Memory Deficits Characterized by Patterns of Lesions to the Hippocampus and Parahippocampal Cortex

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ABSTRACT: Spatial and nonspatial memory tests were given to patients with small thermal lesions administered to the medial temporal lobes in an attempt at alleviating pharmacologically resistant epilepsy. In all three spatial memory experiments presented in this paper, patients with lesions that included the right parahippocampal cortex were seriously impaired. Their impairment, together with the performance of patients with lesions to the right hippocampus (sparing the right parahippocampal cortex), provides the different patterns of deficits that lead to different interpretations of the function of the parahippocampal cortex. The distinction between the effects of functional damage in hippocampus and the effects of a lesion to the hippocampus or to regions surrounding the hippocampus, such as the parahippocampal cortex, is emphasized. We conclude that the right parahippocampal cortex participates in spatial memory beyond serving as a gateway to the hippocampus.

INTRODUCTION

Important contributions to our understanding of human memory come from the study of brain-damaged patients whose etiologies differ widely, including cerebrovascular damage (infarct), progressive diseases (such as Alzheimer's and Parkinson's), infectious diseases (herpes encephalitis), closed or open head injuries, surgical removal of tumors or cysts, resections of epileptogenic tissue, and hypoxia. Much of the past and current research on human memory focused on patients with extensive brain damage resulting from one of the above-mentioned etiologies.[1–9] There are, however, reports of memory deficits after lesions restricted to small areas.[10–12] Important contributing factors to these kinds of studies are the recent advances in neuroimaging techniques allowing high-resolution visualization of the brain (such as magnetic resonance imaging, MRI); visualization of brain damage had traditionally been limited to postmortem analyses.

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Studies of brain-damaged patients that have large lesions do not allow for the study of the mnemonic role of single structures (defined by distinct cytoarchitecture). In the medial temporal lobe for example, the hippocampus (proper and dentate gyrus) and amygdala are surrounded by the tail of the caudate nucleus and the parahippocampal gyrus, composed of the peri-amygdaloid cortex, the subiculum, the piriform, entorhinal, perirhinal, and parahippocampal cortices. In addition, structures neighboring the medial temporal lobes include the fusiform cortex, lateral temporal neocortices, and, medially, the lingual gyrus and the posterior tip of the cingulate gyrus.[13] Despite the knowledge that cytoarchitectonic fields other than the hippocampus were compromised in studies with human subjects, for several decades it has been thought that the hippocampus was the medial temporal lobe structure primarily responsible for the memory loss observed in amnesic patients. In addition to the hippocampus, lesion studies of rodents, nonhuman primates, and brain-imaging studies with positron emission tomography (PET) and functional MRI (fMRI) now point to regions surrounding the hippocampus, as also contributing to memory processes.[14–24]

The encoding and recall of verbal material[6] or of the location of objects[25,26] and other spatial memory processes[27–29] has been thought to rely on the hippocampal region (hippocampus, subicular complex, and entorhinal cortex[30]). The patients in these studies had unilateral damage that included other neocortical regions of the medial temporal lobe. Thus, damage to structures surrounding the hippocampal region might have contributed to the memory loss.

Topographical amnesia, on the other hand, has been linked to more posterior regions, including areas around the occipital–parietal–temporal junction.[31–33] Topographical amnesia is the inability to find one's way in the environment, in the context of intact visuo-spatial perception. A study by Habib and Sirigu[32] showed that the area common to their patients who suffered from topographical amnesia was the parahippocampal gyrus. Because a lesion to the parahippocampal gyrus will also largely de-afferent the hippocampus, it is possible that topographical learning requires the contribution of the hippocampus.

Given that the various regions of the medial temporal lobes are interconnected, studies that dissociate regions from one another are necessary in order to establish which region is critical for a task.[34–36] Consider the following two possibilities.

(1) *Functional lesion in hippocampus*: Suppose that the parahippocampal cortex was involved in processing *perceptual* information about scenes, but was not involved in *memory* for scenes, then a lesion to the parahippocampal cortex could deprive target structures such as the perirhinal cortex, entorhinal cortex, and hippocampus of their "scene" input. It would not be surprising then to find *memory* deficits for scenes in patients with lesions of the parahippocampal cortex, even if their hippocampus was intact. One could conclude that the parahippocampal cortex was involved in memory, whereas in reality the deficit was produced by a functional lesion of the hippocampus.

(2) *Memory representation in parahippocampal cortex*: Suppose that patients with lesions to the parahippocampal cortex are impaired at remembering "scenes" after a delay period, and patients with lesions to the hippocampus, sparing the parahippocampal cortex, are not impaired, then the interpretation of a functional lesion in the hippocampus can be eliminated. In this case the parahippocampal cortex itself assumed the memory capacity for scenes.

TABLE 1. Subjects

Group	Sex		Age		Wechsler 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	2	36.9	29–49	103.7	88–131	102.9	84–126
Right parahippocampal	3	2	45	38–59	94	82–105	102	81–129
Left hippocampal	1	3	44.5	37–53	91.8	87–96	94.8	89–103
Left parahippocampal	1	0	34	—	99	—	87	—

In the present paper, we attempted to make the distinction between the effects of functional damage in the hippocampus and effects of a lesion to the hippocampus or to regions surrounding the hippocampus, such as the parahippocampal cortex. The patients studied had small stereotaxic thermal lesions performed in an attempt at alleviating intractable epilepsy. Despite the fact that our patients had small lesions, their lesions invaded several different cytoarchitectonic fields. Our contribution, however, is based on the fact that the small lesions do not invade all the different cytoarchitectonic fields, in the same way, in all patients. Consequently, the patients with lesions to the right or left hippocampus or parahippocampal cortex had either an intact entorhinal or perirhinal cortex, and some patients with lesions to the parahippocampal cortex had intact hippocampi. Importantly, all the patients in the parahippocampal lesion groups had damage to the parahippocampal cortex (FIG. 1), and all the patients in the hippocampal groups had intact parahippocampal cortices (FIG. 2). The three experiments described below provide evidence for three different patterns of deficits (1) a functional hippocampal lesion and critical involvement of the hippocampus, (2) involvement of both the hippocampus and parahippocampal cortex, and (3) critical involvement of the parahippocampal cortex.

METHODS AND RESULTS

Subjects

Two control groups and four brain-operated patient groups were tested in the present experiments (see TABLE 1). These patients have been described elsewhere.[12] One control group consisted of patients with back pain problems, but no epileptic problems, and the other consisted of patients with epilepsy who did not undergo brain surgery. Of the two control groups, the epileptic patient control group resembles more closely the experimental groups and therefore serves as a better control.

Back Pain Control Group

Eight patients with back pain were chosen as controls because, as the experimental groups, they were patients who suffered a disorder; however, the disorder was not localized to the brain.

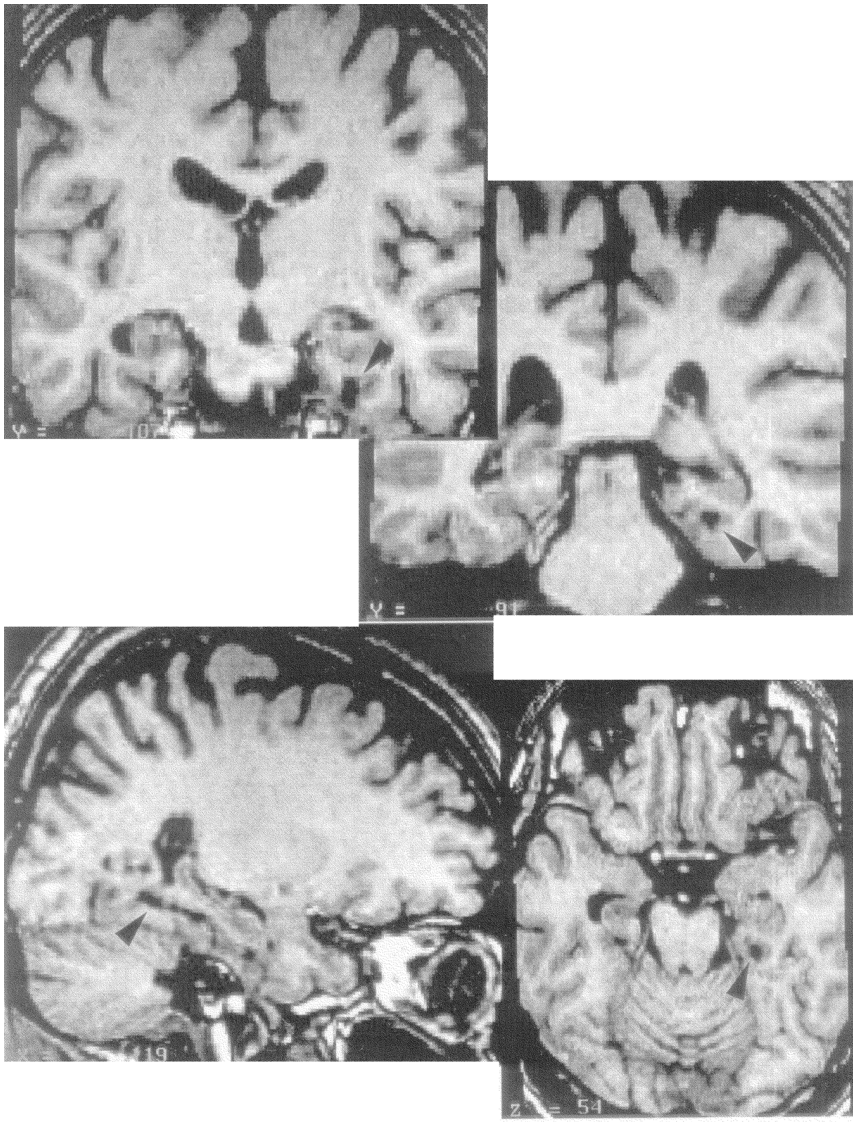

FIGURE 1. Thermal lesion to the right parahippocampal cortex. MRI sections in coronal, horizontal, and sagittal planes of a brain transformed into Talairach[42] standard stereotaxic space. *Arrows* point to the lesion in the right parahippocampal cortex sparing the hippocampus.

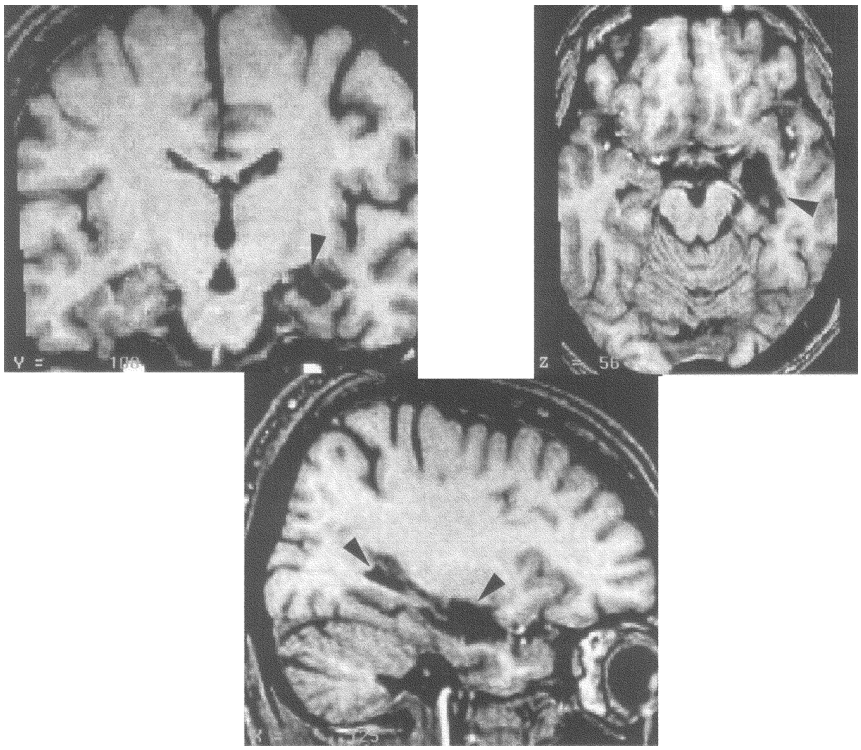

FIGURE 2. Thermal lesion to the right hippocampus. MRI sections in coronal, horizontal, and sagittal planes of a brain transformed into Talairach[42] standard stereotaxic space. *Arrows* point to the lesion in the right hippocampus sparing the parahippocampal cortex.

Epileptic Patient Control Group

Ten epileptic patients without brain resection or thermal lesion were used as controls. They were on nontoxic antiepileptic drug (AED) therapy similar to that received by the operated patients, but their epilepsy was controlled with medication, and they were not surgical candidates. Their epilepsy was of probable temporal origin. This group was considered a good control group because they suffer from the same neurological disorder as the brain-operated patients.

Brain-Operated Groups

Fourteen of 17 patients who underwent selective thermo-coagulation lesions (FIGS. 1 and 2) in an attempt to alleviate pharmacologically intractable epilepsy are reported in each experiment. Patients with Wechsler IQs below 75, psychiatric disorders, or with gross brain atrophy were excluded from the study. All patients were right-handed. The patients were tested 4 to 17 years postoperatively. All patients were on antiepileptic drug therapy at the time of testing. None of the patients had clinical symptoms of overdose, and the patients' performance was not affected by clinical or EEG seizures on the day of testing.

The patients with thermal lesions were divided into four groups: right hippocampus, right parahippocampal cortex, left hippocampus, and left parahippocampal cortex. The anatomical landmarks that were used to identify the patients' lesions have been described elsewhere.[12] In summary, patients with lesions were divided into groups depending on whether or not they had damage to the parahippocampal cortex. Lesions to the hippocampus can include the hippocampus proper, the dentate gyrus, and the subicular complex (FIG. 2). Lesions of the parahippocampal cortex refer to the posterior parahippocampal gyrus (FIG. 1), the neocortical region posterior to the entorhinal cortex and perirhinal cortex. Many but not all patients in these groups had damage to the entorhinal and perirhinal cortices, see Bohbot *et al.*,[12,37] for more details.

Analysis

Because the assumption of a normal distribution cannot be made in groups with small sizes, a nonparametric analysis of variance, the Kruskal-Wallis H test, was used to analyze 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 BPC group to the EPC group, and there were no significant differences on any test. The BPC group and the EPC group were compared with each brain-operated patient group.

Object Location Task

Procedure

This recall task was designed to test memory for several objects and their different spatial locations. The subject was allowed to observe the location of four objects (briefcase, stand, kettle, and flowerpot) in the experimental room, for 10 seconds. 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. 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 and their relation to the room.

Results

The mean error for the estimated position of each one of the four objects for the different groups is shown in FIGURE 3. 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

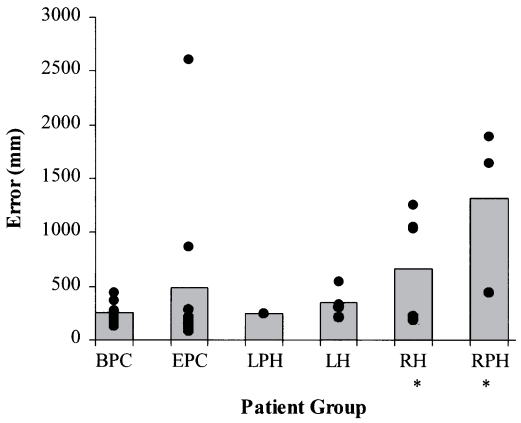

FIGURE 3. Object location task. The error (in millimeters) is the difference between the estimated position of the objects and the real position. Each bar represents the mean of a group. The scores of individual subjects for each group are displayed. BPC: back pain controls; EPC: epileptic patients controls; LPH: left parahippocampal cortex; LH: patients with damage to the left hippocampus; RH: right hippocampus; RPH: right parahippocampal cortex. *Different from EPC, $p < 0.05$.

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.

Although there was only one left parahippocampal patient, precluding statistical analysis, descriptively it appeared that the left parahippocampal patient was unimpaired on this task.

Spatial Oddball Task

Procedure

Computerized tasks were developed to assess memory for two types of information about objects: changes in the spatial configuration of objects and changes in the particular objects displayed. These tasks were designed in the oddball fashion for use with evoked potentials.[38] In each task, a standard display depicting five unrelated objects appeared on 80% of the trials (standards), and alterations of this standard display appeared on 20% of the trials. On 10% of the trials, a new object appeared in place of one of the objects on the standard display (object identity change). On another 10% of the trials, two of the objects from the standard display switched locations (spatial configuration change). In each sequence of 10 displays, one spatial configuration change and one object identity change occurred, with a standard display following each of these changes. The standard displays that followed the object identity or the spatial configuration changes were never included in the analyses, as these represented a change back to the standard condition.

In the spatial task, subjects were instructed to respond to spatial configuration changes (targets) and ignore the object identity changes (distractors). They indicated

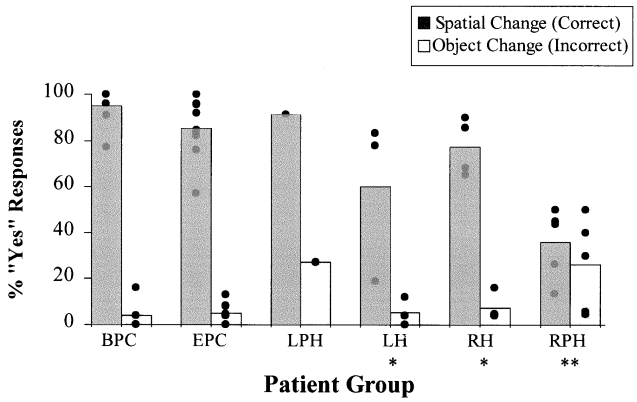

FIGURE 4. Spatial oddball task. Percent scores of correct detection of the spatial configuration change (target), and incorrect detection of the irrelevant object identity change (distractor). Each bar represents the mean of a group. The scores of individual subjects for each group are displayed. Details and labels are described in the legend of FIGURE 3. *Significantly different from the BPC group in responses to spatial changes (p <0.05). **In responses to spatial changes, significantly different from the BPC and EPC groups (p <0.005) and from the RH group (p <0.05); in responses to the object changes, significantly different from the BPC (p <0.01) and EPC (p <0.05) groups.

their response by pressing the left key for standards and distractors ("NO" response), or a right key for the targets ("YES" response). The subject's target detection was "correct" if the right key was pressed for the change in configuration of objects in the spatial task. A response was incorrect if the right key was pressed for either the standards or irrelevant changes. Only the results from the spatial task are presented here. Further details on an object task equivalent to the spatial task are published elsewhere.[37]

Results

The patients with lesions to the right parahippocampal cortex, and to some extent the patients with lesions to the right and left hippocampus showed poor discrimination of the spatial configuration from the object identity changes in the spatial task (FIG. 4). The detection of spatial configuration change ("YES" response) was different across the groups (Kruskal-Wallis rank test, $H = 17.71$, $df = 4$, p <0.001). The Wilcoxon rank sum test for two independent samples showed that the two control groups performed similarly. The right parahippocampal subjects were impaired relative to the EPC subjects ($z = 2.93$, p <0.005), and relative to the BPC subjects ($z = 2.89$, p <0.005). The left and right hippocampal subjects were impaired relative to the BPC subjects (*left*: $z = 1.98$, p <0.05; *right*: $z = 2.33$, p <0.05); however, they were not impaired relative to the EPC subjects (*left*: $z = 1.48$, n.s.; *right*: $z = 0.85$, n.s.). This implies that the left or right hippocampal thermal lesion itself did not significantly change the performance beyond that seen in individuals with epilepsy. The group with lesions to the right parahippocampal cortex was impaired relative to the

group with lesions to the right hippocampus ($z = 2.33$, $p < 0.05$), indicating that the impairment resulting from the right parahippocampal cortex lesion could be dissociated from any impairments caused by dysfunction in the right hippocampus.

While subjects were engaged in the spatial task, there were differences (Kruskal-Wallis rank test, $H = 9.76$, $df = 4$, $p < 0.05$) in the number of incorrect "YES" responses to the object identity change (distractors; FIG. 4). The Wilcoxon rank sum test showed that only patients with lesions to the right parahippocampal cortex were impaired relative to the patient control group with epilepsy ($z = 2.15$, $p < 0.05$) and relative to the BPC subjects ($z = 2.59$, $p < 0.01$). None of the other tested comparisons differed. These results show clearly that the only patients who were affected by the presence of distractors in the spatial task were those with lesions to the right parahippocampal cortex.

Invisible Sensor Task

Procedure

A dry version of the Morris water task[39,40] 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 seconds 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-minute delay, trial 3 was administered starting from the same door as in trial 1.

Results

On the first trial, all subjects found the sensor through trial and error by walking around the room. On immediate recall, all groups of patients rapidly found the invisible sensor (FIG. 5); there were no significant differences (Kruskal-Wallis rank test, $H = 1.15$, $df = 4$, n.s.) across all groups. Planned comparisons showed no differences between patients with lesions to the right hippocampus and the epilepsy patient controls in the Wilcoxon rank sum test. Latencies to find the invisible sensor after the 30-minute delay are also shown in FIGURE 5. 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 only the patients with lesions to the right parahippocampal cortex were impaired relative to the BPCs ($z = 2.35$, $p < 0.01$), and relative to the EPCs ($z = 2.45$, $p < 0.01$). Patients with right or left hippocampal lesions were unimpaired on this task.

DISCUSSION

We presented evidence from patients who underwent small stereotaxic thermocoagulation lesions to the medial temporal lobes (FIGS. 1 and 2), done in an attempt to alleviate intractable epilepsy. Patients were tested on various spatial memory tests reported elsewhere.[12,37] Because the lesions were small, we were able to separate the patients into two groups per hemisphere: those with and those without lesions to

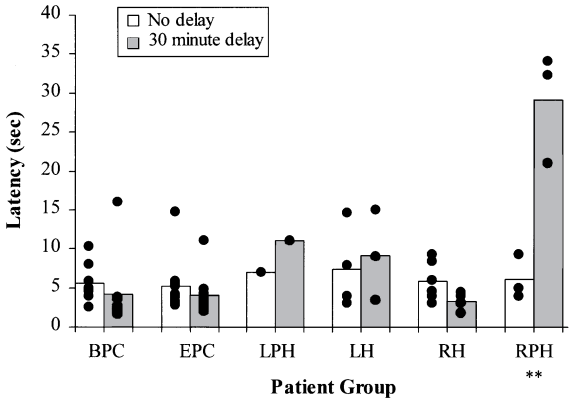

FIGURE 5. Invisible sensor task. Latencies for reaching the invisible sensor (trial 2: no delay and trial 3 at a 30-minute delay). Each bar represents the mean of a group. The scores of individual subjects for each group are displayed. Details and labels are described in the legend of FIGURE 3. **RPH different from BPC and from EPC at the 30-minute delay interval only, $p < 0.01$.

the parahippocampal cortex. Our results showed that patients with lesions to the left hippocampus were unimpaired compared with their epilepsy controls on all spatial memory tasks. Consistent with other reports, only patients with lesions to the right medial temporal lobe were impaired,[26,41] suggesting that the right side is specialized in spatial memory. Within the right medial temporal lobe, three different patterns of deficits were observed.

(1) *Deficit in patients with lesions to the right hippocampus and right parahippocampal cortex.* Patients with lesions to the right hippocampus, sparing the parahippocampal cortex, showed deficits in the object location task (FIG. 3) and the Rey-Osterreith complex figure.[12] Patients with lesions to the right parahippocampal cortex showed similar impairments. Because patients in the right hippocampal group ($n = 6$) had an intact parahippocampal cortex, this suggests that the parahippocampal cortex itself was not capable of sustaining these memory functions. In the group with lesions to the right parahippocampal cortex, one of three patients had an intact hippocampus; this patient's deficit can be attributed to a functional hippocampal lesion. These two tests critically require the involvement of the right hippocampus but do not inform us about the role played by the right parahippocampal cortex: it remains unclear whether it is implicated in memory or in processing perceptual information that it transmits to the hippocampus.

(2) *Mild deficit in patients with lesions to the right hippocampus, severe deficit in patients with lesions to the right parahippocampal cortex.* Patients whose lesions included the right parahippocampal cortex were severely impaired (35% correct) relative to patients with lesions to the right hippocampus, on the spatial oddball task (FIG. 4). Patients with lesions to the right hippocampus sparing the parahippocampal cortex showed no deficit (77% correct) relative to control subjects with epilepsy (85% correct) but had a deficit compared with back pain patient controls (95% cor-

rect). This is best interpreted as evidence that the medial temporal lobes are involved, including the participation of the hippocampus. However, when intact, the right parahippocampal cortex alone can sustain some spatial memory function (up from 35% to 77% correct performance in patients with lesions to the right hippocampus). The deficit in patients with right parahippocampal lesions is therefore not due merely to a functional hippocampal lesion. The right parahippocampal cortex itself is critical for this task, in addition to the right hippocampal involvement.

(3) *No deficit in patients with right hippocampal lesions, severe deficit in patients with lesions to the right parahippocampal cortex.* Patients with lesions to the right parahippocampal cortex were severely impaired after the 30-minute delay of the invisible sensor task and not impaired at all on the immediate recall (FIG. 5). Patients with lesions to the right hippocampus showed no deficit on the invisible sensory task, even when recall was tested after a 30-minute delay. Clearly, the deficit in patients with right parahippocampal lesions was not due to a functional hippocampal lesion, showing that the right parahippocampal cortex itself can sustain long-term memory.

We showed that the pattern of deficits in patients with lesions to the right hippocampus and right parahippocampal cortex differed in the three examples provided. In all three experiments, our patients with lesions that included the right parahippocampal cortex were seriously impaired. Their impairment, together with the performance of patients with lesions to the right hippocampus (sparing the right parahippocampal cortex) provide the different patterns of deficits that lead to different interpretations of parahipocampal function. Specifically, patients with right hippocampal damage were no different from control subjects in the 30-minute delay recall of the invisible sensor task, thus showing that their intact parahippocampal cortex can sustain this memory function. In the spatial oddball task, patients with lesions to the right hippocampus were mildly impaired, showing that the right hippocampus may be involved, but that the intact parahippocampal cortex could sustain some memory for this task. And finally, the object location task showed that both right-sided groups of patients were impaired, indicating that the hippocampus was critical for this task, despite the role of the parahippocampal cortex in some aspects of spatial memory. In a normal brain, both these structures may be recruited if they are intact.

Several hypotheses regarding the different roles of the hippocampus and the parahippocampal cortex can be posed.

(1) The hippocampus is important for allocentric spatial memory, and the parahippocampal cortex for egocentric spatial memory. The data from the invisible sensor task do not support this hypothesis since it is an allocentric task and subjects with right hippocampal damage were not impaired.

(2) The hippocampus is important for the computations involved in navigation and the parahippocampal cortex is important for spatial representations. Results on the object location task and invisible sensor task fail to support this hypothesis, suggesting the opposite if anything.

(3) The hippocampus is important for memory of multiple items, the parahippocampal cortex for single items. Because the difference between the object location task and invisible sensor task lies in the number of items stored in memory, not in the nature of the material to be studied, these data support this hypothesis.

(4) The hippocampus is involved in memory for object locations, and the parahippocampal cortex is involved in memory for scenes. These latter would be crucial in navigation, hence the role of the parahippocampal cortex in the invisible sensor task.

(5) The parahippocampal cortex is involved in memory for two-dimensional static spatial information, such as snapshots, and the hippocampus links these parahippocampal snapshots into three-dimensional representations. This is consistent with the results in the invisible sensor task and the spatial oddball task, since snapshots could subserve performance of the right hippocampal group in these tasks, and results in the object location task, where they could not.

(6) The hippocampus is important for episodes that include memory for single events as well as the context, and the parahippocampal cortex is involved in memory for single events alone (this is a variant of #3).

Our results to date seem to eliminate the first two hypotheses, but the remaining hypotheses are consistent with what has been observed so far. Future studies using subjects with damage limited to small areas in the medial temporal lobe should help distinguish among these various possibilities.

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