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Object–location memory impairment in patients with thermal lesions to the right or left hippocampus

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Abstract

Memory for object–location was investigated by testing subjects with small unilateral thermolesions to the medial temporal lobe using small-scale 2D (Abstract) or large-scale 3D (Real) recall conditions. Four patients with lesions of the left hippocampus (LH), 10 patients with damage to the right hippocampus (RH) and 9 matched normal controls (NC) were tested. Six task levels were presented in a pseudorandom order. During each level, subjects viewed one to six different objects on the floor of a circular curtained arena 2.90 m in diameter for 10 s. Recall was tested by marking the locations of objects on a map of the arena (Abstract recall) and then by replacing the objects in the arena (Real recall). Two component errors were studied by calculating the Location Error (LE), independent of the object identity and the configuration error by finding the best match to the presented configuration. The RH group was impaired relative to the NC for nearly all combinations of recall and error types. An impairment was observed in this group even for one object and it deepened sharply with an increasing object number. Damage to the right perirhinal or parahippocampal cortices did not add to the impairment. Deficits in the LH group were also observed, but less consistently. The data indicate that spatial memory is strongly but not exclusively lateralised to the right medial temporal lobe.

Keywords: Medial temporal lobe; Parahippocampal cortex; Stereotaxic thermolesions; Pharmacoresistant epilepsy

1. Introduction

Bilateral lesions of the medial temporal lobes result in profound global amnesia (Scoville & Milner, 1957). Neuropsychological effects of unilateral medial temporal lobe lesions involve milder memory deficits that were often found to be material-specific. Left-sided lesions were associated with verbal memory impairment (Bohbot et al., 1998; Frisk & Milner, 1990; Helmstaedter & Elger, 1996) and episodic memory recall deficits (Spiers et al., 2001) while right-sided damage was accompanied by poor performance on non-verbal and spatial memory tasks (Bohbot et al., 1998; Jones-Gotman, 1986; Smith & Milner, 1981, 1989). Brain imaging protocols supported evidence of lateralisation of information since verbal tasks in fMRI studies activated the left hemisphere more (Kirchhoff, Wagner, Maril, & Stern, 2000), and spatial tasks in PET or fMRI studies preferentially activated the right (Bohbot et al., 2000b; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Maguire et al., 1998). However, there is evidence that subjects with unilateral damage to the hippocampus are deficient at certain memory tasks regardless of the side of the lesion (Dobbins, Kroll, Tulving, Knight, & Gazzaniga, 1998; Kroll, Knight, Metcalfe, Wolf, & Tulving, 1996; Maguire, Burke, Phillips, & Staunton, 1996). Memory impairment for object–location is thought to be part of a broader class of spatial memory deficit observed in patients with lesions of the right medial temporal lobe (O'Keefe & Nadel, 1978). Just how broad the class of hippocampus-dependent behaviours may be, is still a matter of intense speculation (Aggleton & Brown, 1999; Eichenbaum, 2000; Nadel & Moscovitch, 2001; Squire, 1992; Tulving & Markowitsch, 1998; Vargha-Khadem et al., 1997).

Among non-verbal memory tasks, those assessing memory for object–location are unique in the sense that they require a synthesis of two forms of knowledge, object

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identity and its placement. Smith and Milner (1981, 1989) were the first to suggest that object–location memory was mediated by the right hippocampus (RH) in humans. The convergence in the hippocampus of pathways involved in object recognition such as the perirhinal cortex (Murray & Mishkin, 1998) and memory for places such as the parahippocampal cortex (Bohbot et al., 1998) supports this view (Ungerleider & Mishkin, 1982). Smith and Milner (1981, 1989) and Crane, Milner, and Leonard (1995) used small-scale object–location tests in patients with unilateral temporal lobe damage of varying size. Subjects with large hippocampal excisions from the right temporal lobe were found to perform worse than normal controls (NC) when recall of object–locations was tested after a delay of 2–4 min. On the other hand, subjects with left temporal lesions involving small or large portions of the hippocampus and those with small right-sided hippocampal removals performed normally. Smith and Milner (1989) also reported that the recall deficit in their patients was not related to the size of the neocortical excision. Bohbot et al. (1998) showed that a lesion involving the RH leaving the right parahippocampal cortex intact was sufficient to produce an object–location memory impairment. The dissociation between the hippocampus and parahippocampal cortex could not be shown explicitly until then since the patients that were previously tested typically had medial temporal lobe resections that included the parahippocampal cortex in addition to the lesion of the hippocampus, amygdala and other cortical structures (Smith & Milner, 1989). Crane (2000) and Nunn, Graydon, Polkey, and Morris (1999) started to address this issue by finding a positive correlation between memory for object–location and the amount of RH present in patients with right medial temporal resections.

In comparison to the studies with humans, the results of experiments addressing the role of the non-human hippocampus in location and object–location memories are rather controversial. Parkinson, Murray, and Mishkin (1988) and Angeli, Murray, and Mishkin (1993) found that monkeys who underwent bilateral hippocampectomy could not remember two places out of three in a delayed matched to sample location task. Gaffan (1998) also noted that monkeys with lesions to the Delay–Brion system (formed by the fornix, mamillary bodies and anterior thalamic nuclei) showed similar deficits when required to remember one out of two places that were either occupied by identical dots or different objects. Murray and Mishkin (1998), however, demonstrated intact memory for two locations in monkeys with bilateral excitotoxic lesions of the amygdala and hippocampus. When discussing the neural substrates of location memory, the authors pointed out that medial temporal lobe removals in the studies of Parkinson et al. (1988) and Angeli et al. (1993) extended beyond the hippocampus proper, involving also the subicular complex and the parahippocampal cortex. The fact that the cortical structures surrounding the hippocampus could have a specific role in memory for object–locations is supported by the results of Bussey, Duck, Muir, and Aggleton (2000). They used a task requiring rats to discriminate between objects that remained in fixed locations from those that exchanged locations with other objects. The deficit found in rats with bilateral lesions to the perirhinal and postrhinal cortices (rat equivalent of the primate parahippocampal cortex) was more robust than that detected in animals with bilateral fornix lesions.

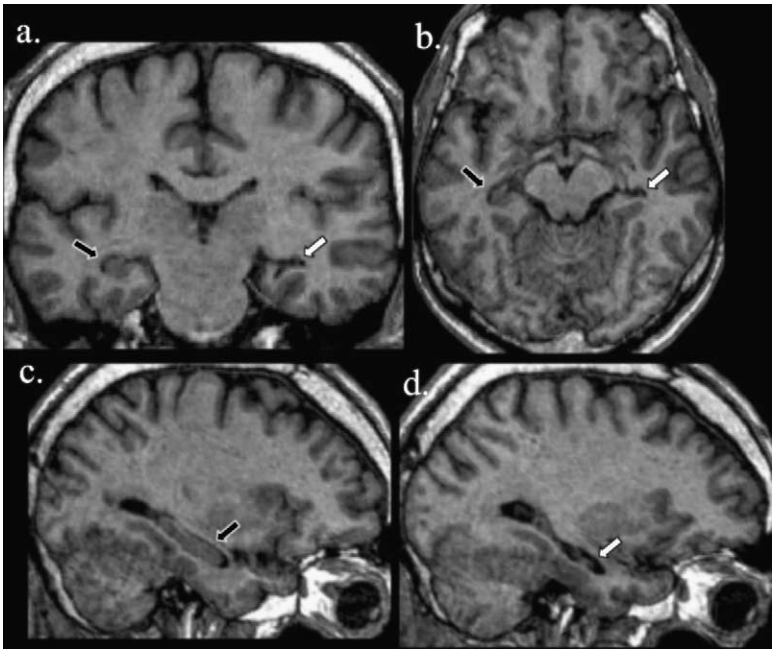

Fig. 1. Coronal, horizontal and sagittal sections in (a), (b), and (d), of the right hippocampal lesion of patient MJa, indicated by the white arrows (Talairach co-ordinates, $x = 32$, $y = -28$, $z = -12$). In contrast, the black arrows point to the intact LH in (a), (b), and (c) ($x = -32$).

The aim of the present study was to clarify the involvement of the human hippocampus and related temporal lobe structures in the memory for object–location in an extended extra-personal space. Unlike the patients described in most of the literature concerned with object–location memory, our subjects had received small stereotaxic thermocoagulation lesions involving different combinations of medial temporal lobe structures. An example of the precise lesion resulting from this type of surgery is shown in Fig. 1. The initial assessment of this population showed that a lesion of the RH led to a deficit in memory for four object–location associations (Bohbot et al., 1998). In that study, the subjects were tested in an open rectangular room with various other objects and features that were presumed to be used only as orienting cues. The present experiment was designed to answer four questions that arise from the initial study. (1) Is the object–location memory impairment primarily caused by inaccurate encoding and recall, i.e. a memory deficit, or could the deficit observed in Bohbot et al. (1998) have originated from a deficient 3D to 2D translation of object–location associations, i.e. a procedural deficit? (2) Do other medial temporal lobe structures contribute to this impairment seen in the patients with right hippocampal damage? (3) Is it possible to define and quantify any components of the object–location memory impairment, such as a deficient memory for the locations alone or an inability to orient the correctly recalled arrangement of objects on the map? (4) Does a higher memory load increase the magnitude of a deficit associated with lesions to the RH and does it reveal an impairment in cases of damage to the left hippocampus (LH)?.

2. Methods

2.1. Subjects

2.1.1. Normal controls

Nine right-handed NC were chosen to match the brain-operated patients with respect to sex, age and education. Their basic characteristics are shown in Table 1.

2.1.2. Brain-operated patients

This group consisted of 14 subjects who underwent stereotaxic thermolesions involving the medial temporal lobes at the Department of Neurosurgery, Central Military Hospital, Prague, Czech Republic as a treatment for their pharmacoresistant epilepsy. The lesions were unilateral in all but three cases (these three people had sustained bilateral lesions to the amygdala). None of the patients had signs of a psychiatric disorder, a pronounced overall brain atrophy or Wechsler IQs below 75. All these subjects had normal binocular vision with the exception of one (KoA) who had

Table 1
Subject characteristics

Group	Subject	Age	Education	Sex	IQ	MQ	Anterior *H*	Posterior *H*	PH	PR	EC
NC	DV	55	12	F							
	HJ	43	13	F							
	HV	48	13	F							
	KM	32	12	M							
	KV	50	14	M							
	LD	35	13	F							
	LL	42	13	M							
	MK	56	11	M							
	VJ	39	17	F							
	Mean	44.4	13.1								
LH	FA	54	14	M	95	90	x	o	o	x	o
	KS	41	11	F	89	89	x	o	o	x	x
	SV	54	10	F	87	97	o	x	o	x	o
	VP	40	17	F	96	103	x	x	o	o	o
	Mean	47.3	13		91.8	94.8					
RH	BS	43	14	M	96	96	x	o	o	x	o
	FL	35	13	F	106	126	x	o	o	o	o
	MH	34	12	M	88	84	x	o	o	x	o
	KJ	41	11	F	98	89	x	o	o	x	o
	KoA	52	11	M	89	97	x	o	o	x	o
	KP	32	12	M	118	116	x	x	o	o	o
	MJ	45	13	M	131	112	x	o	o	o	o
	MJa	48	11	M	101	129	x	x	x	o	o
	PV	45	12	F	84	81	x	o	x	x	o
	PP	62	13	M	105	116	x	x	x	x	x
	Mean	43.7	12.2		102	105					

x: regions that are encroached by the lesion; o: the intact areas. See text for further details.

his left eye removed and could thus only see with his right eye. The patients were tested 7–23 years postoperatively (average = 13.3 years). All of them were right-handed. As for their epilepsy compensation during several months preceding the testing, seven patients were seizure-free, six had their seizure frequency reduced by more than 50% and one by less than 50% in comparison to the state prior to the surgery. All of them except for one (FA) were medicated with one to three of the following antiepileptic drugs: carbamazepin, phenytoin, phenobarbital, valproate, lamotrigine, clonazepam, primidone, vigabatrine. None of the patients had clinical signs of overdose or a seizure on the day of testing. Sex, age, education and neuropsychological characteristics of individual patients are given in Table 1. Eleven of them were described in detail elsewhere (Bohbot et al., 1998). The variability in the lesion locations within the medial temporal lobe is related to the fact that the stereotaxic operations were performed at a time that no MRI guidance was available. See Table 1 for a summary of the regions encroached by the thermo-coagulation lesion.

2.1.2.1. Right hippocampus. Ten patients who had damage to the RH 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. Patient FL had damage to the right anterior hippocampus and additional damage to the amygdala bilaterally. 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. 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. Patient KP had partial damage to the anterior and posterior parts of the RH and additional damage to the right amygdala only. Patient MJ had a right anterior lesion to the hippocampus with additional damage to the right amygdala. In addition to a lesion in the parahippocampal cortex, patient PV had damage to the right anterior hippocampus and the right perirhinal cortex. Patient PP had a large lesion to the RH that was almost complete, including the anterior and posterior segments. In addition patient PP had partial damage to the right parahippocampal, perirhinal and entorhinal cortices and minor damage to the amygdala. Patient MJa had an almost complete lesion to the anterior and posterior hippocampi (Fig. 1) that encroached onto the amygdala and spared the entorhinal and perirhinal cortices. The lesion in MJa extended into the medial border of the parahippocampal cortex. In addition, patient MJa had a small lesion to the left amygdala. Patient KJ had a right lesion to the anterior part of the hippocampus that reached the part of the perirhinal cortex anterior to the amygdala as well as the amygdala. Patient KJ had intact entorhinal and parahippocampal cortices, as well as the part of the perirhinal cortex lateral to the entorhinal cortex.

2.1.2.2. Left hippocampus. Four patients with lesions to the LH were included in this group. Patient FA had damage to the left anterior hippocampus, and left amygdala. Patient KS had damage to the left anterior hippocampus, left amygdala, and minor damage to the left entorhinal and perirhinal cortex. Patient SV had damage to the posterior part of the LH, bilateral damage to the amygdala, and damage to the anterior portion of the left perirhinal cortex. Patient VP had a lesion to the left anterior and posterior parts of the hippocampus and partial damage to the left amygdala.

2.2. Materials and procedure

2.2.1. Arena

The objects were placed in a fully enclosed uniform circular arena (2.90 m in diameter) formed by opaque curtains. Two salient paper cues showing patterns of different colours were attached to the inner wall of the arena at eye level. They were located 90 and 180° clockwise from the entrance.

2.2.2. Design of the object–location test

The subjects were tested one at a time on six subtests that were administered in a pseudorandom order. Common objects such as toys, souvenirs and tools were used. For each subtest, one to six different objects were placed at predefined locations on the floor of the arena using a computerised system (the computer tracked the positions of objects in the signal from the overhead camera). The minimal distance between any two objects was approximately 90 cm. Sixteen positions were available in total. There were four phases in each subtest, following each other in a specified order without any delays: Encoding, Abstract recall, Translation phase and Real recall. No distractor tasks were used.

2.2.3. Encoding

Subjects were instructed to view the object array for 10 s through the arena entrance. In order to view all the objects, subjects had to scan the entire arena by turning their heads about 70° to the right and 70° to the left, therefore requiring an integration of multiple views. They were encouraged to use all this time to memorise the location of each object.

2.2.4. Abstract recall

Immediately afterwards, the subjects were asked to mark the location of each object on a paper, bird's eye view map of the arena (map:arena ratio = 1:17) using sticky 1 cm × 1 cm photo icons of the individual objects. The positions of the cues were indicated on the map. The subjects were free to spend as much time placing the icons on the map as they wished. No feedback regarding the performance accuracy was given at that point.

2.2.5. Translation phase

After placing all the icons on the map during the Abstract recall, this map was hidden from the subject's view and the subject received another blank map with a new identical set

of icons. This time, s/he was instructed to place the icons at appropriate locations on the map while viewing the object array from the entrance. All subjects needed less than 1 min to do so. The reason for performing Translation phase was to allow for assessment of the baseline requirement of the task, i.e. to translate the viewed object positions to a map without a mnemonic component.

2.2.6. Real recall

All the objects were gathered in the middle of the arena by the experimenter at the beginning of this phase (in the absence of the subject). The subject's task was to replace each of the objects to its original location, taking as much time as s/he needed.

2.3. Analyses

When evaluating the Abstract recall and the Translation phase, Cartesian co-ordinates of the icons placed by the subject on the map were measured and expressed in the "arena-scale", i.e. multiplied by the arena:map ratio. Cartesian co-ordinates of the objects placed inside the arena by the subject during the Real recall were measured semi-automatically by the computerised location tracking system. All errors were calculated in the "arena-scale".

2.3.1. Error measures

Object–Location Error (OLE) measured the displacement of an object or an icon representing it from its location, thus reflecting the subject's ability to remember object–location associations (Fig. 2, left). Two other types of error were also calculated. Object Arrangement Error (OAE) was used to assess the subject's capability to encode and recall spatial relationships among multiple objects, ignoring their spatial relationships to the cues on the inner arena wall. To evaluate the OAE, the entire array of objects underwent a rigid imaginary rotation around the arena centre. The rotation angle yielding the minimal sum of distances between the objects and their locations was found and the distances forming this minimal sum were considered OAE (Fig. 2, centre). Location Error (LE) measured the subject's ability to remember locations alone, irrespective of the identity of the objects occupying them. For the purpose of LE evaluation, each object was assigned to one location so that the sum of distances between the objects and the locations assigned to them was as small as possible (Fig. 2, right).

Each type of error (OLE, OAE and LE) was evaluated separately for each test phase (Abstract recall, Translation phase and Real recall) except for the LE during the Translation phase and the Real recall because the number of occasions when any subject confused the positions of objects during these two phases was negligible. Therefore, the LE was the same as the OLE for the Translation phase and Real recall in almost all cases. Given the design of our object–location test where no obligatory recall of object appearances was required, the level of one object differed from those of two to six objects in the sense that memory for location (not object–location association) was sufficient for performance. Thus, the one object subtest was evaluated separately. To compare performance across the levels of two to six objects the average error was calculated as the total error divided by the number of objects in the subtest.

2.3.2. Statistical analyses

Due to the small group sizes, lesion groups were compared primarily to the control (NC) group using the non-parametric Kruskal–Wallis test, followed when necessary by post hoc Dunn's tests. Since the experiment had a repeated-measures design across number of items to remember, and there were multiple lesion groups, two-way repeated-measures ANOVA was used to detect group, memory load effects and their interaction. Since the assumption of normality was often violated, and there is no equivalent non-parametric test, the procedure of Conover (1980) was used. The ANOVA was performed on the error values as well as their ranks, and following Conover (1980) when both results were nearly identical the parametric analysis was considered to likely be valid. Conservative Tukey post hoc tests were used when

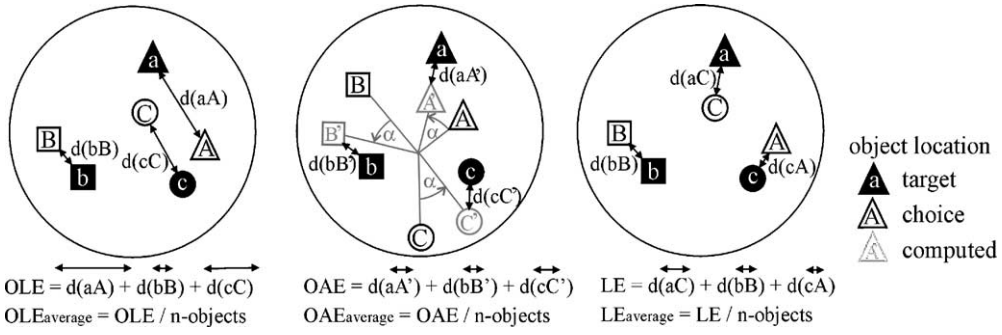

Fig. 2. Left: the OLE measured displacement of an object or an icon ("choice") representing it from its location ("target"): choice A, target a; choice B, target b; choice C, target c. Centre: to evaluate the OAE, the choices were rotated around the arena centre in order to minimise their displacement from the corresponding targets: computed A′ (= rotated choice A′), target a; computed B′, target b; computed C′, target c. Right: for the purpose of the LE measurement, the choices were assigned to targets such that the total sum of choice–target distances was minimal: choice A, target c; choice B, target b; choice C, target a. The average error was used to compare each type of error across subtests. Note that by definition, OLE ≥ OAE and OLE ≥ LE.

necessary. To further explore whether performance was related to memory load (number of object–location associations to remember), Spearman's correlation analyses were performed within each group.

3. Results

3.1. Relationship between performance and various medial temporal lobe structures

The patients were assigned to two groups according to which of their hippocampi was damaged. Patients with lesions to the right hippocampus (RH: $N = 10$) could be subdivided in two ways. One option was to define two subgroups consisting of people with and without additional damage to the right parahippocampal cortex (RH+PH+: $N = 3$; RH+PH−: $N = 7$). The second possibility was to separate patients with and without additional lesions of the right perirhinal cortex (RH+PR+: $N = 6$; RH+PR−: $N = 4$). Two patients (PV and PP) had lesions to all three of the above right-sided medial temporal lobe structures: the hippocampus, the parahippocampal and perirhinal cortices. These patients were not treated as a separate subgroup, i.e. they were included in both the RH+PH+ and the RH+PR+ subgroups. A limited number of subjects in the group with damage to the left hippocampus (LH: $N = 4$) did not allow for its subdivision into smaller groups.

We analysed whether additional damage to the right parahippocampal and/or perirhinal cortex worsened the performance of subjects with lesions to the RH. Table 2 summarises the results comparing the average OLEs of the RH+PH− and the RH+PH+ subgroups. There were no effects of subgroup or interaction in any phase of recall. The corresponding analysis of the RH+PR− and the RH+PR+ subjects is shown in Table 3. There were no effects of subgroup in any phase of recall, but there was a significant interaction on Real recall. The RH+PR+ patients performed worse than the RH+PR− subjects at the level of two objects ($P < 0.001$) but no other comparison was significant.

Since lesions to the right parahippocampal or perirhinal cortices did not consistently influence object–location memory beyond the effect of hippocampal lesion, the patients were divided into two groups according to the laterality of their lesion to the hippocampus for further analyses.

3.2. Laterality of hippocampal damage and overall performance

Overall OLE performance of the NC, LH and RH groups averaged across the levels of two to six objects (Fig. 3) was compared. There were no reliable effects on the Translation performance. The RH group was worse than the NC on both the Abstract and the Real recall while the LH patients were worse than the NC only on the Real recall. The performance of the LH and the RH groups was similar during both types of recall. There were no significant post hoc differences in the Translation test. The ANOVA results concerning OLE at different levels (see Table 4) of Abstract and Real recall were uniform: there was a significant effect of the group and of the number of objects but no significant interaction.

3.3. Laterality of hippocampal damage and the effect of task difficulty

3.3.1. Performance at the level of one object

The OLEs for one object were normally distributed (Fig. 4). Significant differences among the LH, RH, and NC groups were found for both the Abstract and Real recall (Abstract recall: $F_{(2,20)} = 3.6$, $P < 0.05$; Real recall: $F_{(2,20)} = 3.6$, $P < 0.05$). The RH group was impaired

Table 2
Analysis of the average OLE at individual levels of two to six objects: RH+PH+ compared

Two-way RM ANOVA			Values			Ranks		
			Abstract recall	Translation	Real recall	Abstract recall	Translation	Real recall
Subgroups	$F(1, 8)$	P	0.710	0.142	0.759	0.219	0.147	0.570
Number of objects	$F(4, 32)$	P	0.003	0.588	0.005	0.004	0.093	0.009
Interaction	$F(4, 32)$	P	0.581	0.722	0.093	0.244	0.571	0.110

Table 3
Analysis of the average OLE at individual levels of two to six objects: RH+PR− and RH+PR+ compared

Two-way RM ANOVA			Values			Ranks		
			Abstract recall	Translation	Real recall	Abstract recall	Translation	Real recall
Subgroups	$F(1, 8)$	P	0.777	0.692	0.069	0.757	0.118	0.056
Number of objects	$F(4, 32)$	P	0.003	0.154	0.051	0.004	0.023	0.028
Interaction	$F(4, 32)$	P	0.363	0.365	0.039	0.174	0.540	0.012

Table 4
Analysis of the average OLE at individual levels of two to six objects: NC, LH and RH compared

Two-way RM ANOVA			Values			Ranks		
			Abstract recall	Translation	Real recall	Abstract recall	Translation	Real recall
Groups	$F(2, 20)$	P	0.019	0.289	<0.001	0.015	0.265	<0.001
Number of objects	$F(4, 80)$	P	<0.001	0.090	0.015	<0.001	<0.001	0.003
Interaction	$F(4, 80)$	P	0.200	0.958	0.317	0.865	0.624	0.430

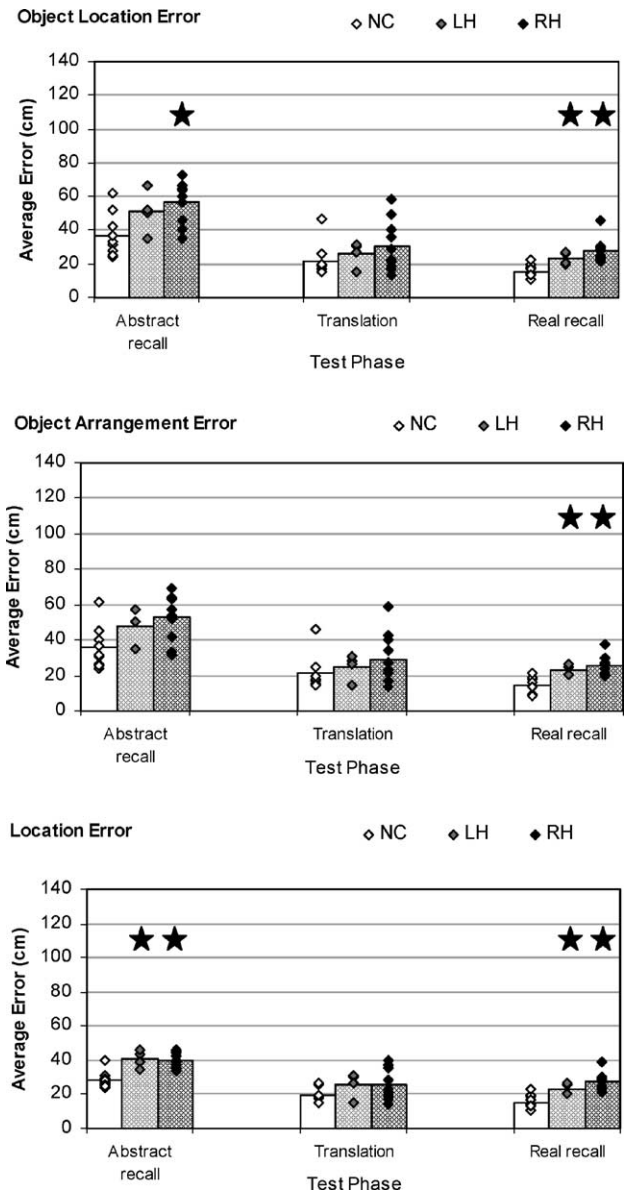

Fig. 3. Overall performance of the NC and patients with damage to the LH and to the RH across the levels of two to six objects as measured by different types of error. Each individual value plotted here corresponds to an overall average error of one subject across all the above levels (for the sake of clarity). The analyses were performed on the average errors calculated for each subject and each level separately, however. OLE, Object–Location Error; OAE, Object Arrangement Error; LE, Location Error. The symbol (★) indicates a significant difference from the NC.

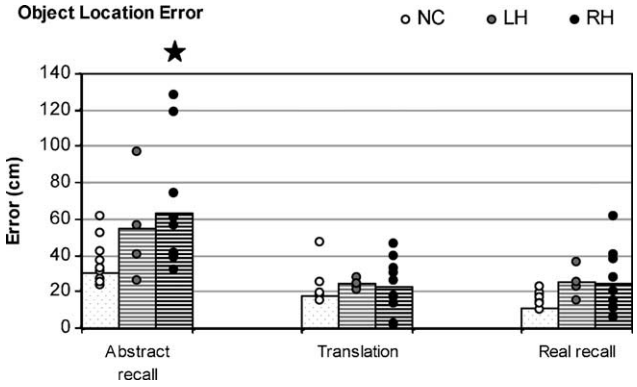

Fig. 4. Object–Location Error of the NC and patients with damage to the LH and to the RH at the level of one object. The performance of the RH group was inferior to that of the NC during the Abstract recall. The symbol (★) indicates a significant difference from the NC.

relative to the NC in the Abstract recall, but in Real recall, the difference only approached significance. The LH group did not differ significantly from any other group in any recall condition. No differences in Translation phase were detected ($F_{(2,20)} = 0.7$, $P = 0.50$).

3.3.2. Performance change at the levels of two to six objects

There was a trend for OLEs to increase with increasing object–location items to remember (Fig. 5). When assessed by correlation analyses, the relationship between the number of items to be remembered and performance was significant in the LH and RH groups during Abstract recall (LH: Spearman coefficient $= 0.46$, $P < 0.05$; RH: Spearman coefficient $= 0.55$, $P < 0.0001$). The correlations were also significant for the NC group during Abstract recall (Spearman coefficient $= 0.45$, $P < 0.001$) but this correlation was only significant in the RH group during Real recall (RH: Spearman coefficient $= 0.35$, $P < 0.05$; NC and LH, n.s.).

3.4. Relationship between Object–Location, Object Arrangement and Location Errors

Since good performance on the object–location task requires that the locations of the objects be correctly identified and associated with the appropriate object, we next examined whether the deficits of the brain-operated groups could be attributed to a selective inability in spatial memory. While

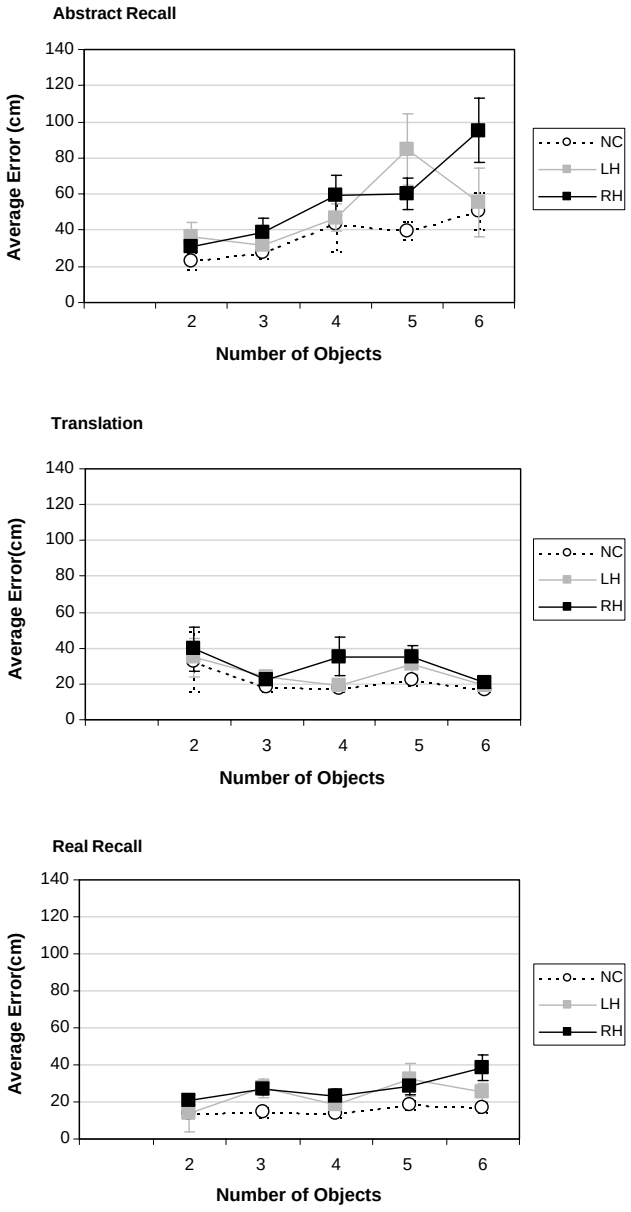

Fig. 5. Object–Location Errors of the NC and patients with damage to the LH and to the RH at individual levels of two to six objects. The OLE performance of both the LH and the RH groups on Abstract recall deteriorated with increasing number of items to remember. Error bars = S.E.M.

subjects may know the correct location of items in the arena, they may perform poorly if they switched two of the objects in the recall task. The LE was therefore evaluated by ignoring the object identities and evaluating the error based on a "best match". Along the same lines, a perfect configuration of object–location associations may have also generated error in the event that the reference frame of the circular arena was off by several degrees. In order to measure whether this was an important source of variability, the OAE was measured by rotating the object–location configuration until a "best fit" was found. It was reasoned that if the pattern of object–location performance deficits was present when either the OAEs or the LEs were analysed, then the reason for the deficit could be attributed to the corresponding specific inability.

When examining the between group differences concerning the Object Arrangement and Location Errors, the pattern of results from the OAE and LE errors was similar to the results of the OLE analyses (Fig. 3). The LH and RH groups appeared to be somewhat worse than the NC group. The OAEs during Abstract recall approached but was not significant ($H = 5.6$, d.f. $= 2$, $P = 0.06$). The groups were different in Translation phase ($H = 7.4$, d.f. $= 2$, $P < 0.05$) and in Real recall ($H = 27.2$, d.f. $= 2$, $P < 0.001$). While no post hoc comparisons were significant in Translation phase, in Real recall the LH and RH groups were worse than the NC group. The groups differed in the average LE on Abstract recall ($H = 13.8$, d.f. $= 2$, $P < 0.001$). Both the LH and RH groups performed worse than the NC group. Within group differences between the three error types were not examined because, by definition, the location and OAEs must be equal to or smaller than the OLE. In summary, the location and object arrangement analyses indicate that subjects suffer a spatial deficit as well as a deficit in placing an arrangement of objects within a spatial frame.

4. Discussion

4.1. Object–locations: a deficit in 3D to 2D translation or encoding and recall?

The patients with lesions of the hippocampus had no consistent deficits in Translation phase, suggesting that they can accurately perceive the object–location associations and translate them to a map. Yet, they were impaired at immediate recall of the object–location associations. When amnesic patients had a greater memory impairment after a delay compared to immediate recall, it was interpreted as a retrieval deficit (Smith & Milner, 1989; Warrington & Weiskrantz, 1970). Most imaging studies (PET and fMRI) show greater amounts of blood flow in the medial temporal regions in response to novel stimuli (Kirchhoff et al., 2000; Martin, 1999; Stern et al., 1996; Tulving, Markowitsch, Craik, Habib, & Houle, 1996), compared to already presented stimuli, suggesting that the medial temporal lobes are involved in encoding. Our data are consistent with these brain imaging studies.

In two studies by Smith and Milner (1981, 1989), patients with large lesions to the RH were impaired at delayed object–location recall only. The fact that not even the large number of objects (16) used was sufficient to produce an immediate impairment in any group of patients with lesions to the hippocampus contrasts with the present result. The difference may have arisen because the locations of their 16 objects on a table could have been learned in a single snapshot view. In our study, the subjects probably had to organise a unified coherent memory of the object arrangement from

several overlapping views of individual parts of the arena space. In an object–location task that required the integration of views from multiple vantage points, King, Burgess, Hartley, Vargha-Khadem, and O'Keefe (2002) showed that their test was extremely sensitive to human hippocampal damage.

4.2. Relationship between performance and various medial temporal lobe structures

We failed to find consistent evidence that damage to the right parahippocampal or the right perirhinal cortex increased the object–location memory deficit associated with a lesion to the RH. The fact that patients with lesions encompassing the RH and the right perirhinal cortex (RH+PR+) performed worse than those with the RH damaged and the right perirhinal cortex intact (RH+PR−) only in the Real recall of two object–locations was not considered convincing evidence of the contrary. This difference was not confirmed by *t* test and there was no trend for the RH+PR+ to perform worse than the RH+PR− at the any other level of the task. While the perirhinal cortex has been implicated in object recognition (Bachevalier, Nemanic, & Alvarado, 2002; Meunier, Bachevalier, Mishkin, & Murray, 1993; Zola-Morgan, Squire, Amaral, & Suzuki, 1989), damage of the parahippocampal cortex seems to be primarily responsible in topographical amnesia (Barrash, Damasio, Adolphs, & Tranel, 2000; Habib & Sirigu, 1987). Neuroimaging studies have shown an important involvement of the parahippocampal cortex for scene perception, encoding and recognition (Aguirre, Detre, Alsop, & D'Esposito, 1996; Aguirre, Zarahn, & D'Esposito, 1998; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Epstein & Kanwisher, 1998; Kohler, Crane, & Milner, 2002). Since both the perirhinal and parahippocampal cortices project to the hippocampus, a lesion to these structures can create a functional hippocampal lesion (Bohbot, Allen, & Nadel, 2000a). Any mnemonic function can thus be ascribed to these cortices only if not disrupted by a selective lesion to the hippocampus. This is clearly illustrated in the article by Meunier et al. (1993), where normal object recognition performance was achieved in subjects with circumscribed ibotenic acid lesions to the hippocampus, attributing the mnemonic capacity to the intact perirhinal cortex. A similar example is found in Bohbot et al. (1998) where subjects with selective lesions to the RH performed normally after a 30 min filled delay on the Invisible Sensor Task while subjects with an additional parahippocampal cortex lesion were impaired. However, this was not the case for object–location memory in the current study and in the study of Bohbot et al. (1998). In both studies, the groups with intact perirhinal or parahippocampal cortices were still impaired, demonstrating a critical requirement of the RH for object–location memory. Recent evidence by Malkova and Mishkin (2003) indicates that memory for two object–place associations and for two different places depends critically on the posterior parahippocampal region rather than on the hippocampal formation. This important result, taken together with the present results, suggests that a key difference in the role of the hippocampus and parahippocampal cortex might be in the integration of scenes from multiple views, as suggested in Bohbot et al. (2000a) and as discussed above. Such an integration was probably not necessary in the Malkova and Mishkin (2003) study since the objects in locations to be remembered were within arm's reach. The hypothesis that a role of the primate hippocampus in object–location memory is in integrating multiple views of the object–location space will require further experiments for which extended spaces like the one in the present study may be critical.

Owen, Milner, Petrides, and Evans (1996) suggest that the entorhinal cortex may have a special contribution to the retrieval of object–place associations. They found that the part of the right parahippocampal gyrus corresponding to the entorhinal cortex was activated when "retrieving location" was subtracted from "retrieving object–location" in their PET and fMRI study on recognition of object–locations or locations alone in healthy humans. No increase in cerebral blood flow was found in hippocampus itself after any of the subtractions. This seemingly surprising finding was explained by the fact that all scanning conditions involved memory for spatial information, the neural correlates of which may have been "subtracted out" (leaving only changes related to memory for locations of objects). Milner, Johnsrude, and Crane (1997) obtained similar results despite using a baseline visual discrimination task without a mnemonic component and making the object–location retrieval task more difficult. They ascribed the lack of hippocampal activation to the static nature of their two-dimensional computerised object–location task. Since there were only two subjects with lesions to the entorhinal cortex in our study (one on the right side and one on the left side), our analysis did not allow to evaluate the specific contribution of this structure. Nonetheless, we point out that the majority of our subjects with right hippocampal lesions and an intact entorhinal cortex were still impaired.

4.3. Can the impaired ability to associate objects with locations be explained by memory impairments for locations per se or the ability to orient the retrieved object configuration in the spatial frame?

Subjects with lesions to the hippocampus were impaired at remembering the object–location associations. We examined whether this deficit could be explained by an impairment in recalling the locations themselves or correctly orienting the arrangement of object–locations by assuming that the OLE is composed of location and orientation components. Since these components are not independent, these analyses only allow us to test if we can account for the object–location memory deficit in terms of each of these related factors.

We minimised the error by ignoring the identity of objects and evaluated the LE and yet we still found a significant

deficit in Abstract recall (Fig. 3). In other words, no matter what the identities of objects were, a deficit emerged when subjects with lesions to the hippocampus were asked to place objects on a map. This suggests that the deficit in memory for object–location includes a specific spatial memory deficit.

We also minimised the error in recalling the object–locations by rotating the entire configuration about the centre of the space until we found the best fit (OAE). While there was no longer an impairment in the Abstract recall, there was still a significant impairment in the Real recall indicating that the subjects' inability to orient the configuration of the set of object–locations could account for the object–location deficit in Abstract but not Real recall. This fact is intriguing and has to be interpreted with caution. Real recall was performed after Translation phase which gave all the subjects an additional opportunity to observe (and possibly better encode) the object–locations. We did not record the exact amount of time the subjects spent on Translation phase but it seems implausible that the control subjects would have taken more time to complete the task than the patients. Furthermore, subjects were not aware of the subsequent Real recall task. It is possible that the control subjects were more able to benefit from this extra encoding because they were operating with fully functional hippocampi. In the event that the controls neither took longer on Translation phase nor exploited it more efficiently, the hippocampus is likely to be especially involved in reconstruction of remembered object–locations within a real space. The data warrant further study to make the comparison between Real and Abstract recall directly. In Real recall, virtually all tested people placed the objects correctly with respect to each other and performed better than at the Abstract recall so an interpretation of the above difference related to task difficulty is unlikely. All together the data show that the object–location memory deficit in patients with lesions to the hippocampus includes a spatial memory deficit, specifically shown in the inability to place objects in space as well as a deficit in placing a configuration of objects within a spatial reference frame.

4.4. Laterality of hippocampal damage, object–location memory and the effect of memory load

Lesions to the RH were associated with worsened memory for the locations of objects irrespective of the retrieval method. This overall impairment of the RH but not the LH group, in the Abstract recall, replicated our previous findings (Bohbot et al., 1998).

The present data showed that the average error during Abstract recall increased with the number of object–location associations to be remembered. This effect of memory load was more evident in patients with the lesions to the RH, than it was for subjects with lesions on the left. The RH group also differed from the other two groups in the following two aspects: it showed a significant increase in the average OLE with the memory load during Real recall and it was impaired at the level of one object already. From the information processing perspective, if a structure is necessary for processing a particular kind of information, then a lesion of the area will compromise the information processing ability of the subject, independently of how much there is to remember. In this view, the failure to find a deficit indicates that the structure is not necessary for this type of information. The fact that there was a deficit observed in the RH group when the location of one object had to be recalled supports the finding that the RH is implicated in processing this type of information.

In agreement with Smith and Milner (1981, 1989), the damage to the RH was associated with poorer object–location memory. However, the current results differ since Smith and Milner (1981, 1989) found no object–location memory deficit in a patient group with damage to the LH. Abrahams, Pickering, Polkey, and Morris (1997) used up to four different objects hidden in four out of nine identical containers on a desktop to test object and spatial memory in subjects after unilateral anterior temporal resection. Patients with right side but not left side lesions had a spatial memory impairment. It is possible that the spatial memory deficits did not emerge in the groups with left-sided medial temporal resections in the above studies (Abrahams et al., 1997; Smith & Milner, 1981, 1989) due to a low memory load. Although we found consistent memory deficits for object–location in patients with lesions to the RH, we showed that by increasing the memory load, an impairment in the group with left-sided lesions to the hippocampus was revealed. A single snapshot view of 16 objects may be less demanding in terms of memory load than memory for several views of a real environment taken from different angles.

The results of Maguire et al. (1996) support the view that both medial temporal lobes are involved when a mental representation of the real world is built using views from multiple perspectives. They found patients with lesions to the left and to the right temporal lobe equally impaired on a topographical orientation task. In a PET study, Maguire et al. (1998) showed that only the RH involvement correlated with accuracy of navigation. The authors interpreted a left activation in hippocampus to indicate its maintenance of the appropriate destination, consistent with its well-known role in episodic memory (Vargha-Khadem et al., 1997; Viskontas, McAndrews, & Moscovitch, 2000). It should be noted that tissue abnormalities contralateral to the excised side can occur and can help explain certain deficits (Incisa della Rocchetta et al., 1995). Other imaging studies have shown bilateral activation of the medial temporal lobes in spatial tasks (Aguirre et al., 1996; Epstein & Kanwisher, 1998; Maguire et al., 1996). Our data support the notion that spatial memory is strongly but not exclusively lateralised the right medial temporal lobe.

In summary, four conclusions can be made on the basis of the data: (1) The hippocampus is critically involved in encoding and retrieval, but not the 3D to 2D translation of object–location associations. (2) Lesions to the right

perirhinal or parahippocampal cortex do not increase the object–location memory deficit associated with damage to the RH. (3) The hippocampus is involved in the memory of locations themselves. (4) While performance correlated with increasing memory load in both the RH and LH groups, the effects of damage to the RH on object–location and location memory tend to be greater than the effects of damage to the LH, suggesting strong but not exclusive lateralisation of information.

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