

## PAPER

# Loss of spatial learning in a patient with topographical disorientation in new environments

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The case is described of a patient who, following cerebral hypoxia, developed severe difficulty in orienting himself in new environments in the context of a mild global amnesic syndrome. Some episodes he related suggested that his main difficulty was remembering the spatial/directional value of landmarks he recognised. A neuroradiological examination documented severe bilateral atrophy of the hippocampi associated with atrophic changes in the cerebral hemispheres, most marked in the dorsal regions. Neuropsychological and experimental evaluation showed a severe deficit of spatial learning with substantially preserved ability to learn verbal and visual-object information. He was also virtually unable to learn a route in a maze task based exclusively on spatial data, but the availability of visual cues substantially improved his learning. Finally, he performed within normal limits on various tests investigating knowledge acquired premorbidly regarding famous buildings, routes in the town he had been living in since childhood, and geography. Topographical disorientation may be subtended by a specific difficulty in storing the spatial/directional value of visual landmarks in novel environments. The hippocampus appears to be involved in the acquisition of new topographical spatial knowledge.

Topographical disorientation is a syndrome characterised by impaired ability to navigate in the real world. Cases of topographical disorientation are typically described in terms of perceptual or mnemonic difficulties.<sup>1–5</sup> In the perceptual type (topographical agnosia), visual processing of places, including landmarks, and space exploration are impaired, thus resulting in a deficient internal representation of the environment. In the mnemonic type (topographical amnesia), visual and spatial characteristics of the environment are normally processed but the patients fail to recall topographical information for the purpose of orientation.

Aguirre and D'Esposito<sup>6</sup> recently proposed a taxonomy of cases of topographical disorientation by distinguishing four categories of the syndrome.

The first, described as *landmark agnosia*, is characterised by the inability to use salient environmental features for orientation.<sup>3,7,8</sup> Most commonly, this disorder is a consequence of damage to the part of the neural system specialised for landmark representation; this is located in the right ventral occipito-temporal cortex (fusiform, lingual, and parahippocampal gyri<sup>9–11</sup>).

The second, *egocentric disorientation* describes people who are unable to represent the location of objects with respect to self even though they are able to identify prominent environmental objects.<sup>12,13</sup> Lesions of the right posterior parietal cortex are generally responsible for this deficit.

Third, *allocentric spatial representation* can also be damaged selectively, so that people affected by *heading disorientation* are unable to remember the direction to go with respect to the external environment. The few cases so far described (perhaps the patients described by Takahashi *et al*<sup>14</sup> and Cammalleri *et al*<sup>15</sup>) had lesions in the retrosplenial cortex (posterior cingulate).

The fourth category of topographical disorientation described by Aguirre and D'Esposito is *anterograde disorientation*. People who have preserved way-finding in environments known before the onset of their impairment, but who are unable to create new representations of surrounding information, are classified in this category.<sup>16–21</sup> Interestingly, in the patients reported so far with clinical manifestations of anterograde disorientation the prevalent impairment is an inability to learn the visual aspect of new environments. The

location of cerebral damage in these individuals is similar to (but does not overlap) that of patients with landmark agnosia. Aguirre and D'Esposito<sup>6</sup> underlined the fact that although the lingual and fusiform gyri were most regularly damaged in the reported cases of landmark agnosia,<sup>22,23</sup> the right parahippocampus was most consistently lesioned in the patients with anterograde topographical disorientation.<sup>17,19</sup>

The specific role of distinct cortical areas in the ventromesial surfaces of occipital and temporal lobes in topographical orientation is an issue of debate. In particular, although convergent evidence from neuropsychological and functional neuroimaging investigation in healthy humans supports the involvement of the fusiform, lingual, and parahippocampal gyri,<sup>9–11</sup> the role of the hippocampus in topographical learning is controversial. The identification of "place cells" (neurons that fire preferentially for a specific position in the environment) in the hippocampus of rodents<sup>24</sup> and of "spatial view cells" (tuned to respond to a view of space) in the hippocampus of monkeys,<sup>25</sup> as well as the impairment of place learning following hippocampal lesions in the rat,<sup>26,27</sup> support the critical importance of the hippocampal function for topographical learning in animals. However, there is little evidence of a comparable role of the hippocampus in humans. The unilateral removal of the hippocampus for the relief of pharmacologically untreatable seizures does not cause relevant way-finding deficits.<sup>28,29</sup> On the other hand, the memory impairment in patients with bilateral damage to the hippocampal formation also involves topographical representations, but it lacks selectivity, involving virtually all kinds of information.<sup>30</sup> Functional neuroimaging studies in healthy humans have also yielded divergent results on the involvement of the hippocampus in topographical orientation. Some studies, using encoding or retrieval navigational tasks, have reported activation in the hippocampus proper,<sup>10,31–34</sup> while others have not.<sup>9,11,35</sup>

In this paper, we report the case of a man who, as a result of cerebral hypoxia, showed a particularly severe anterograde topographical disorientation in the context of a mild global amnesic syndrome. Considering that his difficulties are confined to the learning of spatial relations between visually processed objects, our findings suggest that in this patient topographical disorientation is subtended by a specific

difficulty in storing the spatial/directional value of visual landmarks in novel environments. Moreover, as his neuroimaging investigations showed severe bilateral hippocampal atrophy, the case of this patient is consistent with the hypothesis of involvement of the hippocampus in the acquisition of new topographical spatial knowledge.

### CASE REPORT

The patient was a 41 year old right handed man, employed as a sailboat skipper, with 13 years of formal education when, in January 1998, he was admitted to a hospital in Rome in a comatose state as a result of a heroin overdose. The patient was referred to our laboratory in March 1998. At that time, he complained of moderate difficulty in remembering day to day events and information so that he frequently referred to his notes (mainly appointments and things to do) in a pocket diary. However, his main complaint was a severe impairment of finding his way in unfamiliar environments. At no time during the period of our observation (from March 1998 to May 1999) did the patient show any substantial modification of his difficulty in navigating in places that were unfamiliar to him before the accident. Some episodes he reported suggest that his prevalent difficulty was remembering the spatial/directional value of landmarks he effectively recognised. For example, once when he was leaving a friend's house, he could not tell which direction to go to find his car. First he went right and walked along the street but he was unable to remember anything. So he came back and suddenly recognised the buildings and landscape around him. Continuing to walk in the same direction, he recognised more buildings and places. Finally, he recognised a laundry and, close to it, his car. These orientation problems seemed to be limited to unfamiliar environments. In fact, he said he was well oriented in places he knew well and had no problem in moving through areas of town which were familiar to him before the onset of the disease.

The patient gave informed consent to his participation in this study, and the ethics committee of our institute approved the protocol of the experiment.

### Neuroradiological examination

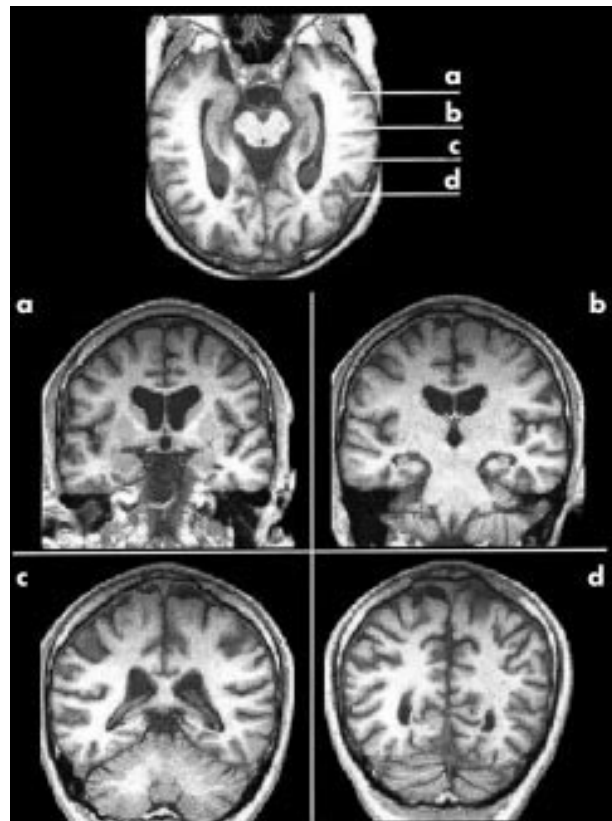
Magnetic resonance imaging (MRI) of the patient's brain, done in July 1998, showed very marked atrophy of the hippocampi bilaterally. There was also moderate cortical atrophy particularly involving the frontal lobe, the parietal lobe, and the dorsal aspect of the temporal lobe. The posterior and ventral areas of the brain appeared less involved. No focal brain lesion was detected (fig 1).

### Neuropsychological assessment

The patient was assessed with a variety of standard neuropsychological tests. The results are reported in table 1. The patient's scores were normal on tests assessing general intelligence, executive function, language, and visual-spatial perceptual abilities.

### Memory

As shown in table 2, the patient scored in the normal range on tests of verbal, visual, and spatial short term memory and on a visual imagery task (the Brook's matrix task) which requires the subject to listen to a sequence of sentences describing the placing of consecutive numbers in consecutive squares of a  $4 \times 4$  square matrix and to form a mental image of the matrix. This test has been used extensively for evaluating visual-spatial imagery and spatial working memory in behavioral experiments with normal subjects. In the long term memory domain, his deficit was specific for spatial information. He performed poorly on episodic memory tests for spatial position or visual-perceptual material involving spatial relations (Rey's figure). Conversely, he scored normally on



**Figure 1** Axial and coronal slices of the patient's brain on magnetic resonance imaging.

memory tests for verbal material or visual stimuli in which spatial relations between constitutive elements were not critical (faces).

The results of the neuropsychological examination confirmed the clinical impression that this patient's topographical disorientation was caused by a memory deficit rather than an agnosic disorder. Indeed, he had normal visual-perceptual and visual-spatial working memory abilities and he was normally able to construct and manipulate new spatial layouts based on mental imagery. Moreover, the fact that he performed normally in the visual domain on memory tests involving visual-perceptual material but poorly on tests involving visual-spatial material suggests that his topographical disorientation was the result of an impairment of spatial learning. However, data supporting this latter claim are not compelling. His normal performance on the face recognition test could reflect sparing of the neural circuitry dedicated to processing physiognomic material, known to be distinct from that involved in memory for places.<sup>48, 49</sup> Moreover, in Rey's figure reproduction, in which our patient obtained abnormal scores, memory for both visual details and spatial relations between constitutive elements is involved, so his deficient memory for visual-perceptual information could not be excluded on the basis of these data.

### EXPERIMENTAL INVESTIGATION

The first goal of the experimental investigation was to confirm the patient's pattern of long term memory impairment disclosed by the neuropsychological analysis (that is, his deficit for spatial material being disproportionately more severe than that for verbal and visual-object material), by directly contrasting performance on memory tests for verbal, visual-object, and visual-spatial information. Second, we analysed the qualitative characteristics of the patient's route learning deficit using a theoretical model that distinguishes memory

**Table 1** Patient's performance on the neuropsychological battery of tests; references are also reported from which normative data, adjusted scores, and centile scores were derived

Test	Patient	Maximum possible score
<i>General intelligence</i>		
Wechsler adult intelligence scale <sup>36</sup>		
Verbal IQ	121	
Performance IQ	103	
Full scale IQ	114	
Raven's coloured progressive matrices <sup>37</sup>	36 (=100%ile)	36
<i>Language</i>		
Phrase construction <sup>38</sup>	25 (=100%ile)	25
Phonological word fluency <sup>38</sup>	36.5 (>50%ile)	
<i>Executive functions</i>		
Modified card sorting test <sup>39</sup>		
Criteria achieved	6 (=100%ile)	6
Perseverative errors	2.3 (>50%ile)	0
Non-perseverative errors	7.3 (>50%ile)	0
<i>Visual-perceptual abilities</i>		
Visual object and space perception battery <sup>40</sup>		
Object perception		
Screening test	20 (=100%ile)	20
Incomplete letters	20 (=100%ile)	20
Silhouettes	22 (>40%ile)	30
Object decision	20 (=100%ile)	20
Progressive silhouettes	12 (>80%ile)	20
Space perception		
Dot counting	10 (=100%ile)	10
Position discrimination	20 (=100%ile)	20
Number locations	10 (=100%ile)	10
Cube analysis	9 (>30%ile)	10
Facial recognition <sup>41</sup>	48 (>70%ile)	54
Street's completion test <sup>42</sup>	9 (>50%ile)	14
Judgement of line orientation <sup>43</sup>	29 (>80%ile)	30
Copying drawings <sup>38</sup>		
Free copy	12 (=100%ile)	12
With landmarks	70 (=100%ile)	70

IQ, intelligence quotient; %ile, centile.

for the visual aspects of landmarks from learning spatial information about the landmarks.<sup>12</sup> Finally, we experimentally evaluated the patient's self report that his topographical disorientation was limited to learning routes in previously unfamiliar environments with substantial sparing of topographical knowledge acquired premorbidly.

On all experimental tasks, the patient's performance was compared with that of five normal male controls matched for education and age. In addition, two pathological controls were also examined to clarify whether the described pattern of memory impairment was specific to this patient or was a common sequel of cerebral damage; the first of these was a 32 year old amnesic patient with bilateral hippocampal atrophy following hypoxia; the other was a 75 year old patient with Alzheimer's disease and diffuse cortical atrophy.

### Experiment 1: comparison of verbal, visual, and spatial learning

To verify the prevalent impairment of long term spatial memory, three tests were administered that directly contrasted the learning of two different types of material: verbal *v* visual-object learning, verbal *v* visual-spatial learning, and visual-object *v* visual-spatial learning. To avoid problems of interpretation related to different absolute levels of performance in the patient and the age matched controls, each subject had first to achieve a minimum of 80% accuracy in learning one kind of material (for example, a word recognition test) and was then evaluated on the other learning test (for example, recognition of the spatial location of the word on a sheet of paper). On all three tests, if the subject did not reach the

learning criterion (80% accuracy) on the first of the two tests on the first attempt, then study and testing phases were repeated until that criterion was achieved.

### Tests

The memoranda of the *verbal-visual recognition test* are 20 coloured pictures of objects. In the study phase, each picture is presented to the patient for three seconds. When the learning criterion is achieved on the multiple choice verbal recognition test (discriminating the name of a previously seen object from two semantically related distractors), the visual-object test is administered. In each of 20 trials, three pictures depicting the same target object coloured with different hues of the same principal colour are presented, and the subject is requested to indicate the picture with the same colour as the one presented in the study phase.

The memoranda of the *verbal-spatial recognition test* are 20 nouns of concrete objects. During each of the 20 trials of the study phase, a word is presented in one of three different positions (left, middle, or right) on a horizontally placed sheet of A4 paper. When the learning criterion is reached on the verbal recognition test, the spatial test is administered. In each of the 20 trials, the patient is requested to indicate in which of the three positions (indicated by a cross on a sheet of paper) the word was placed during the study phase.

The memoranda of the *visual-spatial recognition test* are 20 black and white pictures of objects. During each study phase trial, a picture is presented in one of three different positions (left, middle, right) on a horizontally placed sheet of A4 paper.

**Table 2** Patient's performance on the tests of the memory battery; references are also reported from which normative data, adjusted scores, and centile scores were derived

Test	Patient	Maximum score possible
Wechsler memory scale quotient <sup>44</sup>	103	
<i>Verbal short term memory</i>		
Digit span forward <sup>45</sup>	7 (>50%ile)	9
<i>Visual-spatial short term memory</i>		
Corsi block test forward <sup>45</sup>	6 (>50%ile)	9
Immediate visual memory <sup>38</sup>	22 (=100%ile)	22
<i>Visual imagery</i>		
Brooks' matrix <sup>46</sup>		
Longest correctly reproduced sequences	8 (=100%ile)	8
Errors	13 (>50%ile)	0
<i>Verbal long term memory</i>		
Rey's 15 words learning task <sup>38</sup>		
Immediate recall	38.8 (>25%ile)	75
15 min delayed recall	6.1 (>10%ile)	15
Short story recall <sup>47</sup>		
Immediate recall	4.3 (>10%ile)	8
20 min delayed recall	3.5 (>5%ile)	8
<i>Visual-object long term memory</i>		
Recognition memory of faces <sup>48</sup>	26 (>50%ile)	30
<i>Visuo-spatial long term memory</i>		
Rey's figure A <sup>47</sup>		
Immediate reproduction	5.5 (<5%ile)	36
20 min delayed reproduction	5.5 (<5%ile)	36
Supraspan spatial learning <sup>42</sup>	0 (<5%ile)	30.78*

\*The performance score on the Supraspan spatial learning test is expressed as the logarithmic transformation of the probability of casually reproducing in the correct order the sequence of blocks (or only chunks of it) proposed by the examiner (see Spinnler and Tognoni,<sup>42</sup> page 35 for details).  
%ile, centile.

When the learning criterion is reached on the visual recognition test (by choosing the perspective of the object in the study phase out of three different perspectives of the same object), the spatial memory test is given. On this test the patient is requested to indicate in which of the three positions (indicated by a cross on a sheet of paper) the picture was placed during the study phase.

### Results and comment

The performance scores of the patient and the controls on the tests of experiment 1 are given in table 3. Confirming his overall difficulty in learning new information, the patient needed three and four presentations of the stimulus material to reach the learning criterion on the verbal-spatial and visual-spatial recognition tests, respectively. However, these data also confirm the impression that his memory deficit for spatial information was disproportionately more severe than his memory deficit for verbal and visual data. On the verbal-visual test, after reaching the learning criterion on the verbal test, he also performed at the same level as normal controls on the visual test. In contrast, on the verbal-spatial and visual-spatial recognition tests, even after reaching the learning criterion on the verbal and visual recognition tests, he still performed at chance level on the spatial tests. These findings indicate also that when the patient correctly recognised the names or visual features of objects, he was still severely impaired in remembering their locations in space. Both the pathological controls differed from our patient in that they had a more homogeneous pattern of memory impairment. They obtained scores below the normal limits not only on the verbal-spatial and visual-spatial tests but also on the verbal-visual test.

### Experiment 2: learning of visual, topological, metrical, and vectorial information

It is commonly agreed that route learning involves the acquisition of two main pieces of information about the environment: the identification and representation of salient environmental features (visual landmarks) and the structuring of a sequential representation of the spatial relations among landmarks, including topological, metrical, and vectorial characteristics. In this experiment, we contrasted the patient's ability to recognise visual objects and to memorise spatial relations between objects by evaluating his memory for topological, metrical, and vectorial information separately. As in experiment 1, in order to control the patient's more general memory impairment, he was required to reach the learning criterion for the identity stimuli (80% accuracy) before the administration of visual or spatial tests.

#### Tests

##### *Recognition memory for visual objects*

The memoranda consist of 18 coloured photographs of buildings, cars, monuments, and home tools. During the study phase, the pictures are presented to the patient for three seconds each. When the learning criterion is reached on the verbal test (a multiple choice recognition test discriminating the object seen previously from two semantically related distractors), the visual test is administered. Three photographs, each reporting an exemplar of the same principal object (for example, three cars), are visually presented and the patient is required to indicate the one previously seen in the study phase.

##### *Recognition memory for spatial relations*

The aim of the *reciprocal position learning test* is to assess memory for object location specified by topological information. In this



**Table 3** Performance scores of the patient and of the healthy and pathological controls on tests in experiment 1; the number of trials needed to reach the learning criterion of 80% accuracy in the first testing phase of each test is given in parentheses

	Patient	Normal controls (range)	Pathological controls	
			Patient with hippocampal atrophy	Patient with cortical atrophy
<i>Verbal-visual recognition test</i>				
Verbal	19/20 (1)	18–20/20 (1)	18/20 (1)	18/20 (3)
Visual	13/20	12–16/20	9/20*	8/20*
<i>Verbal-spatial recognition test</i>				
Verbal	18/20 (3)	17–20/20 (1)	18/20 (1)	18/20 (4)
Spatial	3/20*	10–16/20	9/20*	2/20*
<i>Visual-spatial recognition test</i>				
Visual	17/20 (4)	17–20/20 (1)	18/20 (1)	18/20 (5)
Spatial	5/20*	11–17/20	5/20*	4/20*

\*Performance below 2 SD from the mean of normal controls.

test, the memoranda are 40 black and white drawings of concrete objects taken from Snodgrass and Vanderwart's set.<sup>50</sup> During each of the 20 trials of the study phase, a pair of semantically unrelated stimuli is presented visually for three seconds; the two items of the pair are reciprocally located on the page in four standard arrangements (right-left, left-right, top-bottom, bottom-top). When the learning criterion is reached on the visual test (discriminating the object that was paired with the stimulus target during the study phase from three semantically related alternatives), the spatial test is given. On each trial the subject is required to indicate which reciprocal position the two objects of a pair were located in during the study phase.

The *proximity judgement test* evaluates the ability to learn metrical information regarding the spatial relations between two objects. The memoranda are 100 black and white pictures from Snodgrass and Vanderwart's set.<sup>50</sup> During each of 20 trials in the study phase, the drawings of three semantically unrelated objects are presented for three seconds. The reciprocal position of the pictures on the page is such that two objects of the triplet are closer to each other than to the third one. When the learning criterion is reached on the visual test (given two objects, the subject is requested to indicate which,

among three semantically related alternatives, was the third object in the triplet), the spatial test is given. On each trial, a previously studied triplet is presented and the patient is asked which objects were closer together in the study phase.

The *vector judgement test* was administered to investigate spatial memory based on vector information. During the study phase, 20 black and white drawings of concrete objects randomly located on a sheet of A3 paper are simultaneously presented to the patient for 60 seconds. When the learning criterion is reached, the spatial test is administered. On each of the 20 trials, the patient is asked to indicate verbally in which direction of eight alternatives (north, northeast, east, southeast, and so on) he has to go to move from one object to another (for example, "in which direction do you go from the cow to the watering can?").

### Results and comment

The performance scores on the tests in experiment 2 for the patient and the controls are shown in table 4. In these tests also, the pathological controls performed below the normal controls in all cases. With the exception of the proximity judgement test (in which two presentations of stimulus material were needed), the patient reached the 80% accuracy

**Table 4** Performance scores of the patient and of the healthy and pathological controls on tests in experiment 2; the number of trials needed to reach the learning criterion of 80% accuracy in the first testing phase of each test is given in parentheses

	Patient	Normal controls (range)	Pathological controls	
			Patient with hippocampal atrophy	Patient with cortical atrophy
<i>Recognition memory for visual objects</i>				
Verbal	16/18 (1)	16–18/18 (1)	16/18 (2)	16/18 (4)
Visual	18/18	16–18/18	15/18*	10/18*
<i>Spatial relationship learning</i>				
Reciprocal position learning test				
Verbal	19/20 (1)	19–20/20 (1)	18/20 (1)	18/20 (4)
Spatial	4/20*	10–19/20	8/20*	3/20*
Proximity judgement test				
Verbal	18/20 (2)	18–20/20 (1)	18/20 (2)	18/20 (6)
Spatial	10/20*	14–18/20	11/20*	9/20*
Vector judgements test				
Verbal	20/20 (1)	20/20 (1)	18/20 (2)	18/20 (3)
Spatial	3/20*	5–9/20	4/20*	3/20*

\*Performance below 2 SDs from the mean of normal controls.

**Table 5** Performance scores of the patient and of the healthy and pathological controls on the maze learning task

	Patient		Normal controls (range)		Pathological controls			
					Patient with hippocampal atrophy		Patient with cortical atrophy	
	Trial	15 min delayed trial	Trial	15 min delayed trial	Trial	15 min delayed trial	Trial	15 min delayed trial
Without landmarks condition	43*	6/12	10–17	12/12	21*	0/12	32*	3/12
Few landmarks condition	16	4/12	12–17	12/12	19*	5/12	22*	0/12
Full landmarks condition	12	10/12	11–15	12/12	25*	2/12	23*	0/12

\*Task interrupted because the patient appeared to be excessively frustrated by repeated failures. On the 43th trial, he correctly reproduced the first seven blocks of the route.

learning criterion for stimulus identity on all other tests after only one study phase. This showed the substantial sparing of his memory when he could rely on a verbal or a visual strategy of stimulus learning. Another indication of the substantial sparing of his visual memory is that he scored within normal limits on the test for recognition memory for visual objects. In contrast, he performed at chance level or clearly below normal on all other tests investigating memory for spatial relations between objects (reciprocal position learning, proximity judgement, and vector judgement tests), suggesting that he was unable to permanently acquire any kind of information referring to space. The pathological controls did not show any dissociation between memory tests based on stimulus material. They performed poorly on all tests, regardless of the visual or spatial nature of the memoranda.

### Experiment 3: maze learning

The behavioural, neuropsychological, and experimental evidence so far reported strongly suggests that the patient has lost the ability to permanently acquire memory for the spatial components of topographical environments, but that visual information relative to significant landmarks is largely preserved. If this is true, then on a route learning task he ought to benefit from the availability of visual landmarks which should at least partially compensate for the loss of spatial information. In order to verify this hypothesis, the patient underwent a maze learning test, which contrasted a condition in which route learning was exclusively based on the encoding of spatial cues and one in which route learning was at least partially supported by the availability of visual cues.

### Test

The *maze learning task* involves discovering and learning a 12 block route through a  $7 \times 7$  array of blocks, similar in form to that described by De Renzi *et al.*<sup>2</sup> When an error is made, the patient is required to try again from the starting block. The task continues until the route is reproduced without error on three consecutive trials. To assess long term retention of the learned route, the patient is also asked to reproduce the route following a 15 minute delay after completion of the learning trials. Three different mazes are presented, differing in the number of visual cues (drawings from Snodgrass and Vanderwart's set<sup>30</sup>) reported over the blocks. The first maze has no visual cues (*without landmarks condition*), the second has 23 visual cues randomly located on the matrix (*few landmarks condition*), and the third maze has visual cues located over each of the 49 blocks (*full landmark condition*).

### Results and comment

The performance of the patient and the controls on the maze learning task are summarised in table 5. When performance

was evaluated as the number of trials needed to reach the learning criterion, the patient's scores varied strikingly as a function of visual cue availability. He was not able to learn the route in the "without landmarks" condition even after 43 trials; in contrast, the number of trials he needed to learn both the "few landmarks" and the "full landmark" routes was in the range of the normal controls. These results confirmed the prediction of the present experiment—that is, that the presence of visual-perceptual information greatly improves our patient's ability to learn a route. However, his performance on the delayed test was below normal limits in all experimental conditions, probably because effective long term retention of a learnt route requires the integration of both visual and spatial information. Confirming the non-selective nature of the pathological controls' long term memory impairment, their scores were below the normal limits in all test conditions.

### Experiment 4: topographical retrograde memory

The aim of the following experiments was to investigate the patient's self report that his topographical troubles were limited to the learning of routes in previously unfamiliar environments. For this purpose, we explored his geographical knowledge and memory for visual landmarks and routes acquired before the onset of the amnesic syndrome.

### Tests

In each of the 15 trials of the *famous buildings recognition test*,<sup>48</sup> the pictures of one famous building (for example, the Eiffel Tower, the Santa Maria degli Angeli Church in Florence, and so on) and of three non-famous buildings are presented simultaneously. Subjects are required to provide three responses: (a) familiarity judgement (pointing to the famous building); (b) verbally reporting the town in which the building is located; and (c) its name.

The *geographical knowledge test* assesses memory for position over a map of 10 Italian cities and 10 European cities. In each trial, the subject is presented with a blank map and asked to indicate the exact location of a verbally presented town.

In the *route description test*,<sup>48</sup> the subject is given the names of two well known places in Rome and is requested to verbally describe the shortest route linking the two places, mentioning street names, change of direction, notable monuments (for more detailed description, see Carlesimo *et al.*<sup>48</sup>).

### Results and comment

These results are shown in table 6. The patient scored within the normal range on all tests, supporting his self report that the topographical deficit was confined to the acquisition of new information. The pathological control with selective hippocampal damage also performed in the normal range on all tests of experiment 4. The poor performance achieved by the

**Table 6** Performance scores of the patient and of the healthy and pathological controls on tests in experiment 4

	Patient	Normal controls (range)	Pathological controls	
			Patient with hippocampal atrophy	Patient with cortical atrophy
<i>Famous buildings recognition</i>				
Familiarity	15	13–15	14	8*
Town	15	13–15	15	3*
Name	14	12–15	15	5*
<i>Geographical knowledge</i>				
Italy	11.8 mm	9.1–18.5 mm	10.3 mm	26.7* mm
Europe	13.8 mm	5.9–18.1 mm	9.7 mm	36.3* mm
<i>Route verbal description</i>				
	12.2	3.0–13.6	9.8	2.3*

patient with Alzheimer's disease showed that his memory deficit also affected the retrograde domain.

## DISCUSSION

We have described the case of a patient suffering from a particularly severe deficit of topographical orientation in the context of a mild global amnesic syndrome. Qualitatively, his topographical disorientation was characterised by being restricted to the anterograde domain, and by being subtended by a particularly severe impairment in the learning of spatial information.

As described above, in the few reported cases of topographical disorientation confined to unknown environments in the absence of a persistent retrograde deficit, the memory disorder mainly regarded the visual-perceptual domain with a relative (or absolute) sparing of the memory for visual-spatial information.<sup>16–18, 20, 21</sup> In contrast to these cases, our patient's crucial neuropsychological defect was an impairment in learning the spatial relations between visually processed objects. Based on the patient's self report that after he visited new environment or ran through a new route, he was able to recognise the previously seen buildings and places, but that these visual landmarks did not seem to convey any directional information when he tried to run through the same route again or to find some place in the area, we assumed that a spatial memory disorder was the source of his topographical disorientation. Experiments 1 to 3 confirmed the dissociation in the patient's anterograde memory deficit between only mildly impaired ability to learn verbal and visual information and almost complete lack of ability to remember spatial information. In view of this normal performance on visual-spatial working memory and mental imagery tasks, his deficit should not be attributed to difficulty in forming and manipulating spatial representations but rather in consolidating these representations in the long term memory store. The pattern of selective impairment of spatial anterograde memory was specific to this patient. In the two pathological controls—whose brain damage partially overlapped that of the patient (the first with selective hippocampal atrophy caused by hypoxia, the second with diffuse degenerative cortical damage)—performance on the same experimental tasks was homogeneously impaired, affecting anterograde memory for verbal, visual, and spatial data to the same degree.

In the previously reported cases of anterograde topographical disorientation, the lesion site was generally found in the inferior ventral cortex of the right hemisphere, most regularly involving the parahippocampal gyrus<sup>16, 17, 20</sup> (for review, see Aguirre and D'Esposito<sup>6</sup>). Instead, in this patient the crucial neuropathological damage was a severe reduction of hippocampal volume without predominance of side, associated with

neocortical atrophic changes that were more evident in the fronto-parietal dorsal regions. Indeed, within the resolution limits of 1 mm<sup>3</sup>, the MRI investigation did not reveal any other focal lesion in the cerebral parenchyma, particularly in the occipito-temporal ventro-mesial regions.

As previously observed, although the role of the parahippocampal cortex in topographical orientation is well established (based on neuropsychological evidence and functional neuroimaging data), the issue of the relation between the hippocampus and topographical orientation is controversial. In a recent study of a large group of patients with stable and focal brain lesions (127 patients), Barrash and colleagues<sup>51</sup> found a route learning impairment in 10 of 13 subjects with hippocampal lesions and in 12 of 14 patients with lesions involving the parahippocampus. The authors assumed that the hippocampal and parahippocampal cortices have different specificity in topographical memory. The parahippocampus is critically involved in combining visual information about the form of scenes and landmarks with spatial information about their locations in a unified topographical representation, whereas the hippocampus is crucial for consolidating this representation.

In our patient, the finding of topographical disorientation confined to the learning of new routes in unfamiliar environments is consistent with Barrash *et al's* claim<sup>51</sup> of involvement of the hippocampal formation in consolidating new topographical representations, and with the role more generally assigned to the hippocampus in memory functioning. According to a great deal of experimental evidence in both humans and animals, the critical role of the hippocampal circuitry is generally held to be transitory storage of recently acquired information and the successive long term consolidation of memory traces in the associative neocortex.<sup>52–54</sup> Actually, a possible role of the hippocampus as a definitive repository of topographical representations has been hypothesised by some investigators,<sup>55</sup> but neuropsychological data in this regard are controversial.<sup>56</sup> The high performance level achieved by our patient on retrograde topographical memory tests, in spite of his very marked bilateral hippocampal atrophy (in this case, consistent with the performance of the neurological control with hippocampal atrophy) is clearly at variance with this hypothesis.

It is more difficult to understand why the patient's anterograde memory deficit affects spatial rather than verbal and visual information in such a disproportionate way. There are two possible interpretations of this finding. The first relates to the supposed prevalent role played by the hippocampus in the memory for spatial rather than non-spatial material. Based on the evidence of a prevalent role of the hippocampus in spatial learning in rodents,<sup>26, 27</sup> some investigators have advanced the hypothesis that the hippocampus is also mainly involved in

consolidating spatial information in humans, with a less crucial role in consolidating other kinds of information (for example, verbal or visual). However, results of studies experimentally testing this hypothesis in groups of patients with anterograde amnesia are, at the very least, contradictory. Some studies report relatively worse performance on spatial than on non-spatial memory tests in these patients<sup>57, 58</sup> while others report a homogeneous impairment across different categories of information.<sup>59</sup> On the other hand, the dissociation between substantially spared verbal and visual memory and severely disturbed spatial memory observed in our patient is undoubtedly too strong to be assimilated in the relative prevalence of the spatial over non-spatial deficit reported in some of the previous group studies.

Rather, this case seems more in line with previously reported cases of patients with anterograde amnesic syndromes that selectively involved or spared some types of information. The most obvious dissociation in this regard is that between verbal and visual-spatial memory impairment.<sup>60, 61</sup> More recently, a far less obvious dissociation was described between impaired ability to learn different classes of visual objects. For example, Tippett *et al* reported the case of a patient with right temporal lobectomy who was impaired in the learning of previously unknown faces but learned other kinds of visual and non-visual information at a normal rate.<sup>62</sup> Recently, a double neuropsychological dissociation in the anterograde memory impairment for two different classes of visual objects, namely faces and topographical scenes, was reported. In particular, Cipolotti and coworkers<sup>63, 64</sup> reported the cases of two patients with a severe impairment in learning unfamiliar faces but a completely spared ability to recognise recently seen topographical material. Conversely, the patient described by Carlesimo *et al* had a severe deficit in learning verbal, spatial, and visual-topographical material but learned new faces at a normal rate.<sup>48</sup> In the context of these reports, our patient represents the previously unreported case of a person with an anterograde memory impairment confined to (or at least disproportionately more severe for) spatial information, with a relative sparing of the ability to learn verbal and visual-object material.

Taken together, the material specific memory impairment found in these patients argues for a high degree of domain specificity in the neural systems involved in learning new information. It is not a novelty that distinct cortical regions are specifically involved in the processing of verbal, visual, and spatial data and—in the visual domain—of different classes of objects. What emerges from the report of patients with anterograde memory deficits restricted to a single class of visual objects is that this domain specificity is not confined to the cortical areas that are the definitive repository of long term memory traces, but also involves the neural circuits implicated in the storage of new memory representations. In particular, in the hippocampus and in the pathways connecting the hippocampi and the neocortex, the neural circuits involved in the storage of material-specific information could maintain a reciprocal segregation, so that focal damage in these circuits may differentially affect the learning of different kinds of information.

It is interesting to note that the neocortical atrophic changes in the patient's brain most markedly affected the parieto-frontal dorsal regions which have a generally accepted role in the processing of spatial information.<sup>12, 13, 65, 66</sup> Although he did not display any damage in spatial processing (his performance on perceptual, short term memory and visual imagery tasks involving spatial data was largely preserved), we suggest that his specific anterograde memory deficit for spatial data actually resulted from the interaction between atrophic changes in the hippocampi and in the dorsal parietal regions, ultimately affecting the neural circuitry involved in the acquisition and consolidation of new spatial information.

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