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Posterior parahippocampal gyrus lesions in the human impair egocentric learning in a virtual environment

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Abstract

Functional imaging studies have shown that the posterior parahippocampal gyrus (PHG) is involved in allocentric (world-centered) object and scene recognition. However, the putative role of the posterior PHG in egocentric (body-centered) spatial memory has received only limited systematic investigation. Thirty-one subjects with pharmacoresistant medial temporal lobe epilepsy (TLE) and temporal lobe removal were compared with 19 matched healthy control subjects on a virtual reality task affording the navigation in a virtual maze (egocentric memory). Lesions of the hippocampus and PHG of TLE subjects were determined by three-dimensional magnetic resonance imaging volumetric assessment. The results indicate that TLE subjects with right-sided posterior PHG lesions were impaired on virtual maze acquisition when compared with controls and TLE subjects with anterior PHG lesions. Larger posterior PHG lesions were significantly related to stronger impairments in virtual maze performance. Our results point to a role of the right-sided posterior PHG for the representation and storage of egocentric information. Moreover, access to both allocentric and egocentric streams of spatial information may enable the posterior PHG to construct a global and comprehensive representation of spatial environments.

Introduction

Deficits in the area of learning and memory have been found to be one of the most prominent types of neuropsychological impairment after lesions of the human medial temporal lobe (Milner, 1975). The hippocampus is thought to play an important role in allocentric (i.e. world-centered) spatial representations, being independent of the observer, in contrast to egocentric (i.e. body-centered) representations, which relate to the body axes (O'Keefe & Nadel, 1978). Accordingly, neurons within the rat hippocampus were shown to be place-sensitive (O'Keefe & Nadel, 1978), and hippocampal lesions were shown to impair place learning in the rat (Morris *et al*., 1982). A recent study on humans with temporal lobe epilepsy (TLE) confirmed that hippocampal neurons predominantly respond to specific spatial locations during navigation in a virtual town (Ekstrom *et al*., 2003).

A number of studies have reported that individuals with medial temporal lobe damage (including parts of the amygdala, hippocampus and overlying cortex) are impaired in place learning or in finding their way within their locomotor environment ('topographical disorientation') (Maguire *et al*., 1996a; Abrahams *et al*., 1997; Spiers *et al*., 2001b; Astur *et al*., 2002). Single case studies using various spatial memory tests provided evidence that bilateral hippocampal lesions are associated with allocentric memory impairment (Holdstock *et al*., 1999, 2000; Spiers *et al*., 2001a; King *et al*., 2002), whereas other studies reported the right parahippocampal gyrus (PHG) as the common area of damage across cases (Habib & Sirigu, 1987; Bohbot *et al*., 1998, 2000; Nyffeler *et al*., 2005). Selective sparing of topographical memory was reported in a patient with predominantly left-sided temporal lobe damage (Maguire & Cipolotti, 1998).

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Functional neuroimaging studies investigating human navigation in virtual reality large-scale environments also provide evidence that the PHG subserves allocentric memory (Aguirre *et al*., 1996; Maguire *et al*., 1996b, 1998b; Aguirre & D'Esposito, 1997). Specifically, the cortex, being located on the posterior PHG, was shown to be activated when subjects viewed complex scenes such as landscapes and city streets ('parahippocampal place area') (Epstein & Kanwisher, 1998; Brewer *et al*., 1998; Epstein *et al*., 1999, 2003) or building stimuli (Aguirre *et al*., 1998a).

In contrast to allocentric representation and memory formation, egocentric (i.e. body-centered) representation and memory of visual space have received only limited systematic investigation. Egocentric memories of space may include the sensorimotor represention of whole-body, head and gaze motion, the mental representation of distance, time and number of routes that have been travelled, and the temporo-spatial relationship of all these information sources. In everyday life, conjoint use of allocentric and egocentric information in spatial navigation and learning is likely. However, the question arises as to where in the brain allocentric and egocentric information are brought together.

Currently, spatial representation is modeled as a process supported by a network of thalamic/striatal and parietal and temporal cortical regions. The subject's location and the allocentric representation of spatial context is likely to be processed by ventromedial temporal cortices (i.e. hippocampus and PHG), whereas posterior and medial parietal cortices and the striatum are thought to provide representation and encoding of egocentric coordinates (Aguirre & D'Esposito, 1997; Agiurre *et al*., 1998b; Burgess *et al*., 2001a, 2001b; Hartley *et al*., 2003; Iaria *et al*., 2003; Bohbot *et al*., 2004). However, given the fact that the posterior PHG is strongly connected to the posterior parietal cortex and the striatum (Goldman-Rakic & Selemon, 1986; Cavada & Goldman-Rakic, 1989; Suzuki & Amaral, 1994; Suzuki, 1996;

Lavenex *et al*., 2002), one would expect a role of the posterior PHG for egocentric representation and memory formation as well. In line with this assumption, a recent study (Epstein *et al*., 2003) found that the posterior PHG represents scenes in a viewpoint manner, suggesting that the posterior PHG is also involved in encoding the relationship between the observer and the scene.

In the present investigation, 31 subjects with pharmacoresistant TLE and temporal lobe removal were compared with 19 matched healthy control subjects on a virtual reality task affording the navigation in a virtual maze. We used a computer-simulated first-person virtual reality environment in order to simulate navigation in a large-scale space. TLE subjects with lesions of the hippocampus and the PHG were assessed by volumetric analysis based on three-dimensional magnetic resonance imaging (3D MRI). Lesion subgroups were formed based on the presence (TLE+) or absence (TLE–) of posterior PHG lesions. The goal of our study was to investigate whether posterior PHG lesions impair the acquisition of egocentric spatial information in a virtual maze. We further hypothesized that larger posterior parahippocampal lesions would be related to worse performance on virtual maze learning.

Materials and methods

Subjects

Subjects with medial TLE

The sample comprised 31 subjects with pharmacoresistant medial TLE (Table 1). All subjects were regularly seen as outpatients at the specialized epilepsy clinic of the Department of Clinical Neurophysiology, University of Göttingen. Classification of TLE subjects (consensus diagnosis) was based on repeated EEG monitoring, seizure semiology, clinical history and cortical imaging (MRI). All subjects underwent long-term video-EEG telemetry and in some cases single-photon emission computer tomography (SPECT) as part of the preoperative evaluation. Severity of illness was rated according to the scoring system of Engel *et al*. (1993), which is based on frequency and impact of seizures. All subjects were on anticonvulsant medication.

TABLE 1. Demographic and clinical characteristics of the subjects

	Group TLE-left ($n = 13$)	Group TLE-right ($n = 18$)	Control Group ($n = 19$)
Age (years)[a]	36 ± 6	43 ± 11	43 ± 16
Education (years)[a]	10 ± 1	10 ± 1	10 ± 2
Sex (female: male)[b]	8 : 5	11 : 7	11 : 8
Handedness (right: left)[b]	10 : 3	16 : 2	18 : 1
WAIS-R, IQ (preoperative)[a]	96 ± 19	98 ± 19	109 ± 12
WAIS-R, IQ (postoperative)[c]	95 ± 18	103 ± 20	
WMS-R, Verbal memory (preoperative)[d]	104 ± 17	99 ± 16[e]	112 ± 13
WMS-R, Visual memory (preoperative)[d]	106 ± 17	99 ± 23[e]	118 ± 17
WMS-R, Delayed recall (preoperative)[d]	95 ± 16[e]	93 ± 17[e]	116 ± 18
WMS-R, Verbal memory (postoperative)[c]	98 ± 17	95 ± 18	
WMS-R, Visual memory (postoperative)[c]	107 ± 16	98 ± 21	
WMS-R, Delayed recall (postoperative)[c]	96 ± 15	91 ± 23	
Duration of disorder (years)[c]	21 ± 11	26 ± 12	
Seizure frequency (preoperative)[c,*]	8 ± 1	7 ± 1	
Seizure frequency (postoperative)[c,*]	3 ± 2[f]	3 ± 2[f]	
Outcome (no seizures: rare seizures: improvement: no improvement)[b,*]	9 : 0 : 1 : 3	10 : 4 : 2 : 2	

Data are given as mean ± SD unless indicated otherwise. TLE, temporal lobe epilepsy; WAIS-R, *Wechsler Adult Intelligence Scale-Revised* (Tewes, 1991), IQ estimates were derived from Information, Similarities, Picture Completion and Block Design Scores; WMS-R, *Wechsler Memory Scale-Revised* (Wechsler, 1987). *As determined by Engel *et al*. (1993). [a]$P > 0.05$, the groups did not differ significantly (one-way-ANOVA); [b]$P > 0.05$, the groups did not differ significantly (Fisher's exact test); [c]$P > 0.05$, the groups did not differ significantly (*t*-test); [d]$P < 0.05$, the groups differed significantly (one-way-ANOVA); [e]$P < 0.05$, compared with the control group (Bonferroni *post-hoc* test); [f]$P < 0.05$, compared with the preoperative value (*t*-test).

All subjects underwent anterior temporal lobectomy at the neurosurgical department of the University of Göttingen. Eighteen subjects had been operated on the right temporal lobe and 13 on the left temporal lobe. All subjects had an anterior temporal lobectomy with removal of the temporal pole and the anterior perihinal, entorhinal and hippocampal cortices and part removal of the amygdala. Preoperative MRI and postoperative neuropathology revealed structural lesions of the operated temporal lobe in 29 subjects (hippocampal sclerosis, $n = 17$; hamartia, $n = 5$; venous malformation, $n = 3$; ganglioglioma, $n = 3$; gliosis, $n = 1$).

Subjects were administered a comprehensive neuropsychological test battery before surgery as part of the extensive preoperative assessment and were then re-evaluated about 2 weeks, 6 months, and 1 and 3 years postoperatively. Data for the present report were obtained 3 years postoperatively.

Control subjects

TLE subjects were compared with 19 healthy control subjects recruited for the study by an advertisement in a local newspaper. Only subjects without a history of psychiatric or neurological disease were studied. Control subjects were matched according to sex, age and education.

After a complete description of the study was given to the subjects, written informed consent was obtained. The study design was approved by the Ethical Committee of the Medical Faculty of the University of Göttingen, and performed in accordance with the Declaration of Helsinki.

MRI acquisition and analysis

All subjects received an MRI scan using a 1.5-T Philips Gyroscan machine (Philips Medical Systems, Best, The Netherlands) at the time of the assessment. Scanning parameters of the T_1-weighted 3D sequence were as follows: TE = 6.0 ms, TR = 24.0 ms, flip angle = 30°, FOV = 256, slice plane = sagittal, matrix = 256 × 256, slice thickness = 1.3 mm, slice number = 130, acquisition mode = three-dimensional. Lesion analysis and volumetric analysis was done on the basis of 3D MR images. The images were transferred to a computer workstation and processed using the CURRY® software (Neurosoft, Inc., El Paso, TX, USA). Images were reformatted into continuous slices 1 mm in thickness.

Defining regions of interest (ROIs)

Total brain volume was calculated with automated multistep algorithms and 3D region growing methods that are limited by gray value thresholds. Hypothesis-driven calculations of regional volumes were made for the hippocampus and the PHG (Weniger *et al*., 2004). Temporal lobe volume was assessed to estimate total lesion size. Simultaneous 3D visualization of brain structures and manual tracing allowed a precise identification and delineation of all ROIs.

Hippocampus

The hippocampus was outlined on coronal slices by means of manual tracing according to a standardized protocol (Pruessner *et al*., 2000) and by aid of the serial sections provided by Duvernoy (1998).

PHG

The PHG was disarticulated on coronal slices by manual tracing. Medially, the PHG is bordered by the hippocampal formation and the isthmus. The lateral bank of the collateral sulcus served as lateral boundary of the PHG. The anterior and posterior boundaries were defined by the most anterior and most posterior level of the hippocampus in the nonoperated hemisphere. The posterior PHG was defined as the cortex situated behind the gyrus intralimbicus (Pruessner *et al*., 2002).

Temporal lobe

Medially, the temporal lobe was disarticulated from other brain structures by drawing a straight line from the lateral fissure to the inferior horn of the lateral ventricle. The posterior border of the temporal lobe was defined by a plane vertical to the anterior–posterior cortex line (Talairach & Tournoux, 1988) and touching the posterior border of the hippocampus.

Reliability of regional volumetric measurements

Reliabilities were calculated with intraclass correlation coefficients. Intraclass correlation coefficients (absolute agreement) were derived from a two-way mixed-effects analysis of variance model (McGraw & Wong, 1996). All analyses were done blind to subjects' test performance. Intra- and inter-rater reliabilities were obtained with each ten randomly chosen cases. Intra-rater reliabilities were determined for the hippocampus and the PHG. The intra-class correlation coefficients for this procedure were $r = 0.97$ for the hippocampus and $r = 0.99$ for the PHG. For the hippocampus, the inter-rater reliability was also determined. The intra-class correlation coefficient for this procedure was $r = 0.96$.

Virtual reality task

The static 3D model of the virtual environment was designed with Kinetix 3D Studio Max R2 as visualization tool. For programming the task, Realimation VSG 4.4 and Microsoft C++ were used. The virtual environment was presented on a personal computer with two Pentium III processors, 128 MB RAM, two Voodoo2-Add-On graphic cards on a Windows NT 4.0 system, allowing stimuli to be presented at frame rates of 36.1 Hz. Graphics were displayed on a 21-inch monitor. The virtual reality environment was three-dimensional, fully colored and textured, and presented a first-person view. Subjects controlled their movements within the environment with a joystick. Prior to the task, subjects underwent a training session in the virtual reality environment after which they were tested on their ability to navigate.

An aerial view of the virtual maze is presented in Fig. 1. The virtual maze environment comprised six points of two-way intersection and seven cul-de-sacs containing pots, from which one contained money. The maze consisted of brick walls, a similarly colored floor and a blue sky. All intersections appeared identical when approached from different directions (Fig. 1). The maze did not include any landmarks and therefore could only be solved using egocentric navigation strategies. Subjects were instructed to find the shortest way to the pot with money in it. Five trials were applied. In each trial, subjects started at the same location and then had to find the target which remained in the same location across trials. Subjects were not able to see the target from the starting position or from other vantage points in the environments. In the training session that preceded the task, the location of the target was not indicated.

Subjects' learning performance was characterized by the following variables: the number of errors (visiting a pot not containing money) and the time (s) to find the pot with money. After finishing the task, subjects completed a questionnaire indicating what kind of navigation strategies they used in trials 2–4 of the task (storage of egocentric cues or survey perspective).

Statistical analyses

Because of the small number of subjects in each lesion group, comparisons of lesion groups were performed using nonparametric statistical methods (Kruskal–Wallis one-way ANOVA, *U*-test). Multivariate comparisons were performed using a nonparametric version of the classical mixed model (Brunner *et al*., 2002). Pre- to postoperative comparisons were made using Wilcoxon tests. Frequencies were compared using the Fisher's exact test. Effects of hippocampal and posterior PHG volume on performance in the virtual maze were investigated by using regression analyses. All analyses were two-tailed and the alpha was defined as $P < 0.05$. Statistical computations were

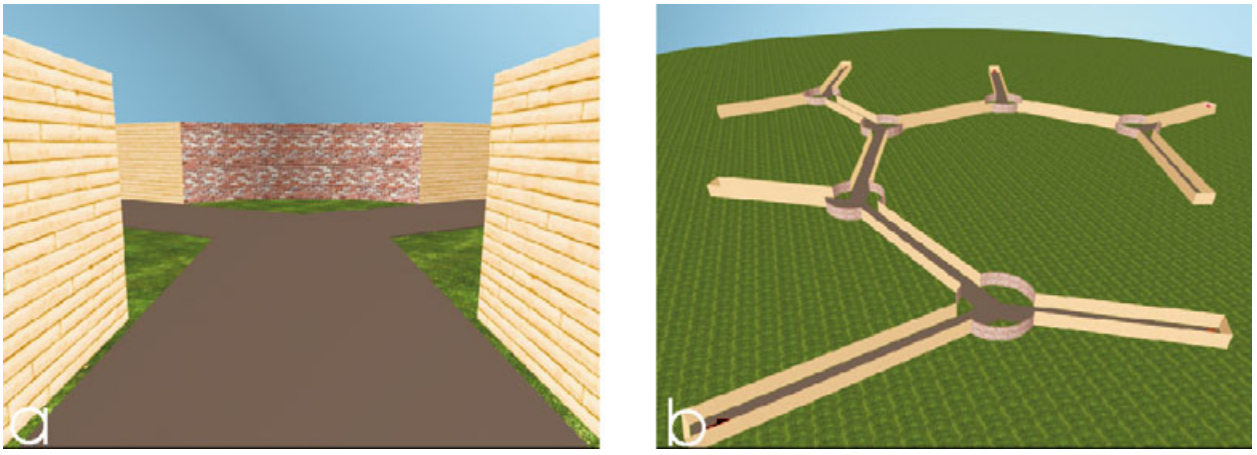

FIG. 1. Gray scale rendering of subject view (a) and aerial view (b) of the virtual maze. Actual stimuli were in full colour.

performed using the Statistical Analysis System (SAS for Windows, Version 8.02; nonparametric ANOVAs and ANCOVAs: http//http://www.ams.med.uni-goettingen.de/de/sof/ld/makros.html) and the Statistical Package for the Social Sciences (SPSS for Windows, Version 11.5.1).

Results

Demographic and clinical variables

The groups did not differ with respect to demographic and intellectual variables (Table 1). Subjects with left-sided and right-sided temporal lobe removals (TLE-left, $n = 13$; TLE-right, $n = 18$) did not differ with respect to duration of disorder and preoperative or postoperative seizure frequency. Groups TLE-left and TLE-right also did not differ with respect to preoperative or postoperative intellectual or memory functioning; however, in the TLE-left group left hippocampal volume was significantly correlated with *WMS-R* postoperative verbal memory performance ($r = 0.74$, $P = 0.004$), indicating better memory performance in subjects with larger hippocampal volumes. For detailed results see Table 1.

The subgroups (groups TLE-left+, TLE-left–, TLE-right+, TLE-right–) did not differ with respect to any demographic or clinical variable as listed in Table 1 (Kruskal–Wallis ANOVA, Fisher's exact test; $P > 0.10$) except for preoperative verbal memory (*WMS-R*), for which subjects of the TLE-left+ group performed worse than subjects of the TLE-left– or TLE-right– groups (*U*-tests; $P < 0.05$).

Anatomical results

All TLE subjects had removals of the temporal pole, amygdala, hippocampus and PHG. In all subjects the hippocampal head was removed in part or as a whole. In many subjects lesions extended into the hippocampal body. The hippocampal tail was always spared. Lesions of the PHG covered in all subjects the perirhinal and entorhinal cortices. The cortices located on the posterior PHG (situated posterior to the perirhinal and entorhinal cortices) (Pruessner *et al*., 2002) were affected by the lesion in six subjects with left-sided lesions (group TLE-left+) and in nine subjects with right-sided lesions (group TLE-right+). The remaining subjects had lesions restricted to the perirhinal and entorhinal cortices (group TLE-left–, $n = 7$; group TLE-right–, $n = 9$) (cf. Table 2 and Fig. 2).

Virtual maze: group comparisons

A 5 (group) × 5 (trial) nonparametric ANOVA (with B = box approximation for small sample sizes with Chi-square df) comparing the errors performed by groups TLE-left+, TLE-left–, TLE-right+, TLE-right– and the control group across the five trials of the virtual maze revealed a significant effect of group [$B(3.5) = 3.1$, $P = 0.019$] and trial [$B(3.2) = 6.5$, $P < 0.001$], indicating worse performance of TLE-right+ subjects when compared with the other groups and better performance in later trials of the task. The interaction of group and trial [$B(9.9) = 1.8$, $P = 0.052$] just missed conventional levels of significance, indicating a trend towards worse improvement of TLE-right+ subjects across trials when compared with the other groups. For detailed results see Table 3 and Fig. 3.

Comparisons of group TLE-right+ with each other group across trials of the virtual maze (nonparametric 2 × 5 ANOVAs) confirmed worse performance of TLE-right+ subjects when compared with controls [group: $B(1.0) = 18.6$, $P < 0.001$; trial: $B(3.1) = 2.8$, $P = 0.036$; group × trial: $B(3.1) = 3.9$, $P = 0.008$], with TLE-left+ subjects [group: $B(1.0) = 7.7$, $P = 0.005$; trial: $B(2.7) = 0.8$, $P = 0.503$; group × trial: $B(2.7) = 1.1$, $P = 0.344$], with TLE-right– subjects [group: $B(1.0) = 4.3$, $P = 0.039$; trial: $B(2.5) = 0.5$, $P = 0.625$; group × trial: $B(2.5) = 1.3$, $P = 0.279$] and with TLE-left– subjects [group: $B(1.0) = 3.4$, $P = 0.067$; trial: $B(3.0) = 1.9$, $P = 0.122$; group × trial: $B(3.0) = 4.2$, $P = 0.005$].

Non-parametric ANCOVAs (with covariates; T = Chi-square approximation with Chi-square df) were performed for virtual maze performance with two subject groups (groups TLE-right+, TLE-right–) and hippocampal volume as covariate. After partialing out hippocampal volume, the factor group remained significant [time to learn: $T(1) = 6.5$, $P = 0.011$; errors: $T(1) = 5.9$, $P = 0.016$].

TABLE 2. Brain volume measures

	Volume (mL)						
	Group TLE-left ($n = 13$)	Group TLE-left+ ($n = 6$)	Group TLE-left– ($n = 7$)	Group TLE-right ($n = 18$)	Group TLE-right+ ($n = 9$)	Group TLE-right– ($n = 9$)	Control Group ($n = 19$)
Total brain[a]	1076 ± 78[b]	–	–	1121 ± 131[b]	–	–	1237 ± 101
Temporal lobe							
Left[a]	41 ± 13[b]	–	–	72 ± 11[c]	–	–	78 ± 10
Right[a]	70 ± 7[b]	–	–	36 ± 10[b,c]	–	–	80 ± 10
Hippocampus							
Left[a]	1.2 ± 0.8[b]	–	–	2.8 ± 0.4[b,c]	–	–	3.6 ± 0.6
Right[a]	2.9 ± 0.4[b]	–	–	1.1 ± 0.7[b,c]	–	–	3.7 ± 0.6
PHG							
Left[a]	2.3 ± 0.8[b]	–	–	4.3 ± 0.8[c]	–	–	3.9 ± 0.9
Right[a]	4.1 ± 0.7	–	–	2.5 ± 1.3[b,c]	–	–	4.2 ± 1.1
Posterior PHG							
Left	–	1.5 ± 0.5[b]	2.2 ± 1.0	–	–	–	2.7 ± 0.7
Right	–	–	–	–	1.4 ± 0.5[b,d]	2.1 ± 0.5	2.7 ± 0.7

Data are given as mean ± SD. TLE, temporal lobe epilepsy; TLE+, temporal lobe epilepsy subjects with posterior PHG lesions; TLE–, temporal lobe epilepsy subjects without posterior PHG lesions. [a]$P < 0.001$, non-parametric one-way ANOVA (Kruskal–Wallis, across TLE-left, TLE-right and control groups); [b]$P < 0.001$, compared with the control group (*U*-test); [c]$P < 0.001$, compared with the TLE-left group (*U*-test); [d]$P < 0.01$, compared with the TLE-right– group (*U*-test).

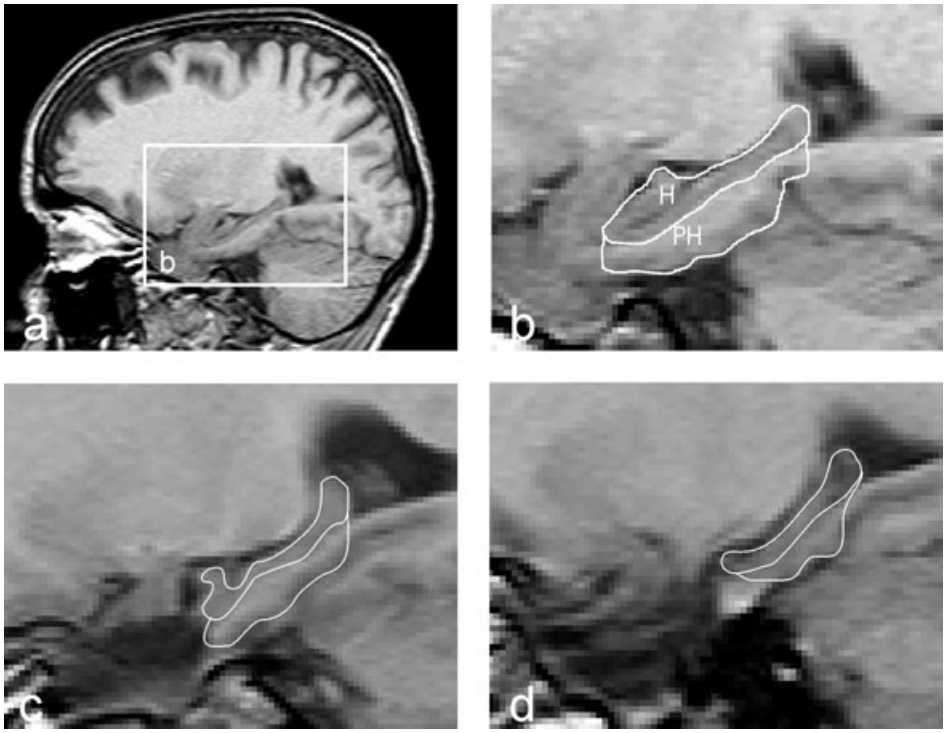

FIG. 2. (a) T1-weighted sagittal MRI of a healthy subject. (b) Magnification of inset shown in (a). Region of the hippocampus and PHG. (c and d) Postoperative T1-weighted sagittal MRIs of the region of the hippocampus and PHG of each one subject of group TLE-right– (c) and group TLE-right+ (d). For definition of the lesion groups, see text. Hippocampus and PHG are delineated by white lines. H, hippocampus; PH, parahippocampal gyrus.

TABLE 3. Virtual maze

	Group TLE-left[a] ($n = 13$)	Group TLE-left+[b] ($n = 6$)	Group TLE-left–[b] ($n = 7$)	Group TLE-right[a] ($n = 18$)	Group TLE-right+[b] ($n = 9$)	Group TLE-right[b] ($n = 9$)	Control Group[a] ($n = 19$)
Errors	20.9 ± 10.6	20.2 ± 8.4	21.6 ± 12.8	27.3 ± 12.4[d]	33.1 ± 9.5[c,e,g]	21.4 ± 12.6	15.6 ± 11.3
Time (s)	988 ± 294	1048 ± 270	937 ± 326	1178 ± 272[d]	1328 ± 159[c,f,g]	1027 ± 283	861 ± 383

Data are given as mean ± SD. TLE, temporal lobe epilepsy; TLE+, temporal lobe epilepsy subjects with posterior PHG lesions; TLE–, temporal lobe epilepsy subjects without posterior PHG lesions. [a]$P < 0.05$, non-parametric ANOVA (Kruskal–Wallis) across groups TLE-left, TLE-right and the control group. [b]$P < 0.05$, non-parametric ANOVA (Kruskal–Wallis) across groups TLE-left+, TLE-left–, TLE-right+ and TLE-right–. [c]$P < 0.05$, compared with the control group (U-test); [d]$P < 0.01$, compared with the control group (U-test); [e]$P < 0.05$, compared with the TLE-left+ group (U-test); [f]$P < 0.05$, compared with the TLE-left– group (U-test); [g]$P < 0.05$, compared with the TLE-right– group (U-test).

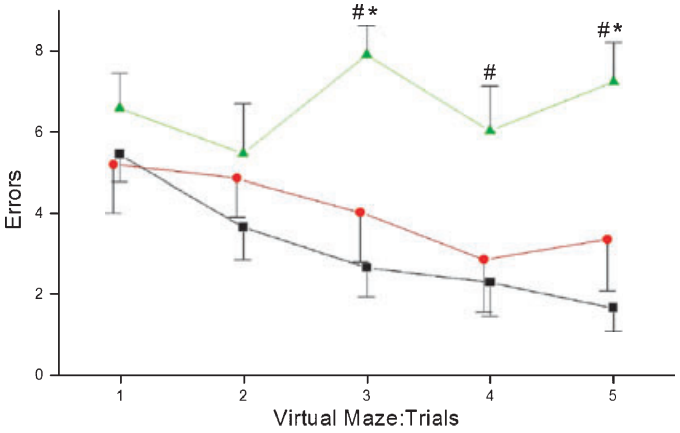

FIG. 3. Mean number of errors performed across the five trials administered in the virtual maze. (▲) Group TLE-right+ (●) group TLE-left+ (■) control group. #$P < 0.05$, comparing group TLE-right+ with the control group; *$P < 0.05$, comparing group TLE-right+ with group TLE-left+.

Navigation strategies in the virtual maze

In the virtual maze, 14 control subjects (74%) reported to have memorized egocentric cues, four subjects (21%) memorized the survey perspective and one (5%) subject did not use any navigation strategy. None of our study subjects reported to have counted left and right turns. Only two (22%) TLE-right+ subjects tried to memorize egocentric cues, three tried to memorize the survey perspective (33%) and four (44%) did not use any navigation strategy. By contrast, the other subgroups (TLE-right–, TLE-left+, TLE-left–) uniformly reported memorizing egocentric cues (18 subjects, 82%) or the survey perspective (four subjects, 18%) as a navigation strategy. It is possible that TLE-right+ subjects more often tried to memorize the survey perspective or did not use any navigation strategy because of their impairment in using and storing egocentric cues. Nevertheless, any navigation strategy used by TLE-right+ subjects was accompanied by a similarly poor task performance (memorizing egocentric cues, mean: 35 errors, 1406 s; memorizing the survey perspective, mean: 38 errors, 1337 s; no navigation strategy, mean: 30 errors, 1283 s).

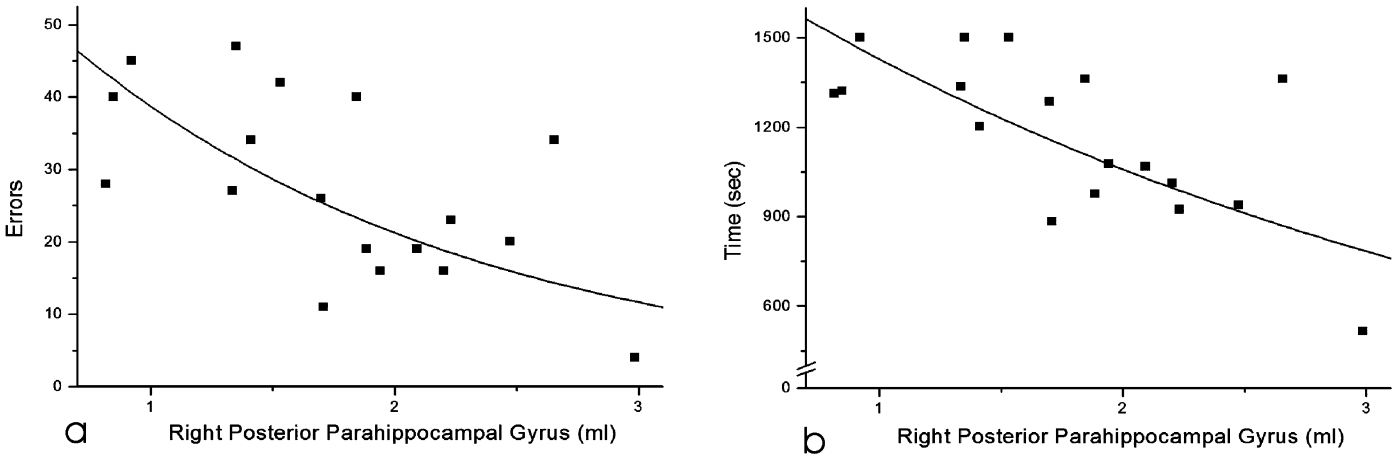

FIG. 4. (a) Relationship between right posterior PHG volume of TLE-right subjects and errors committed in the virtual maze. The best fitting line has an exponential function ($y = 70.6 \times 0.994^x$; $R^2 = 0.41$, $P = 0.004$). (b) Relationship between right posterior PHG volume of TLE-right subjects and the time to learn the virtual maze. The best fitting line has an exponential function ($y = 1929 \times 0.9997^x$; $R^2 = 0.46$, $P = 0.002$).

Anatomico-behavioral relationships

Single regression analyses were performed with the volume of left-sided hippocampus or posterior PHG (group TLE-left) or with the volume of right-sided hippocampus or posterior PHG (group TLE-right). The right posterior PHG volume of TLE-right subjects significantly predicted the time to learn [proportion of explained variance (R^2) = 0.44, $P = 0.003$] and the errors ($R^2 = 0.38$, $P = 0.007$) performed in the virtual maze (Fig. 4). Large volumes were associated with a better performance than small volumes, respectively. All other regression models were not significant.

The volume of left-sided hippocampus and posterior PHG (group TLE-left) or right-sided hippocampus and posterior PHG (group TLE-right) were then entered into multiple regression analyses (method: stepwise; significance level for selecting variables: $\alpha = 0.05$). Total brain volume or temporal lobe volume were entered as further predictors to control for the influence of brain size and total lesion size, respectively. Considering subjects of the TLE-right group, only the volume of the right posterior PHG significantly predicted the time to learn ($R^2 = 0.44$, $P = 0.003$) and the errors ($R^2 = 0.38$, $P = 0.007$) performed in the virtual maze, and the addition of hippocampal volume and total brain volume or temporal lobe volume did not significantly improve the prediction. All other regression models were not significant.

Influence of neuropsychological variables

Multiple regression analyses (method: stepwise; significance level for selecting variables: $\alpha = 0.05$) were performed for the time to learn and the errors performed in the virtual maze by subjects of the TLE-right group with the predictors right-sided posterior PHG volume and pre- or postoperative visual memory measures. Posterior PHG volume significantly predicted the errors and the time to learn the virtual maze (errors: $R^2 = 0.38$, $P = 0.007$; time to learn: $R^2 = 0.44$, $P = 0.003$), and the addition of preoperative visual memory measures did not significantly improve the prediction. Considering postoperative memory capacity, visual memory scores (errors: $R^2 = 0.52$, $P = 0.001$; time to learn: $R^2 = 0.22$; $P = 0.007$) and right-sided posterior PHG volume (errors: $R^2 = 0.19$, $P = 0.006$; time to learn: $R^2 = 0.44$, $P = 0.003$) significantly predicted performance in the virtual maze.

Discussion

Summary of findings

To our knowledge, the present study is the first to investigate egocentric navigation and memory storage in a virtual maze lacking any topographical landmarks, and to test the effects of posterior PHG lesions on task performance. We found that TLE subjects with right-sided removals were significantly impaired in learning the virtual maze (cf. Table 3). An analysis of subgroups of subjects with and without posterior PHG lesions indicated significantly impaired performance of TLE-right subjects with posterior PHG lesions (group TLE-right+) when compared with the other lesion groups (Table 3 and Fig. 3). Accordingly, right posterior PHG volume of TLE-right subjects significantly predicted virtual maze performance, indicating stronger impairments of subjects with smaller volumes (cf. Fig. 4).

The right posterior PHG subserves egocentric memory

Lesions of our TLE subjects principally covered the anterior PHG, i.e. the perirhinal and entorhinal cortices, and the anterior parts of the hippocampus. Those subjects in which lesions extended into the right-sided posterior PHG (group TLE-right+) showed significantly greater impairments in learning the virtual maze than subjects of group TLE-right–, who did not differ significantly from control subjects. It may be concluded that the impairments of subjects of group TLE-right+ mainly depended on lesions of their posterior PHG. The present results are supported by a functional MRI study (G. Weniger, K. Boucsein and E. Irle, unpublished data) which applied the same task as used in the present study in healthy volunteers. Besides parietal and frontal activation, we observed increased activity within the posterior PHG at decision points of the virtual maze. A previous study by Janzen & van Turennout (2004) found parahippocampal responses being selectively increased during recognition of objects having been placed at decision points of a virtual museum, thus also indicating an important role of the PHG for the storage of navigationally relevant locations.

The posterior PHG of the macaque brain was shown to be strongly connected with the posterior parietal cortex (Cavada & Goldman-Rakic, 1989; Suzuki & Amaral, 1994; Lavenex *et al*., 2002) and the striatum (Goldman-Rakic & Selemon, 1986; Suzuki, 1996). Single unit recordings in macaque monkeys have demonstrated that egocentric representations of visual space are modulated by posterior parietal

(Andersen *et al*., 1985) and striatal (Muller *et al*., 1996) neurons. It seems possible that the posterior PHG contributes to the long-term memory consolidation of egocentric spatial information by its feedback projections to the posterior parietal cortex and the striatum. This assumption is supported by lesion studies in humans, demonstrating that lesions of the posterior PHG, but not lesions of the hippocampus or perirhinal cortex, delay memory-guided saccades in a task assessing spatial memory in a retinotopic, egocentric frame of reference (Ploner *et al*., 1999, 2000).

An additional role of the posterior PHG for egocentric representation and navigation in visual space is also likely. Single unit recordings in monkeys suggest that information about whole-body motion as well as about where the monkey is looking in its environment ('spatial view cells') are located in the hippocampus and parahippocampal region (O'Mara *et al*., 1994; Rolls, 1999). Neurons responding to the head direction of an animal ('head direction cells'), independent from the place where the animal is, were found in the presubiculum of rats (Muller *et al*., 1996) and monkeys (Robertson *et al*., 1999). Single unit recordings in humans with TLE have revealed that the majority of parahippocampal neurons respond to views of landmarks within a virtual town; however, place-responsive cells within the PHG were also frequent, and 30% of the view-responsive cells within the PHG responded as a function of the subject's location in the virtual environment (Ekstrom *et al*., 2003). Accordingly, a functional imaging study provided evidence that the human posterior PHG responds equivalently to place changes and viewpoint changes and that these responses are stronger than those to object changes (Epstein *et al*., 2003).

Taken together, there is evidence that the posterior PHG is involved in the memory of object landmarks as well as in the representation and memory of the spatial relationships between the body and its environment, i.e. egocentric spatial information. Access to both streams of spatial information may enable the posterior PHG to construct a global and comprehensive representation of spatial environments. Accordingly, lesions of the posterior PHG should impair both kinds of navigational strategies. The results of the present study support this interpretation: subjects with right-sided lesions of the posterior PHG were strongly impaired in learning the virtual maze, regardless of whether they tried to memorize egocentric information or tried to construct a survey perspective of the maze, i.e. a visual scene or a cognitive map. However, it must be kept in mind that the virtual maze did not contain any landmarks and that all intersections appeared identical when approached from different directions, thus forcing subjects to learn the maze using egocentric navigation strategies. Using egocentric memories to build up a survey perspective of the maze should be possible only in later trials of the task, when most or all of the maze has already been stored in an egocentric frame of memory.

Differential contributions of the hippocampus and posterior PHG to spatial memory

Regression analyses revealed that larger lesions of the right-sided posterior PHG of our TLE subjects were significantly related to increasing deficits in egocentric maze learning, and that hippocampal volume did not significantly improve the prediction. ANCOVAs showed that after partialing out hippocampal volume, subjects with right-sided posterior PHG lesions (TLE-right+ group) were still impaired in virtual maze learning as compared with subjects of the TLE-right– group. Although the results of the present investigation clearly point to an important role of the right-sided posterior PHG in spatial memory, it must be borne in mind that this is in the context of significant hippocampal damage as well. It may be that right-sided posterior PHG damage impairs performance on our virtual reality tasks, given that hippocampal damage exists as well.

Evidence from human and animal experimentation points to differential contributions of the hippocampus and posterior PHG to visuo-spatial representation and memory formation. Single case studies investigating humans with relatively selective bilateral hippocampal damage suggest that the hippocampus has a greater involvement in allocentric than in egocentric spatial memory (Holdstock *et al*., 2000; Spiers *et al*., 2001b; King *et al*., 2002). Accordingly, neuroimaging studies investigating healthy humans in virtual environments have found that activation of the hippocampus mainly reflects processing locations, or route learning or recall from a survey perspective (Maguire *et al*., 1996b, 1997, 1998a; Mellet *et al*., 2000; Burgess *et al*., 2001a; Shelton & Gabrieli, 2002; Hartley *et al*., 2003).

Methodological considerations

Our data do not permit the determination of the influence of temporopolar lesions on virtual maze performance of our TLE subjects, as all subjects had undergone complete removal of the temporopolar cortex. However, subjects without right posterior PHG lesions were less impaired than subjects with right posterior PHG lesions despite removal of the temporal pole in these cases. Multiple regression analyses demonstrated that smaller right posterior PHG volumes were related to increasing deficits and that temporal lobe volume (i.e. total lesion size) did not significantly improve the prediction. The empirical evidence so far suggests that the primate temporopolar cortex has a putative role in object recognition and memory rather than in spatial memory (Nakamura & Kubota, 1996). Furthermore, all TLE subjects of the present study had part removals of the amygdala, which may have had an effect on learning the virtual maze. We are not aware of lesion studies in the human explicitly testing the effects of selective amygdala lesions on spatial memory. However, lesion studies in nonhuman primates suggest that spatial relational memory is not impaired by lesions of the amygdaloid complex (Alvarado *et al*., 2002).

The amount of tissue removal in TLE surgery partly depends on the extent of epileptogenic pathology. Accordingly, TLE subjects with a more severe illness and greater memory impairment probably received larger removals, leading to an assignment to a group with posterior PHG lesions. However, our lesion groups did not differ significantly with respect to illness severity and preoperative and postoperative intellectual and mnemonic functioning (cf. Table 1 and Results, 'Demographic and clinical variables'). Postoperative *WMS-R* performance correlated with postoperative hippocampal volume, and the lesion effects on virtual maze performance were unchanged when preoperative or postoperative mnemonic capacity was controlled for (cf. Results, 'Influence of neuropsychological variables'). TLE subjects with hippocampal sclerosis (see Methods, 'Subjects') did not differ from TLE subjects without hippocampal sclerosis on the performance in the virtual maze ($P > 0.20$). Nevertheless, taking into account the correlation of the various TLE pathologies with resection type, the risk of incorrectly attributing specific functions to particular parts of the temporal lobe cannot be completely ruled out.

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Abbreviations

3D MRI, three-dimensional magnetic resonance imaging; PHG, parahippocampal gyrus; ROI, region of interest; TLE, temporal lobe epilepsy.

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