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Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex

VERONIQUE D. BOHBOT,*¶ MIROSLAV KALINA,† KATERINA STEPANKOVA,‡ NATASA SPACKOVA,‡ MICHAEL PETRIDES§ and LYNN NADEL*

* Psychology Department and ARL Division of Neural Systems, Memory and Aging, University of Arizona, Tucson, AZ 85724, U.S.A.; † Department of Neurology, Hospital Na Homolce, Prague 151 19, Czech Republic; ‡ Neurology Clinic, 1st Medical Faculty, Charles University, Prague 120 00, Czech Republic; § Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada H3A 2B4

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Abstract—Spatial memory tasks, performance of which is known to be sensitive to hippocampal lesions in the rat, or to medial temporal lesions in the human, were administered in order to investigate the effects of selective damage to medial temporal lobe structures of the human brain. The patients had undergone thermo-coagulation with a single electrode along the amygdalo-hippocampal axis in an attempt to alleviate their epilepsy. With this surgical technique, lesions to single medial temporal lobe structures can be carried out. The locations of the lesions were assessed by means of digital high-resolution magnetic resonance imaging and software allowing a 3-D reconstruction of the brain. A break in the collateral sulcus, dividing it into the anterior collateral sulcus and the posterior collateral sulcus is reported. This division may correspond to the end of the entorhinal/perirhinal cortex and the start of the parahippocampal cortex. The results confirmed the role of the right hippocampus in visuo–spatial memory tasks (object location, Rey–Osterrieth Figure with and without delay) and the left for verbal memory tasks (Rey Auditory Verbal Learning Task with delay). However, patients with lesions either to the right or to the left hippocampus were unimpaired on several memory tasks, including a spatial one, with a 30 min delay, designed to be analogous to the Morris water maze. Patients with lesions to the right parahippocampal cortex were impaired on this task with a 30 min delay, suggesting that the parahippocampal cortex itself may play an important role in spatial memory.

Key Words: medial temporal lobes; navigation; spatial; amnesia; human; rat; hippocampus; parahippocampal cortex; anterior collateral sulcus; topographical memory; environmental agnosia.

Introduction

Bilateral damage to the medial temporal lobe (MTL) causes severe learning and memory impairments [10, 24, 47, 58]. These impairments involve the acquisition of new information about facts, faces, events and places. In the past 40 years, many attempts have been made to define the nature of these memory deficits and attribute them to damage of specific brain structures within the broad MTL region. In patients, this task has been complicated because of the difficulty in obtaining lesions localized to specific brain structures. On the other hand, considerable research has been carried out with experimental animals in order to specify the role of particular medial temporal lobe structures, with an initial focus on various components of the hippocampal formation [25, 56, 57].

Although research in rats, monkeys and humans originally took divergent routes, recent findings support a common role for the hippocampus in learning and remembering about space, across species [4, 38, 43, 45, 48]. While broader theories of hippocampal function have been proposed [9, 39, 49, 50], but see [34, 35], all agree that the hippocampus is important in remembering information about space. Work with rats has strongly supported the critical importance of hippocampal function for learning about space, both in terms of the activity

¶To whom all correspondence should be addressed: McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, 3801 University St, Montreal, Quebec, Canada H3A 2B4. Tel.: (514) 398-1996; fax: (514) 398-8952; e-mail: vero@bic.mni.mcgill.ca

patterns of single hippocampal neurons [36, 37, 55] and in terms of the impairments induced by lesions to the hippocampus [5, 10, 38].

Similar findings have been obtained from work in monkeys. Location specific neurons have been recorded from the monkey hippocampus [40, 46]. Lesions limited to the monkey hippocampus do not contribute to an impairment on object recognition memory, for example on the Delayed Non-Match-to-Sample task [21, 22, 25, 30, 31]. In contrast, monkeys with lesions involving the hippocampus and adjacent parahippocampal cortex are severely impaired on a task requiring memory for object location [4, 43]. Thus, the monkey hippocampal formation is critically involved in memory for locations, while recent work [21, 22, 59, 60] suggest that the perirhinal cortex, which receives its main projections from areas TE and TEO [51], may be particularly involved in visual object memory. There is growing evidence that the object-place task [42] as well as topographical memory [18] in humans activate the parahippocampal gyrus rather than the hippocampus, suggesting that the location memory deficit reported in Parkinson *et al.* [43] could have been caused by damage to the former rather than to the latter [26].

In patients, unilateral medial temporal lobe damage yields material-specific impairments. Extensive damage to the right medial temporal region, including the hippocampus, impairs spatial memory, while similar damage in the left hemisphere impairs verbal memory [23, 48]. In a study of memory for the spatial location of objects, Smith and Milner [48] found that patients with left or right temporal lobe excisions performed as well as control subjects when asked to recall the location of objects immediately after presentation. However, the patients with right temporal excisions including extensive resections of the hippocampal region were impaired when a delay of 4 min was imposed between presentation and recall. These results show that patients with right hippocampal region lesions were able to encode the spatial location of the objects, but they rapidly forgot this information relative to patients with left temporal lesions, patients with smaller right hippocampal region lesions and normal control subjects.

The aim of the present study was to characterize further the deficit in learning and memory resulting from lesions to specific structures within of the medial temporal lobe region. The patients had undergone selective thermocoagulation lesions to the amygdalo-hippocampal region in an attempt to alleviate severe and pharmacologically intractable epilepsy. They were tested on a range of verbal, non-verbal spatial and non-spatial memory tasks. Many of the spatial memory tasks were adapted from tasks used to demonstrate impairments in rats with hippocampal lesions, to allow for cross-species comparisons. Digital magnetic resonance imaging (MRI) was used to evaluate the specific areas damaged in these patients. It was expected that patients with lesions to the right hippocampal formation would show impairments in spatial memory, but would not be significantly impaired on non-spatial memory tasks.

Subjects

There were two control groups in the present investigation: one group consisted of patients with back-pain problems, but without epileptic problems and the other, patients who had epilepsy but did not undergo brain surgery.

Back-pain control group

These eight control patients were staying at the Department of Neurology, First Medical Faculty, Charles University, Prague, Czech Republic, for back-pain problems. They were selected to be as similar as possible in age, socio-economic background and education to the patients with lesions within the medial temporal region (Table 1).

Epileptic patient control group

Ten epileptic patients who had not undergone brain surgery, suffering from complex partial seizures of probable temporal origin were used as controls (Table 1). They were out- and in-patients of the Departments of Neurology, First Medical Faculty of the Charles University, Prague, Czech Republic or of the Na Homolce Hospital, Prague, Czech Republic. The patients were on non-toxic anti-epileptic drug therapy similar to that received by the operated patients. This is a good control group because it comprises patients who suffered from the same neurological disorder as the brain-operated patient groups.

Brain-operated groups

These groups consisted of 14 patients who underwent brain surgery at the Department of Neurosurgery, Center Military Hospital, Prague, Czech Republic in an attempt to alleviate pharmacologically intractable epilepsy (Table 1). Patients with Wechsler IQs below 75, psychiatric disorders, or with gross brain atrophy were excluded from the study. One patient (KoA) who had a left glass eye, but had otherwise normal vision, remained in the study. All patients were right handed. They were tested 4–17 years ($M = 9$ years) postoperatively. Three patients were seizure-free after the operation, eight patients experienced a 50% decrease in their seizures, and three patients continued to have seizures after the operation. All patients were on anti-epileptic drug therapy at the time of testing. None of the patients had clinical symptoms of overdose. The anti-epileptic drug therapy included one,

Table 1. Subjects

Group	Sex		Age		Wechsier IQ		Wechsler memory scale	
	M	F	Mean	Range	Mean	Range	Mean	Range
Back-pain patient control	5	3	41.4	29–57	119	96–133	126	98–143
Epileptic patient control	5	5	26.5	17–43	99.3	80–129	107.1	99–143
Right hippocampal	5	1	36.8	29–49	103.2	88–131	105.2	84–126
Right parahippocampal	1	2	40.3	38–42	88.0	82–98	88.3	81–97
Left hippocampal	1	3	44.5	37–53	91.8	87–96	94.8	89–103
Left parahippocampal	1	0	34	—	99	—	87	—

two, or three of the following: carbamazepin, primidone, valprolate, phenytoin, clonazepam, lamotrigine, vigabatrin, barbiturate. The patients' performance was not affected by clinical or EEG seizures on the day of testing.

Localization of lesions

On the basis of the T1-weighted MRIs, the following medial temporal lobe structures were examined in each patient. Some included neighboring structures depending on the resolution of MRI. All brains were transformed into the Talairach and Tournoux standard stereotaxic space [52].

Hippocampus (*H*). This included the hippocampus proper (CA fields), the dentate gyrus and the subicular complex. In classical neuroanatomy terms, the hippocampus includes parts of the uncus, gyrus uncinatus, the band of Giacomini and the intralimbic gyrus.

Amygdala (*A*). All of the amygdala, including the cortical nucleus (semilunar gyrus) and the periamygdaloid cortex.

Entorhinal cortex (*EC*). The part of the medial temporal cortex that surrounds the amygdala (gyrus ambiens) and the hippocampus and which lies medial to the anterior collateral sulcus [3] (Fig. 1). The posterior limit of the entorhinal cortex was defined by the end of the anterior collateral sulcus (Fig. 1). The anterior collateral sulcus in humans can be considered the equivalent of the rhinal sulcus in monkeys in that it maintains a close relation to the entorhinal cortex [44].

Perirhinal cortex (*PR*). This area has the same anterior-posterior border as the entorhinal cortex and follows the entorhinal cortex to form the medial and lateral bank of the anterior collateral sulcus [3] (Fig. 1).

Parahippocampal cortex (*PH*). This is the cortex which lies posterior to the entorhinal cortex and the perirhinal cortex, which continues along the posterior collateral sulcus (Fig. 1), until the posterior limit of the hippocampus (i.e. posterior parahippocampal gyrus).

The parahippocampal, perirhinal and entorhinal cortices are considered here as three distinct areas formed by different architectonic types and not taken together to comprise the classical neuroanatomical parahippocampal gyrus. Other structures that are part of the medial temporal lobes, such as the piriform cortex and adjacent inferior temporal cortex, fusiform, or the retrosplenial cortex, were usually intact in the brain-operated patients and will therefore no longer be considered. Only the areas damaged are described; structures not mentioned were intact. Damage of less than 4 mm in radius was considered to be minor and is not further mentioned. Most of the lesions to the perirhinal or entorhinal cortices were very small and were accompanied by damage to the hippocampus or parahippocampal cortex. Patients with these lesions were therefore included into their corresponding hippocampal or parahippocampal group. Based on the MRI scans, the following groups were identified.

Right hippocampus. Six patients who had damage to the right hippocampus were included in this group. Patient BS had a complete right hippocampal lesion, some damage to the right amygdala, and minor damage to the anterior portion of the right perirhinal cortex and the right inferior temporal neocortex (Fig. 2a). Patient FL had damage to the right anterior hippocampus and additional damage to the amygdala bilaterally (Fig. 2a). Patient MH had damage to the right anterior hippocampus, some damage to the right amygdala, as well as slight damage to the anterior portion of the perirhinal cortex and to the white matter around the parahippocampal cortex (Fig. 2b). Patient KoA had damage to the right anterior hippocampus, with additional damage to the right amygdala and slight damage to the anterior portion of the right perirhinal cortex (Fig. 2b). Patient KP had a right hippocampal lesion and additional damage to the right amygdala only (Fig. 2c). Patient MJ had a right anterior lesion to the hippocampus with additional damage to the right amygdala (Fig. 2c). Most importantly, the subjects in this group did not have damage to the parahippocampal cortex.

Right parahippocampal cortex. Three patients were included in this group. All had damage to the right parahippocampal cortex. In addition to the lesion in the parahippocampal cortex, patient PV had damage to the right anterior hippocampus and the right perirhinal cortex (Fig. 3a). PM had damage to the right parahippocampal cortex, anterior and posterior portions of the right hippo-

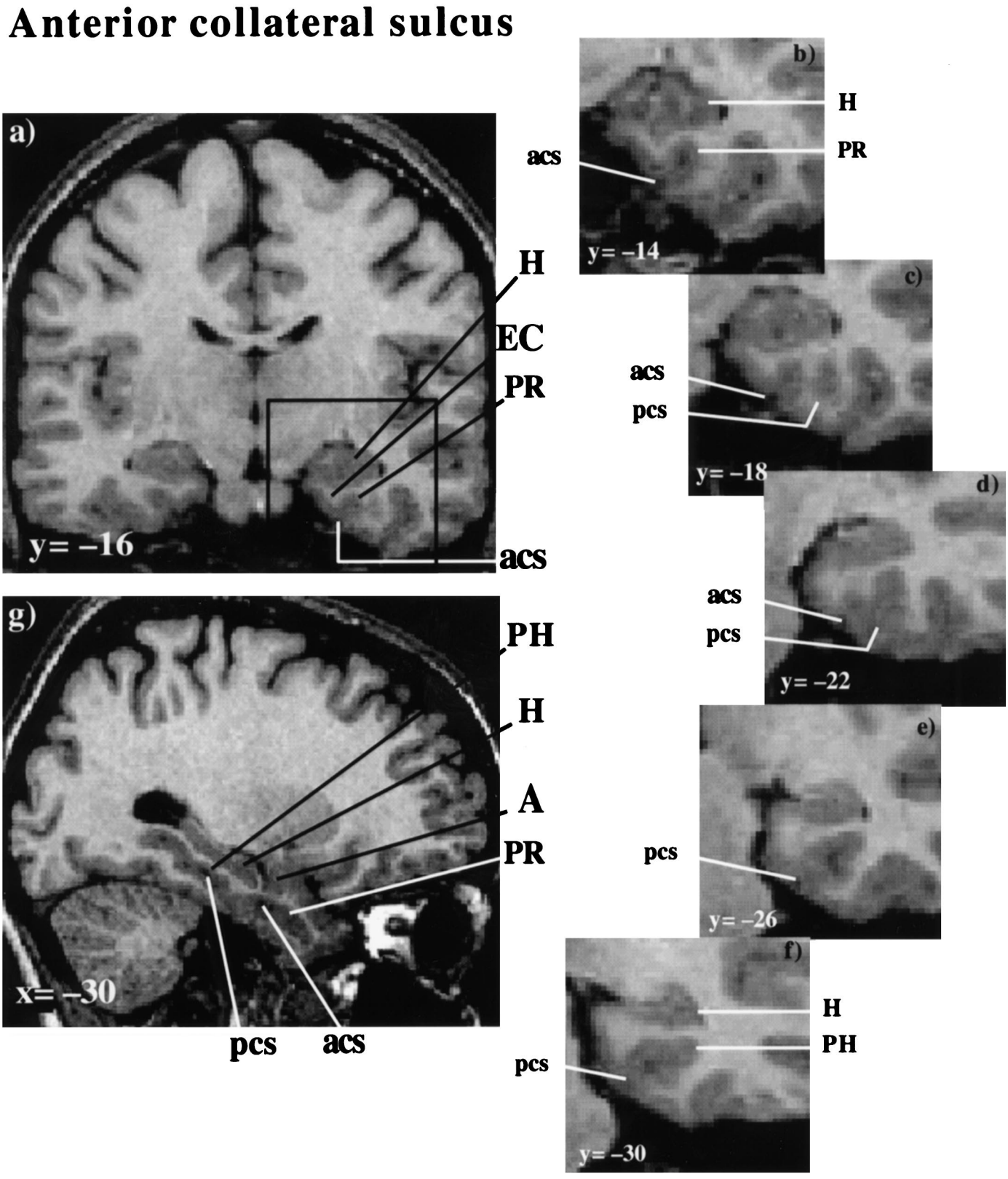

Fig. 1. This figure shows how the anterior collateral sulcus ends while another nearby sulcus, the posterior collateral sulcus, forms and runs posteriorily until the end of the hippocampus. (a) is a coronal section of a normal subject's MRI at the stereotaxic level $y = -16$ to show the hippocampus, entorhinal cortex, perirhinal cortex and the anterior collateral sulcus. The inset square in (a) represents the part of the brain which is displayed in (b–f) (sections every 4 mm). The anterior collateral sulcus is present in (b) and (c) but fades in (d) and disappears in (e). The posterior collateral sulcus appears in (c), lateral to the anterior collateral sulcus and continues until the posterior limit of the hippocampus in (f). This separation of the anterior and posterior collateral sulcus can be seen in the MRIs of the patients with lesions, and it is especially clear in patient PV. In (g) a sagittal section ($x = -30$) shows that the anterior and posterior parts of the collateral sulcus are divided. *Abbreviations*: H: hippocampus, A: amygdala, EC: entorhinal cortex, PR: perirhinal cortex, PH: parahippocampal cortex, acs: anterior collateral sulcus, pcs: posterior collateral sulcus. Coordinates are in the Tailarach and Tournoux [47] stereotaxic space: y refers to the mm behind the anterior commissure and x, mm from the midline.

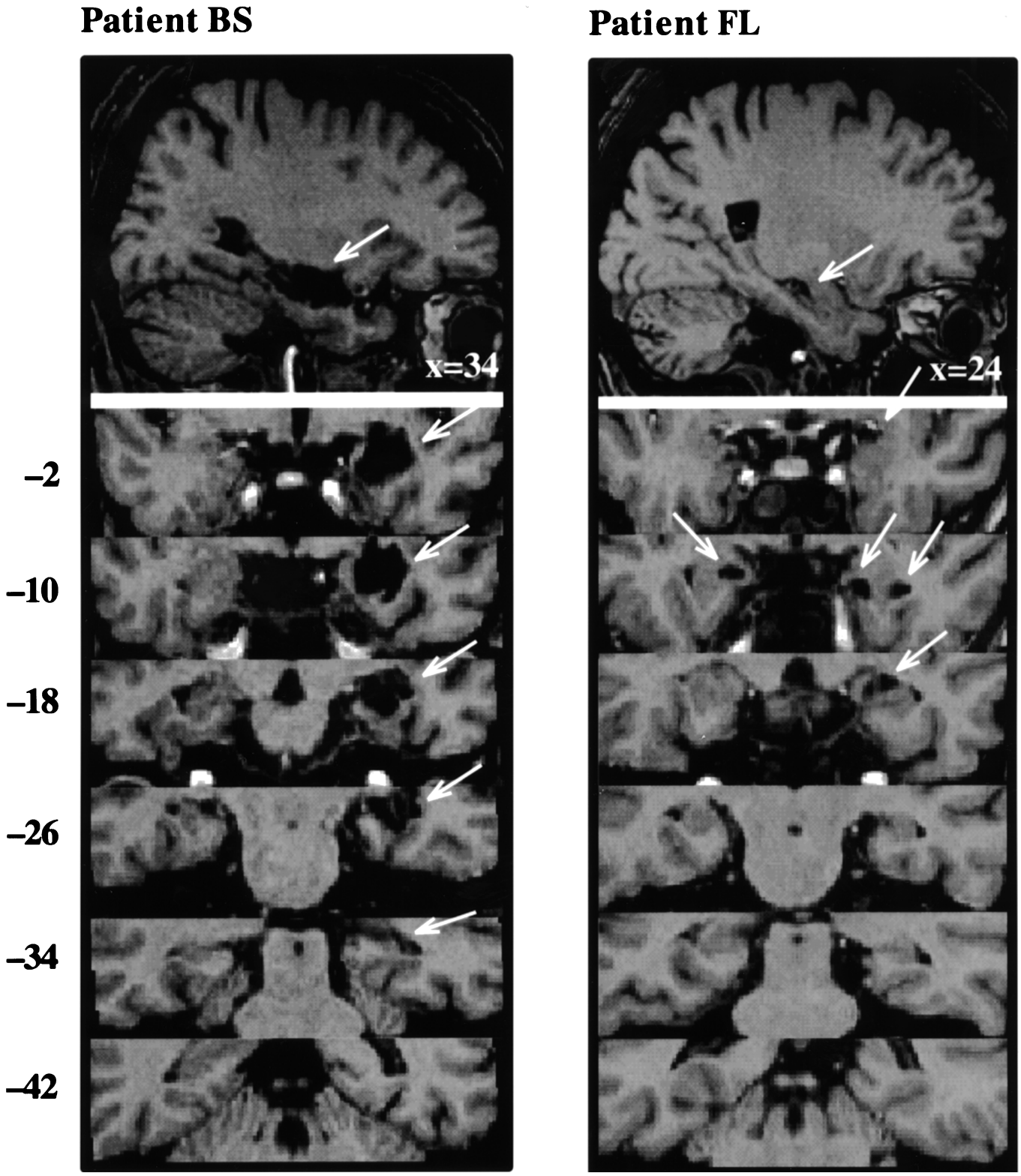

Fig. 2a. A sagittal section and coronal sections from the group with lesions to the right hippocampus. Arrows indicate the location of the lesions. Dark areas which are not indicated by arrows correspond to ventricular space.

campus, the right amygdala, but no damage to the perirhinal or entorhinal cortex (Fig. 3a). KrA had damage to the parahippocampal cortex, the entorhinal and perirhinal cortex, but no damage to the right hippocampus (Fig. 3b).

Left hippocampus. Four patients with lesions to the left hippocampus were included in this group (FA, KS, SV, VP). Patient FA had damage to the left anterior hippocampus, and left amygdala (Fig. 4a). Patient KS had damage to the left anterior hippocampus, left amygdala

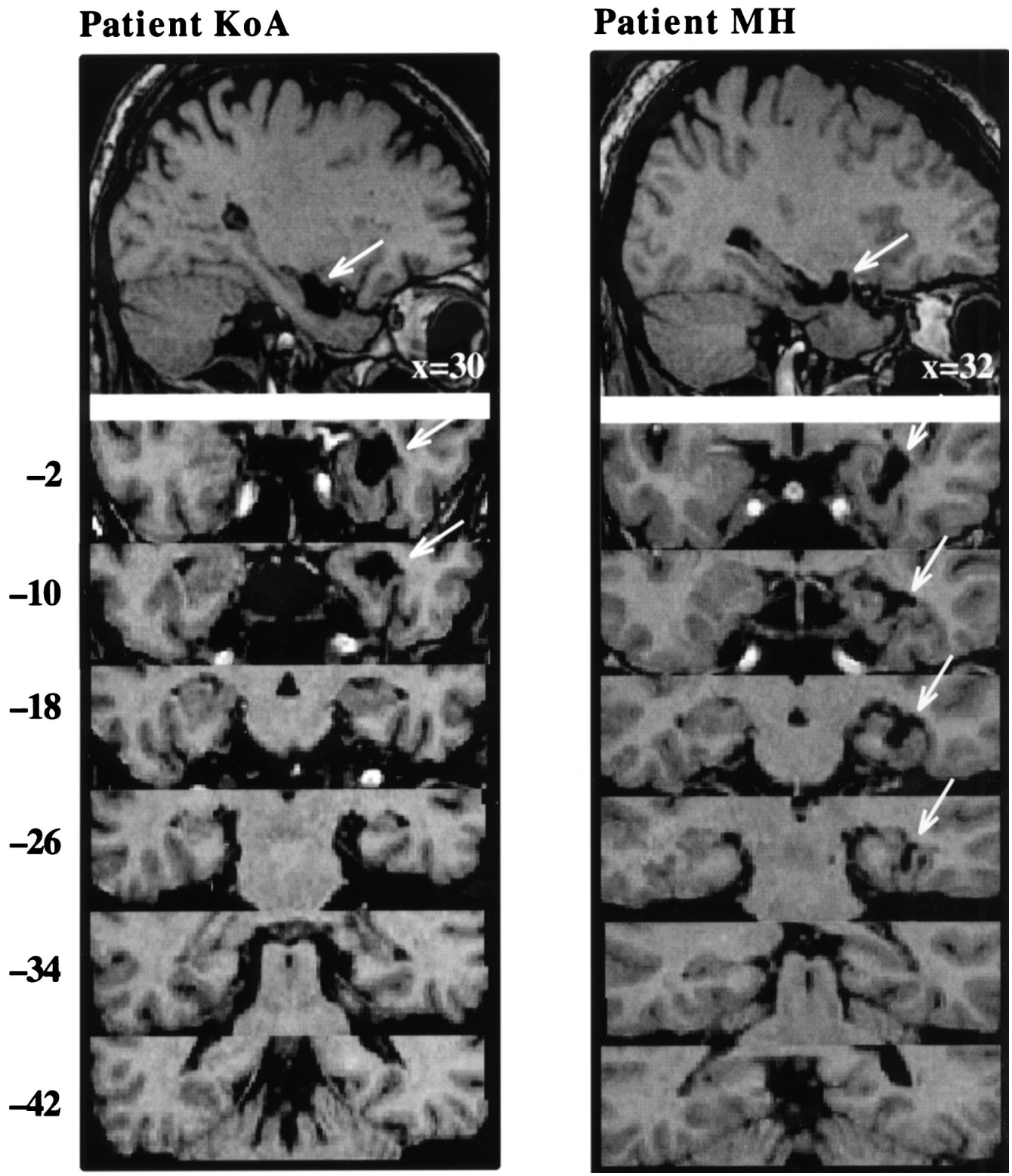

Fig. 2b. A sagittal section and coronal sections from the group with lesions to the right hippocampus. Arrows indicate the location of the lesions. Dark areas which are not indicated by arrows correspond to ventricular space.

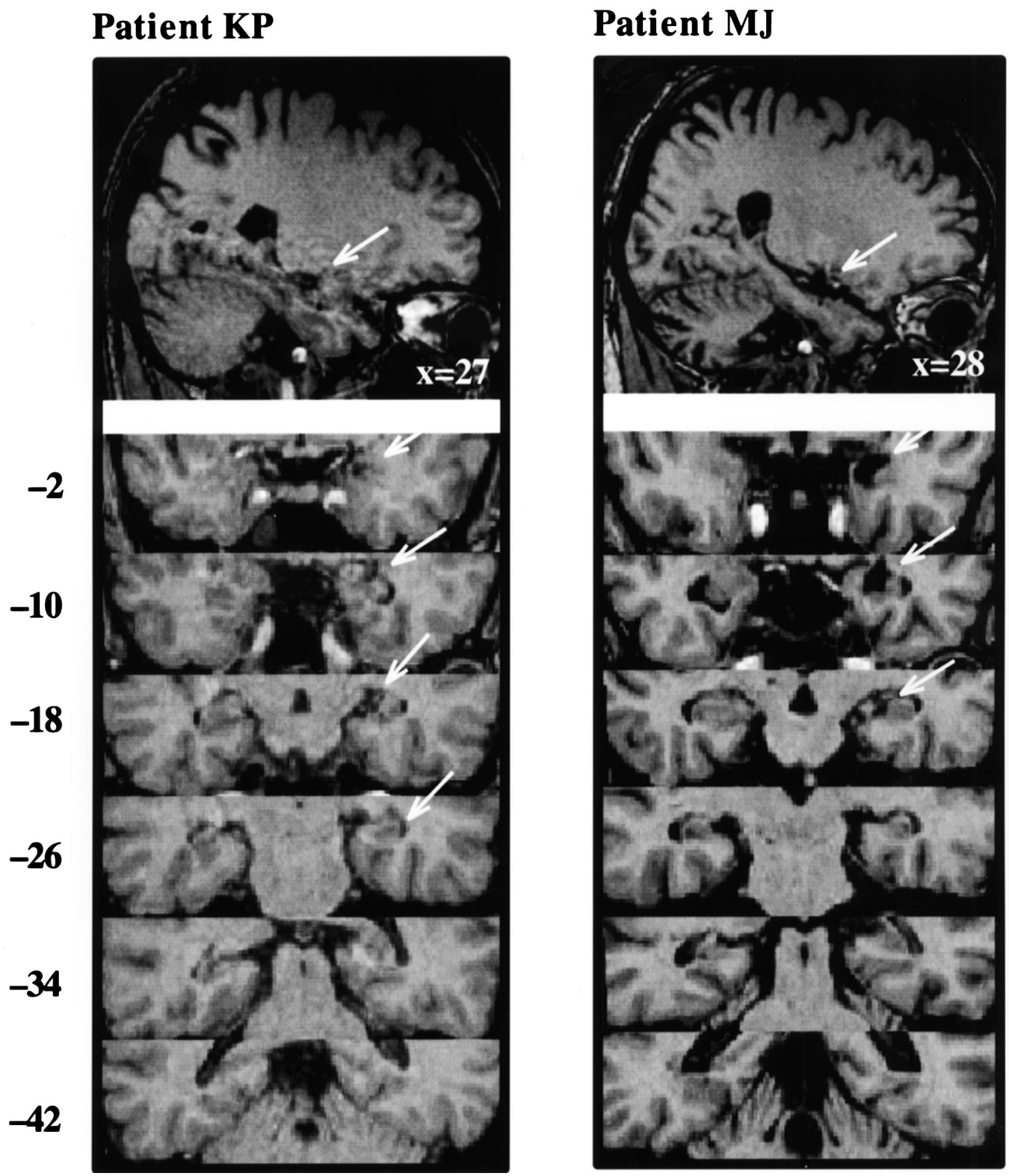

Fig. 2c. A sagittal section and coronal sections from the group with lesions to the right hippocampus. Arrows indicate the location of the lesions. Dark areas which are not indicated by arrows correspond to ventricular space.

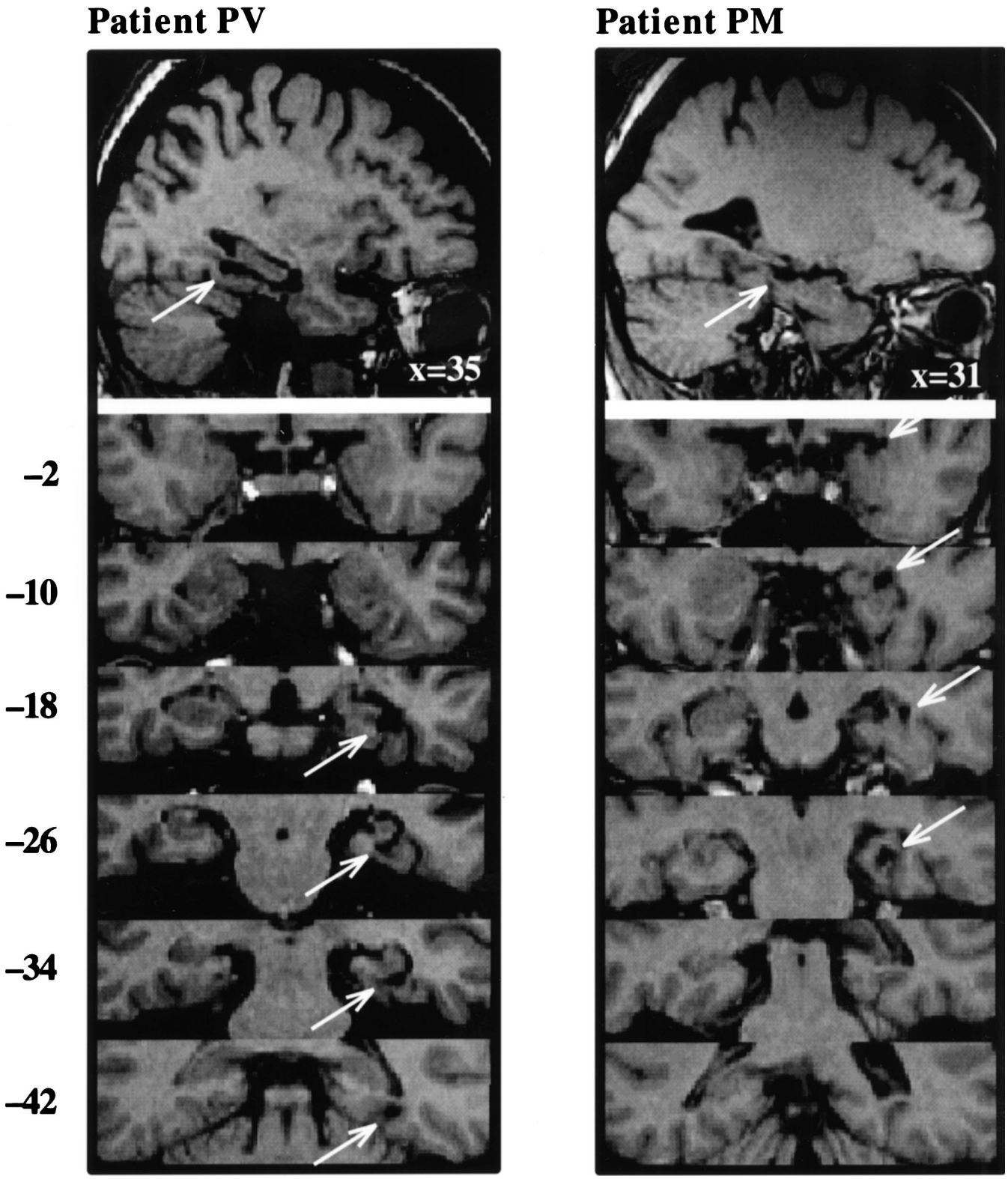

Fig. 3a. A sagittal section and coronal sections from the group with lesions to the right parahippocampal cortex. Arrows indicate the lesions. Dark areas which are not indicated by arrows correspond to ventricular space.

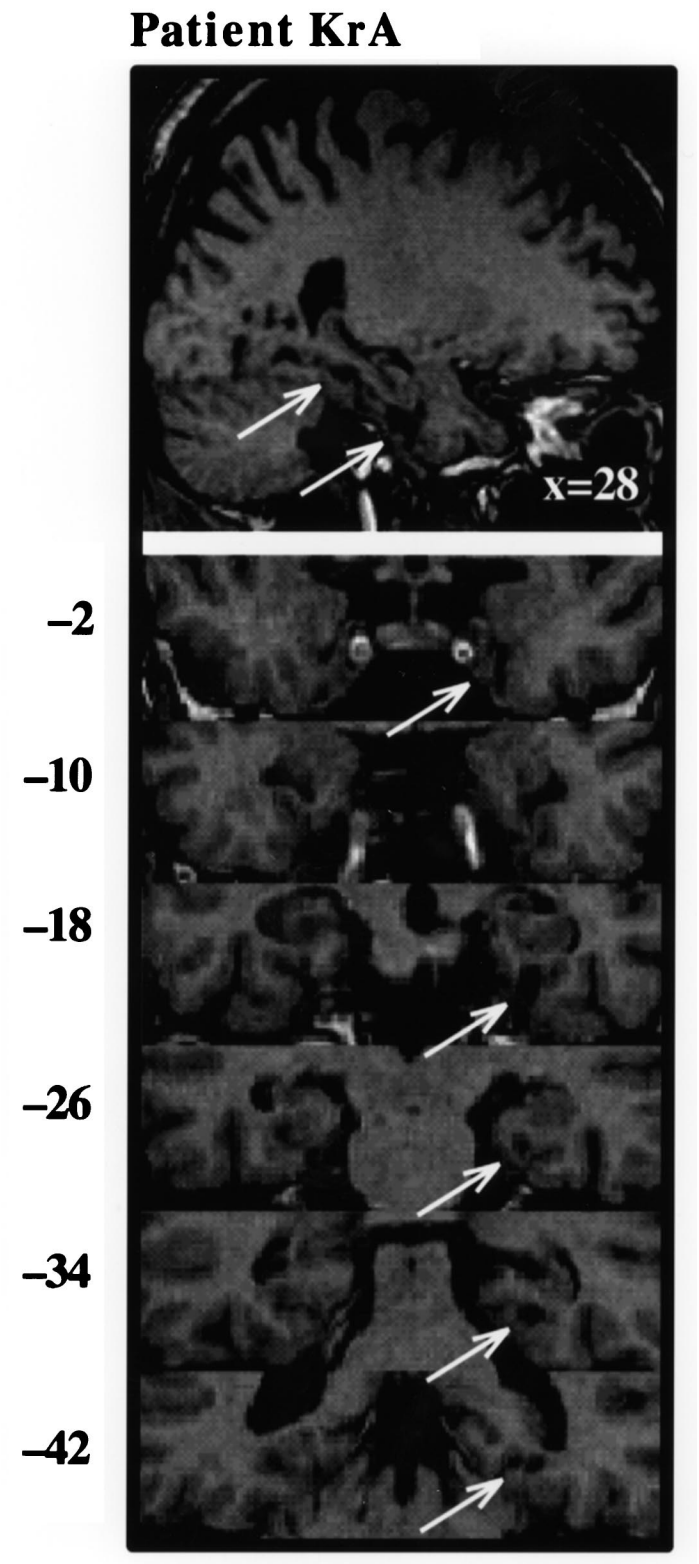

Fig. 3b. A sagittal section and coronal sections from the group with lesions to the right parahippocampal cortex. Arrows indicate the lesions. Dark areas which are not indicated by arrows correspond to ventricular space.

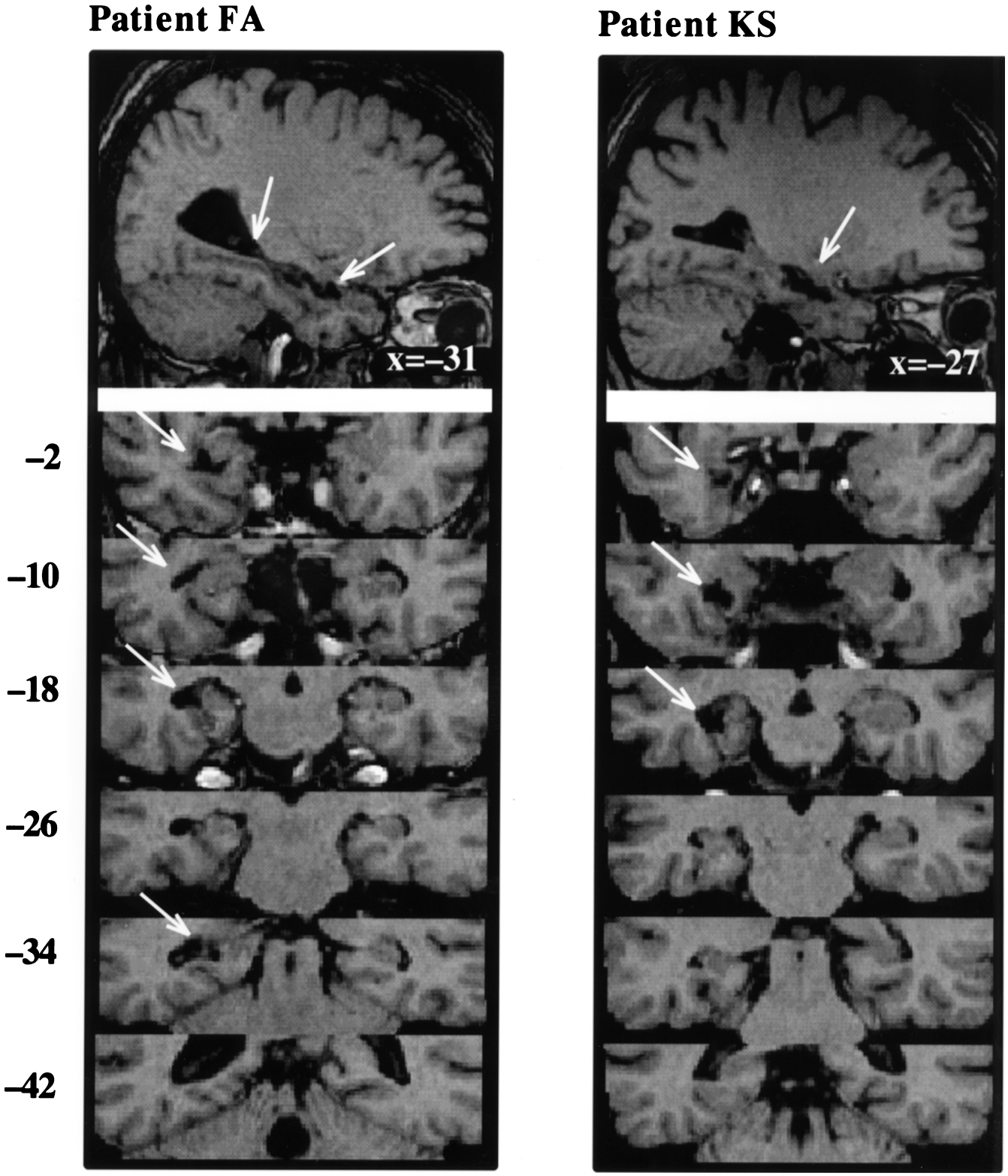

Fig. 4a. A sagittal section and coronal sections from the group with lesions to the left hippocampus. Arrows indicate the lesions. Dark areas which are not indicated by arrows correspond to ventricular space.

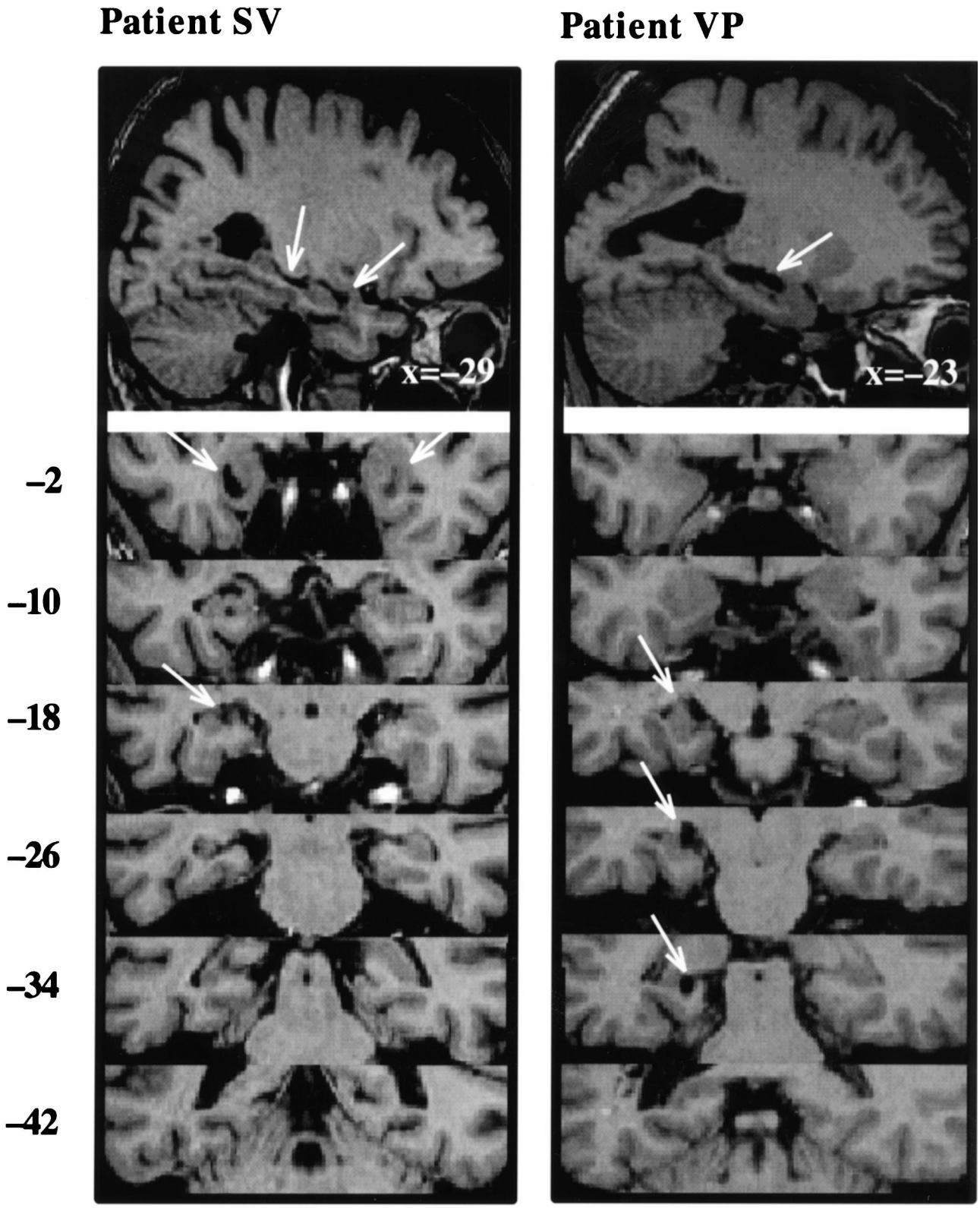

Fig. 4b. A sagittal section and coronal sections from the group with lesions to the left hippocampus. Arrows indicate the lesions. Dark areas which are not indicated by arrows correspond to ventricular space.

and minor damage to the left entorhinal and perirhinal cortex (Fig. 4a). Patient SV had damage to the posterior part of the left hippocampus, bilateral damage to the amygdala, and damage to the anterior portion of the left perirhinal cortex (Fig. 4b). Patient VP had a lesion to the left hippocampus and partial damage to the left amygdala (Fig. 4b).

Left parahippocampal cortex. One patient (SI) had damage to the left parahippocampal cortex. This patient also had some damage to the left amygdala and left perirhinal cortex (Fig. 5).

Materials and Procedure

Testing for all spatial tasks (with the exception of the Rey–Osterrieth Complex Figure) was carried out in a rectangular room, approximately 9 m^2. The room had two doors on opposite walls. There were several fixed cues in the room, such as a heater, a sink and a picture mounted on the wall. The floor of the room was carpeted. Details have been described elsewhere [7].

Non-visual spatial exploration

Three objects (chair, trash can and a stand/box) were placed in different locations in the experimental room, not too close to the walls nor to each other. The subjects were blindfolded and were allowed 3 min to explore the room with the objects for the first time. The subjects were instructed to try to remember the location of the objects for later recall. Visual cues were absent in this situation, and most, though not all, auditory cues were removed. The subjects had therefore to orient themselves mostly on the basis of vestibular, proprioceptive and kinesthetic input. After the 3 min had elapsed, the subjects were led out of the room, the door was shut and the blindfold removed. The patients were then asked to reconstruct from memory the location of the objects on an outline of the room that was drawn on a sheet of paper. The coordinates of the object icons on the paper were measured and translated into real space coordinates. The error was defined as the distance between the real location and the estimated location of the objects.

The invisible sensor task

This task was modeled on the Morris water maze that has been extensively used in studies of hippocampal function in the rat [27, 28]. In the Morris water task, rats search for a hidden platform that is in a fixed location under the surface of a circular pool. Since the platform can not be seen, the rats have to rely on various landmarks in the room to determine the position of the hidden platform. Performance on this spatial task is severely impaired by hippocampal lesions in rats [5, 28]. A dry version of the Morris water task was created for human subjects by hiding a sensor under the carpet of the room. The sensor was placed away from the walls and away from major cues, such as the heater or the sink. The sensor emitted a pleasant sound when stepped on and the subject was asked to locate it as quickly as possible, note its position with respect to the room landmarks, and then to return to the entrance (trial 1). About 30 s later, the subject was asked to enter the same room by the other door and to try to go straight to the location of the invisible sensor (trial 2). After a 30 min delay, trial 3 was administered starting from the same door as in trial 1.

Object location task

This recall task was designed to test memory for several objects and their different spatial locations [45, 48]. The subject was allowed to observe the location of four objects (briefcase, stand, kettle and flowerpot) in the experimental room, for 10 s. Soon afterwards, the subject had to reconstruct the spatial layout of the four objects on an outline of the room presented on a sheet of paper. As in the non-visual spatial exploration, the coordinates of the object icons on the paper were measured and translated into real space coordinates. The error was defined as the distance between the real location of objects and their estimated location by the subject. To solve this task, the patients must encode spatial relations and the location that each object occupied.

Immediately after the recall task, subjects were shown 4 maps with different arrangements of the 4 objects and they were asked to choose the map representing the previously seen objects (recognition). Subsequent to the recognition task, two objects from the testing room were switched positions, one was displaced and one remained at the same spatial location. The subjects were asked to enter the testing room, look at the objects for 10 s and step out of the testing room. The subjects were then asked whether anything had changed and one by one, whether each object had changed location, and finally whether two of the objects were switched. The subject had to correctly identify which two objects were switched, which object was displaced and which object remained at the same location in order to get a full score on this novelty detection task.

Eight-arm radial-maze

This task was modeled on another spatial memory task typically used to demonstrate impairments in spatial memory in rats with lesions to the hippocampus, namely the 8-arm radial-maze [39]. In this task, the animals must retrieve rewards from all eight arms without re-entering arms already visited. An analog of this task for patients was created by placing eight identical stands, 1.4 m from a central point at an equal distance from each other. On top of each one of these stands, there was an identical cup containing one coin. The subjects were instructed to retrieve all the coins, within the limit of 16 choices. Between each choice, the subjects had to return to the center of the room, the lights were turned off for approximately 10 s during which subjects were instructed to make a series of right or left turns in the dark. Before the next choice the lights were turned on again. Subjects had to select each stand only once for perfect performance on this task. The error score of each subject consisted of the number of stands re-visited during the first eight choices.

Non-spatial working memory

We also used a non-spatial memory task, presumably not dependent on the hippocampus, that could easily be compared with the eight-arm radial maze. We designed a task in which human subjects had to select from a collection of eight white cards placed on a table. These cards, made from thin cardboard, were folded in two or three to form various shapes. They differed only in shape, and each contained a number from 1–8, visible only after opening up the card. The subject sat in front of a table with all the cards on it and had to select each card

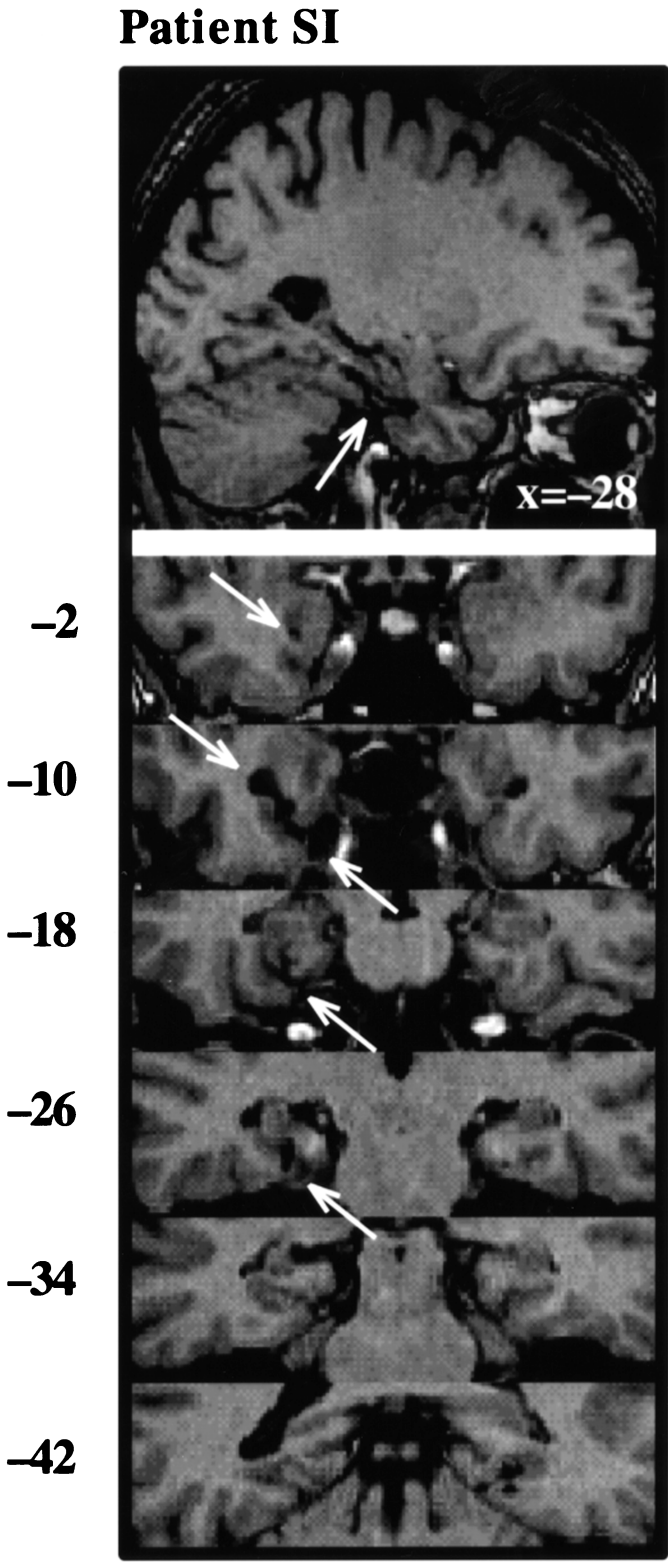

Fig. 5. A sagittal section and coronal sections from the patient with a lesion to the left parahippocampal cortex. Arrows indicate lesions. Dark areas which are not indicated by arrows correspond to ventricular space.

only once (based on the shape) in order to perform correctly in the task, within a limit of 16 choices. The subjects rotated their body (180° with the turning chair), while the cards were shuffled between choices, in order to prevent them from occupying the same spatial location from one choice to the next. Performance was measured by the number of errors made in the first eight trials, where the choice of an already selected card counted as an error.

Rey–Osterrieth complex figure

This is a standard neuropsychological test in which subjects must reproduce a complex drawing after having copied it [8]. Additionally, subjects were asked to reproduce it after a delay of 30 min.

Rey auditory verbal learning task

This is a standard neuropsychological test which involves learning a list of 15 words, by first hearing the list, then repeating it. After the five learning trials, an interference trial, composed of words not studied, is given. This is followed by the immediate recall trial reported in this study where subjects must recall the studied list. Subjects were asked to recall the list again after 30 min.

Results

Because the assumption of a normal distribution cannot be made in groups with small sizes, a non-parametric analysis of variance, the Kruskal–Wallis H test, was used to analyse the data. The single patient with a left parahippocampal lesion was not included in any of the statistical analyses. The five groups included in the analyses were: the back-pain control (BPC) and the epilepsy patient control (EPC) groups, as well as the patient groups with lesions to the right hippocampus (RH), right parahippocampal cortex (RPH), and left hippocampus (LH). Further analysis was done with the Wilcoxon Rank Sum Test for comparing two independent samples. First we compared the Back-Pain Control group to the Epilepsy Patient Control group and there were no significant differences on any test. The Back-Pain Control group and the Epilepsy Patient Control group were compared with each brain operated patient group. Planned comparisons were carried out where a prediction had been made, such as in the comparisons of the control group with the group with left hippocampal lesions on verbal memory tasks and the one with right hippocampal lesions on spatial memory tasks.

Non-visual spatial exploration

The mean error for the estimated position of each of the three objects in the blindfolded condition is shown in Fig. 6 for all groups. The statistical test approached significance, but there were no significant differences between the groups (Kruskal–Wallis rank test, $H = 8.75$, df. = 4, n.s.).

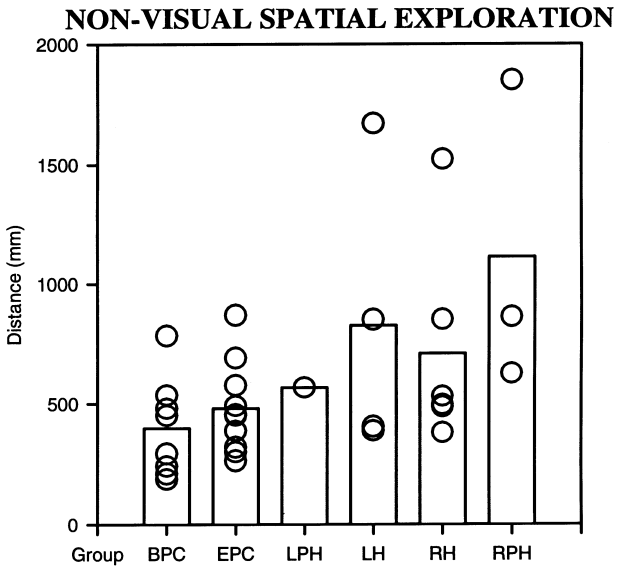

Fig. 6. Non-visual spatial exploration task: The error (in mm) is measured by the difference between the estimated position of the objects and the real position. Each bar represents the mean of a group. The scores of individual subjects for each group are also displayed. BPC: Back-Pain Controls; EPC: Epileptic Patient Controls; LPH: left parahippocampal cortex; LH: patients with damage to the left hippocampus; RH: right hippocampus; RPH: right parahippocampal gyrus.

The invisible sensor task

On immediate recall, all groups of patients rapidly found the invisible sensor (Fig. 7); there were no significant differences (Kruskal–Wallis rank test, $H = 1.15$,

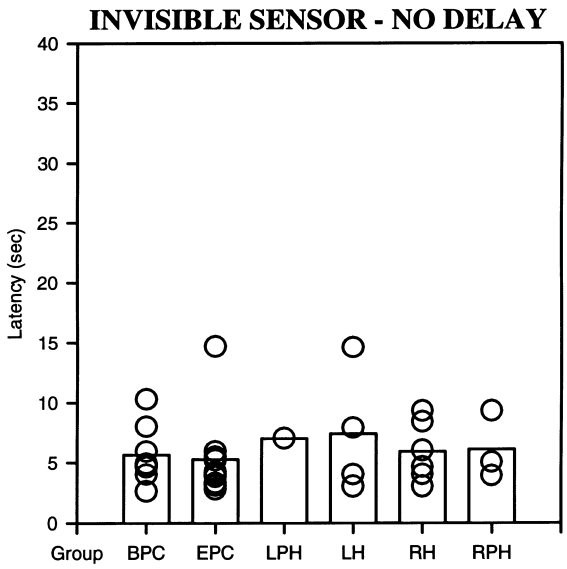

Fig. 7. Latencies for reaching the invisible sensor (trial 2), no delay. Details and labels are described in the legend of Fig. 6.

df. = 4, n.s.). Planned comparisons showed no differences between patients with lesions to the right hippocampus and the epilepsy patient controls in the Wilcoxon Rank Sum Test. Figure 8 shows the latencies to find the invisible sensor after the 30 min delay. After this delay, significant differences between the groups on the recall of the location of the invisible sensor were found (Kruskal–Wallis rank test, $H = 11.33$, df. = 4, $P < 0.05$). The one-tailed Wilcoxon test showed that the patients with lesions to the right parahippocampal cortex were impaired relative to the back-pain controls ($z = 2.35$, $P < 0.01$), and relative to the epilepsy patient controls ($z = 2.45$, $P < 0.01$). Patients with right or left hippocampal lesions were unimpaired on this task.

Object location task

The mean error for the estimated position of each one of the four objects for the different groups is shown in Fig. 9. The Kruskal–Wallis analysis of variance indicated that there were significant differences between the groups ($H = 9.65$, df. = 4, $P < 0.05$). Further analysis with the Wilcoxon Rank Sum Test showed that relative to the epileptic patient controls, both the right hippocampal group ($z = 1.90$, $P < 0.05$) and the right parahippocampal cortex group ($z = 1.77$, $P < 0.05$) were significantly impaired; in addition the right parahippocampal cortex group was significantly impaired relative to back-pain controls ($z = 2.14$, $P < 0.05$). The left hippocampal group was unimpaired on this task.

All subjects from the back-pain control group, epileptic control group, and brain-operated patient groups (right and left hippocampus, right and left parahippocampal cortex), recognized correctly the map representing the objects they previously observed, with the exception of one subject from the right hippocampal group and one subject from the right parahippocampal cortex group. All subjects were able to notice that changes were made to the layout of objects in the room with the exception of one subject from the right parahippocampal group. In summary, the back-pain control group scored 90% correct on our measure of novelty detection, the epileptic patient controls scored 83%, the left parahippocampal cortex subject scored 25%, the left hippocampus group scored 75%, the right hippocampus group scored 50%, and the right parahippocampal group had a 41% score.

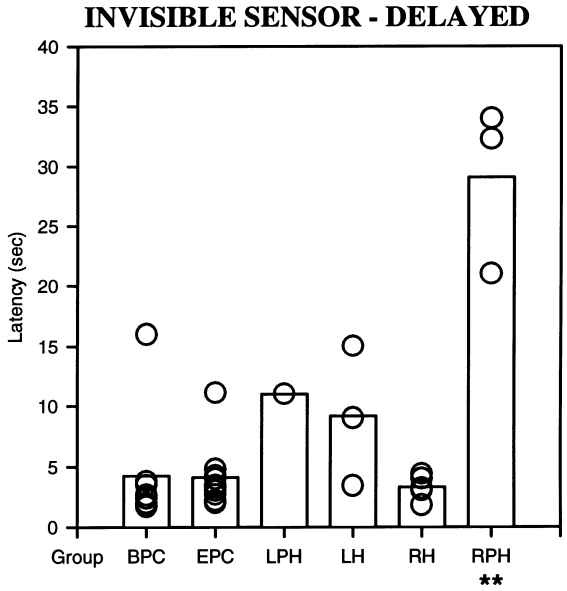

Fig. 8. Latencies for reaching the invisible sensor (trial 3) at a 30 min delay. Details and labels are described in the legend of Fig. 6. **: different from BPC and from EPC, $P < 0.01$.

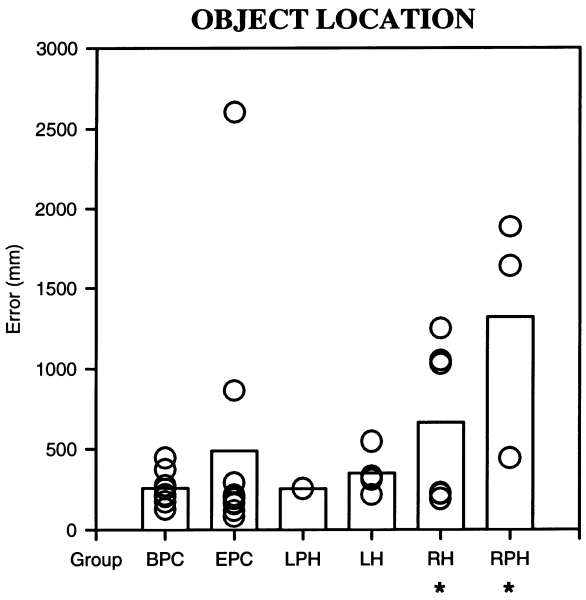

Fig. 9. Recall of the object location task: The error (in mm) is the difference between the estimated position of the objects and in the real position. Details and labels are described in the legend of Fig. 6. *: different from EPC $P < 0.05$.

Eight-arm radial-maze

The number of errors made in the first eight choices between the different groups are shown in Fig. 10. There were no significant group differences (Kruskal–Wallis test: $H = 4.16$, df. = 4, n.s.). Planned comparisons showed no differences between patients with lesions to the right hippocampus and the epilepsy patient controls with the Wilcoxon Rank Sum Test.

Non-spatial working memory

The number of errors made in the first eight choices are shown in Fig. 11. No significant group differences were detected (Kruskal–Wallis rank test, $H = 2.74$, df. = 4, n.s.).

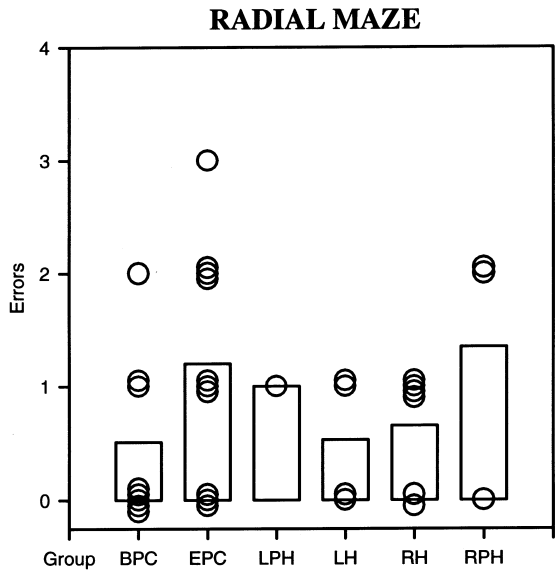

Fig. 10. Errors on the eight-arm radial-maze in the first eight choices. Because many ties occurred, the data were slightly separated in order to show the distribution of scores. Details and labels are described in the legend of Fig. 6.

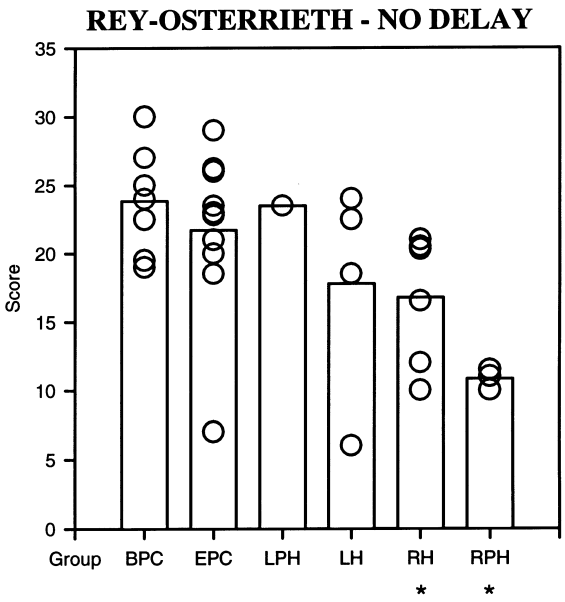

Fig. 12. Scores on the Rey–Osterrieth complex figure drawing task at zero delay. Details and labels are described in the legend of Fig. 6. *: different from BPC and from EPC $P < 0.05$.

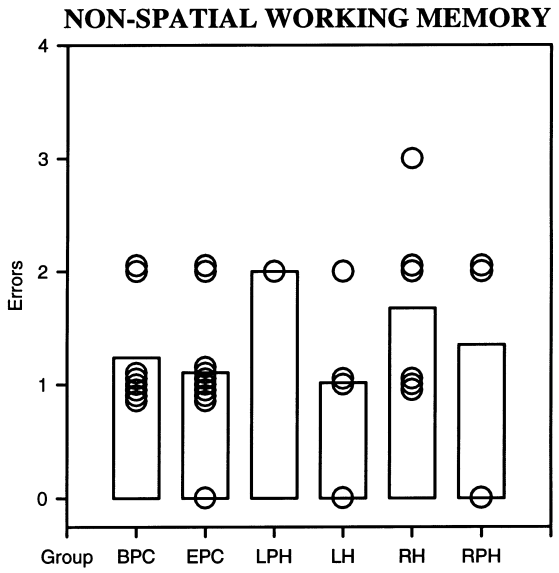

Fig. 11. Errors on the non-spatial working memory in the first eight choices. Because many ties occurred, the data were slightly separated in order to show the distribution of scores. Details and labels are described in the legend of Fig. 6.

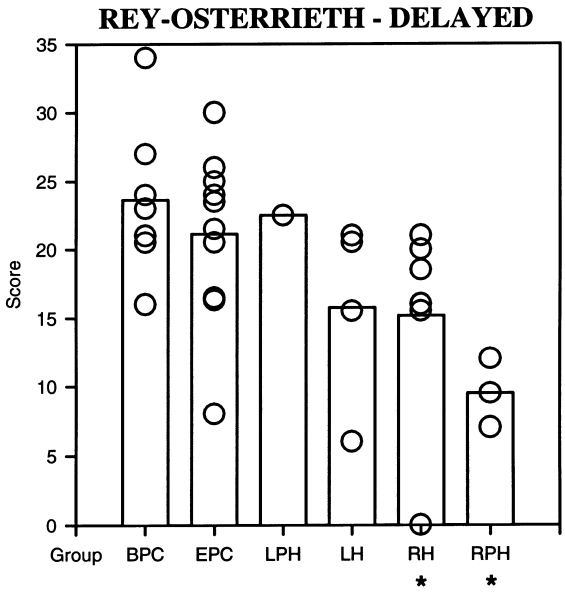

Fig. 13. Scores on the Rey–Osterrieth complex figure drawing task at a 30 min delay. Details and labels are described in the legend of Fig. 6. *: different from BPC and from EPC $P < 0.05$.

Rey–Osterrieth complex figure task

All patients were able to copy the figure. Four patients showed signs of perceptual fragmentation. The scores during immediate recall and after a 30 min delay are shown in Figs 12 and 13, respectively. In both conditions, there were significant group differences (immediate recall: $H = 10.64$, df. $= 4$, $P < 0.05$; delayed recall $H = 12.31$, df. $= 4$, $P < 0.05$). Paired comparisons with the Wilcoxon Rank Sum Test showed impairments in the right hippocampal group (immediate recall: $z = 1.85$, $P < 0.05$; delayed recall: $z = 1.90$, $P < 0.05$) and the right parahippocampal cortex group (immediate recall: $z = 1.95$, $P < 0.05$; delayed recall: $z = 2.12$, $P < 0.05$) relative to epileptic patient controls, and impairments in the right hippocampal group (immediate recall: $z = 2.07$, $P < 0.05$; delayed recall: $z = 2.22$, $P < 0.05$) and the right parahippocampal cortex group (immediate recall: $z = 2.28$, $P < 0.05$; delayed recall: $z = 2.28$, $P < 0.05$) relative to back-pain patient controls. Patients with lesions to the left hippocampus were unimpaired on this task.

Rey auditory verbal learning test

The scores during recall after the interference trial and after a 30 min delay are shown in Figs 14 and 15, respectively. No main effects were detected for either condition (after the interference trial: Kruskal–Wallis rank test, $H = 5.37$, df. $= 4$, n.s.; after the 30 min delay: Kruskal–Wallis rank test, $H = 8.74$, df. $= 4$, n.s.), although the 30 min delay condition approached significance. Patients with lesions to the left hippocampus are usually impaired in this task. It was therefore important to determine if direct comparisons would yield any statistical differences.

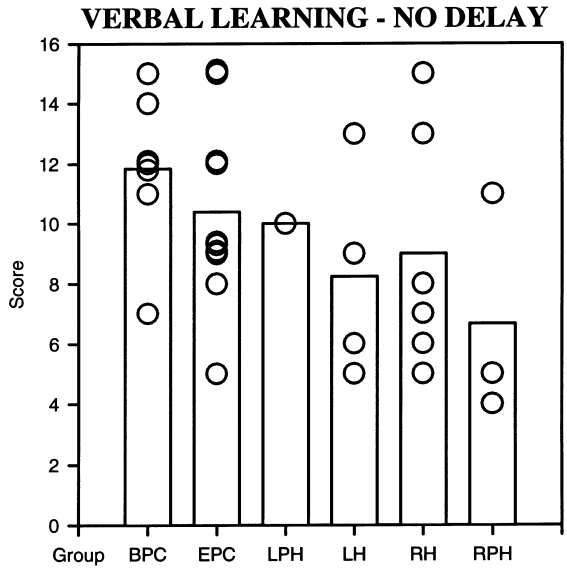

Fig. 14. Scores on the Rey Auditory Verbal Learning Test at zero delay (after the interference trial). Details and labels are described in the legend of Fig. 6.

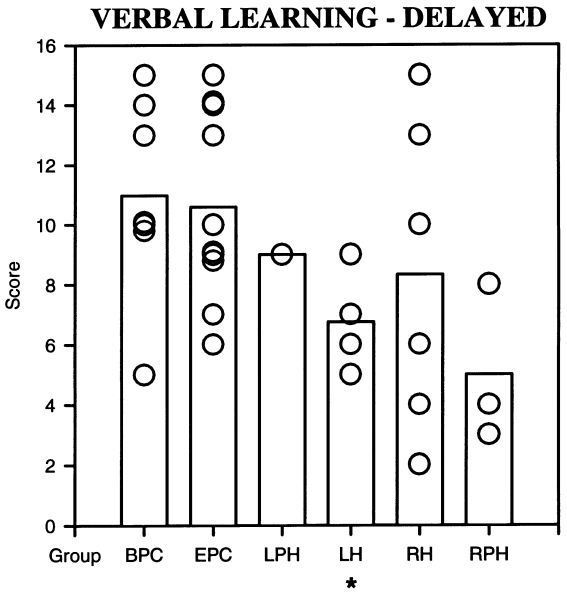

Fig. 15. Scores on the Rey Auditory Verbal Learning Test at a 30 min delay. Details and labels are described in the legend of Fig. 6. *: different from EPC $P < 0.05$.

Patients with left hippocampal lesions were compared with the epilepsy patient controls with the Wilcoxon Rank Sum Test. They performed similarly when asked to recall the list of words after a short delay during which an interference trial was given, but they were significantly impaired relative to epileptic patient controls after a 30 min delay ($z = 2.00$, $P < 0.05$).

Discussion

The present study investigated the effects of unilateral damage to various medial temporal lobe structures on tasks modeled after paradigms known to be sensitive to hippocampal lesions in rats, such as analogs of the Morris water maze, here referred to as the invisible sensor task, and the radial maze. The patients were also tested on a non-spatial working memory task, a task requiring recall of the location of three objects explored in the dark and a task involving memory for the spatial location of four visually presented objects. In addition, the patients were assessed with standard neuropsychological tests, such as the Wechsler IQ, the Wechsler Memory Scale, the Rey–Osterrieth Complex Figure Task, and the Rey Auditory Verbal Learning Task. The patients had undergone thermo-coagulation with a single electrode along the amygdalo-hippocampal axis in an attempt to alleviate their epilepsy. The precise localization of their lesion was assessed with digital high-resolution magnetic resonance imaging with in-house software allowing a 3-D reconstruction of the brain. For each patient, we estimated the extent of damage to the hippocampus, amygdala, entorhinal cortex, perirhinal cortex and the parahippocampal cortex. Because of our interest in distinguishing the parahippocampal cortex from the hippocampus, the patients were classified into two groups: those involving the hippocampus without damage to the parahippocampal cortex, and those with damage to the parahippocampal cortex.

The epileptic patient controls

Patients with epilepsy, but without brain surgery were used as controls for the brain operated patients. These control patients did not differ from the back-pain controls. Patients with severe epilepsy often have neuronal loss, or atrophy associated with the side of the epileptic focus, as shown by volumetric measurements from MRI scans [14]. Such patients were found impaired on specialized memory tests [1, 14]. The side of the epileptic focus was correlated with a memory impairment for locations [1] or abstract designs [14] in the case of the right hemisphere, or abstract words in the case of the left hemisphere [14]. Since the epileptic control patients in the present study were not surgical candidates and that their epilepsy was less severe, MRI data were not available, and therefore, brain atrophy could not be quant-

ified. In some tasks, a slight non-significant reduction in performance was observed relative to the back-pain controls and therefore these two control groups are presented separately for comparative purposes only.

The right hippocampus

Patients with right hippocampal damage were impaired on the object location task (Fig. 9) and the Rey–Osterrieth after immediate (Fig. 12) and 30 min delayed recall (Fig. 13). Both tasks require memory for spatial arrangement, either of objects or lines on a sheet of paper. Such impairments were observed even with the absence of lesions to the right parahippocampal cortex, suggesting that the right hippocampus is essential for learning in visuo–spatial memory tasks. Both tasks are visual and may require the combination of inputs from ventral temporal cortex processing object quality, which enters the hippocampus via the perirhinal and entorhinal cortices, and spatial information processed in parieto-occipital cortical areas, which amongst other areas, enter the hippocampus via the parahippocampal and entorhinal cortices [50]. This selective pattern of deficits after right, but not left, hippocampal damage is consistent with other evidence for specialization of information processing within the medial temporal lobes, as shown before by others [1, 23, 45, 48, 53].

The right hippocampal lesion group was not impaired on the Rey Auditory Verbal Learning Task (Figs 14 and 15) or other non-verbal tasks such as the non-spatial working memory (Fig. 11), the Invisible Sensor task at a 30 min delay (Fig. 8), and the non-visual spatial exploration task (Fig. 6). It has been shown before that patients with right hippocampal damage perform well on verbal learning tasks [23, 19]. Normal performance was observed on the non-visual spatial exploration task, but a deficit was observed on the object location task. Both tasks required the subjects to remember the location of objects. The main differences between the tasks involved the modality of input and the duration of encoding. Because subjects were allowed to walk amongst the objects, touch them, and perhaps estimate distances from the walls, during the 3 min allowed for the non-visual spatial exploration, it is likely that, in this condition, information was encoded using different strategies than in the visual observation condition.

There were no significant differences between the groups on the radial maze and the Invisible Sensor task without a delay. Rats with bilateral hippocampal lesions are dramatically impaired on similar tasks [28, 39]. The different results in the two species could be explained in several ways. For instance, the human subjects had unilateral lesions while rats are typically given bilateral lesions. Up to a point, the intact left hippocampal region may be sufficient to sustain performance on certain spatial memory tasks. Abrahams *et al.* [1] found spatial memory impairments in patients with unilateral medial temporal damage (resections or epileptic focus), when tested on the nine box maze, a radial maze analog, which encourages allocentric encoding. The task was considerably more difficult than the one presented here, evidenced by the number of errors made by normal controls (0.5 errors in the present study and 4 errors in Abrahams *et al.* [1]). Increasing the difficulty of the radial maze may reveal impairments in the patients with selective right hippocampal lesions.

The eight-arm radial-maze task used with patients in the present study may be solved differently than the way rats solve the typical eight-arm radial-maze. For example, human subjects are closer to the walls of the room and to local cues, and could therefore remember the eight spatial locations using simple cue-arm associations. On the other hand, rats, who are much smaller in relation to the room, have to remember the arms of the maze by using the arrangement of cues in the room as opposed to a single cue. In future studies, both of these factors can be independently manipulated either by increasing the difficulty of the task with additional stands on the human radial maze or by testing the patients in a larger room.

Another factor that must be considered is the portion of the hippocampus that is damaged. In the rat, it has been shown that there are behavioral and electrophysiological differences between the dorsal and ventral hippocampus [15, 29, 32, 33]. Bilateral lesions to the ventral 2/3 of the hippocampus in the rat do not cause spatial memory deficits in the Morris water maze, while damage to the dorsal 1/3 alone is sufficient to cause a severe impairment [29]. The dorsal hippocampus in the rat may be equivalent to the posterior hippocampus in the human. If the human posterior hippocampus is necessary for spatial navigation, as it is in the rat, then the present right hippocampal group in which 4/6 subjects had an intact posterior hippocampus, may not be expected to show a deficit on the invisible sensor task. If this is true, perhaps a parahippocampal lesion in the human would lead to a functional posterior hippocampal lesion, thus producing the spatial memory deficits observed in the invisible sensor task (note that this deficit was not observed on the eight-arm radial-maze). Since two of the six patients with damaged right posterior hippocampus were unimpaired on the invisible sensor task, the difference in dorsal-ventral hippocampal function can not be supported until more data are acquired.

The right parahippocampal cortex

The main cortical inputs to the hippocampus come via the entorhinal cortex, from the perirhinal and parahippocampal cortex. If lesions outside the hippocampus block inputs to the hippocampus, this could result in a functional hippocampal lesion [54]. Thus, impairments caused by a right parahippocampal lesion could reflect such a functional lesion. As in patients with lesions to the right hippocampus, patients with right parahippocampal

cortex lesions were impaired in the object location task (Fig. 9) and the Rey–Osterrieth at both delays (Figs 12 and 13). Since RH patients, in whom the RPH was largely intact, were impaired on these tasks (object location and Rey–Osterrieth) the impairments in the RPH group could indeed reflect a functional hippocampal lesion. The RPH may be involved in the object location task and the Rey–Osterrieth but the RH may be "essential" for these tasks.

Several patients in both the RH and the RPH groups were unimpaired at the object location task. It is therefore unclear whether the RH and the RPH groups were impaired due to extra damage to other areas (e.g. the REC or RPR) or whether the unimpaired patients solved the tasks using different strategies. Additional data are necessary in order to resolve this problem. The results reported here indicate that the right hippocampus is critical for remembering the object location task and the Rey–Osterrieth Complex Figure.

On the invisible sensor task with a 30 min delay, patients with right parahippocampal lesions were severely impaired in comparison with epileptic patient controls, patients with right hippocampal lesions or those with left hippocampal lesions. Surprisingly, patients with right hippocampal lesions, in some cases involving nearly complete removals, or patients with left hippocampal lesions were not impaired on this task (Figs 7 and 8; see Discussion in the section above). This implicates a structure other than the right hippocampus in performing the delayed invisible sensor task. The left hippocampus is a possible candidate; however, the patients with right parahippocampal cortex lesions, in whom the entire left medial temporal lobe was intact, were impaired on the invisible sensor task. This suggests that the left hippocampus (or left medial temporal lobe) is not sufficient for normal performance on this task, but that the RPH is.

Note that the RPH group consists of two patients with some additional damage to the right hippocampus and one with the right hippocampus intact. Still the lesions of patients in the RPH group are about the same size or smaller than those in some patients in the RH group (BS and MH), so the resulting impairment in the invisible sensor task is not associated with the size of the lesion. As argued before, the parahippocampal cortex sends efferents to the hippocampus, probably relating spatial information, so deficits arising from a lesion to the parahippocampal cortex are often ascribed to a functional hippocampal lesion [54]. This is not the case in the present situation because six patients in the RH group were not impaired on the invisible sensor task after a 30 min delay, allowing us to conclude that the right parahippocampal cortex may be a structure critically involved in certain kinds of spatial memory.

While patients with right parahippocampal cortex lesions were impaired on the 30 min delayed recall version of the invisible sensor task (Fig. 8), they were not impaired on the immediate recall version of the same task (Fig. 7). This finding is consistent with a previous report [48] showing that patients with damage to the right medial temporal lobe are only impaired after some delay on spatial memory tasks.

The left hippocampus

Patients with left hippocampal damage were not impaired on the short delay (Fig. 14) of the Rey Auditory Verbal Learning Test (trial after interference), but they were impaired with longer delays (Fig. 15). Note that the only patient with a left parahippocampal lesion performed as well as controls on this task at both delays (Figs 14 and 15). The present data show that the left hippocampus is required in remembering word lists, a finding consistent with earlier work which suggested that the left hippocampal system was important in verbal memory [19, 23].

Note that the right parahippocampal group scored lower than the left hippocampal group on the Rey Auditory Verbal Learning Task with delay. No statistics were performed because this group was not part of a planned comparison. Interestingly, several studies reported a verbal learning impairment after right sided temporal resection [13, 20]. The verbal learning impairment can precede the surgical intervention [13], so further research is needed in order to clarify this issue.

Amygdala

The two patients with partial bilateral amygdala damage (SV and FL) were not impaired on spatial or object memory tasks, which is consistent with monkey work, showing that the amygdala is not critically involved in spatial memory [43] or memory for objects [59, 60].

Relation to other studies

Although animal studies have established the important role of the hippocampus in spatial memory, in studies of patients, the evidence has come from lesions that included not only the hippocampus, but also the surrounding entorhinal, perirhinal, and parahippocampal cortex. The present study attempted to see whether lesions limited to the hippocampus are sufficient to impair spatial memory. The results reported above are in agreement with other lesion studies of spatial memory with humans, as well as recent neuroimaging studies of spatial memory.

Pigott and Milner [45] reported a study of memory for complex visual scenes in which patients with right temporal removals that included a large portion of the hippocampal region were impaired in the recognition of the relative location of objects in a scene, suggesting that the right hippocampus and/or parahippocampal region are critical in the processing of the spatial location of

objects. Smith and Milner [48] reported an impairment in object location memory in patients with right temporal lesions involving extensive damage to the hippocampal region. These patients remembered the locations of 16 toy objects as well as the control subjects immediately after learning, but not after a 4 min delay. These results showed that patients with right hippocampal lesions were able to encode the spatial location of the objects, yet they rapidly forgot this information relative to controls. As with most other studies involving resections of epileptic foci [1, 19], in addition to the hippocampal damage, the patients studied by Smith and Milner had a temporal resection which included the anterior temporal pole, the amygdala, as well as the adjacent cortex, i.e. the entorhinal and perirhinal cortices. Thus it is difficult to ascribe the impairment to damage of the hippocampus *per se*. The present findings provide further evidence suggesting that damage limited to the right hippocampus is sufficient to impair performance on spatial memory tasks.

Several studies of topographic memory (spatial memory in a large scale environment) or route learning, have been reported in patients with lesions to the right medial temporo-occipital gyri [12, 16], right or left inferior mesial occipital, occipitotemporal, mesial temporal and right inferotemporal or inferior parietal regions [6]. Habib and Sirigu [12] found that the critical region involved for topographical orientation was the parahippocampal gyrus, because this was a common area of damage to the four patients studied. So far, the brain damage associated with studies of topographical learning, was very large, encompassing various cortical fields and no agreement could be reached on which areas were critical, amongst those in medial or lateral temporal, occipital or parietal cortices.

In the current study, none of the patients had object agnosias, visual field neglect, encoding deficits, or impairments in visual perception; yet patients with lesions to the right parahippocampal cortex were impaired after a 30 min delay, and no lesions to the occipital, parietal or lateral temporal cortices were detected with high-resolution MRIs. The invisible sensor task and topographical learning are very different but both require spatial orientation and thus probably share common neural mechanisms. The question remains whether the right posterior hippocampus is required in addition to the right parahippocampal cortex in large scale spatial learning paradigms, both of which were included in the above mentioned studies of topographical learning [6, 12, 16]. Our data can not directly answer this question since we did not test patients on a large scale spatial memory task; however, in a small scale spatial memory task, the right parahippocampal cortex was critically involved.

In a study reported by Maguire *et al.* [17], patients with either right or left temporal resections were impaired on a spatial memory task in which subjects learn about an environment while visualizing a videotape of the real world. Patients with right or left temporal lesions were impaired relative to controls, on measures of scene recognition, route planning, route execution, and other measures related to the formation of a cognitive map. The difficulty of this task was considered to be an important variable explaining the requirement for both medial temporal lobes, relative to standard tasks used in the laboratory.

Functional neuroimaging studies with positron emission tomography (PET) have reported activation of the medial temporal lobe during performance of spatial memory tasks. While subjects performed spatial navigation tasks or route learning tasks, studies reported activation of the parahippocampal cortex [2], whereas others reported activation in the hippocampus and parahippocampal cortex [18] or both entorhinal cortex and parahippocampal cortex [11]. Other studies reported activation of the right hippocampus in a spatial working memory task [41], and the right entorhinal cortex during the recall of objects and their locations [42]. Altogether, many activation studies have shown that the right parahippocampal cortex was involved in certain kinds of spatial memory, providing support for the present findings.

Most human studies of the medial temporal lobe and memory function have concentrated on the hippocampus; other regions in the medial temporal lobe such as the parahippocampal cortex have received little attention, although the lesions often go beyond the hippocampus proper and dentate gyrus to include the subicular complex, the entorhinal cortex, perirhinal cortex and the parahippocampal cortex. Our results suggest that the right hippocampus is certainly important for some spatial memory tasks (object location, Rey–Osterrieth with and without delay), and the left hippocampus for verbal (episodic) memory tasks (Rey Auditory Verbal Learning Task with delay). However, the present findings also suggest that even after a right hippocampal lesion, some spatial information can still be computed and remembered (invisible sensor task). The right parahippocampal cortex appeared to be responsible for this residual function.

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