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Bilateral Hippocampal Pathology Impairs Topographical and Episodic Memory but not Visual Pattern Matching

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ABSTRACT

A virtual reality environment was used to test memory performance for simulated - 'real-world' spatial and episodic information in a 22-year-old male, Jon, who has selective bilateral hippocampal pathology caused by perinatal anoxia. He was allowed to explore a large-scale virtual reality town and then tested on his memory for spatial layout and for episodes experienced. Topographical memory was tested by assessing his ability to navigate, recognize previously visited locations and draw maps of the town. Episodic memory was assessed by testing the retrieval of simulated events which consisted of collecting objects from characters whilst following a route through the virtual town. Memory for the identity of objects, as well as where they were collected, from whom, and in what order was also tested. While the first task tapped simple recognition memory, the latter three tested memory for context. Jon was impaired on all topographical tasks and on his recall of the context-dependent questions. However, his recognition of objects from the virtual town, and 'topographical' scenes (as evaluated by standard neuropsychological tests) was not impaired. These findings are consistent with the view that the hippocampus is involved in navigation, recall of long term allocentric spatial information and context-dependent episodic memory, but not visual pattern matching.

INTRODUCTION

The human hippocampus has long been associated with episodic memory (Scoville and Milner, 1957), while the hippocampus in rodents has been associated with spatial navigation (O'Keefe and Nadel, 1978). O'Keefe and Nadel (1978) proposed that a possible link between topographical and episodic memory is the existence of an allocentric (world-centered) cognitive map, stored in the hippocampus. They suggested that a spatial system in rats might have developed into an episodic memory system in humans with the addition of verbal and temporal inputs. This hypothesis predicts that hippocampal damage in humans should impair both topographical and episodic memory.

Both topographical and episodic memory can be tested in many ways. Topographical memory has previously been evaluated by observation of route learning (Habib and Sirigu, 1987; Katayama et al., 1999), landmark recognition (Whitley and Warrington, 1978; Incisa della Rochetta et al., 1996; Maguire et al., 1996; Katayama et al., 1999), route learning on a table top maze (Semmes et al., 1955; Milner, 1965; Bottini et al., 1990; Katayama et al., 1999), the ability to describe common routes (Incisa della Rochetta, 1996; Teng and Squire, 1998), view discrimination of the same building (Whitley and Warrington, 1978, Suzuki et al., 1998), orientation and distance judgements (Maguire et al., 1996, Teng and Squire, 1998) and map drawing (Habib and Sirigu, 1987; Bottini et al., 1990; Maguire et al., 1996; Suzuki et al., 1998). Small-scale tasks such as remembering the spatial location of an object or stimulus on a table top or a display have also been applied to test allocentric spatial memory (Smith and Milner, 1981; Morris et al., 1996; Abrahams et al., 1997; Nunn et al., 1998; Bobhot et al., 1998; Holdstock et al., 2000).

Episodic memory has also been tested by a number of methods. One method is to test the ability to remember autobiographical events that occurred prior to the lesion (e.g. Sanders and Warrington, 1975). Another method is to present to patients a list of words or set of pictures (e.g. Warrington and Weiskrantz, 1968) or to ask them to recall paired associates (Meyer and Yates, 1955), or prose passages (Milner, 1958) and subsequently test recognition.

While these tests have been successful in demonstrating that topographical and episodic memory are complex processes that involve many brain regions, not just the hippocampus (see Aguirre and D'Esposito, 1999), it is not clear how these tests map onto the real world behaviors of actually navigating or remembering a real event. Navigation requires more than solely the recognition of landmarks or just the judgement of distance and angle. Equally, episodic memory can be distinguished from both semantic and recognition memory by the additional ability to retrieve the rich spatio-temporal context of events (Tulving, 1983). Furthermore, testing patients with lesions of more than one structure, such as temporal lobectomy patients, does not allow us to accurately identify the structure responsible for a selective impairment (e.g. hippocampus versus other medial temporal lobe structures).

Testing the actual navigation performance and the retrieval of context rich episodic memory in controlled conditions is made possible by the use of virtual reality. Whereas, real world environments and events are difficult to control experimentally, virtual environments allow controlled and simulated events to happen, and actions or movements to be measured accurately. Simulated virtual reality environments have been used in a number of functional imaging studies examining topographical memory, showing the involvement of brain regions consistent with those found in clinical studies (Aguirre et al., 1996; Maguire et al., 1998a; Aguirre et al., 1998; Maguire et al., 1998b; Gron et al., 2000). Two of these studies (Maguire et al., 1998b; Gron et al., 2000) have imaged active navigation and found participation of both right and left hippocampus. Indeed, Maguire et al. (1998b) found that blood flow changes in the right hippocampus were related to accuracy of navigation, the more accurate the performance, the more active the right hippocampus. To our knowledge, neurological patients have not been tested on their ability to navigate in a virtual reality environment or to remember events occurring within them.

In this study we tested the ability of a patient with early-onset selective bilateral hippocampal pathology to navigate, remember topographical information and different aspects of episodic memory in a large-scale virtual environment. The patient, Jon, is one of a group of patients previously reported by Vargha-Khadem et al. (1997) and Gadian et al. (2000).

AEITOLOGY AND SYMPTOMS

Jon was born prematurely at twenty six weeks of gestation, weighting 940g and suffering from breathing difficulties, that required intubation at 15 min,, although spontaneous breathing was established 30 mins later. Despite some brief apnoeic attacks, Jon did well until the age of 3 weeks when more severe episodes of apnoea occurred requiring intubation and positive pressure ventilation for 1 week. At this time, he was suspected to have enterocolitis and he suffered from multiple episodes of severe apnoea, again requiring intubation and positive pressure ventilation. He was transferred to an intensive care unit for a period of three weeks after which he improved steadily and encountered no further medical problems. His developmental milestones were slightly delayed for walking but speech and language functions emerged normally. At the age of 3 years and 10 months, Jon suffered an unconfirmed convulsive episode in association with a cold. From an early age he was considered clumsy although he developed no other motor abnormalities. Memory problems were first noted by Jon's parents when he was about 5 to 6 years of age. Following a parental questionnaire, three main areas of memory problems were identified in Jon by Vargha-Khadem and colleagues (1997) (i) Spatial: Inability to find his way in familiar surroundings, remember where objects and belongings are usually located, or remember where he has placed them. (ii) Temporal: Jon is not well oriented in date or time, and he must frequently be reminded of regularly scheduled appointments and events, such as particular classes or extracurricular activities. (iii) Episodic: Inability to provide a reliable account of the day's activities or reliably remember telephone conversations or messages, stories, television programs, visitors, holidays, and so on.

NEUROPATHOLOGY

Three methods were used to assess Jon's neuropathology (Vargha-Khadem et al., 1997). These were MRI volumetric measurements (Van Paeschen et al., 1997), T2 relaxometry (Jackson et al., 1993) and proton magnetic resonance spectroscopy (^{1}H MRS, Gadian, 1995). These techniques were selected because of their sensitivity to temporal-lobe pathology. From volumetric measurements, Jon's hippocampi were found to be bilaterally shrunken by approximately 50%. His hippocampal volume was found to be reduced along the length of both hippocampi, as indicated by the cross-sectional areas (see figure 1). Furthermore, T2 relaxometry, which provides a means of quantifying the abnormalities that are responsible for the signal increases seen on T2-weighted MRI (Jackson et al, 1993), showed elevated T2 values bilaterally, suggesting that the remaining hippocampal tissue in Jon is compromised. Finally, ^{1}H MRS provides a noninvasive method of detecting diffuse temporal lobe pathology by examining the ratio of certain metabolites within the brain, such as N-acetylaspartate (NAA) to creatine plus phosphocreatine (Cr), and choline containing compounds (Cho). A reduction in the ratio of the NAA signal to the Cr and Cho signals, commonly is interpreted as a reflection of neuronal loss or damage. Spectra were obtained from a 2 x 2 x 2 cm volume within the medial region of the temporal lobes, encompassing a small portion of the hippocampus. Although this selected region of the temporal lobe contains a contribution from hippocampal tissue, this contribution is so small that any spectral changes are considered to arise predominantly from extrahippocampal tissue, i.e. the spectral abnormalities reflect relatively diffuse or widespread pathology that is additional to any pathology detected on volumetric or T2 measures of the hippocampus (Gadian et al., 1999). The ^{1}H MRS values obtained for Jon were in the normal range on the left and marginally below on the right, suggesting that the extrahippocampal regions sampled were largely preserved.

A more recent analysis using voxel based morphometry involving Jon and four other patients who had suffered perinatal or infantile hypoxic-ischaemic episodes further confirmed that within the medial temporal lobes the damage is confined to the hippocampus (Gadian et al., 2000). Outside the medial temporal lobes there was reduced grey matter density in the putamen and the ventral thalamus bilaterally.

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see Fig. 1 at end

PREVIOUSLY REPORTED NEUROPSYCHOLOGY AND EXPERIMENTAL TESTING

When tested in 1996 using The Weschler Adult Intelligence Scale – Revised, Jon's Verbal IQ was 108 and his Performance IQ was 120. He was severely impaired on a range of tests of delayed recall. On the Rey-Osterrieth Complex Figure Test, he recalled only two identifiable fragments (maximum 18) of the figure after a 40 minute delay, and on the 90 minute delayed recall of the Logical Memory subtest of the Weschler Memory Scale (Wechsler, 1947) he recalled only 10 percent of the stories. On the Children's Auditory Verbal Learning Test (Tally, 1993) obtained a standard score of 72, close to the minimum possible of 60. However his Digit Span was 7 forward and 6 backward and his Corsi Block Span was 7 forward and 8 backward, performing better than the average of a group (n=47) of normal controls (Vargha-Khadem et al., 1997).

Using a parental questionnaire (Sunderland et al., 1983) and the Rivermead Behavioural Memory Test (Wilson et al., 1985), his anecdotally described problems with spatial, temporal and episodic memory problems were documented and tested more formally. In the parental questionnaire Jon's parents had to rate how often he forgot 29 typical everyday events. The ratings were at the extreme end of the scale, i.e. often forgetting more than once a day. The Rivermead Behavioural Memory Test requires the subject to remember a route through a room, where a belonging was placed, the date, a message to be delivered, a name for a pictured individual, a story, and recognize line drawings of objects, and faces previously seen. Jon correctly remembered only 3 out of 12 items, which is indicative of a severe impairment.

In addition to the tests described above, 12 computerized, two-choice, recognition tests were developed. These tests consisted of three types: one-trial recognition of lists of items, one-trial associative recognition of lists of paired items, and multitrial associative recognition of lists of items. Stimulus items for both the one-trial recognition and one-trial associative recognition consisted of words, non-words, familiar faces, and unfamiliar faces. One-trial recognition tests consisted of 5 lists of 12 sequentially presented items each; the presentation of each set was followed by forced-choice recognition of the familiar items, with each item paired with a novel distractor. One trial associative recognition tests consisted of 10 lists of 6 sequentially presented pairs of items each, followed by re-presentation of one item and forced-choice recognition of its associate or an item from a different pair. In the four multitrial associative recognition tests, the stimuli consisted of 20 pairs each of non-words, unfamiliar faces, voices and faces, or objects and locations. Multitrial tests involved one presentation of the list of stimuli followed by successive recognition trials with feedback until a criterion (18/20 correct) was reached or 10 trials had been completed. Jon was not significantly worse than eleven control subjects on any of the recognition tests except the voice-face, and object-location tasks, where his performance was equal to that of the worst control subject on the voice-face task but even poorer than the worst control subject on the object location task (Vargha-Khadem et al., 1997).

Jon's recognition memory has been studied further in two recent studies. When tested on The Doors and People Test (Baddeley et al., 1994), his scores were within the normal range on both verbal and visual recognition subtests but severely impaired on the recall subtests (Baddeley et al., 2001). When Jon's event-related potentials (ERPs) were measured during the recognition of previously studied words, he was found to be lacking the late positive component (Duzel et al., 1999a), an ERP index thought to be associated with recollection, a fundamental component of episodic memory (Duzel et al., 1999b). By contrast, his ERP index of familiarity, a basic component of semantic memory, was well preserved.

MATERIALS AND METHODS

Standard Neuropsychological Tests

Jon was 22 years old when tested in the present study. Informed consent for participation was obtained in accordance with guidelines set by the Great Ormond Street Hospital for Children and the Institute of Child Health Ethics Committee. His general intellect was assessed using the Raven's Advanced Progressive Matrices, Set I (Raven, 1976). Mental rotation was evaluated by the Little Man Test (Ratcliff, 1979). In this test the subject is shown a sequence of 32 drawings of a man holding a white ball in one hand and a black ball in the other hand. The man is either upright facing the subject, upright facing away, inverted facing the subject, or inverted facing away. For each picture the subject has to say which hand is holding the black ball. The Camden Topographical Recognition Memory Test (CTRMT), The Camden Pictorial Recognition Memory Test (CPRMT) and The Camden Paired Associates Memory Test (CPAMT) from The Camden Memory Test Battery (Warrington, 1996) were used to provide standardized measures of recognition and recall at the time of the present testing. The Camden Topographical Recognition Memory Test involves a three-way forced-choice recognition test of previously presented scenes. The Pictorial Recognition Memory Test follows a similar format to The CTRMT but the stimuli consist of people, animals, and general objects, as well as places. The Camden Paired Associates Memory Test consists of three sets of eight word pairs, each word pair is read aloud during the presentation. After the presentation of eight words recall of the pairs is tested by the presentation of a single word from each pair. Feedback in the form of re-presenting the pair is given after each response. The test is given twice, without re-presentation of the word-pairs the second time.

Experimental Tests

To systematically evaluate topographical memory and episodic memory, four new tests were developed. Jon's performance on these tasks was compared with that of a group of 13 right-handed, age and IQ-matched (Raven's Advanced Progressive Matrices) control subjects. Two of these control subjects were from Jon's peer group. All subjects gave their informed consent in accordance with UCL/UCLH Ethics Committees. The mean age of the control group was 21.2 years (SD= 2.2 years, see table 1 for IQ scores). All control subjects had had similar experience of video games as Jon.

A virtual reality town provided the environment in which to test Jon's memory. The town was designed by one of us (NB) using the commercially available video game 'Duke Nukem 3D' (© 3D Realms Entertainment, Apogee Software Ltd. Garland TX) with the editor provided (Build © 3D Realms Entertainment) see Burgess et al (2001). The same town was used in Spiers et al (2000), and is a modification of that used in Maguire et al (1998b). The town consisted of a main street intersected by a crossroad. Throughout the town there were various interior locations which included a cinema, an arcade, a bookshop, a bar, a sushi bar, an underground station, a karaoke bar and a bank (Figure 2). Each interior had several entrances, providing overall a large number of routes from one location to another.

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see Fig. 2 at end

A desktop PC with a 19 inch screen was used to display the town at a frame rate of 21Hz. No auditory stimuli were used. To maneuver within the town the subjects used the cursor keys of a keyboard. To match Jon and the control subjects for dexterity with the keys, they were timed whilst they followed a short route of arrows through the town. After this the subjects were given between 15 to 40 minutes to explore the town. During the exploration phase the subjects were instructed to explore until they felt they were ready to be tested on their memory for the town and had been observed to visit all locations.

Following exploration, subjects were tested on the following tasks in the order described. Subjects were told that they would be tested on their navigation and memory for the town but not told any specific details of how they would be tested, such as recognizing scenes from the town or draw a map of the town.

Navigation

In this task subjects had to navigate between different locations in the town using the most direct route available. They were shown a picture of a target location which was continuously present during navigation to that location. When the subject reached the location they were shown a new picture and asked to repeat the process until they had each navigated to all ten places. These target locations were spread evenly across the town and varied in their relative proximity to the start point and difficulty to find. To assess the accuracy of a subject's navigation the average path length was calculated from cursor key presses made by the subject during the task.

Environmental Scene Recognition

Paired forced-choice recognition of twenty pairs of scenes were used to test memory for locations visited during exploration and navigation. One of the scenes in each pair was a view from inside the virtual town. Note that the subject was unlikely to have experienced the exact scene used; indeed some of these were taken from view points which the subjects had never been able to reach. However, all subjects would have experienced similar views and only these target views were consistent with the layout of the town. The other half of the scenes were made by creating new virtual locations. These foil views included objects, surface textures and similar geometry from the original town (but spatially rearranged so as to be inconsistent with it) as well as novel objects, novel textures and novel geometry. Subjects responded by using a mouse to select one scene from each of the twenty pairs. Responding was self paced.

Map Drawing

A computer program was used to assess map drawing in a quantitative manner. The program displayed a 10 x 10 grid and a set of ten icons representing locations in the town. Subjects were required to move icons onto the grid, and thus form a map of the town. Having been placed in one location, the icons could be moved to a new location if the subject changed his mind. A 3D view of the location represented by each icon could be displayed at any time by clicking on it. Subjects were instructed to use the full extent of the grid, and not to cluster the icons in one area. When all ten icons had been placed, subjects could opt to stop or to continue arranging the icons.

The completed maps were compared with an ideal map, constructed to reflect the true layout of the town (as shown in Fig. 2B). A subject's map was scored by calculating the error in the distance between all pairs of icons as a fraction of the mean distance between the icons in the ideal and the subject's maps. This measure is independent of differences in map orientation. Independence from differences in map size was achieved by scaling each subject's map to match the ideal map. Specifically, the error measure reported in Table 2 is:

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

where d^{s}_{ab} is the distance between icons *a* and *b* in the subject's map, d^{i}_{ab} is the distance between icons *a* and *b* in the ideal map, γ is an arbitrary scaling factor and $\langle . \rangle_{ab}$ represents the average over all pairs of icons *ab*.

Episodic Memory

This task assessed Jon's memory for various aspects of events. The test was run twice. Each run consisted of two phases, a presentation phase and a test phase. During presentation the subject followed a route through the town, indicated by pictures of locations along the route. Whilst following this route subjects repeatedly encountered two solitary characters, at 16 fixed intervals along the route. Every time a character was encountered, the subject was required to press a key, causing the character to produce an object, which the subject collected. They collected objects in two of the rooms on each route, but not always in the same section of each room. The objects were common, familiar objects, e.g. a light bulb. Before the subjects started the presentation phase they were informed that their memory for the objects, who gave them the objects, where they received the objects and the order in which they collected them would be tested. For the second run, different objects, characters and places were used.

Subjects' ability to recall the various aspects of the event of receiving an object was tested in a counter balanced paired forced-choice procedure immediately following the presentation phase. Subjects re-entered the rooms in which they had previously collected the objects. The room now contained one of the two characters and displayed on the nearest wall two objects and a word which represented one of four questions: OBJECT - "which of the two objects displayed were you given?", PERSON - "which of the two objects did you receive from the character next to this question?", PLACE -"which did you receive in the room you are currently in?", FIRST - "which did you collect first?". For the OBJECT question the foil was an altered version of the original object or a very similar object from another source. Foil objects in the other conditions were other objects from the set they had received. For the PLACE question the foil object was one of the collected objects that had not been given to them in the current room. For the PERSON question the foil object was one of the objects not given to the subject by the character that was next to the question. From the two replications of the test, a total of 32 questions of each type were asked, resulting in a grand total of 128 questions. The questions were given in the form of eight sets of eight questions and the time taken to answer each set of eight questions was recorded. The question order, and left - right response to each question was counter balanced across the test phase.

Prior to testing-proper, subjects were given practice trials during which they followed each of the two routes and were presented with four practice objects and two practice characters. They were asked whether they had used any particular associational or mnemonic strategies to aid their recall of these practice events. If they had, they were asked to avoid using these strategies and simply pay attention to the aspects of the events in the experimental test. This was done to avert the use of verbally mediated strategies.

See Figure 3 The Episodic Memory Task at end of document

RESULTS

Standardized Neuropsychological Tests

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see Table 1 at end

Results of the standardized tests are shown in table 1. Jon's good performance on The Raven's Advanced Progressive Matrices Test is consistent with his performance on the Weschler Adult Intelligence Scale reported by Vargha-Khadem et al (1997). His performance on the little man test is well within the normal range (Ratcliff, 1979), consistent with the view that he does not have damage to right posterior parietal regions, implicated in egocentric spatial processing (see e.g. Burgess et al., 1999; Karnath, 1997).

Results from The Camden Memory Test show that Jon is within the average range on both The Topographical and The Pictorial Recognition Memory Tests. On The Paired Associate Memory Test his performance was at the low end of the normal range for the first trial, but impaired on the second trial. These results mirror the results of the Vargha-Khadem et al (1997) study, in that his recognition is in the high average end of the normal scale in contrast to his recall which is impaired.

Experimental Tests

See Table 2 at end

Topographical Memory Tests

The results of the experimental tests are shown in table 2. The average path length was used to assess the accuracy of navigation. Jon's mean path length was over six standard deviations longer than those of the controls (see table 2), indicating that his ability to navigate is severely impaired. His ability to discriminate between scenes from the virtual town and altered scenes, or scenes from a different town was also significantly compromised (see table 2). Jon's map of the town appeared disordered compared with an ideal map and was ranked worst of all by our measure of accuracy (see Figure 4). His computed score was impaired by 2.4 standard deviations relative to the control subjects' mean (see table 2). Jon explored the town for longer than the controls, and indeed had experience of similar towns during piloting. The two control subjects from Jon's peer group performed no differently from the other 11 control subjects (Average: exploration time: 21.0 minutes, navigation distance: 91.5 virtual meters, environmental scene recognition: 87.5% correct and map drawing error: 0.323).

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see Fig. 4 at end

Paired Forced Choice Episodic Memory Tests

As expected, Jon's performance on the forced-choice recognition of objects presented was normal (see table 2). Although the performance of the controls was high, only three scored at ceiling (32 / 32). However Jon's ability to retrieve contextual information about receiving objects (i.e. which object was given first, by whom, and in what location) was deficient. Of the 96 contextual questions, 50 responses were correct (i.e. two more than chance), a standard which was significantly lower than controls who averaged 76 correct responses. Examining the individual categories, Jon was at chance on each (see table 2), whereas only 0 / 13, 1 / 13 and 2 / 13 controls were at chance on the FIRST, PERSON, and PLACE questions respectively. On the individual tests, Jon's score was two standard deviations lower than controls on the FIRST question but not on the other two context dependent questions, due to the high variance of the controls scores (see Table 2). To stabilize the variance with respect to the mean of the proportion correct for each type of question, an arcsine transformation was applied to the data, which did not alter the overall finding. On a number of occasions, when answering the PERSON questions Jon would try to position himself in the room so that one of the two objects appeared next to the character while the other object was occluded by the character, i.e. creating a situation similar to presentation of an event. None of the controls did this. Jon's peer group control's performance did not differ from the other controls (Average number of OBJECT questions correct: 31.5/32 and context-dependent questions correct: 78/98).

Both Jon and the controls took the same amount of time to collect the objects at presentation, an average of 8 - 9 minutes, although Jon took significantly longer to answer the questions. However, there was no evidence of a decline in Jon's performance or that of controls over the duration of retrieval.

DISCUSSION

When first interviewed Jon presented with three main symptoms; spatial, temporal and episodic memory problems. Using a computer simulated environment we have characterized his spatial and episodic memory problems systematically. To our knowledge this is the first study to examine both topographical and episodic memory together within the same simulated life-like but controlled environment. Our results indicate that selective bilateral hippocampal damage disrupts navigation, topographical memory and the contextual aspects of episodic memory but does not affect recognition when the stimulus is re-presented exactly as it was at presentation, i.e. visual pattern matching is unaffected.

Topographical Memory

Many previous studies have implicated the medial temporal lobes in topographical memory (e.g. Maguire et al., 1996a; Habib and Sirigu, 1987; Aguirre et al., 1996) although relatively few have specified the role of the hippocampus or simulated actual navigation (Bohbot et al., 1998; Maguire et al., 1998b; Gron et al., 2000). Despite his greater exploration of the town, his navigation, environmental scene recognition, and map drawing were all impaired, consistent with these previous studies. Due to the large-scale nature of the town, all the tasks required long-term storage of the spatial layout of the town, i.e. memory consistent with having stored a cognitive map of the virtual reality town. Whether tested by navigation, map drawing, or identifying scenes of the town, Jon does not appear to have access to this type of representation of the town's layout. Thus bilateral hippocampal damage appears to compromise the ability to form this type of representation.

Complementary to our finding that bilateral hippocampal pathology severely disrupts navigation in large-scale space, unilateral damage to the medial temporal lobe has been shown to disrupt wayfinding abilities (Maguire et al., 1996a). In a previous neuroimaging study on healthy individuals using the same task in the same virtual town, blood flow in both hippocampi was found to be significantly greater during successful navigation than when following a route of arrows through the town (Maguire et al., 1998b). Furthermore, blood flow within the right hippocampus was found to be correlated with accuracy of navigation. The present data on Jon are consistent with the results of this previous study and other neuroimaging studies (Maguire et al., 1996b; Ghaem et al., 1997; Maguire et al., 1997; Maguire et al., 1998; Gron et al., 2000), further demonstrating that the hippocampus is critically required for accurate navigation.

Despite the use of 'topographical' stimuli, Jon's performance was in the average range on The Camden Topographical Recognition Memory Test (CTRMT), thus illustrating the extent of his preserved recognition memory. Although this test can be used to diagnose topographical amnesia (e.g. Whitley and Warrington, 1978; Habib and Sirigu, 1987), it involves recognizing photographs and does not require subjects to form a representation of large-scale space thus enabling good performance solely in terms of the familiarity of the pictures or visual pattern matching. Jon's performance clearly dissociates such a test from more active tests of navigation, and map drawing, suggesting the possibility that, while extra-hippocampal medial temporal regions are sufficient for topographical recognition tests (perhaps posterior parahippocampal cortex, see Epstein and Kanwisher, 1998), active navigation requires the hippocampus.

Our test of environmental scene recognition is different from The Camden Topographical Recognition Memory Test because it requires the identification of scenes that had not been explicitly studied. Control subjects found it relatively easy to identify these scenes from the information encoded during the exposure to the many thousands of scenes experienced during exploration and navigation. However, due to the design of the foils in this task it is not possible to perform consistently by identifying single objects within the scene or by matching the test scenes to a previously encoded template scene as the exact angle view may have been different. Instead, successful discrimination of target views probably requires retrieval of abstracted environmental information, such as the layout. This may explain why the hippocampus is required to solve our environmental scene recognition task. In support of this, Holdstock and colleagues (2000) recently found that bilateral hippocampal damage has a substantial effect on the recognition of allocentric information at a delay of 60 seconds but not the recognition of egocentric information at the same delay. The fact that Jon's delayed recognition of verbal information is unimpaired (Baddeley et al., in press) suggests that it is unlikely that his impaired environmental scene recognition performance is due to the delay between encoding and recognition.

The ability to draw an accurate map of a previously explored environment also requires many skills and is likely to be subserved by many brain regions. In this study we have identified that one of these regions is the hippocampus (Jon's map drawing performance was worse than all the control subjects). Given Jon's impaired performance on the navigation and environmental scene recognition tasks, his map drawing deficit is likely to be due to an inability to accurately recall the relative abstracted locations of elements in the town, consistent with the cognitive mapping hypothesis. Unlike previous studies which have used subjective measurements (e.g. Maguire et al., 1996a; Suzuki et al., 1998), we have used an objective measure of map drawing accuracy, rather than subjective ratings. Note that, in this test, the pictures indicating locations were designed to be as salient as possible and were all highly distinguishable from each other in contrast to the environmental scene recognition test, in which foils were designed to resemble targets. This result is also consistent with the finding that damage to the medial temporal lobes can cause a deficit in map drawing (Maguire et al., 1996a).

In addition to the impairments shown on the three topographical tasks, Jon took significantly longer to explore the town than control subjects. Given the impairments on the other tasks, this finding can be attributed to Jon's inability to learn about the layout of the town, as subjects were asked to finish exploration when they thought they knew where everything was.

The finding that Jon is unimpaired on The Little Man Test (Ratcliff, 1979), performance on which is considered to be sensitive to right posterior cortical damage, suggests that his spatial navigation deficit is not attributable to some hidden damage in the right posterior cortex, or more general problems with egocentric spatial processing such as mental rotation. This finding together with Jon's unimpaired performance on The Camden Topographical Recognition Memory Test raises the possibility that spatial navigation as an example of a real world function, may not be adequately tested by standard 'spatial' neuropsychological tests.

Episodic Memory

Our test of episodic memory involved the recognition of certain aspects of events, such as receipt of objects from people in particular locations within a virtual reality town. When Jon's memory of the objects he had received (OBJECT questions) was tested, his score was within the normal range (the performance of 6 / 13 controls was equal to or worse than Jon). Although three of the 13 controls' scores were at ceiling, the number of correct responses made by Jon exactly matched the mean of the control subjects indicating that his memory for the objects is unimpaired (Jon is also unimpaired when an arcsine transformation is applied to the data, showing the value of 0.52 standard deviations from the mean). Such spared recognition for the objects is consistent with the results from previous tests of Jon (Vargha-Khadem et al., 1997) and with meta analyses of recognition in other amnesic patients (e.g. Aggleton and Shaw, 1996, but see Manns and Squire, 1999, for an alternative point of view).

In contrast, the hippocampus does appear to be required for remembering the context-dependent aspects of the events (i.e. PERSON, PLACE and FIRST questions). Jon was impaired relative to the control subjects on these types of questions and his performance was not significantly different from chance. This is evidence that the hippocampus is required for context-dependent memory. Whereas the OBJECT questions can be solved without reference to context (using the visual familiarity of the objects as the cue), the other questions demand access to the spatio-temporal context in which the object was presented. Thus the results are consistent with view that the hippocampus is involved in the retrieval of context-dependent information but not necessarily familiarity-based recognition (e.g. Aggelton and Brown, 1999). These findings are also consistent with the observation of left hippocampal involvement in the PLACE and PERSON conditions, but not in the OBJECT condition as reported in an fMRI study (Burgess et al., 2001). Note that Jon's poor context-dependent memory cannot be explained by a failure to recognize one object from another, as Jon was able to correctly recognize the objects even among very similar foils. His unique strategy of trying to 'line up' one of the objects with the character in the PERSON questions is of interest. He reported that he was attempting to recreate the situation at the time of presentation, which suggests that he was trying to make use of his spared ability to match visual patterns.

The finding that hippocampal damage impairs performance on the context-dependent questions is consistent with Cohen and Eichenbaum's (1993) relational theory of hippocampal function, in that hippocampal damage has disrupted the ability to bind together associations between different stimuli. However, it is not clear that Jon's particular pattern of results (including his preserved recognition memory for pairs of words, and pairs of faces, and preservation of much semantic memory) is best described by a deficit in relational processing. It could be argued that the three different associations in our episodic task, object - location, object - time (temporal order) and object – person, require integration of information represented in different cortical areas, although these different areas have not all been identified. However it is not clear whether this explanation (or the relational theory) accounts for Jon's impairment on the recognition of scenes from the town or his more general recall failure with numerous tests evaluated through unimodal or crossmodal tasks.

It has been suggested that developmental hippocampal damage does not affect familiarity-based recognition in the same way as late-onset hippocampal damage (which can severely impair it, see patient R.B., Zola-Morgan et al., 1986, and Manns and Squire, 1999). At present, it is difficult to know whether the differences in the level of spared recognition memory between adult-onset damage and developmentally sustained damage are primarily due to the selectivity of the hippocampal pathology, or the increased capacity for reorganization and compensation of memory function in developmental cases, or a combination of both. However a simple distinction between early onset and late onset damage seems unlikely given that patient Y.R., with late-onset selective bilateral hippocampal damage shows a similar pattern of impairment to Jon: preserved recognition but impaired recall (Holdstock et al., 1999; Holdstock et al., 2000).

It could be argued that Jon's topographical memory deficit forms part of a more generalized deficit in episodic memory, i.e. topographical memory forms part of episodic memory. However, there is reason to believe that topographical and context-dependent episodic memories are dissociable. In a recent study of adult patients with unilateral temporal lobectomy using the same tasks (Spiers et al., 2000), right temporal lobectomy patients were impaired on all the topographical tests, whereas left temporal lobectomy patients were impaired on their memory for the context-dependent episodic memory questions. Thus, it is possible that, rather than reflecting a general non-lateralized deficit, Jon's impairments are due to the loss of what would be a right lateralized hippocampal spatial system and a left lateralized hippocampal context-dependent episodic system in the normal brain. Of course in Jon the laterization of the remaining parts of these systems may have be reorganised (see Maguire et al., in press).

In summary, the performance of patient Jon on our virtual reality tasks confirms and quantifies the real-life symptoms of impaired wayfinding and episodic memory he originally presented with. It also supports the view that the hippocampus is vital for supporting topographical memory and context-dependent episodic memory. By contrast, it indicates that familiarity-based recognition memory can be spared, even on tasks requiring 'topographical' scene recognition.

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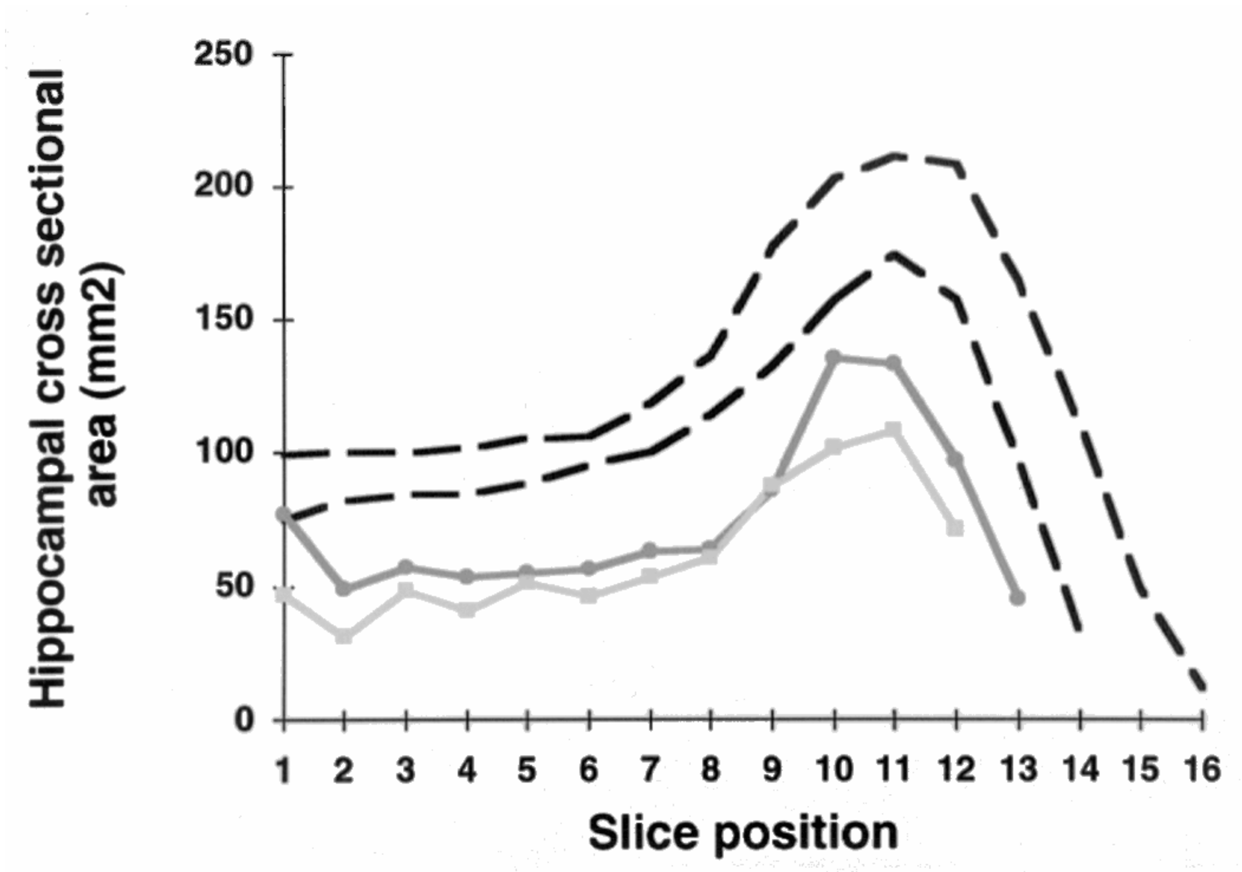
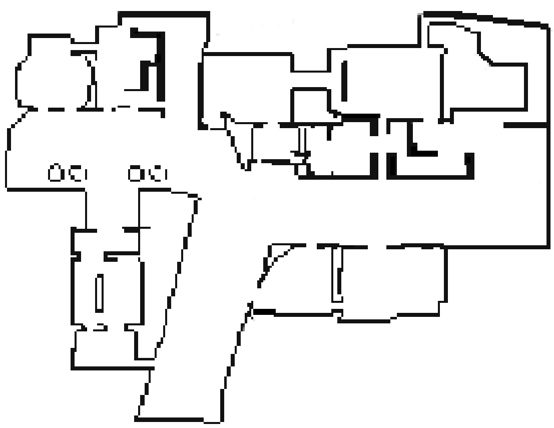
Figure 1.



Hippocampal Cross-sectional Area
Hippocampal cross-sectional area as a function of slice position, sectioned posterior to anterior. The connected lines are Jon's cross sectional hippocampal areas (right hippocampus dark shaded). The dashed lines are 2 standard deviations above and below the of mean hippocampal cross sectional area of a group of 22 normal healthy subjects (Van Paesschen et al., 1997). Cross sectional areas are uncorrected for intracranial volume (as in Van Paesschen et al., 1997, but not Vargha-Khadem et al., 1997).
Figure 2. The Virtual Town

Figure 2.
A

B



The Virtual Town
(A) A screen shot view of the crossroads with the cinema on the right.
An aerial plan perspective of the virtual town (which subjects never saw during testing).

Figure 3 The Episodic Memory Task

A

B

C

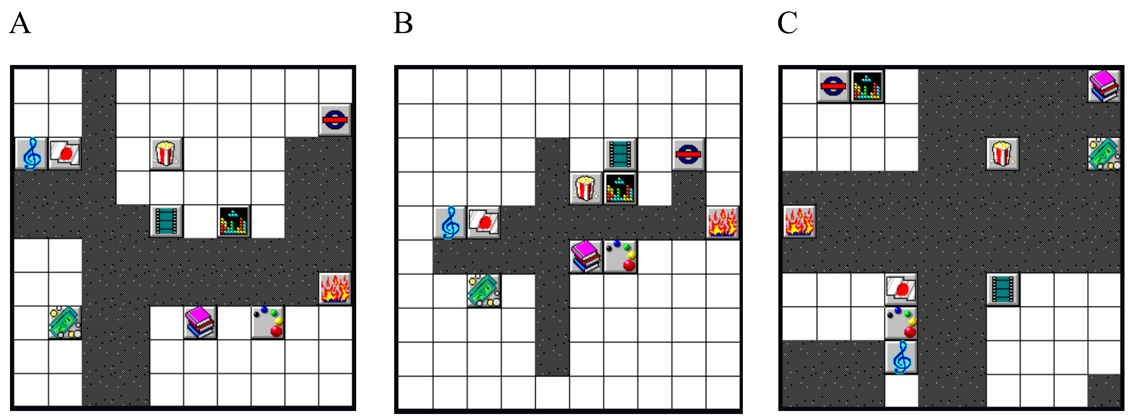
Caption for Figure 2. The Episodic Memory Task

A) The presentation phase: a view of one of the events.

B) The recall phase: an example of one of the OBJECT questions. In this example the object on the left is a collected object and the object on the right the foil object. The person next to the question is irrelevant for the OBJECT questions.

C) The recall phase: an example of one of the context-dependent questions, a PLACE question. In this question the subject has to remember which of the two objects they collected in the question location. For the other context-dependent questions the word PLACE was replaced by the words PERSON or FIRST and the subject had to remember which object the person next to the question had given them or which of the two objects had been collected first respectively.

Figure 4. Map Drawing Results



The ideal map to which the patient and control maps were compared. Road sections were not analyzed. (B) A map drawn by the median control subject, score = 0.28. (C) Patient Jon's computer drawn map of the town. Jon's map had an associated score of 0.45.

Table 1. Results of standard neuropsychological tests

Test	Jon's Score	Control Score	
		13 Control Subjects Mean (St. Deviation)	
Raven's Advanced Progressive Matrices Set I	**11 / 12**	**9.5 (1.7) / 12**	
The Little Man Test		Control data from Ratcliff, 1979	
Total	26 / 32	27 / 32	
Upright	13 / 16	14 / 16	
Inverted	13 / 16	13 / 16	
The Camden Memory Test		Percentile	Interpretation
Topographical Recognition Memory Test	25 / 30	25th – 50th	Average
Pictorial Recognition Memory Test	30 / 30	100th	Superior
Paired Associates			
1st Test	16 / 24	10th –25th	Low-average
2nd Test	16 / 24	< 5th	Impaired

Table 2. Results of Experimental Measures

Measure	Jon	13 Control Subjects Mean (St. Deviation)
Duration of Exploration (minutes)	33*	19.8 (5.8)
Topographical Memory Tests		
Navigational Accuracy (Mean Path length / virtual meters)	151*	83.4 (10.5)
Environmental Scene Recognition	12 / 20*	18.2 (1.1) /20
Map Drawing Accuracy (Computed score)	0.45*	0.30 (0.06)
Episodic Memory Test		
Object Recognition		
OBJECT	30 / 32	30 (1) /32
Context-dependent Memory		
Average (PERSON, PLACE & FIRST)	50 / 98*	77 (11) / 98
Breakdown of Context-dependent Memory		
PERSON	19 / 32	26 (4) / 32
PLACE	14 / 32	24 (6) / 32
FIRST	17 / 32*	27 (3) / 32
Average Presentation Duration (minutes)	8.75	8.15 (1.5)
Retrieval Duration (Average question block time / minutes)	3.32*	2.32 (0.32)

* Impaired scores (> 2 standard deviations from the control mean)