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Spatial memory deficits in patients with unilateral damage to the right hippocampal formation

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Abstract—Patients with unilateral temporal lobe damage resulting from intractable temporal lobe epilepsy (TLE, $n = 30$) or from temporal lobe resection (temporal lobectomy, TLR, $n = 47$) were investigated on the Nine-box Maze. The task, analogous to the radial arm maze, was designed to compare spatial mapping and working memory theories of the functions of the hippocampus. The task provides measures of spatial, object, working and reference memory, incorporated into a within subjects design. The spatial component was designed to encourage the formation of allocentric rather than egocentric spatial representations. Spatial memory deficits were found (across working and reference memory components) in both TLE and TLR patients with right temporal lobe damage, with intact spatial memory in patients with corresponding left temporal lobe damage. Performance on the matched non-spatial (object) working memory component was equal to healthy controls for all groups. However all patient groups showed a deficit on object reference memory. These findings are discussed in relation to the underlying temporal lobe pathology and particularly atrophy of the hippocampal formation. Overall, the results support the cognitive mapping theory of hippocampal function, with the demonstration of a selective (and probably allocentric) spatial memory deficit in patients with right hippocampal damage. Copyright © 1996 Elsevier Science Ltd.

Key Words: hippocampus; temporal lobe epilepsy; temporal lobe resection; allocentric space.

Introduction

One of the most prominent theories of hippocampal function to have emerged from the vast body of literature on the functional role of the mesial temporal lobe structures was proposed by O'Keefe and Nadel [55] *The Hippocampus as a Cognitive Map*, (see also O'Keefe [52] and Nadel [46] for reviews). The authors presented a system in which allocentric spatial information is represented in the hippocampus in the form of a cognitive map, which an organism uses to define their position within an environment. In non-humans this system was suggested to be exclusively spatial, with representations describing environments, including distances and directions, processed and stored within the neural system of the hippocampal region [52]. The human hippocampus was also proposed to involve the ordering of representations into a structured context, but modified to take into account human hemispheric specialisation. The right hippocampus was responsible for processing of spatial information (spatial mapping), whilst the left was concerned with the manipulation of verbal semantic representations.

The cognitive mapping theory has been the focus of substantial research and has gained support from investigations across species, (for example, rodent [3, 44, 56], primate [61, 63] and human [79, 80]). It was based fundamentally on the results of cell recording studies showing neuronal discharges in single hippocampal pyramidal cells corresponding to the animal's position within a controlled environment (most commonly a maze) [49, 50, 51, 53, 54, 57]. Spatial memory impairments were also found following hippocampal lesions in rodents and primates (e.g [28, 29, 44, 63]). However, evidence against an exclusively spatial system emerged from investigations which implicated the hippocampus in a variety of non-spatial behavioral functions (e.g [16, 41, 83]). The combined results of these studies led many researchers to support a disproportionately large (but not exclusive) role for the hippocampus in spatial processing and memory [30, 61, 63].

In humans the spatial theory of hippocampal function has gained some support from investigations of amnesic

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patients [40, 77], in which the spatial memory deficits appeared to be more pronounced than the overall level of memory loss. More fundamentally, there is strong support from data obtained from patients who have undergone unilateral temporal lobe resection, enabling researchers to focus on the differential roles of the right and left hippocampus [13–15, 22, 42, 65, 66, 68, 79, 80]. Specifically, right temporal lobe resections have been found to produce, for example, deficits in maze learning tasks [14, 43], the recall of spatial sequences [15], simple location recall [15, 73], and the recall of object arrays [79, 80]. In addition, the size of these deficits are related to the extent of the hippocampal excision in some instances [32, 35, 78].

Several theorists have proposed that the spatial memory impairment cited above may reflect damage to alternative systems to that concerned with cognitive mapping. For example, the 'working memory' model of hippocampal function, proposed by Olton *et al.* [58], suggests that the function of the hippocampus is to hold and manipulate information pertinent to the present situation or context. The 'working memory system' encodes the temporal context in which an event occurs.* Under this view, spatial memory impairment exists because the spatial location is encoded as a type of event or context. Working memory can be contrasted with 'reference memory' where information remains constant across situations, and is therefore independent of time. This theory has been frequently contrasted with cognitive mapping and supported by the demonstration of non-spatial working memory deficits, as compared with intact spatial reference memory processes in rat hippocampal lesion studies [33, 59, 74].

The radial arm maze is an animal paradigm which has been used to distinguish between cognitive mapping and working memory theories [60]. The original task consisted of a central platform, with eight radiating arms, with the rat trained to traverse all arms in turn to obtain food rewards. In the spatial version the animal was dependent on extramaze cues situated around the room to determine their position within the maze, forming a topological map of the environment. In the non-spatial task the animal uses intramaze cues, situated within each arm, to determine which arms it has entered previously. Jarrard and colleagues [28, 29, 31, 36] expanded the design to incorporate measures of working and reference memory. Within the design, working memory was defined as information that was trial dependent (relevant to a present situation only). The working memory component therefore consists of the animal remembering which arms it has entered within a particular trial and working memory errors were defined as repeated visits to previously entered arms. In contrast reference memory relates to information that is trial independent (relevant across all trials of the task) and is investigated using a limited baiting procedure. Four of the eight arms within the maze remain unbaited across all trials and reference memory errors consist of visits into consistently unreinforced arms.

Jarrard and his colleagues used this procedure in rats with selective hippocampal lesions, providing strong support for the spatial role of the hippocampus [6, 30, 36]. However, the finding of transient spatial memory impairments following post-training removal of the hippocampus has led Jarrard to suggest the possibility of an extra-hippocampal storage site for spatial information [30]. These findings are complicated further by studies in which a range of lesions to the hippocampus and related structures have implicated both theories, with deficits in both spatial and working memory components [28, 48], (see Jarrard [30] for review).

Investigations into spatial deficits in human subjects have often neglected a fundamental aspect of the cognitive mapping theory, the element of *allocentric* space. In the model proposed by O'Keefe and Nadel a clear distinction is made between spatial information which is independent of the observer (allocentric), and information which relates to the body axes (egocentric). These processes were suggested to be subserved by two different systems, termed locale and taxon respectively. The authors emphasized that hippocampal functions were limited to the locale processing of allocentric spatial representations. However, many humans studies have used spatial memory tasks which were not specifically designed to test for allocentric spatial encoding [12, 40, 79, 80]. Goldstein *et al.* [22] addressed this issue by employing separate testing conditions to measure egocentric and non-egocentric components of spatial memory in patients with unilateral temporal lobectomy. The task involved the recall of shapes in relation to clustered and distributed cues presented on a card. Based on a design by O'Keefe and Conway [54], distributed cues were employed to encourage the formation of place (i.e. spatial) representations and were thus proposed to relate to hippocampal function. The non-egocentric condition was produced through the rotation of the cues in relation to the observer during recall, and subjects were required to draw the remembered shapes with respect to the new cue position. These instructions encouraged the subjects to form allocentric (non-egocentric) representations of the to-be-remembered material. Both right and left temporal lobectomy patients were impaired only in the non-egocentric condition when compared to controls, but these effects were not lateralized according to side of resection. However a lateralized difference was found in the formation of place representations, since the right temporal lobectomy patients responded differentially to clustered and distributed cues, demonstrating a selective spatial learning deficit.

The task used in the current investigation is structurally

* It should be noted that the concept 'working memory' applied to human beings is most similar to long-term episodic memory [86], rather than to the conventional use of it in the 'human' literature, which refers to the simultaneous manipulation and storage of information.

analogous to the radial arm maze, providing measures of the four elements central to the two theories; spatial, non-spatial (in this test 'object'), working and reference memory. These measures are incorporated into a complete within-subjects design. In the task a number of objects are hidden within containers presented in an array fixed to a board (see Fig. 1). As in the animal paradigms the spatial element involves the use of extramaze cues, the containers remaining constant relative to the items within the room throughout the task. The formation of allocentric spatial representations is facilitated by altering the subject's viewpoint of the to-be-remembered spatial information between presentation and recall. This, in effect, discourages the subject from being dependent on egocentric encoding because it makes it particularly difficult to use such processing strategies to remember the spatial array.

To investigate the selectivity of spatial memory impairment, non-spatial memory was measured as well using object recognition, a common comparative procedure employed in both human and non-human primate studies [12, 19, 63, 79, 80]. The design encourages the subject to dissociate the two types of memory item (object and container) in both encoding and recall. During the learning phase the subject is presented with the to-be-remembered objects and containers sequentially, and in recall

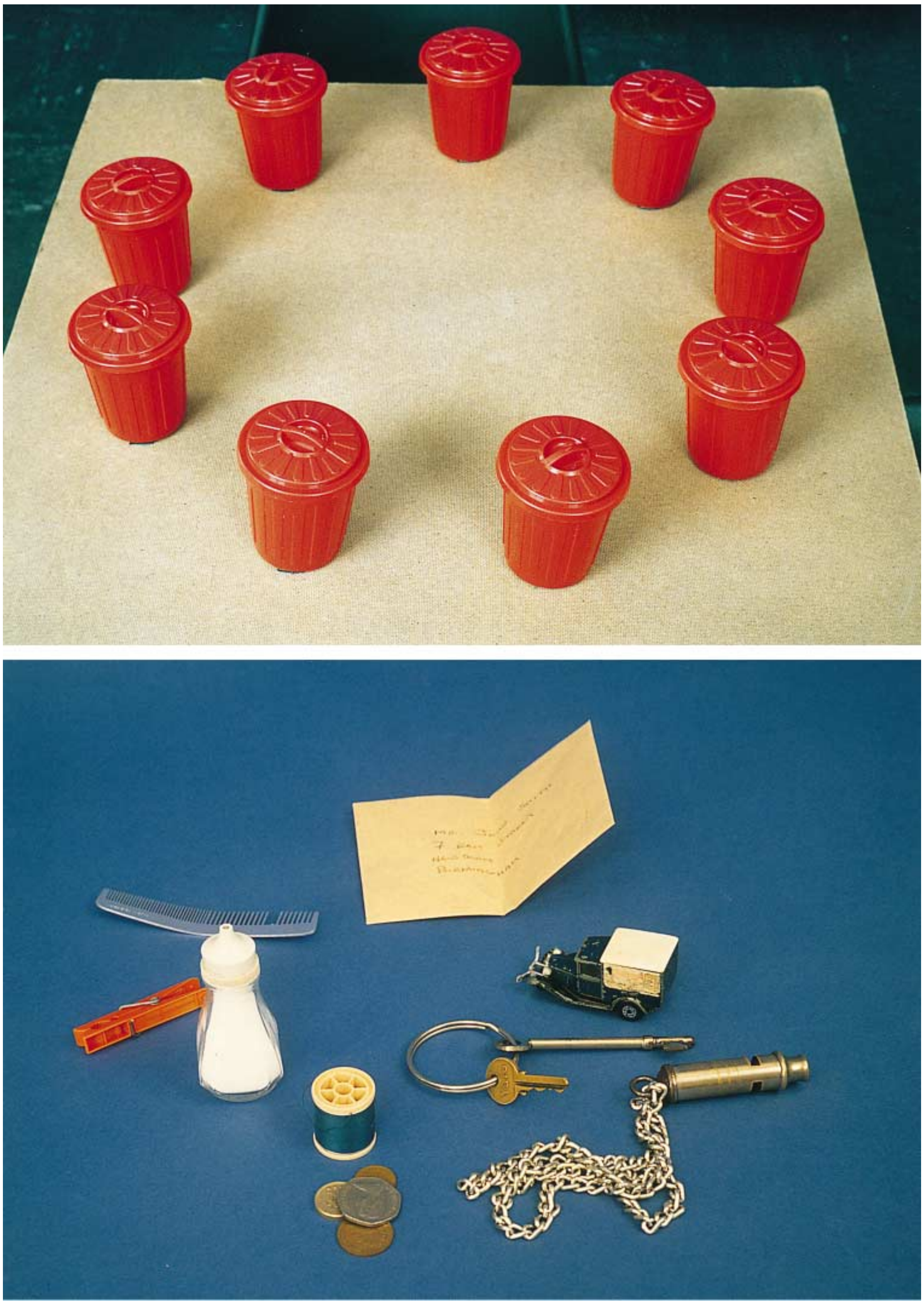

Fig. 1. Nine-box Maze (spatial and object memory test). Above:- Array of nine identical containers used to obtain measures of spatial memory. Below:- Nine everyday objects used to obtain non-spatial measures of object memory.

dissociation is encouraged through the administration of two separate recognition tasks. In addition, the instructions also de-emphasize object–location associations: subjects were required to recognize the location of containers in which an item (object) was hidden, rather than remembering which object was in which container.

The working and reference memory components incorporated in this design consisted of a delayed matching-to-sample procedure, with trial dependent (working memory) and trial independent (reference memory) components. In the latter the same locations (containers) and objects were consistently selected by the experimenter across all trials and so provided a trial independent measure of reference memory. The additional items selected varied between trials, giving a trial dependent working memory component for both object and location.

Two groups of patients with unilateral temporal lobe damage were investigated in this study: (1) those with temporal lobe epilepsy (TLE) being neurologically investigated with a view to neurosurgical treatment, and (2) those with unilateral temporal lobe resections (TLR) as treatment for intractible epilepsy. Post-operative pathology investigations of TLE patients have revealed that the majority (70–80%) suffer from mesial temporal sclerosis (MTS, also known as Ammon's horn or hippocampal sclerosis [18]), where atrophy and neuronal loss is restricted to either the right or left hippocampal formation and adjacent mesial temporal lobe structures (uncus, amygdala, [5, 8]) (see also the Method). The TLR patients had all undergone an *en bloc* temporal lobectomy, for the treatment of intractable focal epilepsy. This procedure includes resection of the left or right anterior temporal lobe and mesiotemporal lobe structures (the amygdala, anterior hippocampus and uncus, [23, 69]). The extent of resection in this patient group overlays pre-operative atrophy and in addition incorporates a more extensive region of cortical tissue.

The unilateral damage of such patients provides an opportunity to explore the lateralized predictions of the cognitive mapping theory with respect to spatial memory. The theory predicts that subjects with right hippocampal damage will show deficits in the formation and utilisation of allocentric spatial representations. Such processes should remain intact in patients with unilateral left hippocampal damage. In addition a selective spatial deficit should occur independently of working and reference components. In contrast the working memory model would be supported through the detection of deficits in working memory elements, with intact reference memory abilities. This pattern of impairment should be apparent across both spatial and non-spatial elements of the task.

Method

Subjects

Temporal lobe epilepsy (*TLE*) *patients*. Thirty patients (16 male, 14 female) with TLE were tested, all of whom were undergoing assessment for surgical treatment. Patients were included on the basis of clear evidence of a unilateral epileptogenic focus as demonstrated by foramen ovale Electroencephalography (EEG) recordings. Fourteen demonstrated evidence of a left focus (LTLE, 5 male, 9 female) and 16 a right epileptogenic focus (RTLE, 11 male, 5 female). Standard assessment procedures also included a neuropsychological assessment, Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI). Patients were excluded from this study if the neuroimaging results revealed evidence of a structural lesion such as harmatoma or glioma, which have been reported to occur in 15–20% of cases of TLE patients with similar sampling characteristics [9]. Such criteria increased the likelihood of MTS being the source of pathology in the majority of the patients studied. In addition 14 (8 male, 6 female) TLE patients tested underwent volumetric assessment of MRI images as part of a pilot investigation [2]. This procedure consists of separate volumetric measurements of the left and right hippocampal formations, parahippocampal gyri, temporal cortices (excluding mesial structures) and remaining cerebral tissue (see Press, Squire and colleagues [72, 82] for measurement protocol). Subsequent left/right asymmetries were analyzed in relation to the predicted side of the epileptogenic focus as determined by EEG recordings. The analysis of the hippocampal measurements revealed a pronounced asymmetry between volumetric estimates of the epileptogenic focal hippocampus and corresponding non-focal structure [$T=4.15$, $P<0.005$]. No significant asymmetries were revealed in the analyses of the remaining temporal cortex [$T=0.73$, $P>0.5$] and cerebral tissue [$T=1.66$, $P>0.1$]. In previous studies similar patterns of left/right mesial temporal asymmetries have been supported by post-operative confirmation of MTS [7, 11, 34]. The current findings suggest that the subgroup of TLE patients who underwent MRI quantification display localised unilateral atrophy, restricted to the mesial temporal lobe structures and most prominent in the hippocampus, a pattern consistent with the nature of MTS.

Temporal lobe resection (*TLR*) *patients*. Forty-seven patients (20 male, 27 female) who had undergone an anterior temporal lobectomy were tested. This surgical procedure consists either of a 5.5–6.5 cm *en bloc* resection of the right (non-dominant) temporal lobe, or of a 1–2 cm resection of the left (dominant) temporal lobe [69]. Twenty-three patients underwent a right temporal lobe resection (RTLR, 11 male, 12 female) and 24 a left resection (LTLR, 9 male, 15 female).

Patients in both TLE and TLR groups were included only if they displayed evidence of left hemisphere language dominance as demonstrated through the intracarotid sodium amytal test, conducted preoperatively [45]. Additional exclusion criteria consisted of evidence of psychotic symptoms or a low intelligence quotient (<75, Wechsler Adult Intelligence Scale—Revised, [87]). It should be noted that the TLE and TLR patients formed completely separate groups, a cross-sectional approach adopted. All patients were under the care of Professor C. E. Polkey (now Academic Neurosurgery, King's Neuroscience Centre, London).

Healthy controls. Twenty healthy controls (11 male, 9 female) were recruited from the temporary employment section of a local job centre.

Subject characteristics

All patient groups were matched for age when tested, with an analysis of variance revealing no significant differences between right- and left-sided damage and TLE and TLR groups. In addition there were no significant differences between patients and controls, using a one-way analysis of variance with a Dunnett's t comparison to compare each patient group against

Table 1. Temporal Lobe Epilepsy (TLE) patient characteristics

	RTLE	LTLE
Age	30.6 (11.4) 16.4–51.8	29.1 (7.0) 18.8–40.2
Age at first seizure	9.9 (10.0) 1.0–27.0	5.0 (5.3) 0.4–18.0
Age at onset of regular seizures	11.4 (11.1) 1.0–39.0	8.3 (5.5) 1.2–19.0
Duration of epilepsy	19.2 (11.5) 4.1–45.8	20.6 (7.9) 6.8–32.6
Partial seizure frequency	16.8 (30.0) 1.3–120	29.2 (62.0) 0.1–240

Means (S.D. and ranges). RTLE—Right epileptogenic focus, LTLE—Left epileptogenic focus. Age and Duration variables are reported in years, pm = per month.

controls separately. Mean age in years for the control group was 28.6 (S.D. 10.9, range 19–67). Mean ages for TLE and TLR groups are displayed in Tables 1 and 2, respectively.

TLE patient characteristics. The clinical variables for the RTLE and LTLE patient groups are shown in Table 1. A series of parametric and non-parametric analyses revealed no significant differences between groups.

TLR patient characteristics. The RTLR and LTLR patient characteristics are shown in Table 2. The only significant differences between groups were on *Age at first seizure* [$T = 2.58$, d.f. = 16, $P < 0.025$] and *Age of onset of regular seizures* [$T = 3.11$, d.f. = 36.5, $P < 0.005$] with the RTLR group displaying a later epileptic onset than the LTLR patients.

Table 2. Temporal Lobe Resection (TLR) patient characteristics

	RTLR	LTLR
Age	34.8 (11.2) 17.1–58.8	38.9 (10.6) 19.1–60.4
Age at first seizure	10.1 (9.1) 0.5–32.0	3.5 (3.4) 0.5–11.0
Age at onset of regular seizures	13.2 (7.6) 2.0–32.0	7.4 (4.7) 1.0–16.0
Age at surgery	30.9 (9.6) 14.8–55.8	29.1 (10.4) 13.7–51.5
Time from onset to surgery	17.5 (7.4) 3.8–31.3	21.7 (9.8) 5.7–40.5
Time from surgery to testing	3.9 (4.0) 0.2–15.4	4.7 (3.9) 0.3–12.2
Preoperative seizure freq. (pm)	28.6 (42.7) 2.0–180.0	25.8 (59.2) 1.0–300.0
Outcome—seizure reduction (%)	87.5 (22.5) 8.3–100.0	94.3 (13.0) 56.3–100.0

Means (S.D. and ranges). RTLR—Right Temporal Lobe Resection, LTLR—Left Temporal Lobe Resection. Age and Time variables are reported in years, pm = per month, Outcome—percentage of seizures reduced following resection.

Neuropsychological assessment

A routine neuropsychological assessment was conducted on the TLE and TLR patients (see Table 3), including the National Adult Reading Test (NART) [47], the short form of the WAIS-R [10], providing prorated measures of Verbal, Performance and Full scale IQ scores. Memory tests included the Logical Memory passages with immediate and 1-hr delayed recall [88] and the Rey–Osterrieth Complex figure, copy and delayed recall after 40 min [62, 75].

The results were analyzed using Analyses of Variance (ANOVA), with emphasis placed on the simple main effects, comparing right- and left-sided damage, within both TLE and TLR groups. The use of *a priori* simple main effects addresses the question of variance attributable to side of damage directly, for both verbal and non-verbal (visuoperceptual) tests. There were no significant differences on *NART predicted IQ* within either the TLE or TLR groups. However, an ANOVA including the four patient groups and the controls revealed a trend towards a significant effect of group [$F = 2.1$, d.f. = 4,90, $P = 0.09$] suggestive of a slightly lower patient performance (controls: mean 110.8, S.D. 8.5, range 95–126; patient scores: see Table 3), the LTLE group displaying significantly lower scores than controls, as revealed by a Dunnett's t comparison [difference between means −8.38, $P < 0.05$]. The *WAIS-R* analysis revealed no differences between RTLE and LTLE groups on prorated Verbal IQ [$F < 1.05$ n.s.], but for the oper-

Table 3. Neuropsychological test scores

	RTLE	LTLE	RTLR	LTLR
NART predicted				
Full Scale IQ	106.5 (8.0)	102.5 (8.4)	105.2 (9.9)	105.3 (8.2)
WAIS-R				
Performance IQ	95.7 (10.3)	92.6 (13.4)	96.5 (16.0)	100.4 (15.8)
Verbal IQ	93.5 (12.1)	94.1 (11.5)	99.9 (15.2)	89.0 (13.5)
Full Scale IQ	93.3 (9.0)	92.8 (11.1)	98.4 (14.0)	93.3 (13.3)
Logical Memory				
Immediate	17.7 (6.4)	15.7 (8.8)	18.4 (7.4)	13.2 (5.3)
Delay	10.9 (5.2)	10.0 (9.2)	14.2 (7.2)	8.8 (5.7)
Percentage Delay	63.3 (19.3)	53.6 (27.6)	74.1 (19.6)	61.4 (25.2)
Rey Figure				
Copy	45.3 (2.5)	46.0 (1.7)	44.9 (2.8)	45.4 (3.2)
Delay	24.2 (8.2)	26.1 (7.1)	21.0 (8.2)	26.6 (7.3)
Percentage Delay	49.9 (11.2)	56.5 (14.9)	47.1 (19.1)	58.7 (16.0)

Means (S.D.). NART—National Adult Reading Test. WAIS—R (Wechsler Adult Intelligence Scale—Revised) short form giving prorated estimates of Verbal, Performance and Full Scale IQ. Logical Memory passages of Wechsler Memory Scale, with a 1-hr delay. Rey Figures—Rey–Osterrieth Complex Figure, with a 40 min delay. Percentage Delay—delay score represented as a percentage of immediate memory, or copy score.

ated patients, VIQ was significantly lower in the LTLR group [$F=7.67$, d.f. = 1,94, $P<0.01$] (see Table 3). No differences were found in either group in the prorated Performance IQ measures [TLE and TLR $F<1$ n.s.] or in the overall Full Scale IQ [TLE, $F<1$, n.s.; TLR, $F=1.8$, d.f. = 1,94, $P>0.1$].

The analyses of the *Logical Memory* scores produced a similar pattern of results with no differences between the RTLE and LTLE groups on any of the measures [$F<0.01$ n.s.]. The LTLR group were significantly lower than the RTLR on both the immediate [$F=7.65$, d.f. = 1,93, $P<0.01$] and delayed scores [$F=7.88$, d.f. = 1,93, $P<0.01$]. The pattern of results for visuoperceptual memory as assessed by the *Rey–Osterrieth Figure* also followed the direction of effects predicted by the laterality of resection in the TLR groups only [delay: $F=6.35$, d.f. = 1,93, $P<0.025$]; percentage recall at delay: [$F=6.07$, d.f. = 1,92, $P<0.025$], with no differences occurring in the TLE group [delay: $F<1$, n.s.; percentage delay: $F=1.14$, d.f. = 1,92, $P>0.2$]. In addition there were no significant differences between right- and left-sided damaged patients, in either TLR or TLE group, on the copy condition of the task [$F<1$, n.s.]. This suggests that there was no evidence of a severe perceptual or visual deficit in either patient group with right-sided damage, consistent with the Performance IQ data. These results demonstrate that the predicted pattern of laterality effects, determined by the side of damage was evident for the TLR groups only, in tests of general verbal abilities and in both verbal and visuoperceptual memory.

Materials

The nine-box maze consisted of nine identical cylindrical containers of height 10 cm and diameter 9 cm, with detachable lids (see Fig. 1). These were fixed onto a square board (78×78 cm^2) in a circular formation, at a distance of 19 cm (along the chord of the circle) from each other. The board was positioned on an empty table with four chairs situated around the sides. This apparatus was situated in a room which contained many features including pictures on the walls, cupboards and windows. The apparatus remained constant relative to these features throughout the test. Ten common everyday objects were also used as testing material (salt pot, metal comb, two keys on a ring, cigarette packet, addressed envelope, toy car, clothes peg, reel of cotton, four coins, and a whistle on a chain, see Fig. 1). Materials also consisted of a smaller five-box maze with a 60×60 cm^2 board and five identical containers. An object recognition picture booklet was also used, which contained six pages of photographed or drawn pictures (see Fig. 2c). Five objects were represented on the first page and nine objects on each of the following pages. In addition a mental rotation test was also included which consisted of five complete examples taken from the Flags mental rotation test by Thurstone and Jeffrey [85].

Design

The patients were divided into two groups according to their Operated Status (OS), Temporal Lobe Epilepsy (TLE) and Temporal Lobe Resection (TLR). In addition all patients were further divided into Right (R) and Left (L) groups according to the Side of Damage (SD). This was determined by the predicted side of epileptogenic focus, or side of surgery. This produced a total of four patient groups RTLE, LTLE, RTLR and LTLR and a control group. The analyses was conducted with a three-way mixed design in which there was a between-subjects group factor (five levels, four patient groups and one control), with repeated measures factors of Type of Information (2 levels, spatial vs object) and Trial Dependence (two levels, working vs reference). In analyses of patient data only, the four patient groups were divided by two group factors of Operated Status (TLE vs TLR) and Side of Damage (L vs R), producing a four-way design for these analyses.

Procedure

There were three stages: (1) object familiarisation and free recall test, (2) the five-box maze (practice memory test), and (3) the nine-box maze (spatial and object memory test). This was followed by administering the flags mental rotation test.

Stage 1. During the object familiarisation and free recall stage the subject was presented with 10 objects, each for 15 sec. They were instructed to name and remember them and also respond to the following question, "Would you carry this object everyday in your pockets/handbag?" After a 1-min filled delay, the subject had to recall as many objects as they could. All delays throughout the experiment were filled with simple tasks, such as the National Adult Reading Test (NART) and forward and backward digit span from the WAIS-R.

Stage 2. The practice memory test used five containers and five of the objects from Stage 1. On each trial two objects were placed in two containers and the subjects had to remember, independently, the two objects and the two containers used (four pieces of information in total). During a 1-min delay the subject was asked to change their position to one of three other chairs situated around the table and continue with the simple interval filler task for the remainder of the delay. In the following recognition memory test the subject was shown photographs of the five objects and instructed to point to the two objects that had been hidden. In the subsequent location memory test the subject was asked to point to the two containers that still had the objects hidden in them. Following each response the corresponding container was opened and the contents revealed.

Stage 3. With the nine-box maze, the types of materials used were the same, but with nine containers and nine of the ten objects (one of the items, the cigarette packet was excluded) (see Fig. 1). Instructions were as follows, "On this test instead of choosing two objects, I will choose four objects and put them into four containers, so this time you have to remember eight things. You do not have to remember which object is in which container. You have only to remember the four objects I have chosen and the four containers".

The following five trials consisted of a practice run followed by four test trials. On each trial the experimenter selected four objects and placed them in four containers (see Fig. 2a). This was followed by a 1-min filled delay during which the subject was again required to change their position relative to the apparatus (see Fig. 2b). The remainder of the delay was also filled with an interval task, as described above. In the following memory phase the subject was presented with photographs of the nine items (see Fig. 2c), arranged in different positions on each page, for each trial, which prevented an association being formed between the object and spatial location. The subject was required to point to the pictures of the four hidden objects, and following each response, given immediate feedback as to whether their choice was correct or wrong. The latter was followed by instructions to try again. The object memory test was completed following correct selection of the four items, or after a maximum of ten choices. If the subject repeated a choice of an incorrect item they were told that their response was wrong, but not told that they had previously selected this item. If the subject repeated a correct response they were told that this was correct, but that they had already selected this item. Repetitions of errors were scored as wrong responses and repeated correct choices were discounted. The subject then performed the location memory test by pointing to the containers thought to

Fig. 2. Nine-box Maze (spatial and object memory test). (a) Top Left:- Experimenter selects four to-be-remembered objects and hides them in four to-be-remembered containers. (b) Top Right:- Subject changes position relative to the apparatus, by moving to one of three other positions, between the presentation and memory phases. (c) Bottom Left:- Subject points to the four previously selected containers (each of which contains a hidden object). (d) Bottom Right:- Subject is presented with object recognition picture booklet and points to the four hidden items.

be holding objects (see Fig. 2d). Completion followed correct selection of the four containers, or after a maximum of ten responses. The order of administration of the location and object recognition memory tests was alternated between trials.

Changes with regard to the subject's position around the table within each trial followed a fixed quasi-random sequence for all subjects. This series of movements included both clockwise and anticlockwise rotations. After each trial the subject maintained their new position for the presentation of the to-be-remembered items in the next trial; thus each subject had experienced all four views of the board during the presentation and memory phases.

Throughout all trials two of the selected objects and two of the containers remained constant, in that they were always presented on each trial. These items constituted the reference memory components of the procedure providing separate measures of object reference (Obj–Ref) and spatial reference (Spat–Ref) memory, respectively. The remaining object and location items varied quasi-randomly between trials, in a fixed order. These items provided measures of object (Obj–Work) and spatial (Spat–Work) working memory. This fixed sequence of item selection ensured that all combinations and permutations of reference and working memory elements were tested, and that all of the sample objects and containers were presented to each subject in a testing session. In addition reference objects and containers were rotated between subjects ensuring that all items functioned as reference memory components during the experiment. The performance measure was the total number of errors produced prior to correct selection of both examples of each of the four types of memory item, within each trial. Where items were not correctly selected, the score consisted of the maximum number of errors made, up to and including the tenth choice. The scores for each of the four memory components were summed separately across the four test trials producing four memory measures (Spat–Ref, Spat–Work, Obj–Ref and Obj–Work) for each subject.

Results

Results of spatial and object nine-box maze

Figures 3 and 4 show the performance of the TLE, TLR patients and controls on the four components of the task (Spatial Working and Reference, and Object Working and Reference).

Effects of lateralised lesions

An overall four way ANOVA was then conducted on the patient data only, to explore differences between patients groups with respect to both Operation Status

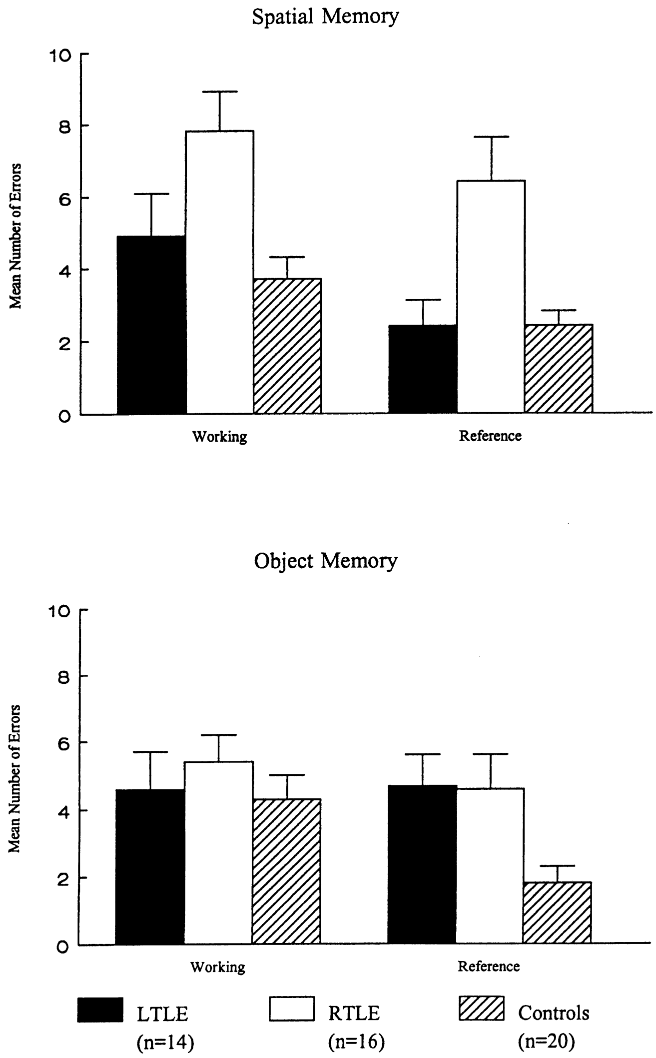

Fig. 3. Temporal Lobe Epilepsy (TLE) Group. Above:- Performance on the two Spatial Memory components of the nine-box maze. Below:- Performance on the two Object Memory components of the task. Mean errors (summed over four trials) and standard error bars.

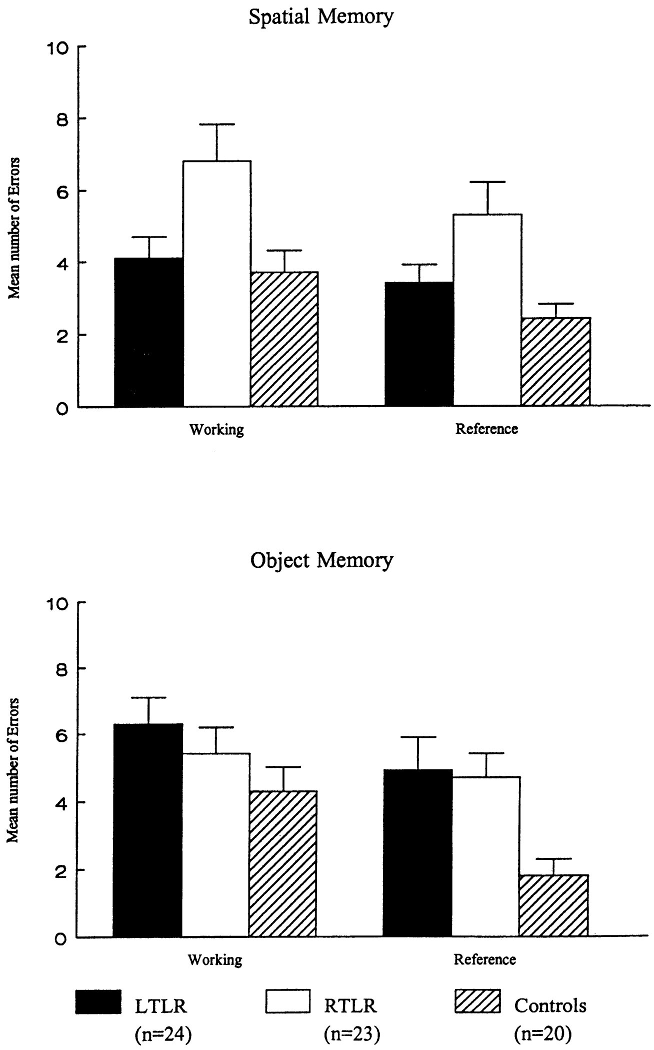

Fig. 4. Temporal Lobe Resection Group (TLR). Above:- Performance on the two Spatial Memory components of the nine-box maze. Below:- Performance on the two Object Memory components of the nine-box maze. Mean errors (summed over four trials) and standard error bars.

(OS) (TLE vs TLR) and side of damage (SD) (Left vs Right). The effects of Type of Information (Spatial vs Object recognition) and Trial Dependence (Working vs Reference) were also explored in the analysis. Thus the two between subject factors were OS and SD, with the two within-subject factors Type of Information and Trial Dependence. This analysis revealed a main effect of SD [$F=4.76$, d.f. $=1,73$, $P<0.05$], and Trial Dependence [$F=9.54$, d.f. $=1.73$, $P<0.005$], but not of OS, with no significant interactions between these factors. This suggests that the right hemisphere damaged groups (RTLE, RTLR) were performing worse overall than those with left hemisphere damage (LTLE, LTLR) and there were more errors overall on the working memory condition. Inspection of the data reveals that the differences between the left and right groups lies specifically in the spatial memory measures, with the right groups having more errors on the spatial memory components, irrespective of the Working vs Reference memory distinction. This is supported by a significant interaction between SD and Type of Information [$F=9.97$, d.f. $=1,73$, $P<0.0025$], but no significant interaction between SD and Trial Dependence, nor between SD, Trial Dependence and Type of Information. There were no significant interactions involving OS, suggesting that the pattern of functioning is the same when comparing TLE vs TLR groups. The latter was confirmed by analysing the data for TLE and TLR groups separately, using 3-WAY ANOVAs. The same significant interactions between SD and Type of Information were seen on both occasions, indicating the robustness of this finding in both types of patients.

Post-hoc comparisons of the means between the right and left groups were conducted using Tukey's HSD test, revealing significant differences in the spatial location scores only. A significant effect emerged in the Spat–Ref scores, between LTLE and RTLE groups [actual difference $=3.94$, minimum significant difference, MSD $=2.76$, $P<0.05$] and in the Spat–Work scores between LTLR and RTLR groups [actual difference $=2.66$, MSD $=2.38$, $P<0.05$]. The Spat–Work score in the TLE group and the Spat–Ref scores for the TLR group also tended towards a significant right-sided deficit with a mean difference of 2.48 (MSD $=3.07$) and 1.89 (MSD $=2.08$) respectively.

In summary, the above analyses demonstrated that the overall interaction between SD and Type of Information was present in the TLE and TLR groups and was dependent on the increase in spatial location errors in both the RTLE and RTLR groups in comparison to the corresponding LTLE and LTLR groups. The object memory scores did not differ between groups.

Comparisons between patients and controls

Further analyses were then conducted with ANOVAs on each memory component separately. Each patient group was compared to the performance of the controls using Dunnett's procedure. The analysis revealed significant increases, relative to the controls, in spatial memory errors for both working and reference memory components, in both the RTLE RTLR groups. The analysis also revealed significant differences between all patient groups and controls on Obj–Ref scores. There were no significant differences between patient groups and controls on the Obj–Work memory component. Overall these results demonstrate a spatial deficit for both patient groups with right-sided damage, coupled with an increase in object reference memory errors independent of laterality of damage, in the comparison of patients to controls. Despite this general deficit in object reference memory, earlier analysis demonstrated that patients still maintained a consistent Trial Dependence effect, with superior performance on reference memory items in both object and spatial components, as compared with working memory items.

Results of object free recall test

The performance measure was the total number of items out of a maximum of 10. An ANOVA with the two between group factors of SD and OS revealed no significant effects or interaction suggesting no differences between patient groups on this task. The patients results were then compared with healthy controls using a one way ANOVA supplemented by Dunnett's procedure. A significant effect emerged in the comparison of the LTLR group and controls only.

Results of flags mental rotation test

The measure was the total number of errors produced on the 30 items used. Because the data differed from the normal distribution, non-parametric Mann–Whitney tests were used to compare right- vs left-sided damage within the TLE and TLR groups. Neither comparisons approached significance.

Discussion

The findings of this study strongly support a specialised role for the right human hippocampus in the processing and manipulation of spatial information. They clearly demonstrate a selective spatial memory deficit in patients with right temporal lobe damage (in both TLE and TLR groups) and intact spatial processes in patients with corresponding left-sided damage, when compared with healthy controls. In contrast, no differences were found between patient groups on the non-spatial object memory components of the task. This pattern of results is consistent with previous findings of a spatial deficit associated with hippocampal damage, across species (e.g. [3, 46, 79, 80]) and add to the series of investigations which demonstrate spatial deficits in patients with right but not left temporal lobectomies (e.g. [14, 15, 22, 79, 80]. Moreover, these findings are more consistent with the cognitive mapping theory [55], since the task discouraged the use of egocentric processing strategies, revealing a selective 'allocentric' spatial deficit. These findings augment those reported by Goldstein *et al.* [22], who demonstrated evidence of a non-egocentric spatial deficit (as compared with a more egocentric condition) in temporal lobectomy patients. However, the present results are more clear cut and wholly congruous with O'Keefe and Nadel's predictions due to the complete lack of an allocentric deficit in patients with left temporal lobe damage (some evidence of a left-sided deficit had been found by Goldstein *et al.* [22]).

The deficit in spatial memory revealed by this investigation was present in both TLE and TLR patient groups with right-sided damage. Temporal lobe resected patients are commonly investigated in studies of lateralized functions (e.g. [15, 25, 26, 43, 65, 66]), an obvious advantage of investigating TLR patients is that the extent of surgical damage can be clearly defined and patients may even be divided according to the amount of hippocampal excision [32, 35, 78]. However, the area of resection in this patient group is often extensive, frequently incorporating a substantial region of cortical tissue, particularly in patients who have undergone a right non-dominant *en bloc* procedure. In the current investigation the TLR patients displayed a similar degree of spatial impairment to the TLE patients, the deficit not increased by the extent of the cortical resection in the TLR group. This suggests that damage to the mesial temporal lobe structures, common to both patient groups, may be the critical factor involved in producing the spatial memory deficits.

In contrast to research conducted on TLR patients, cognitive investigations of TLE patients are less frequently reported, the lack of explicit knowledge concerning underlying pathology possibly discouraging researchers from investigating this patient group. As previously discussed temporal lobe epilepsy is characterised by a type of atrophy known as mesial temporal sclerosis (MTS), which typically occurs unilaterally and consists of dense glial infiltration of the hippocampus and adjacent structures (amygdala and uncus). It is identified when there is 50% or greater neuronal loss, in at least four of the six hippocampal regions, as determined through postoperative pathological reports. The most prominent areas of MTS are the CA1, CA3, CA4 regions of the hippocampus, the subiculum–prosubiculum and the fascia dentata [5, 84]. MTS has been reported to occur in up to 80% of patients who come to surgery [8]. In the current study it is likely that this proportion of patients is increased, due to the exclusion of patients with evidence of structural lesions. Until recently verification of MTS could only occur postoperatively, however several investigations have now demonstrated that this form of pathology can be detected *in vivo*, using quantitative Magnetic Resonance Imaging (MRI) techniques, and is reflected through volumetric left/right hippocampal asymmetries (e.g. [4, 7, 11, 27, 34, 39]). In the current investigation, verification of the extent of hippocampal atrophy was conducted on 14 of the 30 TLE patients tested. The MRI results demonstrated asymmetries reflective of atrophy, which was most pronounced in the hippocampal formation and did not extend beyond the parahippocampal gyrus. This suggests that damage to the hippocampus appears to be the critical factor underlying the allocentric spatial memory deficit.

Lateralized material specific deficits in TLE patients appear to be difficult to elicit and many studies have failed to demonstrate such patterns of impairment using either verbal and non-verbal (visuoperceptual) tests [20, 21, 37, 38, 71]. In the current investigation a lateralized pattern of performance in the TLE group, was exclusive to the spatial and working memory task, and was not present in other more standard neuropsychological tests reported above. In contrast, the TLR patients displayed material specific impairments on tests of visuoperceptual memory (the Rey–Osterrieth Figure test), verbal memory (Logical Memory passages of Wechsler Memory Scale—WMS) object recall (free recall of stage of Nine-box Maze) and verbal IQ. These findings suggest that such impairments may be related to the additional neocortical dysfunction found following temporal lobectomy, and not to the mesial temporal lobe damage associated with temporal lobe epilepsy.*

One other study, which has successfully demonstrated a lateralized spatial deficit in TLE patients, was reported by Helmstaedter *et al.* [24] and involved a serial visual learning test, involving the reconstruction of nine abstract figures following presentation. TLE patients with a right epileptogenic focus demonstrated impaired immediate recall and learning. These cognitive deficits, the current findings with the TLE patients, and the lack of a lateralized deficit on other visuoperceptual tasks (such as the Rey–Osterrieth Figure), may be explained through the nature of the spatial element within the task. It is possible that the complexity of the visual information, incorporated into the design of the tasks, facilitates the construction of allocentric spatial relations between elements within the to-be-remembered presentation.

Cognitive mapping in the spatial domain involves forming a representation between objects in space, independent of the location of the subject. In order to create these spatial maps, both egocentric and allocentric information are needed and the processing of spatial information may take place in regions outside the hippocampal formation [55]. It is possible that both egocentric and allocentric information could be integrated within the hippocampus to enable cognitive maps to be formed. The studies which show spatial memory deficits following right temporal lobectomies [68, 79, 80] could, in principle, support an egocentric memory role for the hippocampus in humans. Nevertheless, these studies were

* There has been some debate as to whether verbal memory as assessed by the Logical Memory passages (WMS) is dependant on the functions of the hippocampus. Several studies have related impairment on percentage delayed recall to left hippocampal damage, using MRI [34], and post-operative cell counts [76]. As in the current study, other investigations have not demonstrated a discrepancy between left and right TLE patients on this measure [20, 21, 71]. When comparing Logical Memory performance in this study to the normative data there is some evidence of an impairment in the LTLE and LTLR groups only on immediate recall [1], but no evidence of impairment with the one hour delay [70]. The significance of these findings is unclear, but one possibility is that Logical memory may involve, but is not wholly dependent on, the effective functioning of the left hippocampal formation, either involving extratemporal regions of the left hemisphere, or possibly the right temporal lobe. Verbal memory impairment associated with right temporal lobe surgery has been observed, but this is in the context of known bilateral impairment, for example, in unselected samples of temporal lobe resection patients, which have included those with pre-existing significant global memory impairments [25]. The current study took care to exclude such patients from the investigation on the basis of their pre-operative neuropsychological assessment.

not designed to differentiate between egocentric vs allocentric strategies and it is possible that they rely partly on allocentric processing. The current task was designed to minimise the use of egocentric memory and found a significant deficit associated with right hippocampal formation damage. The extent to which egocentric processing is excluded is not certain and theoretically, the task could be performed egocentrically, by the subject forming and rotating an image of the spatial array at the recall stage. In practice, this strategy was particularly difficult, mainly because of processing demands involved, making it easier, at least for normal subjects to use an allocentric representation. The apparatus, consisting of an asymmetrical array of identical containers, does not facilitate the construction of egocentric relations that change continually. In addition, the presence of interference effects in the recall of previous viewpoints of the spatial array may serve to encourage the subject to employ an allocentric strategy. Through such allocentric processes, containers may be distinguished by the use of cues around the room, which maintain a constant spatial relationship relative to the apparatus. Subjects were also discouraged from using mental rotation strategies by instructing them to look away from the spatial array when changing viewpoint between presentation and recall.

The results of the Flag's mental rotation test also demonstrates that there was no lateralized difference between groups on mental rotation abilities, which could account for the pattern of spatial impairments. Hence, the selective spatial effects revealed in this investigation can be more confidently ascribed to deficits in the formation and retrieval of spatial representations which are probably allocentric in nature. Just as excluding egocentric memory task requirements enables exploration of the allocentric role of the hippocampal formation, the converse would be the case for egocentric memory and further research is needed in this area in humans.

In relation to the working memory theory of hippocampal function, the pattern of results is clearly inconsistent with such predictions, since spatial deficits occurred across both working and reference memory components of the task. More critically, there was no equivalent impairment in the non-spatial (object) working memory component. A non-spatial working memory deficit is fundamental to the predictions of Olton's theory. Critics of the cognitive mapping hypothesis have suggested that deficits in spatial memory may be the result, or just a component, of an overall general memory disturbance [12, 17, 81]. This proposal receives support from an investigation (conducted by Cave and Squire [12]), in which levels of object memory performance of amnesic patients and healthy controls were matched using varying delays between learning and testing, and subsequent comparisons of spatial memory scores showed no evidence of a disproportionate deficit (although see Pickering [67] for detailed criticisms). In the current study, deficits in object memory, as revealed through the comparison between patients and healthy controls, were restricted to the reference component of the object memory task. No differences were found between groups in the object working memory scores. In addition, there were no differences between the performance of right and left damaged groups on either object memory score.

In the present investigation there was also some evidence of an object reference memory deficit across all patient groups, which was however less marked than the spatial deficit. This impairment was not predicted by either the cognitive mapping or working memory theories and also consistent with animal studies using the radial arm maze, in which non-spatial reference memory deficits have not been reported (see Barnes [6] and Jarrard [30] for review). However, it is consistent with Smith and Milner [79], who found object memory deficits in both left and right temporal lobectomy patient groups, following a 24-hr delay (despite unimpaired immediate recall). In the original Smith and Milner [79] task, the object recall test was administered prior to an object–location memory test, in which the same items were presented. On the delayed recall condition, the performance of control subjects improved, in terms of items correctly remembered, in comparison to the immediate recall condition. Smith and Milner [79] relate this improvement to the additional exposure to the objects during the intermediate object–location test, during which the subjects actively rehearsed (for object recall) those items which they had failed to correctly recall in the immediate memory condition. Hence the control subjects appeared to benefit more from repeated exposure to the objects than either temporal lobectomy group. Similarly, in the current investigation, both the TLE and TLR patient groups did not benefit as much as controls from the repeated presentation of the objects, in the object reference memory component. The working memory condition in the current study can be likened to the immediate memory condition in the Smith and Milner [79] experiment, showing that the basic perceptual processing and retrieval of the objects after one learning trial is intact. These results therefore may suggest that patients with unilateral temporal lobe damage, irrespective of side, are impaired in the learning and consolidation of object memories across repetitions. This deficit cannot be interpreted as part of a more general learning impairment since patients with left temporal lobe damage showed unimpaired performances on the spatial reference memory components of the task.

What then could account for a non-lateralized impairment of object learning across multiple presentations? One possibility is the dual encoding of objects, forming both a verbal (name) and visuospatial memory trace of the item [64]. Verbal encoding was facilitated, for example, by the requirement to produce the name and answer a question about the objects in Stage 1. Such dual coding might not be relevant to the spatial reference task. The findings of the current investigation could suggest that both left and right mesial temporal lobe structures may play a role in the learning of such 'dual-modality' mediated information. A left or right hippocampal lesion may be sufficient to impair the long-term consolidation of verbal or visuospatial information respectively, resulting in an object learning deficit, with intact temporary rehearsal processes involved in immediate recall.

In the comparison of spatial vs working memory theories the results of the current investigation are clearly more consistent with cognitive mapping, with a pronounced deficit in spatial memory in patients with right hippocampal formation damage. There was no evidence of a general working memory deficit, and no indication of both theories being implicated, as reported by a number of rat lesion studies using the radial arm maze [29, 48]. Although there is some evidence for non-spatial memory impairment in the object reference component, this is less pronounced than the impairment in spatial memory. The finding of a disproportionate spatial deficit is consistent with two studies of amnesic patients, including some with bilateral temporal lobe damage [40, 77], in which, in contrast to the study reported by Cave and Squire [12], spatial memory deficits were more pronounced than expected given the level of general memory impairment. In addition, such findings are also consistent with the general opinion expressed in many animal lesion studies, which proposes a strikingly large (but not exclusive) role for spatial processing in the hippocampus [29, 61, 63]. In conclusion, the results of the current study clearly demonstrate that the processing of allocentric spatial information is disproportionately dependent on the effective functions of the right hippocampus.

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