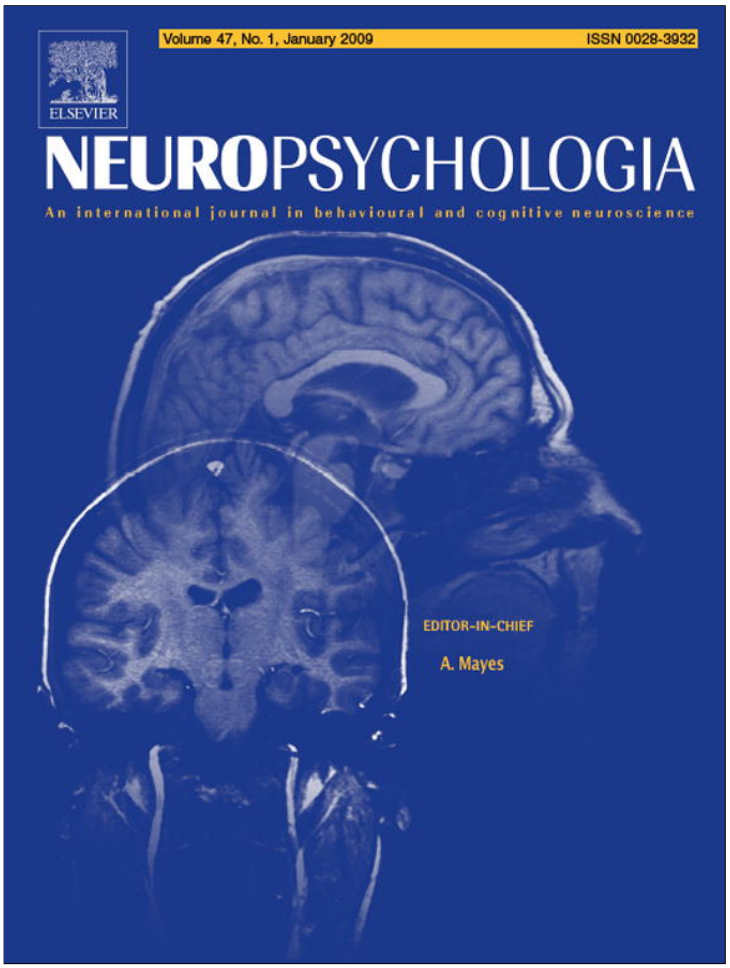

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Developmental topographical disorientation: Case one

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ABSTRACT

Topographical disorientation is the inability to orient within the environment, usually acquired from lesions to different cerebral regions participating in the attentional, perceptual or memory functions involved during navigation. We present the first case of a patient with topographical disorientation in the absence of any structural lesion and with intact sensory and intellectual function. Experimental tests in both real and virtual environments revealed a selective impairment in forming a mental representation of the environment, namely a cognitive map. Consistent with the patient's behavioural findings, a functional magnetic resonance imaging (fMRI) study showed lack of activation in the hippocampal complex and the retrosplenial cortex while forming a cognitive map of the environment. Although the lack of neural activity results in a negative finding that generally has low interpretative value, in this specific case our findings may provide useful information. First, in a group of healthy control subjects performing the same task, activity within the hippocampal complex and retrosplenial cortex were detected in each individual participant. Second, we found that within the same regions (showing lack of neural activity while forming a cognitive map of the environment) increased neural activity was detected while the patient was performing a different navigation task. This case is the first evidence reported in the literature showing that topographical disorientation may occur as a developmental defect causing a lifelong disorder affecting daily activities.

1. Introduction

Topographical orientation is the ability to orient and navigate in the environment. This complex function relies on several cognitive processes such as attention, memory, perception and decision-making skills, all of which play important roles in spatial orientation (Berthoz & Viaud-Delmon, 1999; Burgess, 2006; Corbetta, Kincade, & Shulman, 2002; Lepsien & Nobre, 2006). The proper function of these cognitive processes allows individuals to become familiar with the environment and to use a variety of strategies for navigation (Berthoz, 2001; Wang & Spelke, 2002).

In the last decade, neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have significantly contributed to the understanding of the mechanisms underlying topographical orientation (Aguirre, Zarahn, & D'Esposito, 1998; Maguire, 1997). These studies show an extensive neural network involved in navigation. Regions in the frontal and orbito-frontal cortex subserve attentional and working-memory demands involved in spatial orientation (Corbetta et al., 2002; Hopfinger, Buonocore, & Mangun, 2000; Petrides, 2000; Shulman et al., 1999), while parietal and retrosplenial cortex play critical roles in spatial perception and tracking the subject's movement within the environment (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Culham & Valyear, 2006; Epstein, Parker, & Feiler, 2007; Iaria, Chen, Guariglia, Ptito, & Petrides, 2007; Maguire, 2001). Temporal structures including the hippocampal complex are involved in learning and retrieving spatial information during navigation (Burgess, Maguire, & O'Keefe, 2002; Maguire, 1997). Sub-cortical structures such as the caudate nucleus contribute to the procedural memory that allows individuals to move along familiar paths in an automatic manner (Hartley, Maguire, Spiers, & Burgess, 2003; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003).

Given these complexities, it is not surprising that a variety of cerebral lesions can impair the ability to navigate in the environment (Barrash, 1998), resulting in 'topographical disorientation' (Aguirre & D'Esposito, 1999; De Renzi, 1982; Iaria et al., 2005). As reported in a current taxonomy of topographical orientation disorders (Aguirre & D'Esposito, 1999), patients with lesions of the posterior parietal cortex cannot use egocentric co-ordinates to localize environmental landmarks; that is, they cannot encode the positions of these objects relative to themselves (Stark, Coslett, & Saffran, 1996). Lesions to the retrosplenial cortex impair the

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ability to derive directional information from landmarks: despite recognizing these items, they cannot use them to determine the directions to a given target location (Takahashi, Kawamura, Shiota, Kasahata, & Hirayama, 1997). Lesions to the fusiform and lingual gyri impair the recognition of landmarks, which results in landmark agnosia (Pallis, 1955). Finally, lesions to the hippocampal and parahippocampal cortex often result in a selective disorder known as anterograde disorientation; which is, the impaired ability to learn paths in a novel environment (Habib & Sirigu, 1987).

Despite the growing number of patients reported to have topographical disorientation after acquired brain lesions (Brunsdon, Nickels, Coltheart, & Joy, 2007; Burgess, Trinkler, King, Kennedy, & Cipolotti, 2006; Greene, Donders, & Thoits, 2006; Ino et al., 2007; Nyffeler et al., 2005; Tamura et al., 2007; Wilson et al., 2005), there are no reports of topographical disorientation as a congenital or developmental defect. Nevertheless, congenital cognitive defects have been previously described in other domains, such as the inability to recognize faces, i.e. congenital prosopagnosia (Behrmann & Avidan, 2005), and impaired recognition of music, i.e. congenital amusia (Stewart, 2006). In this study we report the case of a woman who has never been able to orient within the environment. We refer to this case as Pt1. Imaging failed to show brain structural abnormalities and a detailed neuropsychological assessment showed preservation of general cognitive skills. Behavioural studies suggested a selective impairment in the ability to form cognitive maps, mental representations of the environment that allow individuals to reach any target location from different places within the environment (O'Keefe & Nadel, 1978; Tolman, 1948). Moreover, neuroimaging (fMRI) data did not reveal activity within the hippocampus and retrosplenial cortex, brain regions that have been shown to be critical for the formation of a cognitive map (Epstein et al., 2007; Iaria et al., 2007; Maguire, 2001; Maguire, Frackowiak, & Frith, 1996). We refer to her selective impairment as "developmental topographical disorientation".[1]

2. Case history

Pt1 is a 43-year-old left-handed woman employed in a provincial service. Her parents reported that her motor development was within the normal range: she achieved trunk control at about 6 months and walked unsupported before the age of 2 years. Language development was normal and she attended school regularly, successfully completing high school. Despite normal cognitive development, Pt1 has never been able to orient in the environment. She recalls from about the age of 6 years onwards panicking at the grocery store each time her mother disappeared from sight. For the 12 years of her schooling, her sisters or parents brought her to school. She never left home by herself because she got lost each time she tried: as a teenager, she relied on friends to accompany her when she left her parents' house. Neither she nor her parents know of similar navigational difficulties in other family members.

At present she lives with her father. She follows strict stereotyped directions to get to the office where she has worked for 5 years. She knows which bus to take downtown, recognizes a large distinctive square at which she must exit the bus, and then follows a straight route of about 30 m to locate the tall building where her office is situated. She follows the same path in reversed fashion to get home, although sometimes she gets lost in her neighbourhood and needs to phone her father to ask him to come and get her. Aside from this specific path, she cannot find her way to other locations, such as stores or theatres, and gets lost each time she tries. She reports, however, no difficulties in right–left discrimination and no impairments in recognizing familiar places or environmental landmarks. Pt1 was prompted to seek an assessment of her difficulties because she received notice that her office was relocating and knew that this would reduce her already limited independence.

Pt1 participated in a series of detailed investigations. Informed consent was obtained in a manner approved by the local ethics committee in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) as printed in the British Medical Journal (18 July 1964).

3. Neuroradiological examination

Magnetic resonance imaging (MRI) was performed on a 3.0 T Philips scanner equipped with 25 mT/m gradients. A circular polarized head coil with a diameter of 270 mm was used both for RF transmission and for reception of the MR signal. The protocol included axial and coronal T2-weithed fast spin-echo (FSE), axial and sagittal T1-weithed spin-echo (SE) sequences (TR = 600, TE = 14), and coronal fluid-attenuated inversion recovery (FLAIR) sequences (TR = 9000, TE = 119, inversion time = 2470) covering the entire brain. Twenty-one 5 mm-thick sections with no gap, a 23- to 24-cm field of view (FOV), and 256 × 256 matrix were obtained. Axial T1-weithed 3D images (magnetization prepared rapid gradient echo sequence, MPRAGE) were also acquired. The axial and coronal sections ran respectively parallel and perpendicular to a line that connects the anterior and posterior commissure (AC-PC line).

MRI scans were reviewed with an experienced neuroradiologist: these did not reveal any acute intracranial haemorrhage, ischemic change or mass lesion. The extra-axial spaces were clear. The basal ganglia, hippocampi and ventricles appeared normal in volume and symmetry.

4. Neuropsychological evaluation

We administered a series of standard neuropsychological tests assessing general intelligence, attention, memory, visuospatial and imagery abilities (Table 1). Pt1 was alert and fully cooperative. She was fluent and had normal verbal comprehension. No ideomotor, ideative or constructional apraxia was observed. General cognitive level was tested by means of the WAIS-R (Wechsler, 1999): she obtained a Verbal IQ of 93 and a performance IQ of 94 (total IQ = 94). Pt1 did not show any sign of attentional, perceptual or imagery impairment. She performed normally on tests of short- and long-term memory in both spatial and verbal domains.

5. Navigational skills assessment

To assess Pt1's navigational skills we performed a battery of real-world tests aimed at assessing a variety of strategies used in orientation. These tests were performed in a part of the city with which the patient was not familiar, and the paths travelled during testing never overlapped with each other. In addition, the number of left and right turns was balanced in each path. The patient was aware that if she made errors (e.g., a right turn instead of a left one), we would tell her and correct her to allow her to resume her attempt to follow the correct path.

5.1. Route-based navigation

In this test, the patient and the examiner followed a selected path from a specific place to a given target location. Before starting, the patient was told to follow the examiner for the entire journey,

[1] Although the term "congenital" could also be applied, we have no direct evidence showing that the patient's impairment was present since birth.

Table 1
Neuropsychological assessment

Test	Patient's score
General intelligence	
WAIS-R (Wechsler, 1999)	
Verbal IQ	93
Performance IQ	94
Full scale IQ	94
Executive skills	
WCST (Grant & Berg, 1948)	86/128
Orientation	
Left–right orientation (Benton, Hamsher, Varney, & Spree, 1983)	20/20
Memory	
Verbal memory	
CVLT (Delis, Kramer, Kaplin, & Ober, 1987)	46
Digit span (Wechsler, 1999)	
Forward	5
Backward	5
Logical memory I/II (Wechsler, 1999)	44/31
Spatial memory	
Corsi Block Test (Wechsler, 1999)	
Forward	5
Backward	5
Rey's Figure A (immediate/delayed recall) (Osterrieth, 1944)	34/36
Recognition memory (Warrington, 1984)	
Words	50/50
Faces	50/50
Cambridge Face Memory Test (Duchaine & Nakayama, 2006)	
Upright faces	
Intro	18/18
Novel images	30/30
Novel images with noise	24/24
Total score	72/72
Inverted faces	
Intro	15/18
Novel images	19/30
Novel images with noise	16/24
Total score	50/72
Visual memory	
Benton Visual Retention Test (Benton, 1974)	17
Language	
Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983)	54/54
Attention	
Visual search (Spinnler & Tognoni, 1987)	58/60
Stars Cancellation Test (Wilson, Cockburn, & Halligan, 1987)	54/54
Visual-perceptual abilities	
Visual Object and Space Perception battery (Warrington & James, 1991)	
Object perception	
Screening test	20/20
Incomplete letters	20/20
Silhouettes	26/30
Object decision	20/20
Progressive silhouettes[a]	8/20
Space perception	
Dot counting	10/10
Position descrimination	20/20
Number location	9/10
Cube analysis	10/10
Judgement of line orientation (Benton, Sivan, Hamsher, Varney, & Spreen, 1983)	25/30
Hooper Visual Organization Test (Hooper, 1983)	25
Street's Completion Test (Spinnler & Tognoni, 1987)	10/14
Rey's Figure A (copy) (Osterrieth, 1944)	36/36
Imagery abilities	
Mental Rotation Test (Grossi, 1991)	10/10
O'clock Test (Grossi, Modafferi, Pelosi, & Trojano, 1989)	31/32
Road Map Test (Money, Alexander, & Walker, 1965)	31/32

The table shows the patient's score on the neuropsychological assessment evaluating general intelligences, executive functions, memory, language, attention, visuo-spatial perception, and mental imagery skills. WAIS-R, Wechsler Adult Intelligence Scale; IQ, Intelligent Quotient.

[a] Note that this score represents the number of items required to identify the objects (the less is the number of items the better is the performance), Pt1 was not impaired in solving this task.

following which she would be guided back to the starting location by a different route. From the starting location, she was required to follow the same path to the target location that she had travelled with the examiner. While travelling no other information or communication was allowed. Fig. 1A depicts the path travelled from a top-view perspective, which was about 1.2 km, and travelled by the examiner in 11.30 min.

During the test portion, the patient verbalized the name of the landmarks she was looking at while navigating: after testing she confirmed that she was using the buildings and landmarks along the path without referring to the signs showing the street names. Pt1 correctly performed the same path with accuracy of 100% (no errors in left or right turns), reaching the target location in 10.20 min. Thus she was not impaired in the learning and execution of a previously travelled path. Because of her accuracy in performing this test, no control subjects were recruited to perform the same task.

5.2. Landmarks-based navigation

This test was similar to the previous test, in that the patient and the examiner first travelled a route together, which the patient was later required to follow on her own. In this case, however, whenever a crossing was reached, the examiner indicated and named specific landmarks (stores and buildings), which she was required to report during the test phase. Fig. 1B depicts a top-view perspective of the path, which was about 1.1 km long and travelled by the examiner in 12.10 min.

As expected from her performance in the first test, the patient did not have any trouble recalling and indicating all the landmarks named by the examiner, performing the path with no errors (100% accuracy) and reaching the target location in 11.25 min. Because of

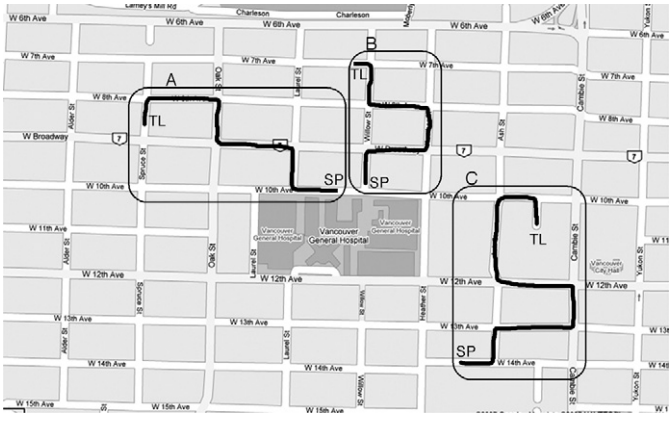

Fig. 1. The figure depicts the pathways performed during the route based (A), landmarks based (B) and verbal based (C) way finding tests. SP, starting position; TL, target location.

this performance, no control subjects were recruited to perform the same task.

5.3. Instruction-based navigation

Before performing this test, the patient was guided to a specific starting location and given a list of instructions that she needed to follow to reach a given target location. Each instruction included the name of the street to follow, the name of the street at which she needed to make a turn, and the direction of the turn (e.g. "*Instruction 3: You are on 13th Avenue, turn left when you reach Cambie Street*"). The list given to the patient included seven instructions that she needed to follow sequentially to correctly perform the path and reach the target location. The path (Fig. 1C) was about 0.9 km long, and the target location was reached by the examiner during a different session, not attended by the patient, in 8.25 min.

The patient did not have any difficulty with this task. She performed the path correctly (100% accuracy) and reached the target location in 7.50 min. Again, because of this performance no control subjects were recruited.

5.4. Map-based navigation

This test included two tasks that were administered separately. In the first task, the patient was given a city map of the neighbourhood involved. On the map both the starting place (where the examiner and patient were located) and the target location were indicated. The map also included the name of the streets. The patient was required to look at the map and describe the shortest path to the target (Fig. 2A). After the examiner took note of the selected path, the patient had to follow this route to the target. In the second task, the patient was given another map, this time already displaying the specific path that the patient was required to follow to reach the target (Fig. 2B).

In task 1, the patient selected a path that was not the shortest one (Fig. 2A). While getting to the target location she made one error, a right turn instead of a left turn. The patient was notified of the error, after which she reached the target without any error. The path that she selected was travelled by the examiner in a different session not attended by the patient in 8.30 min, while the patient performed the same path in 8.40 min.

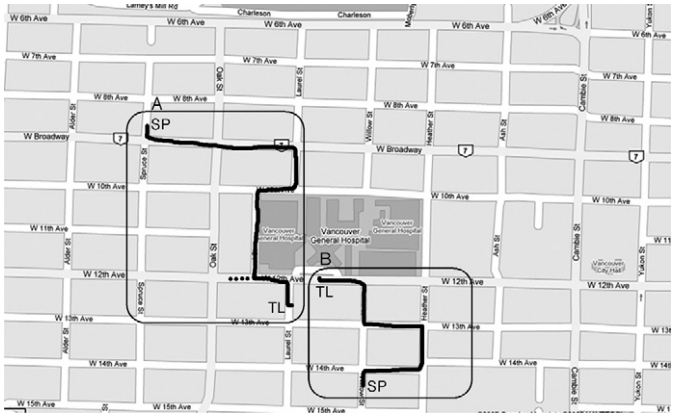

Fig. 2. The figure displays the route selected by the patient while performing the map based way finding test (task 1) including the error (dotted line) she made while travelling along the pathway (A), and the pathway (given on the map) travelled while performing the based map test (task 2), which the patient followed by using the map (B). SP, starting position; TL, target location.

In task 2, the path indicated on the map was about 0.9 km long, and the examiner travelled it in 8.15 min. The patient did not show any impairment in performing the path as reported on the map (100% accuracy) and reached the target in 7.50 min.

Pt1's performance on this test revealed for the first time some difficulties in using a map while navigating. However, she was able to reach the target locations correctly.

5.5. Map drawing

This test was performed in the laboratory. The patient was asked to draw a top-view map of the main floor of the house where she lives, and of the path she follows from the bus-stop where she gets off to the building where her office is located. Both the house and the path performed to reach the office are very familiar to the patient and she does not report difficulty navigating

Fig. 3. In this figure we displayed the schematic outline of the patient's house as drawn by herself at the laboratory (A) and the actual map of the house as reported by the patient's father (B).

these. With respect to the drawing of her house, she reported correctly the number of rooms in the house, but produced a greatly distorted map with inaccurate spatial scaling, as confirmed by contrast with a drawing of the same house by her father (Fig. 3). The drawing of the path she follows to the office showed similar errors in terms of scaling and distances between locations. In both drawing tests, despite the examiner's continuous encouragement, the patient could not locate any item (objects or landmarks) in the environment, which instead she recalled verbally. However, a detailed analysis of her drawings showed that the rooms (in the house) and the streets (along the pathway) were drawn in the correct sequence, despite the spatial inaccuracies. This suggests she can create an approximate schematic representation of overlearned environments, which is consistent with the procedural type of strategy she adopts to navigate these environments. However, for less familiar areas in which she has difficulty navigating, she could not create schematic drawings, for example for the main routes of the city or her neighbourhood, stating that she did not have "in my mind a map to report". This suggests a selective difficulty in forming any mental representation (schematic or spatial) for these environments. To test this more formally, we administered a normed test assessing both the formation and use of cognitive maps in a virtual environment.

6. Formation and use of cognitive maps

6.1. Methods

Since cognitive maps (i.e. mental representation of the environment) are suggested to be critical for orienting within the environment (O'Keefe & Nadel, 1978; Tolman, 1948), we administered to the patient the Cognitive Map Test (CMT), assessing the specific ability to both form and use a cognitive map of the environment (Iaria et al., 2007). This test uses a virtual environment created with the editor of a three-dimensional gaming software (Game Studio A6, La Mesa, CA, USA). The virtual city, composed of several buildings of different sizes and shapes, included four clearly identifiable landmarks: a cinema, a restaurant, a hotel, and a flower shop. The patient moved within the virtual environment by using a three-button keypad, with each button corresponding to movement in one of three directions: left, forward or right. She was asked to perform two tasks, namely the learning and retrieval task, which assess the ability to create and use a cognitive map, respectively.

The experimental design included learning and retrieval tasks. During the learning task, the patient was instructed to explore the virtual environment freely, to learn the locations of the four landmarks and their spatial relationships within the environment. She was told that she would need to create a mental representation of the city, including the landmarks and their spatial relations, because she would later need to use this mental representation to solve the retrieval task that would follow. The patient was asked to report when she felt that she had completed a mental representation of the environment; and told that at that "terminal moment" the examiner would test this ability by asking her to report the locations of the landmarks on a schematic map representing the city from a top-view perspective. If she failed to indicate all four locations correctly, she was returned to the task to continue learning and forming the map. In addition to this terminal assessment, the patient was also aware that during her exploration the examiner would stop her occasionally (every 2 min) to ask her to report the locations of the landmarks on similar maps. This time delay of 2 min was chosen based on pilot data showing that this was the amount of time needed to visit all four landmarks while navigating within the virtual environment. The learning task was considered completed when the patient was first able to indicate the correct locations of all four landmarks, on either one of the every-2-min probes by the examiner or at the terminal moment when she felt that she had formed a cognitive map. The time taken to reach this point was taken to be the time required to form the cognitive map. After this learning task, the patient was given 3 min of rest, following which she performed the retrieval task.

The retrieval task consisted of 12 trials that required the patient to use the mental representation she had formed to reach the location of specific landmarks. On each trial, the patient started by facing one of the four landmarks, chosen randomly, where a sign indicated the target location she needed to reach by the shortest path possible. Both starting and target locations varied across trials, so that the only efficient way to perform the task was to use a cognitive map of the environment: in particular, procedural memory would be of little assistance since a new path was always required, each time from a different starting point. The duration of each trial was recorded as measurement of performance. At the end of the experiment the patient was questioned about the strategy she used for navigation during both the learning and the retrieval tasks.

Before the start of both learning and retrieval tasks, the patient was required to navigate freely for 15 min within a "practice virtual city" different from the experimental one. This allowed her to practice the motor and perceptual aspects of the tasks and familiarize herself with the virtual environment. In this practice phase, the buildings present in the virtual city were similar to the ones present in the experimental trials but they were spatially organized in a different way and no identifiable landmarks were present. After 15 min, the patient was administered three control trials which required her to navigate as quickly as possible a route defined by arrow signs present along the path. The training phase was ended after the third control trial, which she performed with 100% accuracy by following the defined path without stopping along the way. This training was designed to ensure that the patient developed basic motor and perceptual processes needed for manipulation of the virtual environment in the experiment. After completion of the training phase, the patient was given the instructions for both the learning and retrieval tasks, shown the identity of the landmarks available within the environment, and the experiment was started.

6.2. Results

Pt1 needed 1920 s (32 min) to form the cognitive map of the environment. During this time she explored the environment by covering the same routes several times over. When debriefed at the end of the test she reported that she did not have a specific strategy but was trying to encounter the landmarks and to remember where they were respect to each other. She also reported that she had a lot of trouble remembering where the landmarks were with respect to her current location, and got lost each time she encountered a new landmark after visiting a previous one. Her performance was significantly worse (nearly three times longer) that a control group of four left-handed female individuals (average age 41.5 years, S.D. 3.9 years) who solved the same task in an average of 652.5 s (S.D. = 86.2 s).

For the retrieval task we measured the additional time delay for reaching the target location, by subtracting from the subject's times the ideal time used by an observer following the shortest path without stopping. While performing retrieval trials, Pt1's average delay was 75 s, which was significantly longer that the average delayed time of the female control group (mean = 15.7 s; S.D. = 6.3 s).

One week after performing this test, the patient started a training program consisting of six sessions (1 h each, one session per week), during which she performed the same tasks described above (learning and retrieval) in the same virtual environment. Her performance at the last training session showed that she formed the

cognitive map of the environment in 300 s (5 min), and performed the retrieval task with an average delayed time of 4.25 s. Thus Pt1 can acquire and use a cognitive map through intensive overtraining with a simplified environment.

It is of interest that Pt1 has not developed similar mental representations of her familiar environments (e.g., her house and the route to the office). Rather, her life-long strategy appears to have been to minimize the need to form and use such maps. To get to her office, Pt1 uses a straight route from the bus-stop to her building that requires no turns. Evidence that she has not developed a cognitive map from this daily routine includes the fact that she gets lost with even a small deviation from this route. Similarly, when she moves in her house she may orient herself by following very selective and short habitual pathways that do not require a mental representation of the environment, but can use procedural memory.

7. fMRI study

The aim of the fMRI study was to assess Pt1's pattern of cerebral activation while she was engaged in the learning and retrieval tasks of the Cognitive Map Test, which had proved so difficult for her. In a previous study (Iaria et al., 2007) we found that, in addition to frontal, parietal and temporal regions recruited during navigation, the left and right hippocampus play a particularly significant role in acquiring and forming a cognitive map respectively, with an associated increase in activation within the retrosplenial cortex bilaterally during both formation and use of the cognitive map. Because of her impairment in forming a cognitive map, we expected a lack of activity within these brain regions (Iaria et al., 2007). However, because the behavioural data showed that, once she had formed a cognitive map through overtraining she could efficiently retrieve information from such a map, we expect that she would show similar activity found in healthy controls during a retrieval phase of the test.

Pt1's results were compared to those of nine healthy control subjects (mean age 24.9 ± 4.1 years; ranging from 19 to 34 years), whose results were reported in a prior study (Iaria et al., 2007).

7.1. Data acquisition, analyses and protocol

MRI Images were acquired using a 3.0 T Phillips scanner. The scanning session started with the acquisition of structural images with a T1-weighted EPI sequence, recording 170 axial slices of 1 mm thickness (1 mm gap) with an in-plane resolution of 1 mm × 1 mm (FOV = 256). Three functional runs were then administered. Functional images were acquired parallel to the anterior commissure–posterior commissure line with a T2-weighted EPI sequence of 36 interleaved axial ascending slices (TR = 2000 ms; TE = 40 ms) of 3 mm thickness (1 mm gap) with an in-plane resolution of 1.875 mm × 1.875 mm. Scans 1 and 2 consisted of 210 volumes, whereas scan 3 consisted of 360 volumes. The first volume of each functional scan was discarded to allow for scanner equilibration. All MRI data were analyzed using Brain Voyager QX Version 1.8. Preprocessing of functional scans consisted of corrections for slice scan time acquisition, head motion (trilinear interpolation), and temporal filtering with a high pass filter to remove frequencies less than three cycles/time course. Functional scans were individually co-registered to their respective anatomical scan, using the first retained functional volume to generate the co-registration matrix.

During *Functional Run 1* Pt1 was required to form a mental representation of a virtual environment and four landmarks within it, just as was done during the Cognitive Map Test above. Both the environment and the landmarks were new to Pt1 ('novel map'). During *Functional Run 2*, the patient performed the same task but in this case the environment and the landmarks were the ones made familiar to Pt1 through the overtraining exercise above ('familiar map'), which had been completed 2 weeks prior to scanning. During *Functional Run 3*, the patient performed a retrieval task, being required to reach different target locations from different starting points, within the familiar environment used in Functional Run 2. The retrieval task included 12 trials (different than the ones administered in the behavioural tests). As with the behavioural test, in each trial the patient started by facing one landmark and a sign indicating the target landmark that she was asked to reach by the shortest path.

During each functional run, there was also a control task of 2 min duration, during which Pt1 navigated defined routes by following directions present along the path (i.e. arrow signs) in a new virtual city without landmarks. The texture and number of buildings were identical to the ones used in the experimental tasks (novel map, familiar map). These controlled for both the perceptual and motor aspects of the experimental tasks. The patient was familiar with this task, since she had performed similar control trials (but different designed routes) in the behavioural study. During Functional Runs 1 and 2 the patient performed one control task for each scan. During Functional Run 3 subjects performed several control trials intermixed with the 12 trials of the retrieval task.

The software used to create the virtual environment included a script that allowed the linking of different files. Thus, during each run (novel map, familiar map, retrieval) the trials (control and experimental) were linked to one another and the subjects were led automatically to the next trial by simply reaching the end of the defined path in the control task or approaching very close to the target locations in the retrieval trials. Error rates, time and the paths travelled while performing the experimental (novel map, familiar map, retrieval) and control trials were recorded.

For the 'novel map' (Functional Run 1) and 'familiar map' (Functional Run 2) formation runs, whole brain analysis was carried out by contrasting the volumes acquired while forming the mental representation of the environment (i.e. the cognitive map) against the volumes acquired during the control tasks. For the retrieval task (Functional Run 3) whole brain analysis was carried out by contrasting the volumes acquired during the retrieval trials against the volumes acquired during the control tasks. In all cases, significant BOLD signal changes were determined at each voxel, based on a general linear model corrected for autocorrelations. To localize specific neural activity previously found in normal controls (Iaria et al., 2007), the patient's MRI data were normalized to the Talairach stereotaxic space (Talairach & Tournoux, 1988).

7.2. Results

During the patient's attempt at new cognitive map formation (Functional Run 1) there were significant increases in neural activity in frontal, temporal and parietal cortex (Table 2). Within the frontal lobe, there was bilateral activity in the central region involving motor (Brodmann's areas 4 and 6) and sensory (Brodmann's areas 5) cortex, and in the middle and inferior frontal gyrus (Brodmann's areas 8, 9/45, 9, 45/47, 44, 45, and 47/12). Within the posterior cortex, there was symmetric bilateral activity in the superior parietal lobe (precuneus, Brodmann's area 7), and temporal cortex (Brodmann's areas 21, 22). In addition, activity within subcortical structures (i.e. putamen and caudate nucleus) and the cerebellum were found in both hemispheres. These findings are consistent with the neural activity revealed in a group of healthy volunteers while

Table 2
Neural activity related to the formation of a cognitive map in a novel environment (novel map minus control task)

Anatomical region	*x*	*y*	*z*	*t*-Value	BA
Right Hemisphere					
Superior frontal gyrus	8	13	65	4.4	6
	18	53	30	5.72	9
Middle frontal gyrus	43	20	39	5.54	8
Premotor cortex	55	−6	42	4.99	4
Postcentral gyrus (sensory cortex)	5	−42	69	4.36	5
Mid-ventrolateral prefrontal cortex	31	18	−4	5.36	47/12
Anterior cingulate cortex	6	32	−4	5.17	32
Superior temporal cortex	57	−29	4	4.24	22
Superior temporal sulcus	50	−62	23	5.08	39/37
Middle temporal cortex	45	1	−12	5.58	21
	58	−10	−13	5.33	21
Superior parietal lobule (Precuneus)	40	−66	36	4.36	7
Inferior parietal cortex	54	−47	32	3.88	40
Temporo-parietal junction	43	−42	19	4.93	40/22
Fusiform gyrus	32	−90	−13	6.7	18
Cuneus	11	−82	42	4.48	19
Putamen	16	10	−2	4.39	
Cerebellum	36	−40	−39	4.68	
Left Hemisphere					
Superior frontal gyrus	−18	57	36	4.16	9
Postcentral gyrus (sensory cortex)	−17	−40	67	4.04	5
Precentral gyrus	−6	−35	68	3.91	4
Middle frontal gyrus	−33	20	52	5.35	8
Middle/inferior frontal gyrus	−50	20	29	5.14	9/45
Medial frontal gyrus	−6	44	18	5.63	9
Inferior frontal gyrus	−44	35	−7	5.4	45/47
Inferior frontal gyrus	−50	22	5	5.18	45
	−51	7	−15	6.02	44
Orbitofrontal cortex	−2	48	−9	6.71	10
Superior temporal cortex	−41	3	−36	5.28	20/21
Superior/middle temporal cortex	−48	−57	18	6.05	21/22
Inferior/middle temporal cortex	−54	−18	−15	6.82	20/21
Inferior temporal cortex	−27	−4	−37	5.17	20
Superior parietal lobule (Precuneus)	−36	−65	40	4.17	7
Superior parietal cortex	−9	−60	60	4.98	7
Fusiform gyrus	−45	16	−24	4.23	20
Caudate nucleus	−7	7	8	4.49	
Cerebellum	−18	−73	−41	4.31	

BA, Brodmann's area.

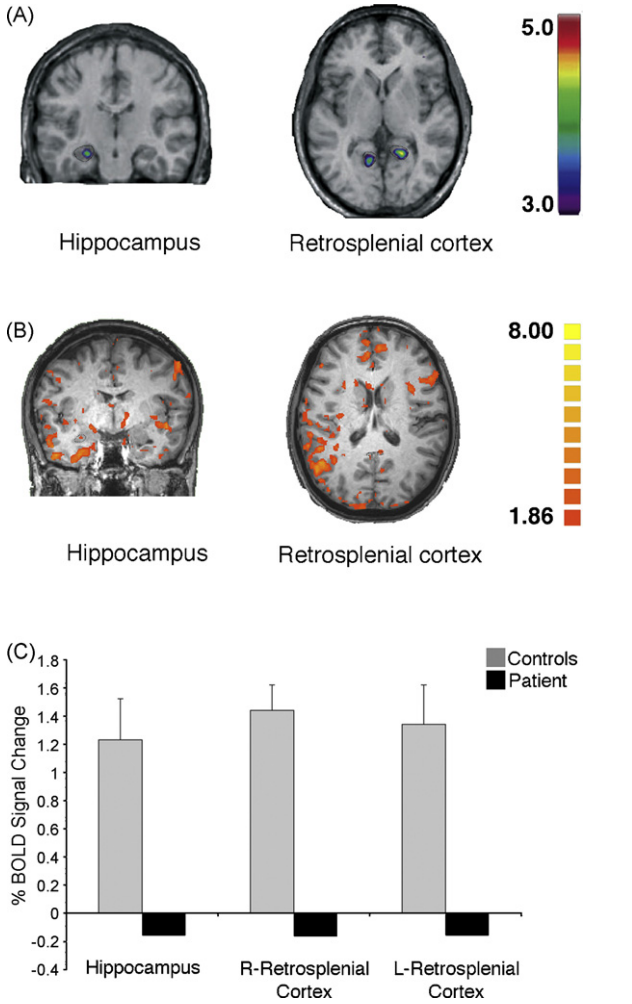

Fig. 4. Coronal and axial view of the neural activity in the left hippocampus and retrosplenial cortex bilaterally as detected in (A) the healthy control subjects and (B) the patient Pt1. Note that the threshold referring to the patient's neural activity has been lowered for the purpose of the illustration, and that such a neural activity was not significantly different than the control task. Dotted lines define the regions of interest (hippocampus and retrosplenial cortex) in both the healthy controls and the patient. (C) The histogram displays the BOLD signal changes detected in the hippocampus and retrosplenial cortex of both healthy controls and the patient while forming a cognitive map of the environment (bars on the controls' average BOLD signal change refer to standard deviations).

performing the same task (Iaria et al., 2007). However, our patient showed no increase in activity within the hippocampal complex and the retrosplenial cortex (Fig. 4), which are known to play a critical role during the formation of a cognitive map (Burgess et al., 2002; Iaria et al., 2007; Maguire, 2001). In contrast, such activation was found in every one of the nine individual subjects who performed the same task (Iaria et al., 2007). The results were similar while Pt1 was engaged in forming a cognitive map of the familiar environment upon which she had been trained (Functional Run 2) (Table 3).

During the retrieval task (Functional Run 3), the patient was able to use the shortest paths to reach the target locations in each trial in this overtrained environment, with an average delayed time of 4.5 s. Significant bilateral increases in neural activity were found in the frontal (Brodmann's areas 4, 6, 8, 9, 45 and 47/12), parietal (precuneus, Brodmann's areas 7 and 40) and temporal (Brodmann's areas 21, 22 and 37) cortices, as well as in the cerebellum bilaterally and the right putamen (Table 4). Also, there was significant activity within the right hippocampus and parahippocampal cortex, and the retrosplenial cortex bilaterally (Fig. 5), consistent with previous findings in normal subjects engaged in retrieving information from a cognitive map during navigation task (Burgess et al., 2002; Iaria et al., 2007; Maguire, 2001) as well as in our healthy control group performing the identical task (Iaria et al., 2007).

Although the fMRI data suggest failure to activate the hippocampus and retrosplenial cortex during cognitive map formation in Pt1, this conclusion requires some caution. There is lower statistical power in assessing fMRI results in single subjects: indeed, most fMRI studies perform group analyses to achieve reasonable statistical power at a single voxel level (Desmond & Glover, 2002). Thus the lack of activity in the left hippocampus and retrosplenial cortex in Pt1 during the learning tasks may be simply due to low power. However, against this is the fact that Pt1 did show activation during the learning task in the frontal, temporal and parietal cortex, as in our healthy controls, suggesting a degree of selectivity to the lack of activation in the hippocampus and retrosplenial cortex. Second, activation in these two structures during cognitive map formation was seen in all nine controls, suggesting that such activity is normally robust enough to be detected at a single-subject level. Third, our protocol did reveal hippocampal and retrosplenial activation during the retrieval task in Pt1 using the overlearned environment, indicating that it was possible to detect activity in these two structures during some part of cognitive map use. While not definitive,

Table 3
Neural activity related to the formation of a cognitive map in a familiar environment (familiar map minus control task)

Anatomical region	x	y	z	t-Value	BA
Right Hemisphere					
Superior frontal gyrus	20	21	62	5.89	6
Middle frontal gyrus	47	24	37	5.61	8
	36	31	12	4.75	9/46
Inferior frontal gyrus	53	25	28	4.91	9/45
Precentral gyrus	63	−1	22	4.04	6
Middle temporal cortex	61	−27	−11	4.91	21
	60	−43	3	4.82	21
	54	−54	10	4.72	21
Superior parietal lobule (precuneus)	41	−68	34	5.34	7
	28	−71	42	5.35	7
	4	−63	54	6.06	7
Inferior parietal cortex	53	−52	26	6.3	40
	54	−34	42	5.42	40
Cerebellum	27	−83	−32	4.15	
Left Hemisphere					
Superior frontal gyrus	−3	27	62	6.01	8
	−6	−18	68	4.65	6
	−27	52	37	6.42	9
Middle frontal gyrus	−25	22	56	5.43	6
	−37	30	41	7.01	8
Inferior frontal gyrus	−39	20	1	4.42	45/47
Superior temporal cortex	−51	−54	24	6.23	39
	−52	10	−4	4.33	22
Middle temporal cortex	−59	−28	−9	4.31	21
Superior parietal lobule (precuneus)	−8	−63	52	5.63	7
	−22	−56	60	4.13	7
Superior parietal cortex	−31	−69	40	5.39	7
Fusiform gyrus	−38	−67	−20	6.61	19
Cuneus	−6	−74	37	5.18	19
Cerebellum	−34	−64	−35	5.94	

BA, Brodmann's area.

Table 4
Neural activity related to the use of a cognitive map. i.e. retrieval (retrieval minus control task)

Anatomical region	x	y	z	t-Value	BA
Right Hemisphere					
Superior frontal gyrus	24	43	38	7.12	9
	8	30	36	8.43	8
Middle frontal gyrus	35	50	19	9.89	9
	32	26	48	8.77	8
Mid-ventrolateral prefrontal cortex	25	29	−1	6.85	47/12
Inferior frontal gyrus	49	18	30	6.98	9
Superior temporal cortex	54	−46	20	8.73	22
Middle temporal cortex	51	2	−9	6.46	21
	64	−47	9	9.8	21
	61	−53	−8	9.78	37
Inferior temporal cortex	54	−30	−15	6.26	20
	52	−69	9	8.66	37
Superior parietal lobule (precuneus)	17	−47	53	9.18	7
	1	−60	54	9.23	7
Superior parietal cortex	33	−45	47	11.73	7
Inferior parietal cortex (Supramarginal gyrus)	55	−56	32	7.98	40
Inferior parietal cortex	44	−43	35	8.48	40
Retrosplenial cortex	15	−47	0	6.13	
Fusiform gyrus	49	−46	−18	6.86	37
Hippocampus	27	−26	−10	5.77	
Hippocampus/parahippocampal cortex	35	−10	−20	7.88	
Putamen	23	4	7	6.43	
	19	−27	−1	7.08	
Cerebellum	46	−58	−33	6.12	
Left Hemisphere					
Superior frontal gyrus	−2	20	54	9.71	8
	−21	13	56	6.81	6
Paracentral lobule	−9	−42	56	6.33	4
Mid-ventrolateral prefrontal cortex	−26	29	−2	6.98	47/12
Inferior frontal gyrus	−40	37	7	8.35	45
	−41	15	35	6.98	9
Superior temporal cortex	−47	7	−1	5.44	22
Superior parietal lobule (precuneus)	−23	−59	40	9	7
	−13	−60	41	7.93	7
Superior parietal cortex	−17	−52	55	7.67	7
Inferior parietal cortex	−32	−60	37	6.98	40
Retrosplenial cortex	−14	−55	21	6.27	
Fusiform gyrus	−45	−53	−8	5.84	37
Cerebellum	−17	−76	−33	7.53	

BA, Brodmann's area.

these points strengthen the significance of the lack of activation in Pt1's hippocampal and retrosplenial cortex during cognitive map formation.

8. Discussion

Topographical disorientation is usually described in patients with acquired brain lesions (Barrash, 1998). The patient we reported in this study differs from these cases with acquired brain damage in two key respects: first, her neuroimaging shows no gross structural damage, and second, her topographical disorientation appears to be confined to the specific ability to form a mental representation of the environment. Patients with acquired topographical disorientation usually have other cognitive impairments, such as attentional, perceptual or memory defects affecting spatial processing (Barrash, 1998; De Renzi, 1982), making it difficult to determine how much of the navigational problem is due to more general spatial processing deficits rather than a specific orientation skill. From a behavioural point of view, one interesting aspect of the case in our study is the highly select nature of our patient's topographical disorder. The patient did not report any learning or memory difficulties in any other cognitive domain, which was confirmed by the neuropsychological assessment. Moreover, we were not able to detect any other mental imagery defect related to objects or even imagery of her own body moving within a map drawn on a paper. This suggests that the learning process involved in the formation of mental imagery may be selectively impaired for cognitive map formation.

Topographical orientation is not a unitary skill. Rather, individuals may use a number of complementary functions and strategies to navigate within the environment (Berthoz, 2001; Redish, 1999). Locations may be reached by remembering a sequence of turns or a sequence of displacements guided by landmarks encountered along the path (Packard & McGaugh, 1996). On the other hand, when deviating from a habitual pathway, one must access a mental representation of the environment (Tolman, 1948). Such cognitive maps allow us to reach a given location by any route available in the environment.

To assess Pt1's ability to use these different strategies, we asked her to perform a series of navigational tasks in both real-world and virtual surroundings. The patient's performances of real-world tasks showed that she could replicate a previously travelled path, with or without the explicit use of the landmarks, and could follow verbal instructions to reach specific locations. In addition, these tasks revealed that Pt1 could perform right–left turns correctly and recognize both familiar places and environmental landmarks. Such tasks do not require the processing and manipulation of a cognitive map (Iaria et al., 2003). Following a specific route by a sequence of displacements (e.g. go straight, turn left at second intersection, etc.) can rely on procedural memory, whereas the ability to select any route to reach any location in the environment requires a cognitive map. In this specific context, however, procedural memory does not necessarily involve remembering without awareness of retrieval since the patient is engaged in instruction-based navigation requiring to perform the same pathway. In navigational tasks, indeed, procedural memory implies the following of selec-

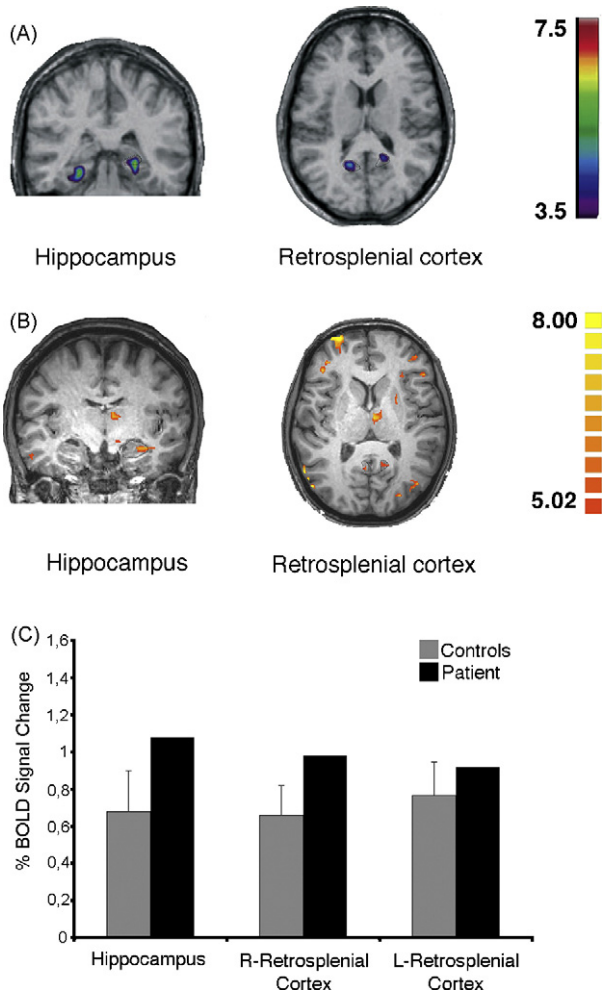

Fig. 5. Coronal and axial view of the neural activity within the right hippocampus and retrosplenial cortex bilaterally as detected in (A) the healthy control subjects and (B) the patient Pt1 (hippocampus: $x = 35$, $y = -10$, $z = -20$, t-value = 7.88; left retrosplenial cortex: $x = -14$, $y = -55$, $z = 21$, t-value = 6.27; right retrosplenial cortex: $x = 15$, $y = -47$, $z = 0$, t-value = 6.13). Dotted lines define the regions of interest (hippocampus and retrosplenial cortex) in both the healthy controls and the patient. (C) The histogram displays the BOLD signal changes detected in the hippocampus and retrosplenial cortex of both healthy controls and the patient while performing the same retrieval task (bars on the controls' average BOLD signal change refer to standard deviations).

tive routes with or without reliance on environmental landmarks, and without relying on any spatial representations concerning the layout of the environment, the route itself, or the spatial relationships between landmarks (McDonald & White, 1994, 1995; Packard & McGaugh, 1996). That is, by definition, procedural memory is of no use once an individual needs to follow a different (alternative) pathway (rather than the usual one) in order to reach a given location (Packard & Knowlton, 2002). This is consistent with Pt1's own experience: she can learn and follow a few select routes of limited complexity, but is severely disoriented with even minimal deviation from these routes.

We also found that Pt1 could follow a route drawn on a map, although she had some difficulties in using the map to select and follow a self-determined route. In both cases, however, she reported that these tasks involving maps were more difficult than the other tasks. Pt1 was also unable to create accurate maps of environments familiar to her: although she was able to report the information available within the environment (number of rooms or name of streets), the layouts of these familiar surroundings revealed spatial distortions. Altogether, her pattern of performance suggested a specific difficulty with using cognitive maps. This was confirmed by her performance on the Cognitive Map Test. Pt1 had a severe deficit in the formation of the mental map of the environment; however, once she had acquired such a map through overtraining, her performance on the retrieval task was similar to that of a control group. These findings point to an impairment specific to the acquisition rather than the retrieval and use of a mental representation of the environment.

Evidence from neuropsychological (Abrahams, Pickering, Polkey, & Morris, 1997; Bohbot, Iaria, & Petrides, 2004; Bohbot et al., 1998; Feigenbaum, Polkey, & Morris, 1996; Goldstein, Canavan, & Polkey, 1989; Holdstock et al., 2000; Maguire et al., 1996) and neuroimaging (Aguirre, Detre, Alsop, & D'Esposito, 1996; Hartley et al., 2003; Iaria et al., 2003; Maguire et al., 1998; Mellet et al., 2000) studies points to a critical role for the hippocampal complex in topographical orientation. We recently reported activation of the hippocampus and retrosplenial cortex during both formation and use of a cognitive map (Iaria et al., 2007), and used diffusion tensor imaging to show that both the formation and use of a cognitive map are strongly related to the microstructural properties of the hippocampus (Iaria, Lanyon, Fox, Giaschi, & Barton, 2008). Like healthy controls (Iaria et al., 2007), Pt1 showed activity within the parietal, temporal and frontal regions while she attempted to form a cognitive map (Tables 2 and 3), consistent with their role in attentional and perceptual processing of spatial information (Andersen & Gnadt, 1989; Burgess et al., 2002; Gnadt & Andersen, 1988; Maguire, 1997; Milner & Goodale, 1995; Petrides & Pandya, 2006), but not within either the hippocampus or retrosplenial cortex. On the other hand, while she was using the cognitive map she had formed through overlearning, these areas did show activation, as in our healthy controls. Although some caution needs to be taken with respect to the single-subject level analyses, the neuroimaging data reported in this study seems to be consistent with the conclusions from her behavioural data, that she has difficulty with acquisition rather than retrieval of cognitive maps, and may provide a pathophysiological basis for her developmental topographic disorientation.

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