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Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town

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Summary

A large-scale virtual reality town was used to test the topographical and episodic memory of patients with unilateral temporal lobe damage. Seventeen right and 13 left temporal lobectomy patients were compared with 16 healthy matched control subjects. After they had explored the town, subjects' topographical memory was tested by requiring them to navigate to specific locations in the town. The ability to recognize scenes from and draw maps of the virtual town was also assessed. Following the topographical memory tests, subjects followed a route around the same town but now collected objects from two different characters in two different locations. Episodic memory for various aspects of these events was then assessed by paired forced-choice recognition tests. The results showed an interaction between laterality and test type such that the right temporal lobectomy (RTL) patients were worse on tests of topographical memory, and the left temporal lobectomy (LTL) patients worse on tests of context-dependent episodic memory. Specifically, the RTL group was impaired on navigation, scene recognition and map drawing relative to control subjects. They were also impaired on recognition of objects in the episodic memory task. The LTL group was impaired relative to control subjects on their memory for contextual aspects of the events, such as who gave them the objects, the order in which objects were received and the locations in which they received them. They were also mildly impaired on topographical memory, but less so than the RTL group. These results suggest that topographical memory is predominately mediated by structures in the right medial temporal lobe, whereas the context-dependent aspects of episodic memory in this non-verbal test are more dependent on the left medial temporal lobe.

Keywords: hippocampus; navigation; virtual reality; map drawing

Abbreviations: LTL = left temporal lobectomy; RTL = right temporal lobectomy; VR = virtual reality

Introduction

Remembering where a location is and how to get there (topographical memory) as well as what happened there (episodic memory) are cognitive operations thought to be dependent on the hippocampus and other medial temporal lobe structures (e.g. see Burgess *et al.*, 1999). It has been suggested that the hippocampus stores a cognitive map of the spatial layout of an environment (O'Keefe and Nadel, 1978). It was further suggested that, in humans, it might additionally contain information about the spatiotemporal context of events. The ability to retrieve the context of an event is a defining characteristic of episodic memory, distinguishing it from simple familiarity-based recognition (O'Keefe and Nadel, 1978; Gardiner and Java, 1991; Tulving, 1993; Knowlton and Squire, 1995).

Temporal lobectomy patients, who have undergone selective removal of the hippocampus and adjacent temporal lobe tissue for intractable epilepsy, have provided a valuable resource in our understanding of the contributions of the temporal lobe to memory. Early studies found that bilateral medial temporal lobectomy patients, such as H.M., suffer from severe episodic memory deficits (Scoville and Milner, 1957), whereas patients with unilateral temporal lobectomies do not show such severe amnesia (Milner, 1972).

Nonetheless, unilateral patients show less pronounced but material-specific anterograde memory deficits. Patients with temporal lobectomy of the left or dominant hemisphere have been found to be impaired on tests of delayed recall of prose passages, recalling only fragments of the passage, whereas right temporal lobectomy (RTL) patients perform as well as matched controls (Milner, 1958; Frisk and Milner, 1990). The same dissociation between the two groups has been observed on tasks such as paired associate learning (Meyer and Yates, 1955; Milner and Kimura, 1964), the learning, recall and recognition of word lists (Milner and Kimura, 1964; Dennis *et al*., 1988; Baxendale, 1997) and the recall of object names (Incisa della Rocchetta and Milner, 1993).

The opposite pattern of material-specific impairments is found when patients are tested on tasks requiring memory for pictures of objects that are difficult to verbalize (e.g. Jones-Gotman, 1986) or spatial memory, with deficits following RTL (or non-dominant lobe surgery) but not left temporal lobectomy (LTL). A large number of tasks have been designed to examine the effect of RTL on spatial memory. Most of these tasks have studied memory for spatial information in small-scale environments, i.e. a table top, a computer screen or within a room. Patients with right temporal lobe damage are impaired in their ability to remember the location of objects on a table top (Smith and Milner, 1981, 1989; Nunn *et al*., 1999), or in a scene (Pigott and Milner, 1993; Baxendale *et al*., 1998). They are also impaired in their performance of table top maze learning (Corkin, 1965; Milner, 1965) and spatial conditional associative learning (Petrides, 1985). Right temporal damage has also been shown to affect performance on tasks mimicking rodent spatial tasks, with either 'table top' tasks (Goldstein *et al*., 1989; Feigenbaum *et al*., 1996; Morris *et al*., 1996; Abrahams *et al*., 1997; Bohbot *et al*., 1998; Morris *et al*., 1999) or navigation in a room (Bohbot *et al*., 1998; Worsley *et al*., 2001). It has been shown that deficits on these tasks are particularly sensitive to damage in the medial temporal lobe region, and the hippocampus in particular (e.g. see Smith, 1989; Nunn *et al*., 1999). On many of these tests of spatial memory the LTL group performed marginally, but not significantly, worse than the control group.

While small-scale tests of spatial memory and verbal tests of episodic memory have been useful in elucidating the material-specific nature of the memory deficits, they do not test directly the 'real-world' abilities of way-finding in large-scale (multiple perspective) environments, nor do they test memory for the events experienced by patients in their daily life. 'Real-world' topographical and episodic memory can sometimes be dissociable from word-list memory and table top spatial tests in neurological patients (e.g. Kapur and Pearson, 1983; Habib and Sirigu, 1987; Maguire *et al*., 1996; Maguire and Cipolotti, 1998).

Neuroanatomical studies examining 'real-world' topographical memory have employed a number of techniques such as identifying landmarks (Whiteley and Warrington, 1978; Incisa della Rocchetta *et al*., 1996), monitoring actual navigation (Habib and Sirigu, 1987; Clarke *et al*., 1993) or route following (Barrash, 2000) and judging changes in view point (Suzuki, 1998). Such studies have identified a range of brain regions involved in topographical memory (for a recent review, see Aguire and D'Esposito, 1999). To our knowledge only one study has examined the effect of unilateral temporal lobectomy on topographical memory. In this study, Maguire and colleagues showed unilateral temporal lobectomy patients and control subjects film footage of two overlapping walked routes though a town (Maguire *et al*., 1996). The footage was repeated until all subjects could correctly identify scenes from the town, after which they were tested on their topographical memory for the town. Both RTL and LTL patients took more viewings to reach the scene recognition criterion than controls. RTL patients were impaired relative to a matched control group in their ability to judge proximity between groups of three landmarks (presented as pictures), distances between pairs of landmarks, the correct sequence of landmarks along the walked routes and their ability to draw accurate sketch maps of the town. With the exception of the proximity judgement test, the LTL group were also impaired on all topographical tasks relative to the control group, although to a lesser degree than the RTL group. Functional neuroimaging studies of the recall of real-life routes have produced complementary results, activating medial temporal lobe regions including the right hippocampus (Ghaem *et al*., 1997; Maguire *et al*., 1997).

'Real-world' episodic memory for events experienced in patients' daily lives has been studied by examining the events recalled in autobiographical interviews. In three studies, left temporal lobe damage has been found to impair the number of memories recalled (Barr *et al*., 1990; Kapur *et al*., 1997; Viskontas *et al*., 2000). However, in a study by Viskontas and colleagues, performance was found to be equally impaired by right temporal lobe damage (Viskontas *et al*., 2000). Indeed other authors have argued for preferential involvement of the right temporal lobe in autobiographical memory (Kopelman *et al*., 1999; Markowitsch, 1995). Thus, the material specific differences shown on standard neuropsychological tasks are not so clear cut for 'real-world' episodic and topographical memory.

There are acknowledged problems associated with studying 'real-world' memory. Studies of topographical memory typically involve a trade-off between experimental control and allowing subjects to interact with an environment in a 'real-world' manner. Often it is difficult to find suitable environments and accurately measure performance. Similarly, memories for remote real-life events are hard to validate, are not the same between individuals and often rely on verbal processing at recall (see Hodges, 1995; Kapur, 1999).

Virtual reality (VR) provides a method for utilizing a large-scale environment whilst controlling the encoding situation and permitting the accurate measurement of navigational performance. VR has been used to investigate whether the navigational performance of neurological patients is impaired (Skelton *et al*., 2000) or spared (Maguire and Cipolotti, 1998). It has also been employed in a number of neuroimaging studies examining topographical memory

(Aguirre *et al.*, 1996, 1997; Maguire *et al.*, 1998*a*, 1998*b*, Gron *et al.*, 2000), which have implicated a network of brain regions including the parahippocampus and the hippocampus. In a study by Maguire and colleagues, subjects navigated through a large complex town and blood flow in the right hippocampus was found to be significantly correlated with the accuracy of navigation: as accuracy increased so did blood flow (Maguire *et al.*, 1998*b*).

In the present study we investigated the effects of right or left anterior temporal lobectomy on topographical memory within a realistic and large-scale environment by adapting the VR town previously employed by Maguire and colleagues (Maguire *et al.*, 1998*b*; Burgess *et al.*, 2001). Furthermore, we were able to examine the effects of temporal lobectomy on episodic memory by using this VR environment as a context-rich setting in which the patients experienced simulated events in which they could participate actively, as with personally experienced events in real life. In testing memory for these events, we were able to distinguish between responses demanding retrieval of the context of the event from responses that could be made on the basis of familiarity, thus probing context-dependent (i.e. episodic) and context-independent memories separately.

Material and methods

Subjects

A total of 34 patients and 21 control subjects were recruited. Two patients and three controls felt uncomfortable (nausea) viewing the VR town, an occasional side-effect of the optic flow. These subjects did not continue in the study. Two left-handed LTL patients with bilateral speech representation were excluded from the study. In order to match the IQ of the control group to the patient groups the control subject with the highest IQ was excluded, as assessed by the NART (National Adult Reading Test) (see below). One further control subject was excluded as English was not her first language (a prerequisite of the NART). The final groups tested were: 17 RTL patients, 13 LTL patients and 16 neurologically normal control subjects. The control subjects were recruited through advertisements in the area around Queen Square, London. They were all right-handed and had no history of neurological illness, neurosurgery or psychiatric problems. All gave informed, written consent to take part in accordance with the Joint Medical Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Patient and control groups did not differ significantly in terms of age [$F(2,45) = 2.28$, $P = 0.11$], FSIQ (Full Scale Intelligence Quotient) [$F(2,44) = 2.39$, $P = 0.10$] and dexterity [$F(2,44) = 2.25$, $P = 0.12$]. Subjects' dexterity was tested by having them follow a timed route through the virtual town using the video game controls provided, and FSIQ was estimated by the NART (Nelson and Willison, 1991). The groups were also matched for gender ratio, prior video games experience and number of subjects with further education. See Table 1 for details.

Patient characteristics

All patients had undergone unilateral temporal lobe surgery for the relief of intractable epilepsy at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. Patients selected for testing were aged between 20 and 60 years, all were seizure free (for at least the preceding 6 months), were >1 year post-surgery and without serious psychiatric or medical conditions. The surgical procedure involved the removal of 3.5–5.5 cm of cortical tissue from the anterior temporal pole in the posterior direction, with the excision of 2.5–3.5 cm of the hippocampus and a varying amount of parahippocampal gyrus and amygdala (as noted by the surgeon). Four RTL patients and five LTL patients had mild upper quadrant visual field defects, contralateral to the surgery. Four RTL patients had undergone surgery for a tumour, three for a dysembryoplastic neuroepithelial tumour and the other for a ganglioma of the temporal lobe. All other patients had undergone surgery for mesial temporal lobe sclerosis. As a group, these patients' removals were predominantly anterior medial temporal, but also included anterior superior and lateral temporal regions (see Kitchen *et al.*, 1994). For convenience we refer to these lesions as medial temporal in the following text, with consideration of the anterior and superior nature of the lesion in the discussion.

Two LTL patients included in the study were left-handed. Sodium amytal testing demonstrated that these patients were left hemisphere dominant for speech. All other patients were right-handed, left hemisphere dominant for speech. At the time of testing, 22 of the patients were taking anti-epileptic medication (nine LTL, 13 RTL). See Table 2 for details of the patients' standard postoperative neuropsychology and epilepsy characteristics.

Experimental tests

A VR town provided the environment in which the patients and the control subjects were tested. The town was designed and constructed by Neil Burgess using the commercially available video game 'Duke Nukem 3D' (3D Realms Entertainment; Apogee Software Ltd, Garland, Tex., USA) with the editor provided (Build 3D Realms Entertainment), and was adapted from the virtual town used in the study by Maguire and colleagues (Maguire *et al.*, 1998*b*; see Burgess *et al.*, 2001). The town consisted of a main street intersected by a crossroad with various interior locations, which involved, for example, a cinema, a bookshop, a bar and an underground station (see Fig. 1). The town was sufficiently complex to provide a large number of possible routes from one location to another.

The town was displayed to the subjects at a frame rate of 21 Hz on a desktop PC with a 19 inch screen. Subjects used the cursor keys of a keyboard to manoeuvre within the town. After the subjects had completed having their dexterity tested by timing how long they took to follow a route of arrows, they were instructed to explore until they felt they were

Table 1 *Group matching details*

Subject group (n = 16)	LTL (n = 13) Mean (SD)	RTL (n = 17) Mean (SD)	Controls Mean (SD)
Age (years)*	34.8 (8.1)	37.5 (9.6)	31.1 (8.1)
Males : females	6 : 7	9 : 8	9 : 7
Premorbid FSIQ [NART]*	100.5 (14.4)	100.9 (15.7)	108.7 (7.3)
Dexterity (s)*	73.3 (24.0)	89.0 (48.4)	61.1 (36.4)
Number with video games experience	7	9	9
Number with higher education qualification	5	5	6

FSIQ = full scale IQ score; NART = National Adult Reading Test. *No significant differences were noted between any of these variables with a one-way ANOVA. All except two patients were in full time employment.

Table 2 *Patient post-operative neuropsychology and epilepsy characteristics*

Patient group	LTL (n = 13) Mean (SD)	RTL (n = 17) Mean (SD)	t-values*
VIQ	97.8 (17.0)	96.6 (14.8)	0.3 n.s.
PIQ	112.7 (20.9)	101.2 (18.7)	1.6 n.s.
RMTW	42.9 (6.1)	46.1 (3.4)	1.8 n.s.
RMTF	45.5 (3.2)	40.2 (4.9)	3.1 (P = 0.004)
Rey–Osterrieth figure immediate recall (max 100)	81.6 (19.1)	76.1 (19.5)	0.7 n.s.
Rey–Osterrieth figure delayed recall (max 100)	80.5 (16.6)	69.6 (23.1)	1.4 n.s.
Story recall immediate (max 60)	22.3 (10.8)	23.1 (12.1)	0.2 n.s.
Story recall delayed (max 60)	17.9 (11.3)	21.3 (11.7)	0.7 n.s.
Time since operation (months)	48.4 (27.1)	60.2 (24.6)	1.2 n.s.
Age of seizure onset (years)	8.5 (5.7)	10.9 (6.8)	1.0 n.s.
Duration of seizure disorder (years)	31.2 (9.6)	32.8 (10.3)	0.4 n.s.

For details of the Story Recall, see Coughlan and Hollows, 1985 and for the Rey–Osterrieth complex figure, see Osterrieth, 1944. Verbal IQ (VIQ) and performance IQ (PIQ) were measured with the WAIS-R (Wechsler Adult Intelligence Scale—Revised). RMTW = Warrington Recognition Memory Test for Words; RMTF = Warrington Recognition Memory Test for Faces (Warrington, 1984); SD = standard deviation. *Independent samples t-test comparing the performance of the two groups.

ready to be tested on their memory of the town (and had been observed by the experimenter to visit all locations). Subjects were required to explore for a minimum of 15 min but not more than 60 min.

Subjects were not warned that they would be tested on their ability to draw a map of the town but were informed that they would be tested on their navigation and memory for the town. Subjects were tested on the following tasks in the order described.

Navigation

Subjects had to navigate between 10 different locations in the town using the most direct route available. They were shown a picture of a target location which was continually present whilst they were navigating to that location. When subjects reached the location, they were presented with a new picture and asked to repeat the process until they had navigated to each of the 10 places. These target locations were the same for each subject, evenly distributed across the town, never visible from the starting view and varied in their relative proximity and difficulty of locating. The subject's average path length, calculated from cursor key presses or joystick moves made by the subject during the task, was used to assess the accuracy of navigation.

Environmental scene recognition

Forced-choice between pairs of scenes was used to test memory for the locations visited by the subject during exploration and navigation. Twenty pairs were tested. One of the scenes in each pair (the target) was a view of a location from the virtual town. Note that the subject was unlikely to have experienced the exact scene used and some of these were taken from viewpoints that subjects had never been able to reach. The other scenes (the foils) were created by altering the town or by creating new virtual locations. Some of these foil views had novel objects, novel textures and novel geometry. Other foils had familiar objects, familiar surface textures and similar geometry, but were spatially rearranged so as to be inconsistent with the original town. Responding was self-paced.

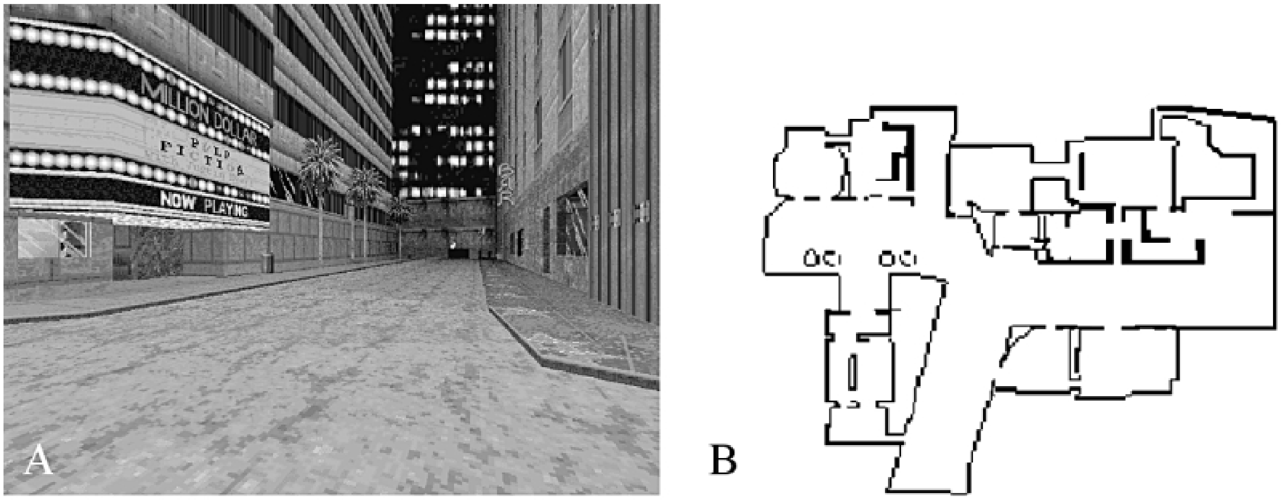

Fig. 1 The virtual town (viewed in colour by the subjects). (**A**) A view of the crossroads with the cinema on the left. (**B**) An aerial perspective of the virtual town (which was not shown to the subjects). This plan is also shown in Spiers *et al*. (2001).

Map drawing

Map drawing was assessed in a quantitative manner with a computer program. A 10×10 grid and a set of 10 icons representing locations in the town were displayed on the computer monitor. Subjects were required to move icons onto the grid to form a map of the town. The icons could be moved to a new location after having been placed initially. A 3D view of the location represented by each icon could be displayed at any time. Subjects were instructed to use the full extent of the grid and to avoid clustering all the icons in one area. After all 10 icons had been placed, subjects could opt to stop, or to continue arranging the icons until they were satisfied.

An ideal map (see Fig. 5A.) was constructed that reflected the true layout of the town (as shown in Fig. 1B). Each subject's completed map was scored by calculating the error in the distance between all pairs of icons as a fraction of the mean distance between the icons in the ideal and the subject's map. This measure is independent of the map's orientation. Scaling each subject's map to match the ideal map achieved independence from map size. Specifically, the error measure reported in Fig. 4C is:

$$\min \left\{ \left\langle \frac{|\gamma d^{s}_{ab} - d^{i}_{ab}|}{\frac{1}{2}(\gamma d^{s}_{ab} + d^{i}_{ab})} \right\rangle_{ab} \right\}$$

where d^{s}_{ab} is the distance between icons a and b in the subject's map, d^{i}_{ab} is the distance between icons a and b in the ideal map, γ is an arbitrary scaling factor (which provides a scale invariant measure) and $<.>_{ab}$ represents the average over all pairs of icons ab.

Episodic memory

The aim of this task was to test memory for events analogous to those experienced in daily life. Following a practice run, two trials were given, each comprising a presentation phase and a test phase. During presentation, the subject followed a route through the town and repeatedly encountered two single characters, at 16 intervals along the route. Every time a character was encountered, the subject was required to press a key, causing the character to produce an object, which the subject then collected by moving up to it. One of these events is depicted in Fig. 2A. The characters were present in two of the rooms on each route, but not always in the same section of each room, and not always approached from the same direction. The objects were common, familiar objects, e.g. a hammer. Before the subjects started the presentation phase, they were informed that their memory for the objects, who gave them the objects, where they received the objects and the order in which they collected them would be tested. For the second route, different objects, characters and places were used. Subjects were given practice by following each of the two routes and collecting four practice objects from two practice characters. They were asked whether they had used any particular associational or mnemonic strategies to aid their recall and, if they had, they were asked to avoid using these strategies and simply pay attention to the aspects of the events in the experimental test.

Immediately following the presentation phase, the subject's memory for the events was tested in a counterbalanced paired forced-choice procedure. Subjects re-entered the rooms in which they had previously collected the objects, which now contained a character and, displayed on the nearest wall, a word that represented the question, and two objects (see Fig. 2B for an example of a question). Paired forced-choice questions were of four different types. One type consisted of old–new recognition questions: OBJECT, 'which of the two objects displayed did you collect?'. The other three were context-dependent episodic memory questions: PERSON, 'which of the two objects did you collect from the character next to this question?'; PLACE, 'which of the two objects

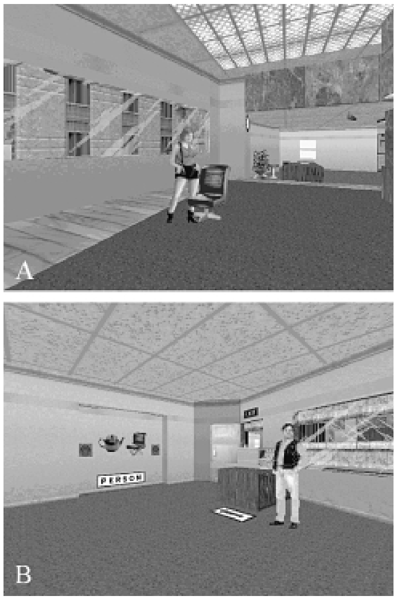

Fig. 2 The episodic memory test. (**A**) The presentation phase: a view of one of the 16 events encountered during presentation of the objects on the first route. (**B**) The recall phase: an example of one of the context-dependent questions, a PERSON question. In this question the subject is asked 'which of the two objects did you collect from the person standing next to the objects?' The two objects above the word PERSON were two of the objects collected, one collected from the person next to the two objects and the other from another person. For the other context-dependent questions the word PERSON was replaced by the words PLACE or FIRST where the subject had to remember which object they had collected in the current location or which of the two objects had been collected first, respectively. Again, the two objects were ones that had previously been collected. When the word under the objects was OBJECT, the question was 'which of the two objects did you collect?' and one of the objects was from the set collected and the other was a similar new object.

did you collect in the room you are currently in?' and FIRST, 'which of the two objects did you collect first?'. For the OBJECT question, the foil was a very similar object but not one that had been collected. Foil objects in the other conditions were other objects from the set the subject had received. For the PLACE question the foil object was one of the collected objects that had been given to them in the other room. For the PERSON question the foil object was one of the objects given to the subject by the character other than the one next to the question. A total of 16 × 4 questions were asked after each of the two trials. The questions were given in the form of eight sets of eight questions, and the time taken to answer each set of eight questions was recorded. The left–right response and question order to each question were counterbalanced across the test phase.

Results

The overall performance of the patients and the controls was compared on the topographical and episodic memory tests. Due to scaling differences in the topographical tests, the performance of all subjects in each test was converted into a Z-score relative to the control mean and standard deviation. The overall score for topographical memory was calculated as the mean of the Z-scores for the navigation task, the environmental scene recognition task and the map drawing task. The overall Z-score for episodic memory was calculated from the context-dependent questions: PERSON, FIRST and PLACE questions (the OBJECT question was excluded because, unlike the other questions, it can be solved by stimulus familiarity, see Introduction). A 2 × 2 ANOVA (analysis of variance) was used to test whether the two patient groups (LTL and RTL) differed in their performance on these two test types (topographical memory, context-dependent episodic memory). There was no main effect of test type or subject group but there was a significant subject group × test type interaction [$F(1,53) = 6.31$, $P = 0.015$], see Fig. 3.

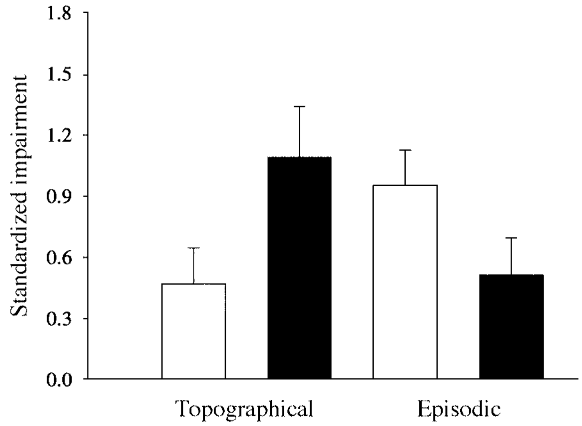

Fig. 3 Impairments in topographical and episodic memory. The scores shown are the mean standardized Z-scores of the LTL (open columns) and RTL (filled columns) patient groups' performance relative to the control group mean and standard deviation. On the left the scores are for the topographical tasks (navigation, environmental scene recognition and map drawing) and on the right for the context-dependent episodic memory questions (PERSON, FIRST, PLACE questions). Statistical analysis of this data shows a significant group × test type interaction [$F(1,53) = 6.31$, $P = 0.015$].

Topographical memory

To further explore this finding, the performance of the groups on each of the individual tests was examined. The performance of the patients and the controls on the topographical tasks is shown in Fig. 4.

Navigation

The performance of each of the three groups is shown in Fig. 4A. There was a significant effect of subject group on navigational accuracy [$F(2,43) = 4.37$, $P = 0.019$]. The RTL group's performance was significantly worse than that of the control group. The LTL group's performance was

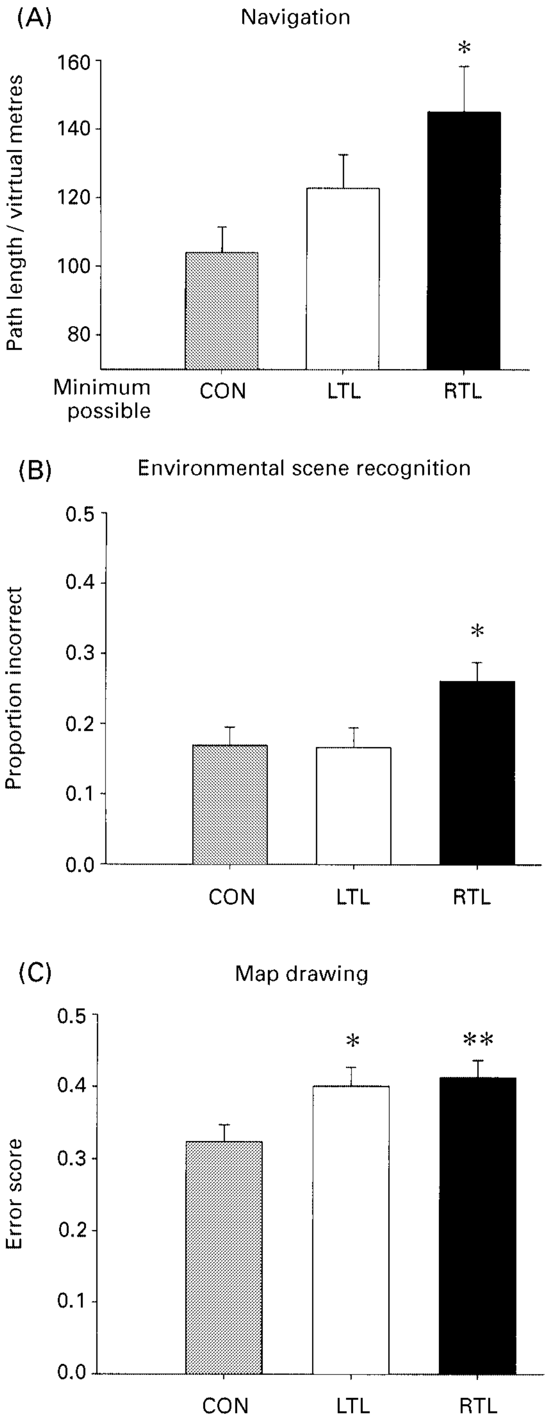

Fig. 4 The topographical memory test results. (**A**) The extent of error on the navigation task is measured by mean path length for each group. Error bars are the standard error of the mean. *Indicates significantly impaired relative to the control group ($P < 0.01$). The minimum path length was 70 virtual metres. (**B**) The mean proportion of incorrect responses on the environmental scene recognition test for each group. Error bars are the standard error of the mean. *Indicates significantly impaired relative to the control group ($P < 0.01$). Chance is 0.5. (**C**) The mean score for each group on our computed measure of map drawing error. Error bars are the standard error of the mean. Significant impairments relative to the control group are indicated by * for $P < 0.05$ and ** for $P < 0.01$.

intermediate to the control and RTL groups (the difference from controls approaching significance), see Table 3 and Fig. 4A for details.

Environmental scene recognition

The performance of each of the three groups is shown in Fig. 4B. There was a significant effect of group on environmental scene recognition [$F(2,43) = 4.35$, $P = 0.019$]. *Post hoc* testing revealed that the RTL group was significantly worse than the control group (see Table 3) and significantly different from the LTL group (see Table 3). The LTL group was not significantly worse than the control group.

Map drawing

The performance of each group is shown in Fig. 4C and the map of the median subject in each group and the ideal map to which they were compared are shown in Fig. 5. There was a significant effect of group on map drawing performance [$F(2,43) = 4.15$, $P = 0.023$]. Both the RTL and LTL patients were significantly impaired relative to the control subjects in their ability to draw accurate maps of the town (see Table 3). The difference between the LTL and RTL groups was not statistically significant.

The impaired performance by the RTL group on the topographical tests could not be accounted for by poor dexterity or a shorter exploration time as there was no statistical difference in the dexterity scores (see subject matching details) or exploration times of the two groups. Indeed both LTL and RTL patient groups spent longer exploring the town than the controls, although not significantly so [$P = 0.061$]. Means and standard deviations for exploration times in minutes were: LTL = 34.3 (18.0), RTL = 33.1 (14.5) and control subjects = 23.3 (7.2).

Episodic memory task

Due to time constraints on some patients' availability, one LTL patient and two RTL patients were not tested on the episodic memory test. Additionally, five LTL patients, five RTL patients and two control subjects were only tested on their memory for the events on the first route (i.e. 16 of the events). Subjects' scores were converted into percentages and entered into the analysis along with the percentage scores of subjects who had completed both routes. The results of these analyses are shown in Table 3. There was no significant difference between the performance of the patients who completed either both routes or only one, and the data from the first route alone showed the same statistical differences and the same trend as the data from both routes, as noted below.

Object recognition

The ability of each group to discriminate new objects from objects that they had collected whilst following the route is

Table 3 *Statistical comparison of patient group and control group performance*

Experimental test	LTL vs Con	RTL vs Con	LTL vs RTL
Topographical memory (Navigation, environmental scene recognition, map drawing)	n.s. ($P = 0.033$)	$P = 0.0005$	n.s. ($P = 0.072$)
Details			
Navigation	n.s. (0.062)	$P = 0.004$	n.s.
Environmental scene recognition	n.s.	$P = 0.009$	$P = 0.020$
Map drawing	$P = 0.017$	$P = 0.005$	n.s.
Object recognition (Object)	n.s.	$P = 0.001$	n.s.
Context-dependent episodic memory (Person, First, Place)	$P = 0.004$	n.s. ($P = 0.055$)	n.s. ($P = 0.092$)
Details			
Person	$P = 0.011$	$P = 0.038$	n.s.
First	$P = 0.011$	n.s.	$P = 0.034$
Place	$P = 0.044$	n.s.	n.s.

P-values shown in the table were calculated following a significant main effect of group with a one-way ANOVA (analysis of variance). n.s. indicates $P > 0.05$. *t*-Tests were 1-tailed when the patient groups were compared with the control group and 2-tailed when the patient groups were compared with each other. Con = control.

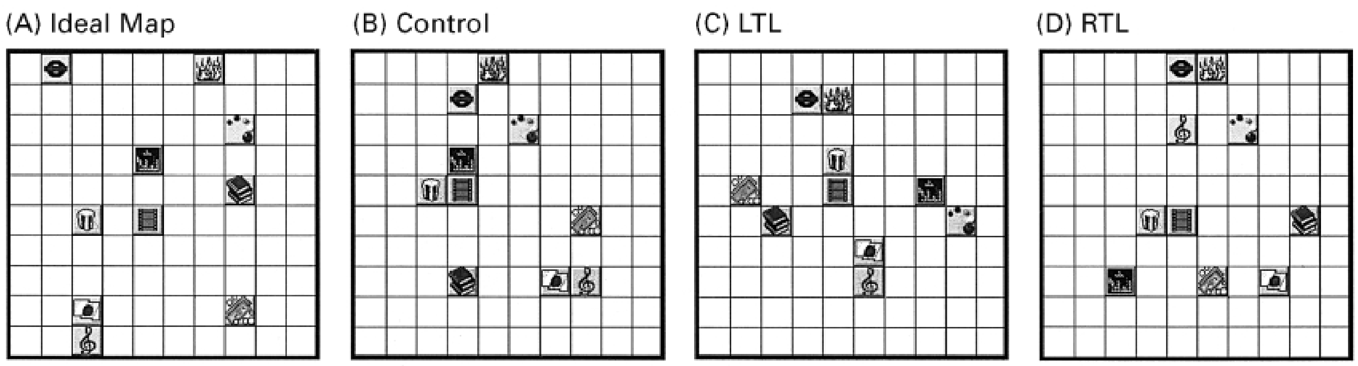

Fig. 5 The ideal map and representative maps of each group. (**A**) The ideal map with which the patient and control maps were compared. (**B**), (**C**) and (**D**) are representative maps from the control, LTL and RTL groups, respectively. The illustrated maps were those where the calculated error score was closest to the group mean. The scores were 0.320 (control), 0.393 (LTL) and 0.415 (RTL). Road icons could also be added to the map by subjects, but were not scored and have been omitted from the figure.

shown in Fig. 6A, expressed as the proportion of correct responses. All subjects correctly identified at least 75% of the total target objects in the OBJECT condition. There was a significant effect of group on object recognition performance [$F(2,40) = 4.72$, $P = 0.014$]. The RTL patients' recognition of the target objects was found to be significantly worse than that of the control subjects, see Table 3. This is present as a trend in the objects on route A and a significant difference for the objects on route B. The LTL group were not significantly worse than the control group.

Context-dependent episodic memory

The context-dependent questions (FIRST, PERSON and PLACE) were those questions for which the subjects had to remember information about the context in which the objects had been collected. The effect of subject group on performance on the three context-dependent memory questions was investigated with a 3×3 ANOVA. This revealed a significant effect of subject group [$F(2,120) = 6.86$, $P = 0.002$] and test type [$F(2,120) = 19.0$, $P < 0.001$], but no interaction. The overall performance of the LTL group on the context-dependent questions was found to be significantly worse than the control group. The difference between the LTL and RTL groups and the difference between the RTL and control groups, approached, but did not reach significance (see Table 3). The performance of the patients and the controls on each of the context-dependent questions is shown in Fig. 6B. When each group's performance was compared on the individual context-dependent questions, the LTL group was found to be significantly impaired relative to the controls on the PERSON, FIRST and PLACE questions (see Table 3). The RTL group's performance was significantly worse than the control group on the PERSON question and

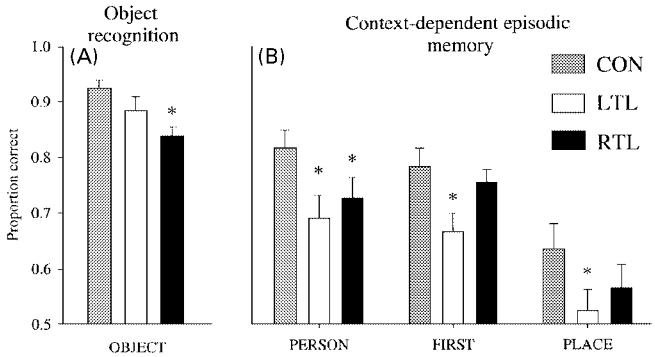

Fig. 6 The episodic memory test results. (**A**) The mean proportion of correct answers made by each group on the OBJECT questions. Error bars are the standard error of the mean. *Indicates significantly impaired relative to the control group ($P < 0.05$). Chance is 0.5. (**B**) The mean proportion of correct answers made by each group on the PERSON, FIRST and PLACE questions. Error bars are the standard error of the mean. *Indicates significantly impaired relative to the control group ($P < 0.05$). Chance is 0.5.

worse on average but not significantly different from the control group on the FIRST and PLACE questions (see Table 3). In terms of individual comparisons, differences between the LTL and RTL group reached significance for the FIRST question, but not for the PERSON or PLACE questions.

The performance of all the groups on each question type was found to be significantly different from chance ($P < 0.05$, chance = 50% correct) except for the PLACE questions where the performances of the RTL group [$t(14) = 1.49$, $P = 0.16$, 2-tailed] and the LTL group [$t(11) = 0.66$, $P = 0.52$, 2-tailed] were not significantly different from chance. When the data from route A were examined separately, no group's performance was significantly different from chance on the PLACE question.

The time taken to collect the objects (presentation time) and the time taken to answer each block of eight questions (retrieval time) were not different between the patient groups, but were significantly shorter for the controls ($P < 0.05$). Means and standard deviations for presentation time in minutes were: LTL 15.3 (3.2), RTL 14.8 (4.0) and control subjects 11.0 (2.4). Retrieval times were: LTL 4.4 (1.0), RTL 4.7 (1.3) and control subjects 3.5 (0.8). When the number of errors made in the first and second halves of the retrieval phase was examined, no decline over the retrieval phase was observed for the patient groups. Thus, the patients' impaired performance could not be due to the increased time taken to answer the questions.

Strategies

When the answers to debriefing questions were examined, four control subjects, three RTL patients and two LTL patients explicitly reported having used a specific strategy to aid their recall of the events. The strategies employed were heterogeneous and included both verbal and non-verbal strategies. Examples of strategies were: creating a story involving the people, objects and places; the verbal repetition of the names of people, objects and places; and imagining a film plot related to an event.

Further analyses

Given that LTL patients are known to perform poorly on verbal memory tests (e.g. Frisk and Milner, 1990), we examined the relationship between LTL patients' performance on the context-dependent episodic memory tests with standard verbal measures. Context-dependent episodic memory performance was not significantly correlated with delayed story recall (Coughlan and Hollows, 1985), the Warrington Recognition Memory Test for Words (Warrington, 1984) or verbal IQ.

As previous studies have reported visuospatial deficits following RTL (e.g. see Smith and Milner, 1989), topographical memory performance (average *Z*-score of errors on tests) was examined in relation to other visual memory tasks and performance IQ. Topographical memory was found to be significantly correlated with delayed recall of the Rey–Osterrieth figure (Osterrieth, 1944) [$r = -0.58$, $P = 0.03$], and performance IQ [$r = -0.63$, $P = 0.007$], but not with performance on the Warrington Recognition Memory Test for Faces (Warrington, 1984).

The performances of the patients on the topographical memory tasks and the context-dependent episodic memory questions were compared with other variables of interest to test for possible relationships. Across all patients, the age of seizure onset, the duration of epilepsy (as a proportion of age) and frequency of pre-operative complex partial seizures were not found to correlate with topographical memory or episodic memory performance.

Further factors affecting topographical and episodic memory were examined with independent samples *t*-tests, namely the effect of anti-epileptic drugs, gender and prior experience with video games. No significant effect of these factors on topographical memory or context-dependent episodic memory performance was found.

Discussion

The aim of this study was to assess the effect of unilateral temporal lobe damage on topographical and episodic memory in a large-scale environment. Patients with unilateral temporal lobectomy were tested on their ability to navigate, recognize scenes, draw maps and remember events occurring in a large-scale VR town. Right temporal lobe damage was found to primarily impair topographical memory and the recognition of objects, whereas left temporal lobe damage was found to primarily impair context-dependent episodic memory. Whilst the temporal lobectomy patients in this study have damage to both lateral and medial regions of the superior and anterior temporal lobe, previous studies have found compelling evidence that the memory deficits were contingent upon damage to the medial temporal regions, and the hippocampus in particular (e.g. Smith and Milner, 1981; Nunn *et al*., 1999).

Topographical memory

The finding that the RTL patients, were much more impaired relative to control subjects than the LTL patients on all the topographical tasks that require long-term memory for spatial information is consistent with previous studies of small-scale or 'table top' spatial memory (Corkin, 1965; Milner, 1965; Smith and Milner, 1981, 1989; Goldstein *et al*., 1989; Piggot and Milner, 1993; Feigenbaum *et al*., 1996; Morris *et al*., 1996, 1999; Abrahams *et al*., 1997; Baxendale *et al*., 1998; Bohbot *et al*., 1998; Nunn *et al*., 1999; Worsley *et al*., 2001). As in many previous studies, the LTL group's performance was intermediate to that of the RTL and control groups, being significantly worse than the control group for map drawing and significantly better than the RTL group for environmental scene recognition. The overall difference in performance on topographical tasks between RTL and LTL groups approached significance. This suggests that spatial memory for large-scale environments is preferentially dependent on the right temporal lobe, but may also involve some left temporal lobe contribution. A number of previous studies have shown that it is the medial temporal regions that are the key structures involved in deficits on such tasks (e.g. Smith and Milner, 1981; Nunn *et al*., 1999), so we therefore ascribe these deficits to medial temporal lobe structures.

Our results and this interpretation are also consistent with neuroimaging studies using VR environments examining topographical memory, which activate both left and right medial temporal lobe regions, but with right medial temporal lobe activation more strongly associated with accurate navigation (e.g. Maguire *et al*., 1998*b*). The results are theoretically consistent with O'Keefe and Nadel's assertion that, in the human, topographical memory functions have become more right lateralized, with the addition of linguistic functions to the left hemisphere (O'Keefe and Nadel, 1978).

This is the first study to quantify the deficit in unilateral (right) temporal lobectomy patients in their ability to navigate in a large-scale environment. Our findings are at odds with De Renzi's view that unilateral damage to the medial temporal lobe regions does not affect way-finding (De Renzi, 1982), and Aguirre and D'Esposito's interpretation that either hemisphere is sufficient to support this function (Aguirre and D'Esposito, 1999). In the present study, it is not clear whether this navigational deficit is caused by damage to the right hippocampus, right parahippocampus or a combination of both.

The ability to discriminate scenes of the virtual town from very similar foil scenes was also found to be impaired in the patients with RTL surgery. This result differs slightly from that found on a test of scene recognition administered by Maguire and colleagues, who found that both RTL and LTL patients were impaired (Maguire *et al*., 1996). This could be due to differences between the large-scale environments used, how they were explored and how the scene recognition was assessed. Previous studies have suggested that the ability to process topographical stimuli is dependent on the posterior parahippocampal cortex (e.g. Epstein and Kanwisher, 1998), an area not removed in patients in the present study. However, the scene recognition task in our study involves more than the ability to recognize landmarks, i.e. most target views were taken from a view that subjects would not have experienced, and foils contained the same or similar visual features as the targets. The ability to identify changes in the spatial composition of a scene has been shown to be impaired in RTL patients (Pigott and Milner, 1993) and pre-operative right temporal lobe epileptics (Baxendale *et al*., 1998). Furthermore, Baxendale and colleagues found that poor spatial memory performance in their Aspect of Spatial Memory Test was correlated with MRI volume measurements of the right hippocampal atrophy, suggesting that the right hippocampus is important for accurate performance on our environmental scene recognition task (Baxendale *et al.*, 1998).

As well as having significant difficulties navigating through and recognizing scenes from the virtual town, RTL patients could not construct maps of the town as accurately as the control subjects, adding further evidence that the ability to form a cognitive map of a large-scale environment is dependent on the right medial temporal lobe region. Previously, patients with right hemispheric lesions have been found to have difficulty drawing maps of their environment (e.g. Clarke *et al*., 1983; Habib and Sirigu, 1987). Interestingly, the LTL patients were also impaired on this task. This finding is consistent with a study by Maguire and colleagues who found both RTL and LTL patients impaired (Maguire *et al*., 1996), similarly the RTL patients in this study performed worse, but not significantly worse, than the LTL patients. Thus, drawing maps also recruits processes dependent on left temporal regions, possibly including retrieval of verbal or episodic information. In contrast, environmental scene recognition showed the greatest difference between groups of all the topographical tasks and, thus, is presumably less reliant on these left-lateralized functions. We note that this task is the most similar to the table top spatial tasks in which differences between RTL and LTL patients have been observed previously (e.g. Smith and Milner, 1981).

Episodic memory

In this task, subjects were presented with a sequence of events that consisted of collecting a set of objects, each collected from one of two people in one of two locations in the town. Paired forced-choice of old versus new objects (OBJECT) was tested, as well as discriminations regarding which of the two objects had been collected from a given person (PERSON), a given place (PLACE) or first in the sequence (FIRST).

The results of the OBJECT questions were similar to those of the topographical memory tests, with RTL patients impaired relative to controls and the LTL performance intermediate but not different from the other two groups. Previous studies have found RTL patients impaired at object recognition when the foil objects are of the same category as the objects to be recognized (Maguire, 1994; Morris *et al.*, 1995), as they are in present study; but not when old and foil objects are from different categories (Maguire, 1994), or when objects simply need to be identified by a verbal label (Smith and Milner, 1981; Nunn *et al.*, 1999). Studies testing the delayed recognition of visual patterns have also found RTL patients but not LTL patients to be impaired (Kimura, 1963). Whether the ability to recognize visual patterns is dependent upon the hippocampus or not is unclear. Kimura found there was no difference between patients with small or large hippocampal removals (Kimura, 1963). A recent study found that patients with hippocampal removals showed impaired recognition of designs, whereas patients without hippocampal removals were not impaired (Gleissner *et al.*, 1998). Primate research has suggested that recognition of visual images depends upon the neocortex surrounding the hippocampus (the perirhinal cortex in particular) rather than the hippocampus itself (see Murray and Miskin, 1998; but for an alternative point of view, see Zola and Squire, 2000).

The pattern of performance produced by the three groups in the context-dependent episodic memory questions was found to be the reverse of that found in the topographical memory tests and the OBJECT question. The LTL patients were significantly impaired in all three questions relative to the control group, while the RTL group's performance was intermediate to the LTL and control groups, being significantly worse than the control group on the PERSON question and significantly better than the LTL group for the FIRST question. The overall difference in performance on context-dependent episodic tasks between RTL and LTL groups approached significance. This pattern of results is similar to those using tests of autobiographical memory, where left temporal lobe patients (Barr *et al.*, 1990; Kapur *et al.*, 1997) or both LTL and RTL patients (Viskontas et al., 2000) are significantly impaired. Our data accords with neuroimaging studies of autobiographical memory where the left hippocampus was observed to be differentially active, using a verbal paradigm. The results are also similar to the findings of previous studies of verbal episodic memory (Milner, 1958; Frisk and Milner, 1990) where subjects had to remember a prose passage, suggesting that similar brain mechanisms may be involved in both types of task. However, our test is not verbal. Furthermore, the performance of the LTL patients on the context-dependent memory questions was not significantly correlated with performance on the delayed story recall, the Warrington Recognition Memory Test for words or verbal IQ. This is similar to the results of the study by Barr and co-workers, who found that there was no relationship between LTL patients' performance on recall of remote events and confrontation naming (Barr *et al.*, 1990), and suggests that the deficit in performance on the episodic memory test cannot be entirely dependent on verbal memory.

In a recent study, a patient with focal bilateral hippocampal pathology was tested on these same tasks (Spiers *et al.*, 2001). He was impaired relative to a matched group of controls on both episodic and topographical tasks, but not the OBJECT question. This suggests that, within the medial temporal lobes, the hippocampus is a crucial structure for topographical and context-dependent episodic memory, but not for object recognition. The damage to the perirhinal cortex (anterior parahippocampal gyrus) in anterior temporal lobectomy may well be pertinent to the deficit in object recognition.

It is interesting that the FIRST condition showed the greatest difference between the LTL and RTL group. In contrast to the PERSON and PLACE questions, the FIRST question requires temporal information regarding the entire episode. The ability to perform temporal discriminations has been shown to be impaired by lesions to frontal brain regions (Janowsky *et al.*, 1989; Milner *et al.*, 1985, 1990; Shimamura *et al.*, 1990). Our results suggest that left medial temporal lobe regions also contribute to temporal order judgements. Temporal lobectomy patients have previously been found to be impaired on their memory for temporal order, although with no difference between left and right temporal lobectomy patient performance (Dennis *et al.*, 1988). It is possible that, in principle, the temporal order question can be solved by using the familiarity of the objects. However, this would be difficult as the individual objects are repeatedly encountered during the retrieval phase. The relatively poor performance of all groups in answering the PLACE question means that a specific involvement of the right temporal lobe in this question might be present but obscured by a floor effect.

In conclusion, this study is the first to show deficits in unilateral temporal lobectomy patients during interactive large-scale navigation and context-dependent episodic memory for realistic but controlled events. We have shown a neural dissociation exists between topographical memory and context-dependent episodic memory, with the former being preferentially mediated by the right medial temporal lobe, and the latter being preferentially mediated by the left medial temporal lobe despite not using a verbal paradigm. The fact that the patients showed little difference on standard tests of memory (Table 2) highlights the importance of using 'real-world' situations in studying memory problems in these patient populations.

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