Allocentric spatial memory in humans with hippocampal lesions

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Abstract

An immersive virtual reality (IVR) system was used to investigate allocentric spatial memory in a patient (PR) who had selective hippocampal damage, and also in patients who had undergone unilateral temporal lobectomies (17 right TL and 19 left TL), their performance compared against normal control groups. A human analogue of the Olton [Olton (1979). Hippocampus, space, and memory. Behavioural Brain Science, 2, 315] spatial maze was developed, consisting of a virtual room, a central virtual circular table and an array of radially arranged up-turned ‘shells.’ The participant had to search these shells in turn in order to find a blue ‘cube’ that would then ‘move’ to another location and so on, until all the shells had been target locations. Within-search errors could be made when the participants returned to a previously visited location during a search, and between-search errors when they revisited previously successful, but now incorrect locations. PR made significantly more between-search errors than his control group, but showed no increase in within-search errors. The right TL group showed a similar pattern of impairment, but the left TL group showed no impairment. This finding...
implicates the right hippocampal formation in spatial memory functioning in a scenario in which the visual environment was controlled so as to eliminate extraneous visual cues.

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1. Introduction

The hippocampus, as well as having a more general mnemonic role has been shown to be a key structure in supporting spatial memory, as indicated by a range of studies involving rodents (Aggleton, Hunt, & Rawlins, 1996; Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Burgess, 1996), non-human primates (Angeli, Murray, & Mishkin, 1993; Ono, Nakamura, Fukuda, & Tamura, 1991; Parkinson, Murray, & Mishkin, 1988; Rolls, 1999; Rolls & O'Mara, 1995) and humans (Burgess, Maguire, & O'Keefe, 2002; Morris, Nunn, Abrahams, Feigenbaum, & Recce, 1999; Morris & Parslow, 2003). The precise neural mechanisms supporting spatial memory have yet to be fully established, but one of the main theories is that spatial information is maintained in the hippocampus in the form of Cognitive Maps, which specify the directions and relative distances between locations in the environment (O'Keefe & Nadel, 1978; O'Keefe & Burgess, 1996). Spatial information is integrated into a viewer independent or allocentric representation and this is then maintained in long term memory. The allocentric representation contrasts with representing distances and direction specifically in relation to the body axis, termed egocentric memory, thought to be independent of hippocampal function.

In humans, spatial memory deficits have been found to occur following unilateral temporal lobectomy (TL), specifically when the operation is in the right hemisphere (right TL). This includes impairment in memory for location, as demonstrated in a landmark series of experiments by Smith and Milner (1981, 1989) in which participants were shown a layout of objects and subsequently had to place these objects from memory. More recently, this impairment has been found to be proportionately greater than that for recall or recognition of patterns or objects (Nunn, Graydon, Polkey, & Morris, 1999; Nunn, Polkey, & Morris, 1998) and to correlate with the degree of hippocampal damage (Graydon, Nunn, Polkey, & Morris, 2001; Nunn et al., 1999).

Many of the tasks used to initially to measure spatial memory in patients with hippocampal lesions have used static spatial arrays, with the possibility that spatial location can be encoded egocentrically, i.e. in relation to the bodily frame of reference. However, theories linking the hippocampus to spatial memory incorporate the notion of an allocentric representation (O'Keefe & Nadel, 1978; O'Keefe & Burgess, 1996; see also Neggers, Schölvinck, van der Lubbe, & Postma, 2005). Accordingly, some neuropsychological studies have used procedures in which the participant views three-dimensional arrays of objects or locations from different directions, or has to navigate through complex spatial environments (see: Burgess et al., 2002; Morris & Parslow, 2003). An early example of this is the development by Feigenbaum, Polkey, and Morris (1996) who showed a specific impairment in right TL patients on a computerized...
human analogue of the Olton Maze test (Olton, Becker, & Handelmann, 1979), in which arrays of locations were presented on a computer screen, with the arrays rotated in between responding to particular locations.

The above study relied on rotation of the spatial array in order to induce allocentric representation, rather than participant movement. This has the potential problem that the participant can simply ‘mentally rotate’ the array and hence remember the location using egocentric memory. An alternative task in which this type of strategy is harder to implement was developed by Abrahams, Pickering, Polkey, and Morris (1997), an analogue of the Olton Maze (Olton et al., 1979), using a circular layout of small containers, placed on a central table. The participant observed objects being placed into the lidded containers and then had to indicate which containers had been used and which objects had been hidden. To emphasize allocentric memory functioning, the participants had to walk round the table in between placement of the objects and memory testing, relying on room cues to remember specific locations. Only right TL patients were impaired in memory for location, whilst both left and right TL participants were impaired on one aspect of object recognition memory. A further study by Abrahams et al. (1999) found the same pattern of results in patients with unilateral hippocampal sclerosis.

In a similar vein to the Abrahams et al. (1997, 1999) container task, Bohbot et al. (1998) developed a human analogue of the Olton Maze, requiring participants to locate coins hidden in cups mounted on stands while not going back to ‘successful’ cups. They found no impairment in patients with unilateral hippocampal or parahippocampal lesions produced by thermocoagulation as treatment for epilepsy. However, the design of this task may not have been sufficiently sensitive to detect spatial memory impairment, with the participants able to trace a simple route between the stands, one after the other to avoid ‘return’ errors. This result compares to their human analogue of the Morris Water Maze (Bohbot et al., 1998), based on searching for hidden floor locations, which did find impairment in only the patients with parahippocampal lesions, and may not have been so susceptible to strategy formation. Indeed, in a further study (Bohbot, Iaria, & Petrides, 2004), they developed a computerized human analogue of the Olton Maze and split patients into those who did and or did not use a strategy, finding that those who did not were impaired.

Holdstock, Mayes, Cezayirli, Aggleton, and Roberts (1999) have also investigated allocentric memory in a study that included one patient who had selective bilateral hippocampal damage. The patient was required to remember the location on a circular display board, signified by light emitting diodes. In an allocentric condition, the patient had to walk round the display board in between inspecting the locations and subsequent recall, making use of room cues to identify the position. The egocentric memory condition involved having to recall the location, but from the same inspection condition. In this and a subsequent study using an additional patient (Holdstock et al., 2000), they found impairments only in the allocentric experimental condition of the experiment. More recently, King, Burgess, Hartley, Vargha-Khadem, and O’Keefe (2002) explored allocentric memory in a patient who had early focal hippocampal damage, called Jon. They used a desktop virtual reality method to test
allocentric memory in which participants were placed on the outside of a ‘courtyard’ and had to view objects placed within. Subsequently they had to view the courtyard and decide which objects had been displaced. Mild impairments were found when the patient viewed the courtyard from the same direction, but these were substantial when the patient was moved around the outside of the courtyard.

The above studies support the link between allocentric spatial memory functioning and either the right temporal lobe, or more specifically, the hippocampus. A potential criticism, however, is that they lack sufficient experimental control to determine the specific mental processes involved in solving the task. For example, in the study by Abrahams et al. (1997) the participant could use extraneous room cues not just to orientate themselves within the spatial domain in an allocentric sense, but link to locations more directly with individual proximal room cues. To some extent this could be solved by darkening the room, as in the study by Holdstock et al. (2000), or manipulating the room cues, but it is difficult to control these factors completely. In relation to desk top three-dimensionally presented tasks, such as the Rotate task used by Feigenbaum et al. (1996) or the courtyard task by King et al. (2002) there is the potential confound that the participant can use either subtle markers around the computer monitor, combined with mental rotation of the display in a non-allocentric mnemonic manner. Alternatively, they can use mental rotation of the displays to avoid true allocentric memory.

For this reason, immersive virtual reality (IVR) was adopted as a means of providing complete control of the visual environment and for testing allocentric memory. A human analogue of the Olton Maze was developed that required the participant to walk around a virtual ‘room’, inspecting locations, in the form of ‘shells’ placed upturned and concentrically on a virtual ‘table,’ to find one with a ‘blue cube’ underneath one of them (see Fig. 2). When the cube is found, it moves to a new location and had to be found again, and so on until all the shells have been used as target locations. Thus the task shares one of the main features of the Olton Maze (Olton et al., 1979), in that the participant was rewarded for exploring certain locations and not for returning to previously successful ones. In common with the approach of previous studies by Abrahams et al. (1997) the IVR also enabled spatial memory to be assessed during whole body movement, thus reflecting a possible characteristic of the spatial memory system, that it is developed to integrate bodily motion and spatial representation (Morris & Parslow, 2003; Worsley, Recce, Spires, Marley, & Morris, 2001). In this case, however, IVR linked the movement of the participant isometrically to the imaginary world in which the memory task was administered.

The present paper reports the results of an individual (PR) who has selective hippocampal damage, sustained in early adulthood through an anoxia incident. The patient has been scanned using magnetic resonance imaging (MRI) to provide volumetric measurements of the hippocampus and surrounding cortical tissue, such as the perirhinal, entorhinal and parahippocampal cortex and the remainder of the temporal lobe using an adaptation of the Insausti et al. (1998) method.
The case study investigated whether damage restricted to this brain region is sufficient to result in allocentric spatial memory impairment as measured using our immersive virtual reality technique. As well as the support from animals implicating the hippocampus specifically in cognitive mapping (O’Keefe & Burgess, 1996), this is suggested by functional neuroimaging studies where hippocampal or parahippocampal involvement has been shown specifically, but activity is not reported in surrounding cortical tissues. For example, such activation is reported in studies of normal participants by Aguirre, Detre, Alsop, and D’Esposito (1996), who used a virtual reality maze with landmark objects, showing bilateral hippocampal activation. Maguire, Frith, Burgess, Donnett, and O’Keefe (1998) explored neural activity using a virtual reality maze to investigate encoding of topographical information with and without salient objects. They found increased activation in the right hippocampal region during exploration of large-scale space with salient objects present. Maguire, Burgess, et al. (1998) employed a large-scale spatial virtual reality environment and compared activation on successful versus unsuccessful navigation with following arrows. This revealed right posterior parahippocampal activation extending into the hippocampus. Other neuroimaging studies spatial have also found parahippocampal or hippocampal activation, including those using imaginary or filmed navigation (Ghaem et al., 1997; Maguire, Frackowiak, & Frith, 1997). Our own studies have shown bilateral (mainly right activation) of the hippocampal/parahippocampal region during a performance on a human analogue of the Morris Water Maze (Parslow et al., 2004).

It becomes important to verify whether the association between brain activity in the hippocampal regions during allocentric memory tasks truly indicates function. Hence there is the need to explore whether focal hippocampal lesions can produce allocentric spatial memory impairment. This has not been shown conclusively in previous studies. For example, allocentric memory has been investigated in patients with reported focal hippocampal lesions have used older patients (e.g. Holdstock et al., 1999, 2000), where discriminating between whether or not non-hippocampal tissue has been damaged is more problematic because of the more variable neurodegenerative age-relative changes. Alternatively, King et al. (2002) used a bilateral hippocampal lesion patient who had a lesion developmentally, in which case there is the possibility of neuronal plasticity resulting in abnormal brain representation of allocentric memory. In all these cases, no measurement of the integrity of the other temporal lobe regions were conducted, so it remains and additional possibility that the deficits reported could have been influenced by non-hippocampal damage.

Hence, this paper presents the first investigation of young adult patient with acquired focal bilateral hippocampal damage to be investigated with respect to allocentric memory functioning. This was backed up by the only study to date to use structural neuroimaging to measure specifically the volume of extra-hippocampal mesiotemporal lobe structures in to explore the extent of focality of the lesions in relation to allocentric memory. Hence the study provides a way of exploring whether any putative deficit could be explained by more widespread damage to mesiotemporal lobe tissue. The study also investigated the performance of patients with
unilateral hippocampal lesions using groups of patients with right and left unilateral temporal lobectomies. These patients have more extensive lesions, including removal of large portions of the anterior temporal lobe and the parahippocampal gyrus. This group enabled us to extend the scope of the investigation to determine whether the allocentric memory tested in the current study is localized in the right hemisphere as suggested by previous studies of patients with unilateral temporal lesions and also the neuroimaging studies reviewed above. Hence, whilst patient PR provides information about the specificity of the hippocampus regarding allocentric spatial memory, the patients with unilateral lesions indicate whether allocentric memory, as tested by the immersive reality paradigm, is supported by the right hemisphere.

2. Method

2.1. Participants

2.1.1. Patient with bilateral focal hippocampal damage

PR sustained his anoxic brain damage when aged 24 years and was tested aged 29 years. Prior to this he had three episodes of major depression, the third of which prompted him to attempt suicide using car exhaust fumes. He was resuscitated, but had sustained anoxic brain damage, resulting in specific impairment in memory function, including his complaints of severe forgetfulness and inability to take in new information, but with intact remote memories preceding the incident.

His neuropsychological assessment included an estimate of premorbid intellectual functioning using the National Adult Reading Test-R (NART-R) (Nelson & Willison, 1991) and measurement of current intellectual functioning using the Wechsler Abbreviated Scale of Intelligence (WASI) (1999). His memory was measured using the memory tests from the Adult Memory and Information Processing Battery (AMIPB; Coughlan & Hollows, 1985). Additional tests of executive functioning were administered, including the Trail Making Test (cf. Spreen & Strauss, 1991), and the Stroop Neuropsychological Screening Test (Trenerry, Crosson, DeBoe, & Leber, 1989).

His background neuropsychological functioning is given in Table 1. His estimated premorbid Full Scale IQ using the NART-R was 121, his WAIS-R Verbal IQ was 130 and Performance IQ 128. His memory performance suggests moderately or severely impaired verbal and non-verbal episodic memory functioning. He was not impaired on the tests of executive functioning.

2.1.2. Normal controls

For the experimental investigation, PR was compared with a group of 10 healthy controls, matched approximately for mean age (30 years; SD = 1.53) and mean NART-R (119.0; SD = 6.68) and selected on the basis that they did not have a history of psychiatric or neurological disorder.
2.1.3. MRI scanning of PR

Structural MRI scanning was obtained for PR and a further comparison set of 10 healthy age matched controls, using a 1.5T GE NV/I Signa System (General Electric, Milwaukee, WI, USA) (Maudsley Hospital, London, UK).

For examination by a neuroradiologist, two sets of images were acquired, including coronal FLAIR (TR = 8000ms, TI = 200ms, TE = 13.3ms, slice thickness = 3.5mm, slice gap = 0.5mm, one data average), and coronal T2-weighted images (TR = 3060ms, TI = ms, TE = 81ms, slice thickness = 3.5mm, slice gap = 0.5mm, one data average). The coronal images were oriented according perpendicular to the axis of the hippocampus. Image contrast for all datasets was chosen with automated optimizing image contrast.

For volumetric measurements T1-weighted 3-D inversion recovery images were obtained in the coronal plane, again orientated perpendicular to the line of the

Table 1
Neuropsychological functioning of PR

<table>
<thead>
<tr>
<th>WASI</th>
<th>IQ Score</th>
</tr>
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<tbody>
<tr>
<td>Verbal intelligence</td>
<td>130 (98 percentile)</td>
</tr>
<tr>
<td>Performance intelligence</td>
<td>128 (97 percentile)</td>
</tr>
<tr>
<td>Full scale intelligence</td>
<td>133 (99 percentile)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AMIPB</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Story recall</td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>12 (moderate impairment)</td>
</tr>
<tr>
<td>Delayed</td>
<td>0 (severe impairment)</td>
</tr>
<tr>
<td>List learning</td>
<td></td>
</tr>
<tr>
<td>Total A1–A5</td>
<td>28 (moderate impairment)</td>
</tr>
<tr>
<td>A6</td>
<td>1 (severe impairment)</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td>Intrusions</td>
<td>1</td>
</tr>
<tr>
<td>Figure recall</td>
<td></td>
</tr>
<tr>
<td>Copy</td>
<td>100%</td>
</tr>
<tr>
<td>Immediate</td>
<td>0% (severe impairment)</td>
</tr>
<tr>
<td>Delayed</td>
<td>0% (severe impairment)</td>
</tr>
<tr>
<td>Design learning</td>
<td></td>
</tr>
<tr>
<td>Total A1–A5</td>
<td>19 (moderate impairment)</td>
</tr>
<tr>
<td>A6</td>
<td>3 (moderate impairment)</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td>Intrusions</td>
<td>0</td>
</tr>
<tr>
<td>Trail making</td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>27 (75–90 percentile)</td>
</tr>
<tr>
<td>Part B</td>
<td>57 (75–90 percentile)</td>
</tr>
<tr>
<td>Stroop</td>
<td>Score</td>
</tr>
<tr>
<td></td>
<td>112/112</td>
</tr>
</tbody>
</table>

Wechsler Abbreviated Scale of Intelligence (WASI); Adult Memory Information Processing Battery (AMIPB).
2.1.4. Neuroradiological examination of PR

The scans for PR and the 10 control participants were examined by a neuroradiologist, who identified bilateral hippocampal lesions in PR, but no other neuropathological features in either PR or the 10 controls.
2.1.5. Volumetric MRI measurements

Volumetric analyses were performed on PR and the 10 controls using the disprim image display (David Plummer, Medical Physics Department University College London: http://www.medphys.ucl.ac.uk). Measurement of the hippocampus, para-hippocampal gyrus, temporal lobe and cerebral hemispheres were obtained using methods adapted from Abrahams et al. (1999). Measurements of the perirhinal and entorhinal cortices were based on the methods described by Insausti et al. (1998). Measures were duplicated for PR and one control participant to check to check the reliability of measurement. Chronbach’s alpha was computed for each brain region and the resulting coefficients varied between 0.89 and 0.99.

2.1.6. PR volumetric measurement data

The brain region volumes are shown in Table 2. These were calculated by summing across the area measurements for the coronal slices and multiplying by the slice thickness. They were then converted into Z scores based on the control data and corrected for whole brain volume by adding the Z score for the whole brain volume. To explore whether PR showed significant differences in volumetric measurements from the control group the Crawford and Howell (1998) method for estimating point estimates of the abnormality of measurement scores was applied to the data. This showed only that the right and left hippocampi were significantly reduced in volume.

2.1.7. Temporal lobectomy patients and controls

The study included 36 participants who had undergone unilateral temporal lobectomies as treatment for intractable epilepsy out of which 17 had right temporal lobectomies (right TL; 10 male and 6 female; mean age 36.4, SD = 10.2) and 19 left temporal lobectomies (left TL; 8 male and 11 female; mean age 38.6; SD = 7.9) at the Neurosurgical Unit, King’s College Hospital, London. The standard en bloc resection method was used (Falconer, 1971), which consisted of removal of between 5.5 and 6.5cm of the temporal lobe tissue from the temporal pole with removal of amygdala and approximately the anterior two thirds of the hippocampus and parahippocampal gyrus. The cortical removal involves relative sparing of the superior temporal

Table 2
Volumetric measurements (mm³) for PR and neuroimaging control group, including the hippocampus, perirhinal, entorhinal, parahippocampal, temporal lobe, and whole volume measurements

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Control volume</th>
<th>PR volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>125.0 (8.6)</td>
<td>130.1 (7.8)</td>
</tr>
<tr>
<td>Perirhinal</td>
<td>118.5 (28.4)</td>
<td>138.11 (29.2)</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>100.0 (12.4)</td>
<td>97.9 (18.4)</td>
</tr>
<tr>
<td>Parahippocampal</td>
<td>145.5 (12.7)</td>
<td>158.5 (24.6)</td>
</tr>
<tr>
<td>Temporal Lobe</td>
<td>921.5 (90.4)</td>
<td>881.5 (68.8)</td>
</tr>
<tr>
<td>Hemisphere</td>
<td>2826.3 (205.6)</td>
<td>3816.3 (216.6)</td>
</tr>
</tbody>
</table>

The raw measurement volumes are given and the measurements of PR as a percentage of the controls.
lobe gyrus in the language dominant hemisphere (described in more detail, with MRI analysis in Graydon et al., 2001; Morris & Parslow, 2003; Nunn et al., 1999). The participants were seen a minimum of 6 months after neurosurgery and had to have a National Adult Reading Test-Revised (NART-R) predicted full scale IQ of 85 or above to be included in the study (right TL; mean = 104.4, SD = 8.3; left TL; mean = 111.9, SD = 9.6). Their performance was compared to a group of 18 normal controls (CON; 9 male; 9 female; mean age 38.8; SD = 5.9; NART-R mean = 115.0, SD = 5.9), selected on the basis that they did not have a history of psychiatric or neurological disorder. The three groups were matched approximately for age and predicted IQ and the difference between the groups on these variables were not statistically significant.

2.1.8. Equipment

Fig. 2 shows the equipment used for virtual reality testing. A head mounted display (HMD), the Virtual Reality 4 (VR4) headset, was used to project the visual images which subtended a viewing angle of approximately 130°. The position of the head was tracked using a Polhemus FasTrak Sensor system, responsive to head orientation as well as lateral, forward, backward, and up and down movements. The World Tool Kit software package was used to construct the virtual environment and maintain the appropriate image within the head mounted display. Online processing of tracking data and image construction was conducted using a PC attached to the tracking system and HMD. Thus, the participant could move as in the real world and see a correspondingly moving virtual world, which had isometric dimensions. The administration required two people, one to operate the computer during the task and another to ensure that the VR4 headset cable did not interfere with the movement of the participants.

2.1.9. Procedure

The procedure is called the Shell Task. The participant was positioned in an empty room, and could see a similarly orientated virtual room (2 × 2 m) via the HMD. In the center of this room was the Virtual Table (diameter 1.5 m) and placed on top of the table was a ring of identical upturned ‘shells’ (concave and colored hemispheres), arranged in radial fashion (see Fig. 3a–d). During the task, the participants could move around the room with the constraint that they were asked not to walk into the walls (they were warned if this is about to happen) or the table (it turned purple if the participant ‘touched’ it).

The participants walked round the virtual table and inspected the shells by looking under them with the aim of finding a hidden blue cube. To inspect a shell the participants walked in front of it and said ‘lift,’ which cued the examiner to press an appropriate key on the PC keyboard, at which point the shell disappeared temporarily. If there was a blue cube ‘hidden’ by the shell, then this appeared in view on the table. When a cube was found, it was moved ‘under’ another shell for the subsequent search. The participants had to search for this next location and so on until a cube had been found under all of the shells, defining the end of a trial. The participants
were instructed to avoid repeatedly inspecting shells within the same search and inspecting a shell that had a cube under it previously in the same trial (failure in either case constituted respectively within- or between-search errors).

In order to prevent the participants from using a simple search strategy (Miotto, Bullock, Polkey, & Morris, 1996), such as moving round the table and inspecting the shells in turn, they were only allowed only to inspect a subset of the shells in any particular search. The shells that could be inspected were colored coded green and those that could not be inspected were colored red. This subset changed systematically

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Fig. 2. The set-up for the Shell Task. The dashed lines represent the Virtual Room, with the Virtual Table in the center. The experiment is controlled through a microcomputer, connected to a receiver in order to track head position and to a VR4 headset to present the visual display (the head mounted display). The patient walks around the ‘real room’ whilst inside the virtual room. Inside this room, centrally placed, is the virtual reality table, with the shells concentrically arranged.
Fig. 3. A sequence of views for the six shell version of the Shell Task. The viewpoint shown here is from an observer rather than that seen by participant, in order to illustrate the sequence of viewpoints. The figure shows the arrays of upturned shells, that can be inspected to reveal a blue cube if the correct one is selected. (a)–(f) shows the sequences of views as the blue cube (the smaller cube on the virtual reality table in the figure) is found in the different locations in turn. Note that only those shells that are color coded green (the darker shells in the figure) can be selected on any one search, the shells that are coded in this manner determined in a pseudorandom fashion to prevent the participant forming a strategy (see main text for further procedural details).
between searches. A constraint within this procedure was that there always was an available (green shell) that had not been used as a target in previous searches. Hence the participant could always find a new target within a search.

After two practice trials with four shells, each participant was tested using four trials with four shells (4A, 4B, 4C) and three trials with six shells (6A, 6B and 6C). At the end of the four-shell trials there was a further trial with four shells (4D) that had a minimal memory load and was used to check that the participants could follow the procedure before moving on to the more difficult six-shell level. For the four-shell task, only two shells could be inspected in any one search, whilst for the six shell game, three shells could be inspected. The order of the ‘correct’ shells was different for each trial. An example of a series of searches with six shells is given in Fig. 4. This shows a successful search path around the table, with the participant correctly locating the hidden cubes.

3. Results

3.1. Measurement of errors

In summary, two types of memory errors could be made during the test: Firstly, within-search errors, in which the participant returned to a location already inspected within a search; and secondly, between-search errors consisted of going back to a previously successful location in a subsequent search in the same trial. The number of errors in each case was averaged across the trials for each level of difficulty, defined by the number of shells used (Levels 4 and 6).
Neither PR nor the controls made any within-search errors. However, both PR and the controls made between-search errors (Fig. 5). PR was compared to the controls using the Crawford and Howell (1998) method for estimating point estimates in single cases studies. This showed no significant impairment at Level 4, with no errors made, but a highly significant impairment at Level 6 ($t(9) = 15.88$).

### 3.2. Unilateral temporal lobectomy patient results

For the RTL and LTL patients, the mean within-search errors were very few. For Level 4, no errors were made in the patient groups and the mean for the controls was 0.02 (SD = 0.02). For Level 6, errors were as follows: right TL; mean = 0.98 (SD = 0.03); left TL mean = 0.08 (SD = 0.05); control mean = 0.07 (SD = 0.06). A Kruskall Wallis test showed no overall difference between the groups at either Level 4 or 6.

In contrast, many between-search errors were found at both levels. Fig. 6 shows this data collapsed across trials for each level of difficulty. The resulting measures were analyzed using a two-way MANOVA with Group (right TL, left TL and controls) as the between-subject factor and Level (4 versus 6) as the within-subject factor. This revealed a main effect of Group, $F(1,51) = 5.19$, $p < 0.01$, and Level, $F(1,51) = 33.61$, $p < 0.01$, with a significant interaction between the two factors, $F(2,51) = 3.73$, $p < 0.05$. The groups appear to differ in performance on Level 6, rather than on Level 4. This was confirmed by a separate ANOVA comparing the groups at the two levels. At Level 4 the ANOVA was not significant. At Level 6 it was, $F(2,51) = 2.68$, $p < 0.01$, and a post-hoc analysis using least squares differences (LSD) analyses showed the right TL group to be significantly worse than the control group.
group and the left TL group. The latter was not significantly impaired in comparison to the controls.

As a further analysis, the data for each trial were considered (see Fig. 7). In part the error rate varied in response to the difficulty of the particular trial. For example, as indicated in the methods section the last four-shell trial (4D) was designed to
check the ability of the participant to follow the instructions, with the search paths deliberately set to minimize the possibility of error. In each search of this trial one of the choices was always a shell under which the blue cube had just been found. The low error rate (see Fig. 7) on this trial indicates (only one participant, a right TL patient made an error and only on once choice) that all the participants in the different groups were following the procedure correctly. It also suggests that the different groups were easily able to remember the last shell that had been lifted, and the location of the blue cube in the immediately prior search.

The between-search error data were explored comparing task performance within the different levels, but leaving out data from the trial 4D ‘checking’ trial. The data were analyzed using a three-way MANOVA with Group as the between-subject factor and Level (4 versus 6) and Trial (A, B and C) was the within-subject factors. This revealed main effects of Group and Level and interaction between these factors (same analysis as given above, hence $F$ and $p$ values are not provided here), but no main effect of Trial or other interactions. Thus the analysis suggests no relative differences in the pattern of task performance between the groups analyzing individual trials.

Additionally the contributions of age, intelligence and gender differences to the pattern of results for the between-search errors were explored by further analysis. Firstly, the analyses above were repeated but with age and NART-R IQ as combined covariates. This made no difference to the overall findings. Secondly, the MANOVA with Group and Level as factors was repeated, but with Gender (male versus female) as an additional between-subject factor. There was no significant main effect of Gender or interaction between Gender and other factors.

### 3.3. Comparison between PR and the unilateral temporal lobectomy patients

Although PR is not matched for age or IQ with the unilateral temporal lobectomy patients, some indication of the relative extent of impairment can be made by direct comparison. For within-search errors at Level 4 neither PR nor the two TL groups made any errors. For Level 6, PR made no errors and was performing significantly better than the right but not left TL groups (respectively: $t(17) = −2.59; p = 0.02; t(19) = −1.56; p = 0.14$). For the between-search errors at Level 4, again PR made no errors. He was significantly better than both right and left TL groups (respectively: $t(17) = −6.07; p = 0.000; t(19) = −5.84; p = 0.000$). For Level 6 PR was significantly better than the right TL group, but showed only a trend towards being worse than the left TL group (respectively: $t(16) = −1.94; p = 0.035; t(19) = 1.46; p = 0.16$).

### 3.4. Comparison with chance levels

The performance of the participants can be compared to chance levels of responding. In order to calculate these levels it was assumed that they were able to retain an immediate memory of the shell that had contained the blue cube in the prior search.
This was confirmed, for example, in the 4D trial described above, where on each search the participant was always presented a choice between a novel target location and a target location that had been successful on a previous search. In this case, only one error was made in the entire study.

To illustrate the chance calculation further, consider the series of searches in Fig. 4, which involve six shells, and is an easy trial: For the first choice, there is an equal probability that the participant will select one of the three shells. No error can be made at this stage because there has not been a previous target. For second search, one of the three possibilities is the immediately preceding target location. In this case, a random response is assumed to be the choice between the two remaining shells and, since these have not previously been targets, no error can be made under the assumptions of the chance calculation. For the third search, again the immediate preceding target is available, and two other locations, not previous targets, are presented. This is also true for the fourth search. However, for the fifth search, the choice is between two locations one of which has previously been a target (but not immediately preceding) and one which is a new target location. In this case, the probability of an error assuming random responding is $1/2$ ($0.5$). The same is true for the final (sixth) search. Hence, for this trial, the error score assuming random responding is on average one (the combination of $0.5$ and $0.5$).

The chance error rates were calculated based on the cumulative chances of making errors across searches and trials assuming random responding. In this way it is possible to evaluate the chance error rate for each of the trials that would be expected from randomly choosing a novel green shell.

The mean chance error rate for the combined three trials (three sets of searches) of Level 6 was $1.67$. The mean of the error in the right TL group ($1.34$) is close to this level and PR is closer to chance responding than the performance of his respective controls ($PR = 1$; control mean $= 0.23$). In fact, the performances of the right TL group and PR may be closer to chance than indicated by these figures, since there was a slight apparent bias for the participants to choose the nearest novel shell, rather than randomly between all novel shells.

4. Discussion

The study shows that allocentric memory is impaired in PR, who has selective hippocampal brain damage, and also in the right TL group, where the damage is unilateral but incorporating additional temporal cortical tissue, including the perirhinal, entorhinal and parahippocampal cortices. The combination of these findings supports the role of the hippocampus in allocentric memory, and implicates the right hippocampus specifically. The impairment was seen in the between-search error measure in which the participant had to retain the ‘used’ spatial locations over a longer time period. Very few errors were made in all the groups in terms of returning to the locations within a search.

The presence of an allocentric memory deficit in PR suggests specific hippocampal involvement in this type of memory functioning, as would be predicted from the
concept of spatial mapping, ascribing this function to the hippocampus (O’Keefe & Burgess, 1996). PR shows a similar deficit to previous patients with bilateral hippocampal involvement, for example, those studied by Holdstock et al. (1999, 2000) and also Jon, studied by King et al. (2002). One difference between these studies is the age of the patient, with PR sustaining his damage aged 24 years and tested for the purposes of this study about 4 years later. His early age reduces the complications of more variable age-related changes in brain neurodegeneration complicating the analysis of his brain region volume changes. The presence of the spatial memory in the right TL group only is likely to suggest unilateral representation. It should be noted, however, that the lesions are smaller in the left TL patients because of the need to preserve language functioning in the dominant hemisphere. However, previous studies, which have measured the extent of cortical removal of different regions of the temporal lobe following en bloc resection in our neurosurgical unit have shown no difference in mesiotemporal lobe removal between left and right TL group (Graydon et al., 2001). Regions other than the mesiotemporal lobe do show differences, but the extent of removal of these regions have not shown an association with spatial memory impairment (e.g. Nunn et al., 1998), so it is less likely that this is an explanation of the laterality effect.

A potential cause of impaired performance on the Shell Task in patient groups might be difficulties with spatial processing, rather than spatial memory per se. Performance on the task requires a variety of non-mnemonic abilities, for example, keeping track of the layout of the spatial array whilst moving around it and coordinating movement within the Virtual Room. Impairments in spatial processing are associated with right hemisphere lesions, including difficulties with visuospatial constructional abilities and spatial attention (De Renzi, 1982). Tasks that create allocentric processing demands, such as that used by Abrahams et al. (1999) and that in the current study, have produced very robust TL related deficits, and it is important to determine whether these are specifically mnemonic in nature. Nevertheless, there are several reasons for discounting these factors as a cause of the impairment. Firstly, various procedural checks were made during the task and these suggest that both TL groups were able to execute the basic task requirements. In the case of PR, his perfect performance at Level 4 showed that he could follow the procedure at this stage. Additionally on trial 4D, in which the mnemonic load was reduced substantially, the error rate of the right TL group was minimal (one patient made one between-search error) again indicating their later errors was not due to a failure to understand the task procedure. Furthermore on Trial 6A, PR, his controls and the other three groups were equally successful at executing the search path up to the fifth search, but then the task discriminated PR and the right TL group from their respective control groups in the last search, where the memory load was increased. This highlights the specificity of the mnemonic deficit. Also, PR was specifically tested on his mental rotation abilities, and was shown to be unimpaired on the Manikin Test (Ratcliff, 1982). Although not tested for this function in the current study, related studies using patients from the same pool (with overlapping participant selection) have consistently shown no impairment in tests of complex spatial manipulation. This includes the studies by Feigenbaum et al.
(1996), Abrahams et al. (1999), and Worsley et al. (2001) in which the participants were matched in their performance on the Flags Mental Rotation task (Thurstone & Jeffrey, 1956). Additionally, a recent study by Feigenbaum and Morris (2004) indicates that right TL participant show no impairment not only on the Flags task, but two other tests of mental rotation, the Manikin test (Ratcliff, 1982), and a more complex test that involves matching representations of 3-D objects constructed from square blocks. Also, Worsley et al. (2001) have shown that the right TL participants are matched with control participants in performance on the Benton test of right–left orientation (Benton, Hamsher, Varney, & Spreen, 1983) and the Money Road Map test (Butters, Soeldner, & Fedio, 1972), that requires providing a verbal indication of a series left-right turns when looking at a road map. The latter involves tracking a route on the map both away and towards the body of the participant.

The analysis of the data makes a distinction between within-search errors, in which the participant selected a shell already inspected within the search, and between-search errors, where a previously successfully shell was revisited within a trial. Very few within-search errors were made and neither PR nor the right TL group was impaired on this aspect of the task. This result indicates that, even with the distraction of walking found the Virtual Room, both PR and the right TL group had no difficulty in retaining a limited number of locations for a short period. This type of memory may be more akin to the visuospatial component of working memory, for example, the functioning of the visuospatial scratchpad system (Baddeley, 2000). The neural basis for this function is thought to involve the inferior prefrontal (BA 47), premotor and dorsolateral regions (Awah & Jonides, 1998; D’Esposito, Detre, Alsop, & Shin, 1995), which would be intact in PR and also following the temporal lobectomy operation. Temporary storage of small amounts of information appears to be more related to parietal or frontal lobe functioning, as indicated by neuroimaging studies (e.g. Owen, 1997), and it may be that this system is untouched by the temporal lobectomy operation. On the other hand, the between-search comparison highlighted the deficit in the right TL participants, suggesting dependence on mesiotemporal lobe structures. This overall pattern is very similar to that observed with the rotational task by Feigenbaum et al. (1996). A distinguishing feature of the between-search condition is that the relevant locations have to be maintained over a longer period, with more opportunity for interference. This echoes the finding with non-human primates in whom bilateral hippocampectomies produce no impairment on the delayed response task (Correll & Scoville, 1967; Diamond, Zola-Morgan, & Squire, 1989), but have impairments either with long delays or when the complexity of delayed response is increased by requiring the animal to remember two positions (Angeli et al., 1993).

Additionally, a recent study by Feigenbaum and Morris (2004) has shown that unilateral temporal lobectomy patients are unimpaired on a direct test of spatial working memory, an adaptation of Brooks (1967) task by Morton and Morris (1995). This task, which involves recalling of sequences of spatial instructions, with recall dependent on the extent of working memory use, employed a span procedure to avoid floor or ceiling effects. The task, despite being sensitive, did not detect work-
ing memory impairment in right or left TL groups, suggesting that spatial working memory is not impaired following large mesiotemporal lobe lesions. In future studies it would be of interest to determine whether this is also the case for patients with focal bilateral hippocampal lesions.

The *Shell Task* was designed in such a way so as to prevent the participant from using a non-spatial strategy to aid performance. That such strategies can influence performance is illustrated by the results of a study by Iaria, Petrides, Dagher, Pike, and Bohbot (2003). They used a desktop human Olton Maze analogue, developed to explore spatial memory in normal participants and also investigated neural activation during the task measured using fMRI. Their task was designed so as to explore the effect of strategy formation on performance and corresponding neural activation. They used an eight arm maze, with radially arranged locations within an imaginary landscape and viewed from the center. Here, the participants were not prevented from exploring particular locations, and potentially they could use the non-spatial strategy of associating the locations with either letters or numbers, for example counting the arms, either clockwise or anticlockwise, from a single starting point. Probe trials were applied in which landscape cues were removed, with the notion that if the participants were using a non-spatial strategy, performance would not necessarily deteriorate. Hence, these trials could be used to determine whether this was the case. Based on this method it was found that only about half the participants used a spatial strategy. Furthermore, these participants showed right hippocampal activation. A subsequent study by Bohbot et al. (2004) has shown that use of a spatial strategy significantly activated the hippocampus, whilst a non-verbal strategy produced caudate nucleus activation. Furthermore, a set of patients with mesiotemporal lesions were tested. Those who tended to use the spatial strategy made significantly more errors than those that did not, presumably because their reliance on this strategy showed up their spatial memory impairment.

In the *Shell Task* the approach was to block the use of strategy through two approaches. Firstly, the Olton Maze procedure was adapted such that there was only one target location during each search, which would shift to a new location after success. This effectively prevented the participants from simply moving round the table sequentially identifying targets, with minimal memory load. Secondly, to prevent a more sophisticated strategy, such as adopting the same search path for each new target location, but simply skipping successful items, half the shells were ‘locked’ in a pseudorandom fashion for each trial. This effectively obliterated the use of either a verbal or non-verbal strategy, as indicated by our pilot studies, in which participants reported not being able to discover any strategy that they could use to aid performance.

An aspect of the current procedure is that it controls the total visual environment of the participant and, to the author’s knowledge, is the only immersive virtual reality exploration of memory dysfunction in patients with memory disorder. The procedure makes it possible to eliminate the use of associations between spatial location and proximal stimuli, including features of the testing room or even imperfections in the apparatus. The test was also designed to eliminate background cues, such that
these could not be used for orientation in an allocentric sense or for cue guidance. Because of these aspects of the design, in order to remember location, participants could adopt two possible approaches. One would be to use the configuration of the shells and monitor position relative to particular shells. This requires an updating process, as well as building up a configural map of which shells had been inspected or successful. Because all the shells are identical and arranged in a symmetrical circular fashion, this would require continuous updating of information as the participant moved round the table. Another method might be a form of path integration, in which ideothetic and visual information about movement enabled the participant to keep track of position relative to the shells. The previously used shells or successful ones could then be coded as specific locations in the overall map, which would be used to avoid subsequent error. The link between the hippocampal formation and a system of path integration has been considered in animal studies (Maaswinkel & Whishaw, 1999; McNaughton et al., 1996; Recce & Harris, 1996; Whishaw, McKenna, & Maaswinkel, 1998) and there is evidence for impairments in path integration in participants with unilateral right temporal lobectomies (Worsley et al., 2001).

Another related consideration is that it is possible to design procedures that separate out ‘visual’ and ‘spatial’ processing demands in a more pure fashion, were visual refers to memory for structure, shape and pattern and spatial to the geometric relationship between primitive features within the visual domain. In the Shell Task, there are no distinctive visual features relating to each location. This may have implications for theoretical accounts relating to the involvement of the hippocampal formation in spatial memory. For example, theories of hippocampal function that involve the formation of spatial maps (O’Keefe & Nadel, 1978), a ‘purely’ spatial deficit is predicted by the theory. On the other hand, approaches that implicate the hippocampus as integrating object features and spatial locations (Gaffan & Hornak, 1997; Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997) cannot encompass such a deficit in this sense. In previous studies by Nunn et al. (1998, 1999) the spatial memory deficit associated with the right TL was dissociated from pattern recognition memory and recall or object recognition memory by using a temporal titration procedure. Furthermore, there are several studies that relate the amount of spatial memory deficits to the integrity of the right hippocampus (Smith, 1989; Smith & Milner, 1981) including the two studies by Nunn et al. (1998, 1999) in which the extent of the operation was verified by an MRI lesion analysis. Abrahams et al. (1999) conducted structural MRI analyses on pre-surgery unilateral hippocampal sclerosis participants that they had tested using their ‘container’ task. They showed that the extent of spatial memory impairment was specifically related to volume reductions in the right hippocampus, but that object recognition, tested within the same task, was related to the right temporal lobe volume. The link between the right hippocampus and spatial memory is also seen in imaginary or virtual reality studies using functional neuroimaging (Aguirre et al., 1996; Ghaem et al., 1997; Maguire et al., 1997).

In summary, an immersive virtual reality system has been used to create a spatial memory task that shows impairment in both a patient with selective bilateral
hippocampal damage and in right temporal lobectomy patients. This result shows that a task of this sort, in which extraneous visual cues are removed, produces a relatively large deficit. Experimental manipulations of the task can then be used to explore the nature of the deficit more precisely in future research, with the immersive technique enabling the systematic manipulation of the visual environment. The deficit observed in a test of allocentric spatial memory in which extrinsic cues were controlled points towards the specific (but not exclusive) involvement of the right hippocampal formation in spatial memory in humans.

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References


