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Rat Spatial Memory Tasks Adapted for Humans: Characterization in Subjects with Intact Brain and Subjects with Medial Temporal Lobe Lesions

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Summary

In the present paper we describe five tests, 3 of which were designed to be similar to tasks used with rodents. Results obtained from control subjects, patients with selective thermo-coagulation lesions to the medial temporal lobe and results from non-human primates and rodents are discussed. The tests involve memory for spatial locations acquired by moving around in a room, memory for objects subjects interacted with, or memory for objects and their locations. Two of the spatial memory tasks were designed specifically as analogs of the Morris water task and the 8-arm radial-maze tasks used with rats. The Morris water task was modeled by hiding a sensor under the carpet of a room (Invisible Sensor Task). Subjects had to learn its location by using an array of visual cues available in the room. A path integration task was developed in order to study the non-visual acquisition of a cognitive representation of the spatial location of objects. In the non-visual spatial memory task, we blindfolded subjects and led them to a room where they had to find 3 objects and remember their locations. We designed an object location task by placing 4 objects in a room that subjects observed for later recall of their locations. A recognition task, and a novelty detection task were given subsequent to the recall task. An 8-arm radial-maze was recreated by placing stands at equal distance from each other around the room, and asking subjects to visit each stand once, from a central point. A non-spatial working memory task was designed to be the non-spatial equivalent of the radial maze. Search paths recorded on the first trial of the Invisible Sensor Task, when subjects search for the target by trial and error are reported. An analysis of the search paths revealed that patients with lesions to the right or left hippocampus or parahippocampal cortex employed the same type of search strategies as normal controls did, showing similarities and differences to the search behavior recorded in rats. Interestingly, patients with lesions that included the right parahippocampal cortex were impaired relative to patients with lesions to the right hippocampus that spared the parahippocampal cortex, when recall of the sensor was tested after a 30 min delay (Bohbot *et al.* 1998). No differences were obtained between control subjects and patients with selective thermal lesions to the medial temporal lobe, when tested on the radial-maze, the non-spatial analogue to the radial-maze and the path integration tasks. Differences in methodological procedures, learning strategies and lesion location could account for some of the discrepant results between humans and non-human species. Patients with lesions to the right hippocampus, irrespective of whether the right parahippocampal cortex was spared or damaged, had difficulties remembering the particular configuration and identity of objects in the novelty detection of the object location task. This supports the role of the human right hippocampus for spatial memory, in this case, involving memory for the location of elements in the room; learning known to require the hippocampus in the rat.

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Introduction

Laboratory animals are commonly used in attempts to model complex functions such as memory, and to provide the means to carefully explore the neural mechanisms underlying these capacities. Yet the kinds of tasks used in rats and those used in humans have traditionally differed in important ways. Human neuropsychological memory tests typically focus on recognition or recall of stories, paired associates, word lists, digits, designs, and shapes, over various retention intervals (Lezak 1995). These, as well as home-made neuropsychological tests are administered by a clinician or researcher at a desk or sometimes in front of a computer, for example abstract designs or small scale models of the radial maze are used while subjects sit at a desk (Jones-Gotman *et al.* 1997, Morris *et al.* 1996). Tests that allow adult brain damaged patients to move around in an environment have not yet made their way into standard neuropsychological evaluation but are now being incorporated into specialized test batteries (Leplow *et al.* 1998, Barrash *et al.* 2000), more commonly in studies of child development (Overman *et al.* 1996, Lehnung *et al.* 1998). Rats on the other hand, are typically required to produce behavioral responses by moving around the environment during various kinds of learning and memory experiments. This is true for spatial memory tasks, avoidance tasks, tasks requiring stimulus-stimulus associations, stimulus-reward associations, and object discriminations, which often take place in a box, a radial maze or in an open field. The purpose of this study was to develop tasks for humans that are closer to the kinds of tasks used in rat studies, with an emphasis on spatial memory, while accepting the limited space constraints of clinical settings. Results obtained from testing patients with thermo-coagulation lesions to the medial temporal lobes that have been described before, will be discussed (Bohbot *et al.* 1998). Novel results include an analysis of the paths that patients with selective thermal lesions to the medial temporal lobe took to the sensor, in the Invisible Sensor Task. Detailed methods of the proposed tasks are described and are the primary emphasis of this paper[1].

General Methods

Subjects

Sixty-two control subjects and 17 patients with brain damage were tested.

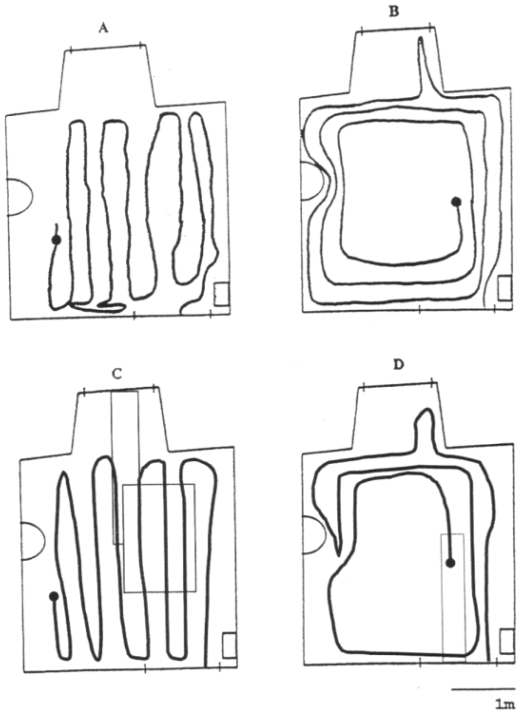

Fig. 1. *Search on Trial 1 of the Invisible Sensor Task. A: Zigzag search strategy used by one subject while searching for the sensor hidden under the carpet. This figure contrasts with the circular search strategy from another subject shown in B. C: Zigzag search strategy used by a patient with a lesion to the right hippocampus. D: Spiral search strategy used by a patient with a lesion to the left hippocampus. There were no differences in the patterns of search between the normal controls and any of the patient groups. Semi-circle: sink, rectangle: heater, the 4 tick marks represent the location of the 2 doors.*

Apparatus

Testing occurred in a rectangular room, approximately 9 m^2 (see Fig. 1). The room had 2 doors, on opposite walls. Several fixed cues were present in the room: a heater, a sink, a picture mounted on the wall. The room was entirely carpeted.

Testing

Before the start of each task, subjects were given instructions so that they fully understood all the task requirements. Subjects were given money reward while tested on the 8-arm radial-maze and the non-spatial working memory task. Specific details about each task are described below.

Experiment 1: The invisible sensor task (IST)

In the reference memory version of the Morris water task (Morris 1981), rats locate a hidden platform in a fixed location under the water surface of a circular pool. In the allocentric version (the most commonly used), the start location varies semi-randomly such that rats find the target with respect to room cues; as opposed to using a route from the same start (egocentric version). The rats use a combination of distal cues to learn the location of the invisible platform. This task is sensitive to bilateral lesions of the hippocampus in rats (Barnes 1988, Morris *et al.* 1982). Here, we adapted the Morris water task to humans by hiding a weight sensor under the carpet of the testing room and varying the start location such that subjects had to find the sensor by using room cues as opposed to a route.

Methods

Control Subjects. Eighteen control subjects were tested. These included eight subjects with back pain problems, without any disorders of the central nervous system (mean age: 41.4 years old; standard error: 2.0) and 10 subjects with epilepsy of probable temporal cause, without brain lesions (mean age: 26.5 years old; standard error: 2.0). These two groups were summed since no significant differences were found between them.

Brain-Operated Subjects. Seventeen patients who underwent selective thermo-coagulation lesions in an attempt to alleviate pharmacologically intractable epilepsy are reported. Patients with Wechsler IQs below 75, psychiatric disorders, or with gross brain atrophy were excluded from the study. All patients were right handed. The patients were tested 4 to 17 years postoperatively. All patients were on antiepileptic drug therapy at the time of testing. None of the patients had clinical symptoms of overdose and the patients' performance was not affected by clinical or EEG seizures on the day of testing.

Table 1. Subjects

Group	Sex		Age		Wechsler IQ		Wechsler Memory Scale		
	M	F	Mean	Range	Mean	Range	Mean	Range	
Back-pain Patient Control	5	3	41.4	29-57	119	96-133	126	98-143	
Epileptic Patient Control	5	5	26.5	17-43	99.3	80-129	107.1	99-143	
Right Hippocampal	5	2	36.9	29-49	103.7	88-131	102.9	84-126	
Right Parahippocampal	3	2	45	38-59	94	82-105	102	81-129	
Left Hippocampal	1	3	44.5	37-53	91.8	87-96	94.8	89-103	
Left Parahippocampal	1	0	34	-	99	-	87	-	

The patients with thermal lesions were divided into 4 groups based on their brain lesions (see Table 1): right hippocampus (RH, n=7), right parahippocampal cortex (RPH, n=5), left hippocampus (LH. n=4) and left parahippocampal cortex (LPH, n=1). The anatomical landmarks that were used to identify the patients' lesions have been described elsewhere (Bohbot *et al.* 1998). In summary, patients with lesions were divided into groups depending on whether or not they had damage to the parahippocampal cortex. Lesions to the hippocampus can include the hippocampus proper, the dentate gyrus and the subicular complex. Lesions of the parahippocampal cortex refer to the posterior parahippocampal gyrus, the neo-cortical region posterior to the entorhinal cortex and perirhinal cortex. Many but not all patients in these groups had damage to the entorhinal and perirhinal cortices, see Bohbot *et al.* (1998) for more details. Due to the fact that a thermo-coagulation electrode was used to surgically resect the epileptic focus, the overall brain damage is very small in comparison to most other causes for brain pathology (Bohbot *et al.* 2000).

Procedure. The invisible sensor is a detector of the subject's position based on a flexible plate capacity sensor, dimensions: 100 x 100 x 1 mm. The sensor was placed away from walls and away from significant cues (heater and sink) so that no single landmark directly marked the sensor. This sensor emitted a pleasant sound when stepped on thus indicating that subjects found the target. On the first trial, subjects must search for the sensor and find it by chance. Once found, subjects must note its position with respect to the multiple room landmarks, and then go back to the entrance. About 30 s later, the subject was asked to enter the same room by the other door and to try to go straight to the invisible sensor (trial 2). After a 30 minute delay a third trial was administered starting from the same door used in trial 1. Since subjects found the sensor by chance on trial 1, it is unlikely that they could follow the same route to find the sensor on trial 3, when starting from the same door. The subjects' search paths were traced on a diagram of the room by the experimenter who was standing by the first door used. Before starting, the experimenter explained that the dimensions of the sensor were 10 cm by 10 cm, so little steps must be taken while trying to find it, otherwise the subject may miss it if steps are too large. The room lights were turned off 10 s after finding the sensor.

After the subject found the sensor, the experimenter said "explore the location, the sensor is under which foot? Move back and make sure you know exactly where it is located". For the second and third trials the experimenter gave the following instructions: "The sensor is at the same location as before. Please try to find it as quickly as you can."

Results and Discussion

Paths: On the first trial, all control subjects seemed to use a planned zigzag (67 %) or spiral (33 %) strategy, while searching for the sensor. The zigzag strategy implied that subjects started searching along one wall, then went back and forth in a parallel fashion until they covered the room (Fig. 1A). The spiral strategy implied that subjects walked around all the walls, and explored in a circular fashion moving gradually towards the center (Fig. 1B). Patients used the same types of strategies as control subjects, in the same proportions as well: 67 % used a zigzag strategy and 33 % used a spiral strategy, when first looking for the sensor. On the second trial, all subjects walked directly to the target.

It is difficult to compare the performance of naive human subjects to naive rats since humans benefit from having been given instructions. When we compare naive humans to experienced rats trained on a new location, the experience may serve a similar function as providing instructions to humans, however rats benefit from having learned procedural aspects of the task.

When rats are naive to the reference memory version of the Morris water task, or to the working memory version which is identical to the reference memory version with the exception that the submerged platform is moved to one of 4 target locations on any given day, they tend to circle around close to the walls of the pool for the maximal allotted time, whether they have lesions to the hippocampus or not. At that point, the rats do not yet know there is an escape platform inside the pool, so they attempt to escape *via* the wall. On the other hand, when a trained rat searches for the platform that is moved for the first time, it will first swim to the previously learned location, then failing to find a platform there, the rat will start swimming around the pool, searching various locations until the platform is found. Interestingly, control rats trained on the working memory version of the Morris water task, swim at a distance from the walls until the target is found, after failing to find the hidden platform at its last location. When rats with bilateral lesions to the hippocampi trained on the reference memory version of the Morris water task search for the location of the platform placed in a new location, also tend to swim in a circle around the pool, at a certain distance to the wall, in order to maximize their chance of hitting the target.

Although control rats trained on the reference memory version of the Morris water task do not seem to use a systematic strategy when searching for a new platform location, as normal human and brain damaged patients do, both rats with lesions to the hippocampus trained on the reference memory version, as well as normal rats trained on the working memory version of the Morris water task, seem to use a similar strategy when searching for the submerged platform in a new location; the search strategy used by these trained rats does not seem as planned as the search strategy of human subjects, i.e. rats do not cover the entire pool area in a systematic way (zigzag or spiral), however, their search may be well adapted to the conditions of the Morris water task, by swimming at a distance from the wall as a result of the training procedure. Since rats with bilateral hippocampal lesions were adopting the search strategy of swimming at a distance from the wall, we can assume that this strategy

does not rely on having an intact hippocampus. Similarly, humans with either a lesion to the right hippocampus or right parahippocampal cortex showed systematic search strategies did not differ from those of control subjects; and these search strategies may rely of structures other than the right hippocampus and parahippocampal cortex.

However, the intact hippocampus and parahippocampal cortex in patients with unilateral lesions, could have contributed to the patient's normal search strategies. We know from the study of patient H.M. that a bilateral lesion to the anterior portion of the hippocampus, including surrounding cortex such as the entorhinal and perirhinal cortices, does not disrupt normal search behavior on the Invisible Sensor Task (Bohbot and Corkin 1999). In humans, the posterior portion of the hippocampus may be the analogue of the dorsal hippocampus in the rat which was found to yield severe spatial memory deficits when lesioned bilaterally (Moser *et al.* 1995). Whether patients with complete bilateral lesions of the hippocampus, including the posterior portion, are enabled with normal search strategies, remains to be investigated. Alternatively, humans and rats could rely on different strategies dependent on different brain areas, when searching for the target.

Latencies: Learning can be measured by latency, in seconds, to find the hidden sensor, and by improvement between successive trials. The first trial shows a lot of variability among control subjects, explained by the fact that the sensor was found by chance (mean: 107.6 s, standard error: 21.1 s). Latencies improved dramatically on trial 2 (to 5.4 s, standard error: 0.7 s), but did not improve on trial 3 (mean: 4.1 s, standard error: 0.8 s), showing that subjects had reached asymptote by the second trial. On trials 2 and 3 there was very little variability indicating that once subjects learned the location of the sensor, they remembered it, and went directly to it on subsequent trials. Latencies of the patient groups have been published elsewhere, but briefly, patient latencies were comparable on the first trial (mean: 78.4, standard error: 21.9). On trials 2 and 3 patients in all groups performed as well as controls (latencies of trial 2: LPH: 7; LH: mean: 7.4, standard error: 2.3; RH: mean: 5.9, standard error: 0.8; RPH: mean: 6.1, standard error: 1.5; latencies of trial 3: LPH: 11.0; LH: mean: 9.1, standard error: 3.1; RH: mean: 3.3, standard error: 0.4) with the exception of the group with lesions to the right parahippocampal cortex, after a 30 min delay on trial 3 (mean: 29.1, standard error: 3.3).

In the traditional version of the Morris water task (reference memory version), rats do not learn in one trial. However, after extensive pretraining on the working memory version of the Morris water task, during which the platform frequently changes locations, rats do learn to go directly to the hidden platform after one trial (Bohbot *et al.* 1996). The extensive pretraining of a rat could serve the same purpose as the instructions given to human subjects. For example, the mean latency of trial 1 for a group of 10 rats trained on the working memory version, was about 30 s while the latency of trial 2 went down to 5 sec (Bohbot *et al.* 1996). This one-trial learning persists for several hours in rats as well (Bohbot *et al.* 1996, Panakhova *et al.* 1984). Rats with bilateral electrolytic lesions to the hippocampus tend to take the maximal allotted time (60 s) on the first trial of the reference memory version of the Morris water task, and with experience they learn to swim at a distance from walls, allowing latencies to decrease to 20-30 s. Changing the location of the platform revealed that the decreased latencies resulted from a non-spatial strategy, evidenced by the fact that latencies to the new platform location remain unchanged (Sutherland *et al.* 1983).

Caution must be taken when establishing comparisons between rats and humans, since they are not tested on the exact same test, but tests that are analogs of each other in theory. Practically, differences such as motivation factors, size of subject vs size of room ratios, visual stimuli available may affect results. Latencies measured from control subjects were similar between humans and rats. However, patients with unilateral lesions to the right hippocampus not only learned the location of the sensor but also remembered it after a 30 min delay. This was not true of patients with lesions to the right parahippocampal cortex who learned the task, but showed a dramatic impairment after a 30 min delay. This indicates that the difference between the disturbing effects of a lesion to the hippocampus in humans was not simply because the rats had bilateral lesions while human subjects had unilateral lesions. Rather, in humans, an intact parahippocampal cortex can permit to some extent, the learning of spatial relationships (Bohbot and Corkin 1999). This is not the case in rats since rats with lesions to the hippocampi with intact postrhinal cortex, the homologue of the parahippocampal cortex in rats (Burwell and Amaral 1998), are severely impaired on the reference or working memory versions of the Morris water task. Despite the evidence that the postrhinal cortex is involved in spatial memory in rats (Aggleton *et al.* 2000), only a lesion to the hippocampus yields severe impairments (Aggleton *et al.* 2000).

Experiment 2: Non-visual spatial exploration (NVSE)

The non-visual spatial exploration task was inspired by path integration experiments done with rats and gerbils (Mittelstaedt and Mittelstaedt 1980) in which successful performance requires that the subjects keep records of paths taken relative to a stable landmark (start or entrance door) in order to orient themselves in space. In standard path integration tasks, learning is measured by observing whether the subject can find a direct route to a target, after having navigated in the dark environment. In our task, learning was measured by asking subjects to place on a map, the location of objects they found while blindfolded. The subjects therefore had to keep track of their movements in order to orient themselves in space while exploring a room with 3 objects. Importantly, subjects had never seen the room before entering it blindfolded. Although visual cues were absent, other sensory cues, for example sounds coming from the corridor, could not always be controlled. The auditory sources were not constant and if they were used, the subjects still had to remember the location of objects with respect to each other and with respect to the room in order to place them on the map. Therefore subjects could orient themselves with idiothetic (self-motion) information, using primarily vestibular, proprioceptive and kinesthetic input. In order to gain more information on the best-to-worst possible performance with the test procedure, subjects were tested on "visual memory" where they had to remember the location of objects after having seen them. Subjects were also tested on "visual observation" where they had to place on the map the location of objects while they were standing in the room, looking at them. Finally, subjects naive to the tasks were asked to randomly place object icons on the map.

Methods

Subjects. Twenty-six normal subjects (mean age: 38 years old; standard error: 1.3) were tested in the blindfolded condition of the non-visual spatial exploration task. In addition, 8 normal subjects (mean age: 26.4 years old; standard error: 0.8) were tested on the visual memory and visual observation trials, and 10 normal subjects (mean age 37.2 years old; standard error: 2.1) served as controls in the random placement of objects of the non-visual spatial exploration.

Procedure. Three objects (chair, trash can, and a stand) were placed in the room, not too close to each other without being placed against the walls, as shown in Fig. 2 (filled shapes). Heavy objects should be used in order to prevent displacement caused by the blindfolded subjects. Subjects were blindfolded and allowed 3 min to

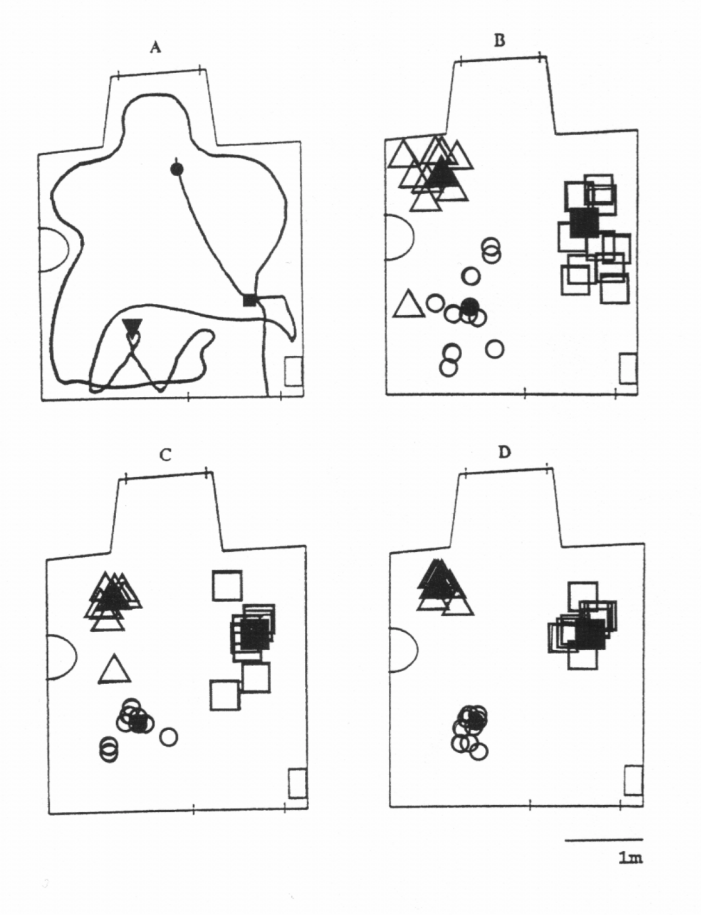

Fig. 2. *Non-visual spatial exploration. A: Top view of the experimental room with an example of the trajectory of a blindfolded subject exploring the room, looking for the 3 objects. Filled shapes represent the location of the 3 different objects. B: Non-visual memory: placement of the 3 objects found during the blindfolded condition (note that different object locations were used in A and B). Subjects placed the objects on the map by sight after having explored the room blindfolded (first 10 subjects tested are displayed). C: Visual memory for object locations: another group of subjects looked at the 3 objects for 10 s and later placed object icons on a map while standing outside the experimental room. D: Visual observation: placement of the 3 objects while the subjects were standing in the room. Semi-circle: sink, rectangle: heater, the 4 tick marks represent the location of the 2 doors. Filled shapes correspond to the real location of objects and unfilled shapes correspond to the location of objects estimated by subjects. Square: chair, triangle: trash can, and circle: stand.*

explore the room to find the objects. Before the experiment started, the experimenter explained that after 3 min of exploration, subjects would be led out of the room and would be provided with a plan of the room showing the entrance door. Subjects were also told that they may encounter a sink and a heater, and that it was not necessary to remember the locations of these two objects.

While the instructions were being presented the experimenter showed the plan of the room with the little icons representing each object that had to be placed on the map. If the subject did not find all the objects within 3 min, then the experimenter would say "continue searching and you will find the object". After another minute the experimenter would say: "is there a place that you did not visit?" Subjects searched for the objects while blindfolded. At that time, the experimenter traced exploration paths on paper for subsequent analysis (for an example see Fig. 2A). After the blindfolded exploration (Fig. 2A), subjects were presented with a sheet of paper containing a schema of the room (9x9 cm), and given sticky paper icons (approximately 1x1 cm, made in proportion to the real objects) to indicate where in the room they thought the objects were located (see Fig. 2B, unfilled shapes).

Visual spatial memory was tested by asking subjects to stand inside the room and look at the 3 objects for 10 s. After having viewed the objects, subjects were led out of the room, the door was shut, and as in the blindfolded condition, subjects were given the schema on which they had to place the objects. Results are shown in Fig. 2C. Subsequently, subjects were asked to place the objects on the schema of the room while they were standing in the room looking at the objects (visual observation condition: Fig. 2D). This test assesses the maximal accuracy possible when translating the visual input to the schema on paper. Chance was defined as the error resulting from placement of the objects in a schema of the room in the complete absence of any knowledge about object location. In order to establish this chance performance, subjects who had no prior knowledge of the room were simply asked to place objects within the same room schema with the instructions: "These paper icons each represent one object (pointing to the paper icons). The identity of these objects is not important. If you wanted to place these objects in the room (pointing to the schema), where would you place them?" The average error in this group of subjects was taken as the level of performance that might be expected when a subject had no knowledge of the room layout and of the objects in it.

Results and Discussion

Performance was measured in terms of the distance between the center of the actual location of objects on the map (e.g. Fig. 2B: filled square), and the location of the center of the objects as indicated by the subjects, on the map (e.g. Fig. 2B: a single unfilled square). The distance on the map was converted to the distance in real space and reported below.

In the random assignment trial, the average error per object, averaged across all subjects was 1921 mm

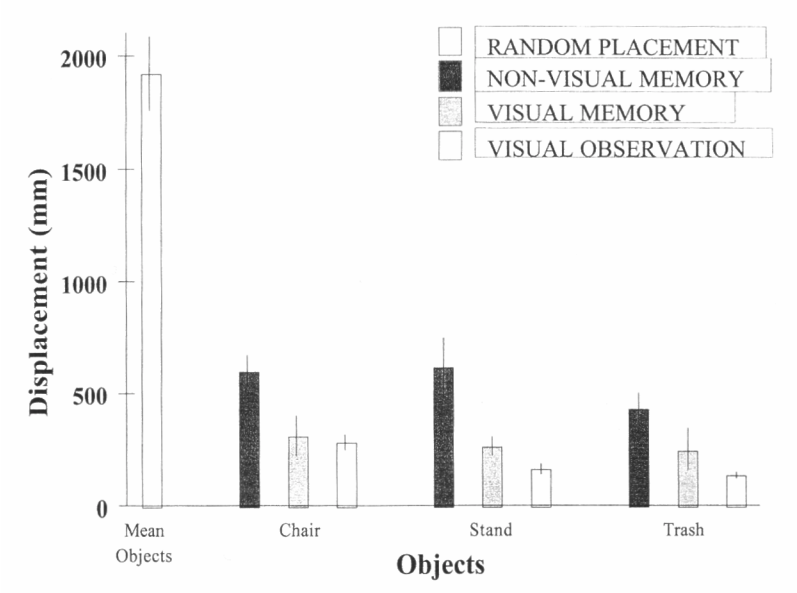

Fig. 3. *Mean displacement error (mm ± S.E.M.) made by normal subjects while placing icons on a map to represent the place where they remember finding each of the 3 objects while blindfolded during the non-visual spatial exploration task.*

(Fig. 3). The average error per object measured after the blindfolded subjects explored the room was far from chance (547 mm; Fig. 2B and 3), showing that blindfolded human subjects were able to construct a mental representation of the space containing objects, derived from movement integration which they later recalled from memory (Fig. 2). When visual confirmation was allowed (visual memory for object location), error was reduced to 276 mm (Fig. 2C and 3) but in the visual observation condition, the error became minimal (194 mm; Fig. 2D and 3). The main differences between the visual and the non-visual memory map formation included the modality of input, one group using idiothetic input, the other visual input, and the time given for encoding the location of objects, which was much longer for the non-visual condition (3 min vs 10 s). The displacement error data show that it is more difficult to use motor integration cues in building a cognitive representation of the relative positions of objects, than it is to use visual cues. However data show that in the absence of visual input, the other information sources can be used to build a cognitive map, as noted above (Gaunet and Thinus-Blanc 1995, Moghaddam and Bures 1996, Save *et al.* 1998). Interestingly, while it was suggested that the hippocampus serves as a path integrator (McNaughton *et al.* 1996, Whishaw *et al.* 1997), patients with lesions to either the left or right hippocampus or parahippocampal cortex were not significantly impaired relative to controls in the non-visual spatial exploration task, the path integration analogue (Bohbot *et al.* 1998). A recent study in which rats with ibotenic acid lesions to the hippocampus were capable of path integration supported our results (Alyan and McNaughton 1999), thus showing that the hippocampus is not necessary for path integration.

While exploring the room blindfolded, 21/26 subjects (81 %) first searched around the walls of the room and then ventured inwards to find the objects (example shown in Fig. 2). The other five subjects headed directly towards the center at the onset of the trial. Two of these later used a zigzag strategy to find the objects, 2 did not seem to have a strategy at all, and the fifth subject used a spiral strategy to locate the objects. Subjects with lesions to the hippocampus or parahippocampal cortex employed similar search strategies as controls did, while searching for objects with a blindfold on. Eleven of 17 brain lesioned patients (65 %) first searched around the walls of the room as control subjects did. Two subjects started a search along the walls, then crossed the room before reverting to the spiral strategy commonly used while being blindfolded. The other 4 subjects ventured towards the center of the room first, two of them adopted a spiral strategy. In summary, subjects tend to first follow the walls of the room while exploring in a novel environment and in the dark. Perhaps subjects need to learn the shape of the room before they can mentally place objects within it. Only later did they seek the objects and try to remember their location. As opposed to the zigzag exploration strategy which most subjects used when visual cues were available, when visual cues were unavailable, most subjects first spiraled around the room.

Experiment 3: Object location task (recall, recognition, and novelty detection)

The object location task is designed to test memory for multiple objects and their spatial locations (Smith and Milner 1989, Pigott and Milner 1993). In order to solve this task, subjects must have the ability to encode spatial relations, and encode which objects were occupying which place. One important difference between the object location task presented here and that of previous studies, is that the subjects are asked to walk inside a room and remember the location of objects that are placed around the subject. Another difference lies in the fact that we used 4 objects in the present study while others have used larger numbers. Other methodological differences were in the encoding time, delay before recall, and recall method.

Methods

Subjects. The same 18 controls subjects that were tested on the invisible sensor task, were tested on the object location task. These included eight subjects with back pain problems, without any disorders of the central nervous system (mean age: 41.4 years old; standard error: 2.0) and 10 subjects with epilepsy of probable temporal cause, without brain lesions (mean age: 26.5 years old; standard error: 2.0).

A. Recall

Procedure. Subjects had 10 s to learn the respective positions of 4 objects (briefcase, stand, kettle, and flowerpot) placed on the floor of a room. Examples of the actual spatial location of objects are shown in Fig. 4 (only one of the 4 layouts was used per subject). Immediately afterwards, subjects had to reconstruct from

memory the spatial location of the 4 objects. They were presented with a piece of paper containing a schema of the room (9x9 cm), and given sticky paper icons (from 7 mm diameter to 15 mm length) to indicate where in the room they thought the objects were located. The experimenter explained to the subjects that they would be provided with a plan of the room, and would be asked to indicate where they thought objects were located. Occasionally, subjects want to stop looking before the 10 s have elapsed. In this case the experimenter said "You must take all the time, it is important that all subjects look for the same amount of time".

The error was measured by the difference between the center of the real location of the objects and the center of the location of the objects estimated by the subject on the plan of the room. This measure was then converted to distance in real space.

Results and Discussion

The average displacement error per object, in the object location recall task, was 255 mm (standard error: 43 mm). This is comparable to the error previously measured in the NVSE (visual memory; mean: 278 mm, standard error: 45 mm), when subjects also viewed objects for the same amount of time and recalled the objects' positions from memory. Normal subjects have excellent memory for the locations of objects, shown by the low displacement error (255 mm).

The object location task involves not only spatial locations but also specific information about the objects which occupy them. The perirhinal cortex is important for learning and remembering previously seen objects (Murray 1996), and the parahippocampal cortex is involved in learning about space (Bohbot *et al.* 1998). A task which requires both types of memory (objects and space) should be especially sensitive to patients with brain damage to the hippocampus since the hippocampus receives input from both the perirhinal and parahippocampal cortices (via the entorhinal cortex). Studies of subjects with selective brain damage to the right hippocampus have confirmed that this structure is critical for object location tasks (Bohbot *et al.* 1998) as earlier studies have suggested (Smith and Milner 1989, Pigott and Milner 1993).

B. Recognition:

Procedure. In order to test whether subjects had difficulty with recall, yet had encoded the information seen in the object location task, we asked the subjects to try and recognize the correct layout of objects by simultaneously looking at 4 plans of different layouts of the objects in the room (Fig. 4).

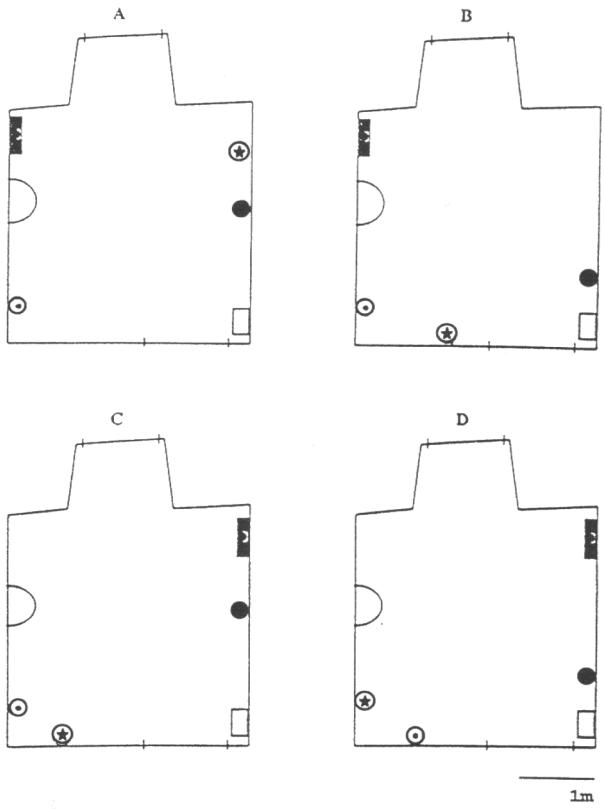

Fig. 4. O*bject location task. Example of the 4 layouts presented during the recognition part of the object location task. One of these 4 was used in the recall task where subjects memorized the location of objects while standing inside the room and looking at them. Objects are placed to scale with the real room coordinates. Rectangle: briefcase, filled circle: kettle, dot inside circle: stand, star inside circle: flowerpot.*

Results and Discussion

All the control subjects identified the correct map. This was expected since all subjects performed well in the recall task, and a recognition task is typically easier. All subjects from the brain-operated patient groups (right and left hippocampus, right and left parahippocampal cortex), recognized correctly the map representing the objects they previously observed, with the exception of one subject from the group with a lesion to the right hippocampus and one subject from the group with a lesion that included the right parahippocampal cortex. A recognition task shows whether some information related to the location of objects was encoded, irrespective of the performance in the recall

task. However, the recognition task is easier than the recall task. Subjects could correctly remember the location of a subset of objects, which could lead to a high score on this task. Good recognition of the map containing the objects does not indicate that the subjects actually encoded the location of all objects, rather this indicates that the subjects can remember at least a partial set of objects.

C. Novelty detection:

Procedure. Another way to test how well the spatial location of objects was encoded can be done by changing the position of objects in the room and asking the subject to describe which changes occurred (Pigott and Milner 1993). After the recognition part of the object location task, we changed one object from its location, switched 2 other objects, and kept one at its original place. The experimenter asked subjects to look around for 10 s and see if they could detect any change in the location of objects. Subjects were asked not to answer while looking at the objects. If subjects tried to answer while they were looking at the objects, they were told to not answer now. Once outside the test room, the subjects were asked: "Was there a change in the position of objects? (If yes or no) Did the briefcase change position? the kettle? the stand? the flowerpot? Was there a switch in the position of two of the objects? (If yes) Which items were switched?" If subjects described their experiences the experimenter asked the subjects to "please answer the questions by yes or no" (except for the last question).

Results and Discussion

All subjects were able to notice that some changes were made to the layout of objects in the room with the exception of one subject from the right parahippocampal group who thought that none of the objects had moved to another location. In summary, the control group scored 87 % on our measure of novelty detection, the single patient with damage to the left parahippocampal cortex scored 25 %, the patient group with damage to the left hippocampus scored 75 %, the group of patients with damage to the right hippocampus scored 50 %, and the group of patients with damage to the right parahippocampal cortex had a 41 % score. Novelty detection brings out further the discrepancy between the effects of lesions to the right vs left hippocampus, in subjects' ability to remember the location of objects.

Experiment 4: Eight-arm radial-maze

Another spatial memory task typically used with rats is the 8-arm radial-maze (Olton and Papas 1979). The 8-arm radial-maze is made from a central platform to which rats can be restricted, for example with Plexiglas doors, with 8 alleys (arms) radiating from the central platform, 45° from each other. Some food reward is usually placed at the end of each alley. In the working memory version of the spatial task, the food wells are not replenished within a single trial, therefore rats rapidly learn to visit each of the 8 arms once only. The rats must use the relation between the cues in the room in order to solve the task (Whishaw *et al.* 1995). Occasionally, rats adopt a non-spatial strategy whereby they visit 8 consecutive arms until all the food is consumed. In these instances the experimenter can selectively block adjacent arms with the Plexiglas doors, thus preventing non-mnemonic strategies.

Methods

Subjects: Twenty-six normal subjects (mean age: 38 years old; standard error: 1.3) that were tested on the non-visual spatial exploration task (blindfolded condition), were also tested on the 8-arm radial-maze.

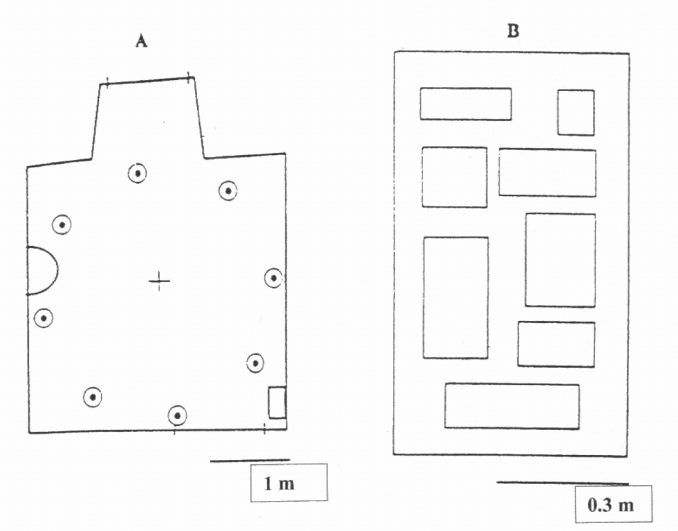

Fig. 5. *A: This figure shows a top view of the testing room with the location of the 8 stands used in the 8-arm radial maze. The cross indicates where subjects have to stand between choices. B: Example of the display of cards of various shapes used in the non-spatial working memory task. The shapes were drawn proportional to those used during testing.*

Procedure. A human 8-arm radial maze was created by placing 8 identical stands 1.4 m from a center point and at an equal distance between adjacent stands (Fig. 5A). On top of each stand was a cup containing one coin. The subjects were instructed to retrieve all the coins, within a limit of 16 choices. They had to select each stand only once and were able to keep the money acquired in the first 8 choices. Errors consisted of responses to previously chosen cups. The experimenter instructed subjects that they will start from the center of the room and retrieve each coin in a random order, and that they should visit each stand only once. Subjects were instructed to make either half or a quarter of a turn, either to the left or to the right before each choice. During this time the lights were turned off in order to reduce the use of non-spatial strategies.

In addition, the experimenter instructed the subject not to use strategies like choosing one stand after the next, or to select 4 stands in a row on one side, then the other 4 in a row from the other side. The experimenter warned the subjects that if they are using such a strategy, their results would not be used. The subject was instructed to solve the task in the following way: "You must choose one stand at random, and remember which stand you selected. Then you must choose one stand, again at random, from the remaining unvisited stands. Again you should choose one stand at random and remember which, until all stands have been visited at least once."

Memory was measured in 2 ways: 1) the number of errors made in the first 8 choices, and 2) the total number of errors made up to 16 choices. The 16 choices are given in order to allow the subject to find the missing coins after the first 8 selections.

Results and Discussion

Subjects made on average 0.73 mistakes (standard error: 0.13) in the first 8 choices. They performed very well in this task, selecting adjacent stands as frequently as they chose stands opposite from each other. When allowed to continue until they had visited all the stands, subjects made on average 1.73 errors (standard error: 0.41).

Normal human subjects performed quite well on the task with less than one error made in the first 8 trials, and less than 2 in total, a performance similar to that obtained in rats. This task is highly sensitive to bilateral lesions of the hippocampus in rats. Patients with unilateral lesions that included the hippocampus or the parahippocampal cortex (right or left) were not impaired on this task. The fact that patients with unilateral lesions, have an intact hippocampus, could have contributed to differences obtained between rats and humans. The scale of the space may be an important contributing factor as well. The ratio between the size of the subject over the size of the room is typically much smaller in rats than it was in our experiment, which could have contributed to differences in the results obtained between the two species (Bohbot *et al.* 1998).

Experiment 5: Non-spatial working memory task (NSWM)

The goal of this experiment was to devise a non-spatial memory task that could easily be compared with the 8-arm radial-maze, similar to an object non-matched to sample task.

Methods

Subjects. Twenty-six normal subjects (mean age: 38 years old; standard error: 1.3) that were tested on the non-visual spatial exploration task (blindfolded condition) and the 8-arm radial-maze, were also tested on the non-spatial working memory task.

Procedure. Subjects had to select each of 8 white cards, made from thin cardboard folded in 2 or 3, thus forming various shapes. The cards were shuffled between choices, while the subjects were facing the opposite direction. The length of the cards varied from 8 cm to 28 cm and were proportional to those shown in Fig. 5B. The cards differed only in shape and each had a number between 1 and 8 inscribed inside. The subject had to select each card only once (based on the shape) and was allowed up to 16 choices. Each card had a monetary value, and subjects were rewarded by keeping the money acquired in the first 8 choices. The experimenter instructed subjects to try not to use any strategies, but rather to just remember all the previously selected cards.

As with the 8-arm radial-maze, there were 2 measures of memory in this task: 1) the number of errors made in the first 8 choices, and 2) the total number of errors made in the first 16 choices.

Results and Discussion

Subjects averaged 0.65 mistakes (standard error: 0.1) on the first 8 choices and 2.92 errors (standard error: 0.65) when allowed to search until all cards were chosen

at least once. The role of the hippocampus in object recognition is still in debate. Research with monkeys suggested that bilateral lesions to the hippocampi yield deficits in object recognition, when tested after a delay with the Delayed Non-Match to Sample (DNMS) task (Mishkin 1978, Zola *et al.* 2000). In the DNMS task, a sample object is presented to the monkey. After a specific delay, the sample object is presented together with a new object. In order to obtain a reward, monkeys need to remember which of the two objects was previously presented, and they have to select the new one. Murray and Mishkin (1998) on the other hand, found no deficit in the DNMS task in monkeys with bilateral ibotenate lesions to the hippocampus, after delays of up to 40 min, but instead found that a lesion that included the perirhinal cortex, which was inadvertently damaged in the earlier studies, led to severe impairments on the DNMS task (Murray and Mishkin 1998). This issue has yet to be resolved in monkeys. In humans, patients with lesions to the right hippocampus or parahippocampal cortex were not impaired on the non-spatial working memory task (Bohbot *et al.* 1998). Methodological differences between the DNMS and NSWM include: 1- Testing procedure: in the DNMS, in the learning phase, one object is shown at one time. In the NSWM all of the items are presented simultaneously. 2- The study material was different in the two studies. Colored objects are typically used in the DNMS, whereas the NSWM uses white cards. 3- Memory impairments in monkeys tested on the DNMS are found after delays of 15 sec and above, varying with the type of lesion (Zola *et al.* 2000), whereas human subjects tested on the NSWM were allowed to choose amongst the various items after a delay of about 10 s Other differences include the fact that in monkeys, lesions to the hippocampus are typically bilateral, whereas patients tested typically have unilateral lesions to the medial temporal lobe.

Subjects' performance is similar in terms of the mean number of errors made on the first 8 choices of the visual object memory task and the spatial memory task (8-arm radial maze). However when subjects made mistakes and were allowed to search until all the cards were retrieved, the performance dropped considerably (from 0.5 to 3 errors), suggesting that this non-spatial task is more difficult than the spatial version. Despite the increased difficulty, patients with lesions to the right hippocampus or parahippocampal cortex were not impaired on the NSWM task (Bohbot *et al.* 1998).

General Discussion

We have assessed tasks that are similar for both rats and humans which can bring new insights for the study of learning and memory as well as facilitate comparisons between these species, specifically the Morris water task and 8-arm radial-maze. A non-visual spatial memory task, which requires path integration, provided a useful platform for comparison with navigation planning when visual input is provided. It showed that the majority of blindfolded subjects tested chose to first walk around the four walls of the room before venturing inwards in order to find the objects, suggesting that they first build a cognitive representation of the room layout before attempting to learn the location of objects. The cognitive representation of the location of objects in the environment can be created using idiothetic information in the absence of visual cues. A non-spatial equivalent to the 8-arm radial maze was found to be slightly more difficult but generally comparable in the first 8 choices of the radial maze. Finally, in order to enrich our test battery, we adapted a task requiring learning of the combination of locations and objects because it was found to be sensitive to lesions of the right medial temporal lobe in humans. In the current version, subjects enter a room and encode the spatial relationships among the elements of that room and a recognition test and novelty detection tests were developed to further enrich the test battery.

In both the water task and the radial-maze analogue, the main advantage over most computerized working memory tasks, is the real life testing environment, examining not only visual abstractions but real movement, monitored by idiothetic, proprioceptive, kinesthetic and vestibular information. These tasks allow subjects to learn while moving about and interacting with their environment. This also allows administering similar tests to humans and rats, contrary to the computerized version which may not provide an analogous situation. The Object Location task was found to be sensitive to lesions of the right hippocampus (Bohbot *et al.* 1998). The Invisible Sensor Task (the water maze analogue) was found to be sensitive to lesions of the right parahippocampal cortex (Bohbot *et al.* 1998). The radial maze and the Non Spatial Working Memory task may depend on an intact cholinergic system (Bohbot *et al.* 1997). So far the Non Visual Spatial Memory task (which requires path integration) was not sensitive to lesions of the right or left hippocampus or parahippocampal cortex.

Human radial mazes have typically been adapted to a small scale or a large scale (Foreman *et al.* 1984, Aadland *et al.* 1985, Glassman *et al.* 1994, Overman *et al.* 1996). The large radial mazes (about 15 m. diameter) have been tested on subjects outdoors (Glassman *et al.* 1994, Mangan *et al.* 1994) thus keeping the subject/maze ratio similar to that used in rats. Keeping the subject/maze ratio is important but unfortunately it does not lend itself well to clinical settings where space is often limited. The large scale mazes are important as they discourage the use of proximal cues (cues that are close to the choices) or intra-maze cues (cues inside the testing apparatus) and encourage the use of distal cues (cues that are far from the choices). Learning the relationship between cues is necessary for the formation of a cognitive map, a key function of the hippocampus (O'Keefe and Nadel 1978), whereas learning an association between a cue and a response may not rely on the hippocampus (O'Keefe and Nadel 1978). The small scale radial mazes (0.5 m.) were used to facilitate testing and are also used with the premise that relationships between the different cues/choices will be learned, that is, learning occurs beyond a simple cue-choice association.

In the small radial mazes, patients often sit at a table (Abrahams *et al.* 1997, O'Connor and Glassman 1993) or in front of a computer (Morris *et al.* 1996, Owen *et al.* 1997) while performing the task. Unless the patient's perspective is explicitly manipulated while performing a task (Abrahams *et al.* 1997), egocentric strategies may be available, i.e. the task is solved by using the spatial information relative to the observer. O'Keefe and Nadel (1978) proposed that the hippocampus processes allocentric spatial memory in the formation of the cognitive map, i.e. the space independent of the subject's position. Allowing subjects to navigate in the environment may help diminish the use of egocentric strategies. Here we set up an 8-arm radial maze (3 m diameter), by using stands, and adapting it to a small room in order to facilitate clinical neuropsychological testing, while encouraging the use of allocentric strategies, by having the subjects move around in the maze during the tasks. Additional measures, such as asking subjects to rotate in the dark, between choices, were taken in order to discourage the use of egocentric strategies.

In the case of the Morris water task, Overman *et al.* (1996) very nicely reproduced it by testing children in a pool filled with plastic chips, thus hiding a treasure box that they had to locate. Testing patients in this situation may be difficult. Another testing method involved covering a circular area with 20 magnetic position detectors, together with light points, several of which were chosen as correct locations to be remembered (Lehnung *et al.* 1998). In our task, subjects had to locate the position of a sensor, placed under the carpet, as quickly as possible by searching through a room. As in the standard Morris water task, the sensor was placed away from the walls, and the surface of the floor was uniform, thus subjects had to use the relationship between a minimum of 2 points or cues in the room, in order to remember the location of the sensor, encouraging the use of an allocentric strategy. As required in rats, this task can not be solved by using a single cue, but requires the use of multiple cues, or by learning the relationship between one cue and another point in space.

Search strategies showed similarities and differences between rats and humans. The search behavior to a new target location, in rats trained on the reference memory version of the water task, and in control rats pretrained on the working memory version of the water task, is similar in such a way that both groups learn to locate the new platform location by swimming at a distance from the wall. Although the strategy employed by rats is different from the systematic strategy employed by humans searching for the target (zigzag or spiral), both species may adopt the strategy most suited to their task. On the other hand, control rats trained to go to one target location of the reference memory version of the water task do not engage in a systematic search when the location of the target is moved, as humans do when first searching for the target. The two species rely on different strategies for searching for the goal and these strategies rely on different brain areas. Humans benefit from a neocortical proliferation, especially marked at the level of the temporal cortex and the frontal cortex, which has been implicated in planning (Shallice 1982). Interestingly, the IST and the NVSE showed that the search strategies tend to vary with the demands of the task, an indication that planning was involved when humans were tested. It is therefore possible that human subjects use more of their frontal or other neocortical areas than rats do, in order to plan a search.

Furthermore, patients with lesions to the right hippocampus or parahippocampal cortex were able to learn the IST, but only the patients with lesions to the right parahippocampal cortex had a deficit in memory after a 30 min delay. Thus, a structure other that the right hippocampus and parahippocampal cortex were involved in learning the IST. This is not the case in rats, since rats with bilateral hippocampal lesions have a severe learning

deficit in the Morris water task. Bilateral lesions to the hippocampus in humans also yield global amnesia, but it has been marked with intact short-term memory (Scoville and Milner 1957), which also must require regions other than the anterior portion of the hippocampus and surrounding structures that are damaged in the case of H.M. Rats rely on their hippocampus for short-term (or working memory) tested on the water task (Bohbot *et al.* 1996).

While rats are devastated at the working memory version of the 8-arm radial maze, humans with lesions to the right hippocampus or right parahippocampal cortex performed normally. Again, this may be an indication that different strategies may be available to humans and that rats rely more on their hippocampus than humans do. Discrepant results between the two species could also be explained by the fact that the patients had unilateral lesions to the hippocampus and/or parahippocampal cortex, whereas rats are typically given bilateral lesions. The non-spatial working memory task was not sensitive to lesions of the right hippocampus or right parahippocampal cortex in humans either. This can also be interpreted as an indication that an area of the brain, other than the right hippocampus or parahippocampal cortex is involved in this task. These results do not eliminate the possibility that the hippocampus or parahippocampal cortex are involved in working memory or perhaps are part of a working memory circuit while these structures remain intact.

The only task that yielded consistent deficits in patients with lesions to the right hippocampus, was the Object Location task, with a marked deficit in the novelty detection part of the task. In the Object Location task, subjects have to learn the positions of several objects simultaneously, together with information regarding the particular objects that occupy the positions. In the novelty detection task, not only did the subjects have to retain the location of object information, but also, they had to notice switches between the position of two objects, as well as a displacement of one object. As previously discussed (Bohbot *et al.* 1998), detailed object recognition information, processed at the level of the perirhinal cortex (Murray 1996) and spatial information processed at the level of the parahippocampal cortex (Bohbot *et al.* 1998) converge in the hippocampus (via the entorhinal cortex). Rats trained to learn a spatial location, such as the location of a target platform in the water task, use the relationship between that location and the room cues; learning that requires an intact hippocampus. Although the Object Location task is quite different from the water task used in rats, both measure the subjects' ability to encode the spatial relationship between room cues (in this case, objects) and both rely on the hippocampus.

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Apendix

[1] I (V.B.) first met Dr. Bureš in September 1993, after I landed in Prague for what was supposed to be a one year collaboration. We worked together, off and on, for nearly 8 years now. Not only has our collaboration been fruitful, but most important, his lessons were invaluable. For instance, while carrying out a "high risk" experiment, Dr. Bureš insisted that we carry out in parallel a "low risk" experiment, which would increase the probability of having publishable results. He was right. He once said to me "the data should be analyzed, before it gets collected". What he meant, of course, was that we should strive for a clear experimental design that would yield publishable results no matter what the outcome. Most important perhaps, Dr. Bureš taught me to ignore the scientific trends and create my own scientific path. But Dr. Bureš isn't all about publications. He really cares about people's success in their career, their well-being, their health, their integration into the laboratory, their friends, and even their romance! Yes, Dr. Bureš has been known to match a few couples… Finally, when he realized how severe my allergies to rats were, he was the one who facilitated my transition into research with humans. For this, I am really grateful because I no longer have chronic fatigue, and my asthma, which arose one year after working with rats, significantly decreased with time away from work with rats. Dear Dr. Bureš, I am grateful for having been given the opportunity to work with you. I can only hope that you enjoyed our collaboration, especially adapting rat spatial memory tasks to humans.

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