 8 |
| Right | 7 |
| Hippocampal sclerosis | 15 |
| Age at epilepsy onset (years), mean (SD) | 17.33 (7.78) |
| Epilepsy duration (years), mean (SD) | 19.73 (14.28) |
| Seizure frequency (per month), mean (SD) | 9.43 (4.76) |
| Wechsler Adult Intelligence Scale III | |
| Full Scale IQ | 84.13 (13.74) |
| Verbal IQ | 84.67 (11.88) |
| Performance IQ | 85.87 (13.78) |
| Wechsler Memory Scale III, mean | |
| Immediate Memory Quotient | 99.07 (11.69) |
| Delayed Memory Quotient | 95.07 (13.37) |
| Working Memory Quotient | 85.87 (10.90) |
| Recognition performance of targets | 34.07 (5.43) |

[a] Values are number or mean (SD).

### 3.3. Relationship between performance in recognition and interictal CMRGlc

In the subgroup of 15 patients with MTLE and HS, recognition of targets correlated positively with ipsilateral entorhinal and perirhinal cortices ($P=0.043$, FDR-corrected; $\rho=0.557$, Spearman's rank test), but neither with the ipsilateral hippocampus (Fig. 1B; Table 2) nor with the contralateral medial temporal lobe. The absence of a significant correlation between recognition of targets and ipsilateral hippocampal metabolism was confirmed using a nonparametric test on CMRGlc values extracted either from the AAL-derived anatomical VOI of the whole hippocampus, or from the hippocampal part of the MTL cluster of significant hypometabolism previously found in comparison to healthy subjects by obtaining the overlap of the SPM cluster and the AAL-derived anatomical VOI ($P>0.260$, Spearman's rank test).

Assessing correlations in the entire group of 25 patients led to a statistically stronger relationship between number of correctly recognized targets and metabolism of entorhinal/perirhinal cortex ($\rho=0.584$, $P=0.004$, Spearman's rank test) (Fig. 1C). This group included 10 additional patients with TLE without HS (age $=34.2\pm9.3$ years; 7 males; 5 left and 5 right TLE; $34.2\pm9.3$ recognized pictures). As previously observed, hippocampal metabolism was not significantly correlated with recognition of targets ($\rho=0.273$, $P=0.181$, Spearman's rank test) (Fig. 1D).

The relationship between performance in recognition memory and the cluster of ipsilateral entorhinal/perirhinal interictal metabolism was found not to be dependent on epilepsy lateralization (left side vs right side) using ANOVA in the entire group of patients, as well as in the subgroup of patients with MTLE with HS ($P=0.562$ and 0.820, respectively).

## 4. Discussion

This voxel-based study, performed in patients with MTLE with ipsilateral hypometabolism of both the hippocampus and the parahippocampal region (relative to the epileptogenic side), demonstrated that the number of correctly recognized targets correlates with interictal CMRGlc of entorhinal/perirhinal cortices, and not with that of the hippocampus. In other words, the ability to recognize targets was weak in patients with low entorhinal/perirhinal CMRGlc and greater in patients with higher entorhinal/perirhinal CMRGlc. This result suggests that assessment of performance on a recognition memory task can be a good predictor of the functional status of the anterior parahippocampal structures metabolically involved in epilepsy. Correlation between recognition memory performance and entorhinal/perirhinal CMRGlc was first obtained in a homogeneous group of patients with HS, and secondarily confirmed in a larger group of patients with TLE including additional etiologies.

In addition to the hippocampus, evidence is growing that the entorhinal/perirhinal cortex is crucial for declarative memory and, in particular, for recognition. For example, selective damage to perirhinal and entorhinal cortices in rats [33] and nonhuman primates [13,19,34] leads to robust recognition memory impairments. Similar findings have been reported in humans [14]. Meunier et al. also showed that damage to the entorhinal cortex, in addition to damage to the perirhinal cortex, notably increased the recognition deficit [13]. Moreover, decreasing fMRI activity of the anterior parahippocampal region has been described when stimuli become familiar, whereas this relationship has not been found in the hippocampus [35–39]. Similarly, recognition memory in TLE does not appear to be related to the presence of HS [40] or to hippocampal MRI volumes, and is not positively correlated with the extent of hippocampal pathology quantified postoperatively [20].

Although our results are in agreement with the literature, they do not directly address the mechanisms underlying the impairment reported in our patients. Several hypotheses have indeed been proposed

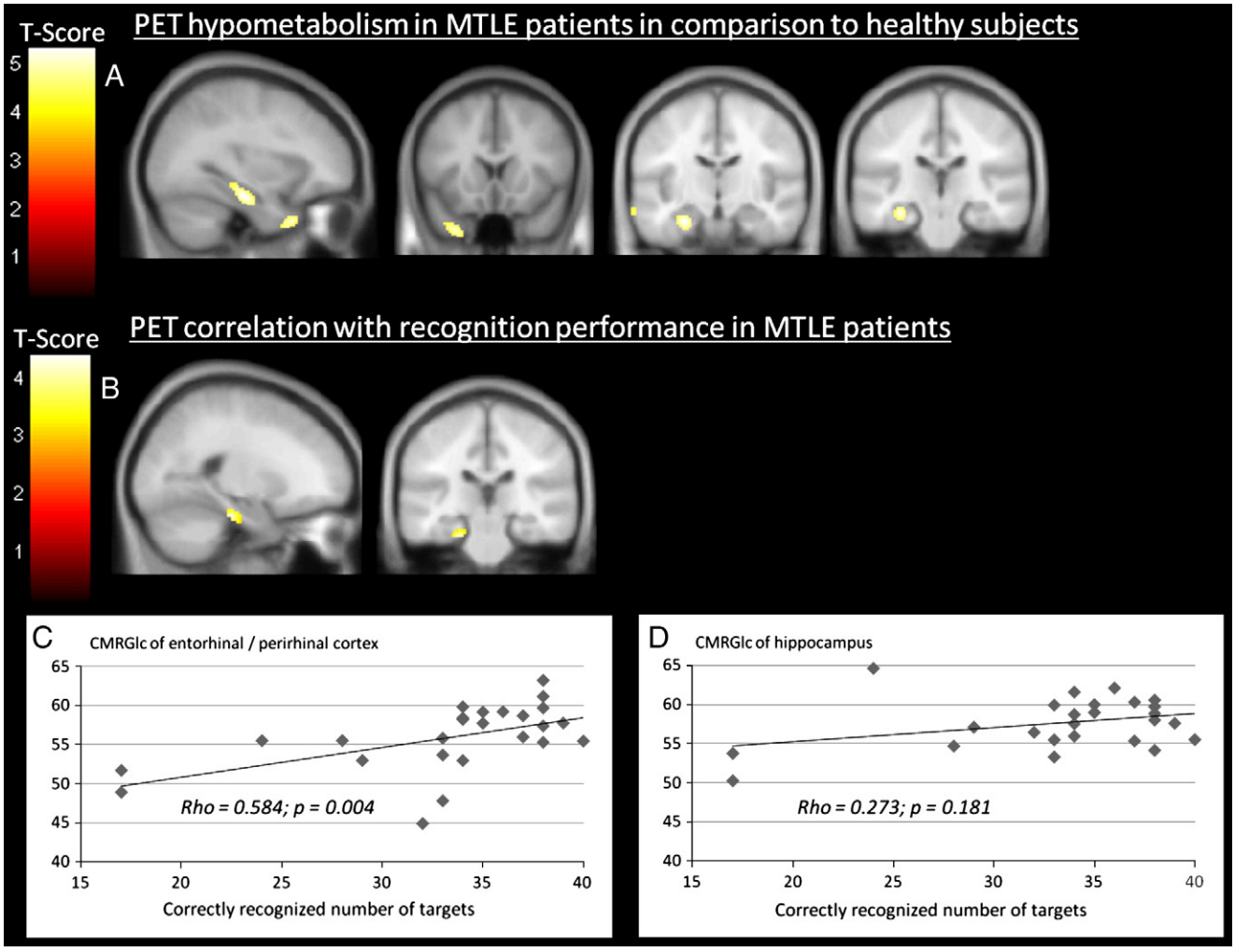


**Fig. 1.** Interictal PET findings in patients with temporal lobe epilepsy (TLE) ($P$ voxel<0.05, FDR-corrected). (A) Hypometabolism of patients with medial TLE (MTLE) with hippocampal sclerosis (HS) in comparison to healthy subjects (whole-brain analysis; hemisphere ipsilateral to HS is on the left side). (B) Metabolism correlated with recognition of targets in patients with MTLE with HS (hippocampal/parahippocampal analysis). (C) Relationship between number of correctly recognized targets and interictal cerebral metabolic rate for glucose (CMRGlc) of entorhinal/perirhinal cortex ipsilateral to the epileptogenic side (mean CMRGlc value = 55.8 ± 4.2), in the entire group of patients with TLE, including patients with and those without HS. (D) Relationship between number of correctly recognized targets and interictal CMRGlc of hippocampus ipsilateral to the epileptogenic side (mean CMRGlc value = 57.6 ± 3.1), in the entire group of patients with TLE, including patients with and those without HS.

that are subject to debate. Although some authors emphasize the role of anterior parahippocampal structures in perceptivo-mnesic transformations [19,41,42], others have developed the idea that this region is critical for familiarity-based recognition [43], whereas the hippocampus is essential for recollection-based recognition [18]. These views are disputed on the basis that recognition memory may be based on a single process that may emit a weak signal (that would depend on parahippocampal structures) or a strong signal (that would depend on the hippocampus) [44]. Interestingly, all these different approaches predict that recognition memory should be impaired after anterior parahippocampal damage, although the mechanisms may differ. Our results confirm the privileged role of anterior parahippocampal structures in recognition memory over the hippocampus. They support the view that assessment of specific MTL structures in TLE should be

**Table 2**
Montreal Neurological Institute coordinates of significant interictal PET findings in the 15 patients with medial temporal lobe epilepsy and hippocampal sclerosis ($P$ voxel<0.05, corrected by false discovery rate method).

| Contrast | Cluster | Voxel | MNI coordinates | | | Localization |
|---|---|---|---|---|---|---|
| | $k$ | $T$ score | $x$ | $y$ | $z$ | |
| Hypometabolism in patients, in comparison to healthy subjects; | 272 | 5.09 | −28 | −16 | −26 | Perirhinal cortex |
| *Whole-brain analysis* | | 4.57 | −22 | −14 | −24 | Entorhinal cortex |
| | | 4.56 | −32 | −28 | −14 | Hippocampus |
| | 161 | 4.78 | −32 | 16 | −40 | Medial temporal pole |
| | 28 | 4.27 | −68 | −10 | −16 | Middle temporal gyrus |
| Metabolism correlated with recognition of targets | 190 | 4.39 | −12 | -6 | −20 | Entorhinal cortex |
| *Hippocampal/parahippocampal analysis* | | 4.04 | −22 | −26 | −24 | Perirhinal cortex |

*Note*. Results from SPM2 are listed in decreasing order of peak $T$ score value within each cluster. Correction of multiple comparisons was obtained with false discovery rate (FDR) method. $k$ value represents the number of significant voxels in the particular cluster. $x$, $y$, and $z$ are the Montreal Neurological Institute coordinates (mm). All localizations are ipsilateral to hippocampal sclerosis.

carried out with specific tests for which there are theoretical, and confirmed anatomo-functional correlations.

There is an increasing body of literature on the relationship between CMRGlc and cognition, in particular in cortical neurodegenerative diseases [45,46]. In TLE, previous studies showed a correlation between [$^{18}$F]FDG-PET metabolism and performance on a variety of memory tasks [47–49]. Moreover, preoperative metabolic asymmetry has been shown to be predictive of memory decline after anterior temporal lobectomy [50]. To our knowledge, only one TLE study previously reported a relationship before surgery between recognition and CMRGlc. Griffith et al. showed a correlation between a face recognition memory task and temporopolar metabolism in an analysis based on an a priori region-of-interest hypothesis (thus excluding the hippocampus and the entorhinal/perirhinal cortex) [51]. This correlation may, however, be consistent with our findings as architectonic studies have demonstrated that the medial part of the temporal pole is in fact related to the perirhinal cortex [30,31].

The pattern of hypometabolism found in patients with MTLE with HS, in comparison to healthy subjects, which included the hippocampus and anterior parahippocampal structures, as well as the medial temporal pole and the middle temporal gyrus, concurs with previous reports in MTLE associated with HS [27]. As such, our group of patients appears representative of patients with MTLE. Performance was significantly decreased in patients with MTLE as a group but, as previously shown and expected for a task based on non-material-specific items, similar for patients with left and those with right MTLE [20–22]. In addition, these two subgroups of patients showed similar ipsilateral/contralateral PET metabolism. Accordingly, we did not find evidence using ANOVA to reject the hypothesis of no difference between patients with left and those with right MTLE for the relationship between recognition memory performance and CMRGlc of the ipsilateral entorhinal/perirhinal cortex. Thus, possibly because we purposely used visual stimuli that were easily named, our results may hold true in both patients with right-sided and those with left-sided TLE.

Interictal changes in CMRGlc have been correlated with ictal electroclinical patterns, ictal discharge frequency, and ictal brain perfusion SPECT [27,52,53]. Interictal hypometabolism topography thus may be related to neuronal networks involved in ictal discharge onset and spread pathways. On the other hand, depth recordings have demonstrated that different medial temporal lobe networks may be involved within the epileptogenic zone [5,6,54]. In particular, distinct subtypes of MTLE have been described depending on the preferential involvement of the entorhinal cortex, the epileptogenicity of which has been correlated with its MRI volumes [6]. Further studies, including depth recordings, will be necessary to demonstrate that hypometabolism in the entorhinal/perirhinal cortices in TLE corresponds to the preferential involvement of these structures in the epileptogenic network of patients with impaired recognition memory.

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