

Retrosplenial and hippocampal brain regions in human navigation: complementary functional contributions to the formation and use of cognitive maps

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Abstract

The ability to orientate within familiar environments relies on the formation and use of a mental representation of the environment, namely a cognitive map. Neuropsychological and neuroimaging studies suggest that the retrosplenial and hippocampal brain regions are involved in topographical orientation. We combined functional magnetic resonance imaging with a virtual-reality paradigm to investigate the functional interaction of the hippocampus and retrosplenial cortex during the formation and utilization of cognitive maps by human subjects. We found that the anterior hippocampus is involved during the formation of the cognitive map, while the posterior hippocampus is involved when using it. In conjunction with the hippocampus, the retrosplenial cortex was active during both the formation and the use of the cognitive map. In accordance with earlier studies in non-human animals, these findings suggest that, while navigating within the environment, the retrosplenial cortex complements the hippocampal contribution to topographical orientation by updating the individual's location as the frame of reference changes.

Introduction

When moving within familiar surroundings, we are able to reach various locations efficiently by relying on a mental representation of the environment. For example, the mental representation of one's neighbourhood, which includes the location of one's home and any other relevant environmental landmark (e.g. the supermarket), allows one to move from one place to another by following correctly a particular route. Such a mental representation, which is built up by exploring the environment and is then used to navigate within the environment, is often referred to as a cognitive map (Tolman, 1948; O'Keefe & Nadel, 1978).

The fundamental role of the hippocampus in establishing and maintaining a cognitive map of the environment was first established in rodents (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978; Wilson & McNaughton, 1993; White & McDonald, 2002) and was extended to the human brain by several neuropsychological studies (Smith & Milner, 1989; Pigott & Milner, 1993; Maguire *et al.*, 1996; Bohbot *et al.*, 1998, 2004; Ekstrom *et al.*, 2003). More recently, functional neuroimaging, following previous findings in rodents, confirmed the role of the hippocampus (Maguire *et al.*, 1998; Hartley *et al.*, 2003; Iaria *et al.*, 2003) and the parahippocampal cortex (Epstein & Kanwisher, 1998; Epstein *et al.*, 2005) in human topographical orientation.

The discovery of head direction cells within the retrosplenial cortex in rodents, i.e. cells that fire when animals are heading towards a certain direction within the environment, suggested that this brain region also plays a critical role in navigation (e.g. Taube, 1998; Cho & Sharp, 2001). Consistent with the rodent research, patients with posterior lesions that include the retrosplenial cortex show a selective topographical disorder referred to as 'heading disorientation' (Aguirre & D'Esposito, 1999). These patients are able to remember the landmarks available within the environment, but they are unable to derive directional information from them (Takahashi *et al.*, 1997). In addition, functional neuroimaging studies investigating navigation in human subjects have often reported increased brain activity within the retrosplenial cortex (e.g. Maguire, 2001).

Although it appears that both the retrosplenial and the hippocampal brain regions are involved in human topographical orientation (Wolbers & Büchel, 2005), it is not clear at what point these brain regions interact functionally. Does the interaction take place during the formation of a cognitive map (i.e. while learning about the environment) and/or while using it to move from one place to another in the same familiar environment? In order to answer these questions, we scanned healthy human subjects with functional magnetic resonance imaging (fMRI) in a virtual-reality environment. First, we asked participants to navigate within a virtual city in order to acquire a mental representation of the environment, i.e. the landmarks available within it and their spatial relationships (learning condition). After forming a cognitive map of the environment, the participants were asked to reach various landmarks starting from different locations, i.e. they were required to use their cognitive map of the environment to navigate within the same virtual city (retrieval condition).

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Materials and methods

Subjects

Nine healthy right-handed human subjects (five women; mean age 24.9 ± 4.1 years) without a history of neurological or psychiatric disorders participated in the study. All subjects gave written informed consent. The study was approved by the Research Ethics Board (REB) of the Montreal Neurological Institute and Hospital. The study conforms with the Code of Ethics of the World Medical Association (Declaration of Helsinki) as printed in the *British Medical Journal* (18 July, 1964).

Virtual environment

The experimental paradigm consisted of a virtual city in which participants navigated by using a three-button keypad, each button corresponding to movement in one of three directions: left, forward and right. The virtual city, which was created by using the editor of a three-dimensional game software (Game Studio A6, La Mesa, CA, USA), was composed of several buildings of different size and shape, but the same texture. Thus, the buildings could not easily be distinguished from each other. However, the virtual city included six clearly identifiable landmarks: a cinema, a restaurant, a bar, a hotel, a pharmacy and a flower shop. Figure 1a and b provide a schematic outline of the city (top-view) and an example of a landmark.

Conditions

The study included two experimental conditions: learning and retrieval. In the learning condition, the participants were instructed to explore freely the virtual environment in order to create a mental representation of the city, i.e. the six identifiable landmarks and their spatial relationships. The subjects were instructed to learn about the environment and the spatial relationships between the landmarks for the entire duration of the condition. Thus, during the learning condition, the subjects were forming a cognitive map of the virtual city. All subjects started the task at the centre of the virtual environment facing the same direction. In a pilot behavioural experiment, we asked 16 different participants to explore freely the environment until they had formed a mental representation of it, including the six identifiable landmarks; then, as soon as they had spontaneously stopped, they were asked to report the locations of the six different landmarks on a schematic map that represented the city from a top-view perspective. All subjects were able to form a perfect mental representation of the environment (100% accuracy) in 13 min or less of exploration. Thus, a cognitive map of the virtual city used in this study could be effectively created in as little as 13 min by explicitly asking the participants to create such a mental representation of the environment. On the basis of these behavioural data, the duration of the learning task in the present fMRI study was 13 min.

During the fMRI scanning, the learning condition was followed immediately by the retrieval condition in which they were required to use the cognitive map. The retrieval condition consisted of 18 trials in which the subjects were required to use the mental representation that they had formed in order to reach the location of specific landmarks. On each trial, the subjects started by facing one of the six landmarks and a sign indicating the target location they needed to reach, as quickly as possible, by following the shortest pathway (see Fig. 1c for an example). Both starting and target locations varied across trials to make the use of the cognitive map the only efficient way to perform the task. Both the accuracy and the duration of each trial were recorded.

There was also a control condition during which the participants navigated a defined route by following directions (i.e. arrow signs) along the path. In this task, a new virtual city was used that did not

contain any of the six landmarks found in the city of the experimental conditions. In addition, in the control task, the structure of the city (i.e. the spatial organization of the buildings) was different from that used in the experimental tasks. In this way, any incidental topographical encoding of the environment while performing the control task, if this occurred, would not contribute to the formation and use of the cognitive map explicitly required during the experimental conditions. However, to control for purely perceptual processing, the texture and number of the buildings were identical for the cities used in both the experimental and the control conditions. That is, the control condition controlled for the motor and perceptual aspects of the experimental conditions. The control trials, which had a duration of 1 min, were administered several times in the scanning sessions (see below) and, on each occasion, the defined route and the structural organization of the virtual city was different.

Procedure

Before scanning, the participants were required to navigate freely for 10 min within a virtual city that was different from the one adopted for the study in order to practise the motor aspects of the tasks and familiarize themselves with the virtual environment in general. In this practice virtual city, there were general buildings but no identifiable landmarks. The subjects were then administered three control trials with different pathways from those administered during scanning. After this preliminary training, the instructions were given for the learning and retrieval conditions to be performed during scanning. For the learning condition, the subjects were told to focus on the formation of the mental representation of the city as its use would be necessary (i.e. the only way) to perform successfully the retrieval condition. Finally, they were told the number and identity of the landmarks available within the environment, and they were asked to perform the scanning session.

The scanning session consisted of two functional runs and one anatomical acquisition. The duration of each functional run was 14 min. The first functional run included one control trial (1 min) followed by the learning condition (13 min). The second functional run included the 18 trials of the retrieval condition mixed with several control trials. In this second functional run, the sequence of trials was as follows: one control trial, six retrieval trials, one control trial, six retrieval trials, one control trial, six retrieval trials, one control trial. In each control trial, the structure of the city and the pathways that the participants were required to take by following the signs along the route were different. The duration of each control trial was 1 min and the duration of each retrieval trial varied depending on the distance between the starting position and the target location.

The software used to create the virtual environment included a script that allows the linking of different files. Thus, during each scan (learning or retrieval condition), the trials 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 trial) or approaching very close to the target locations (in the retrieval trials). At the end of the scanning sessions, each subject underwent an interview during which the experimenters gathered information regarding the strategies used during both the learning and the retrieval conditions. In addition, the accuracy of the cognitive map that was formed was assessed by asking the subjects to draw on a blank sheet of paper the outline of the virtual city and the respective location of each landmark. Error rates, time and paths travelled while performing the experimental (learning, retrieval) and control trials were acquired by a video-recording system located outside the scanner room.

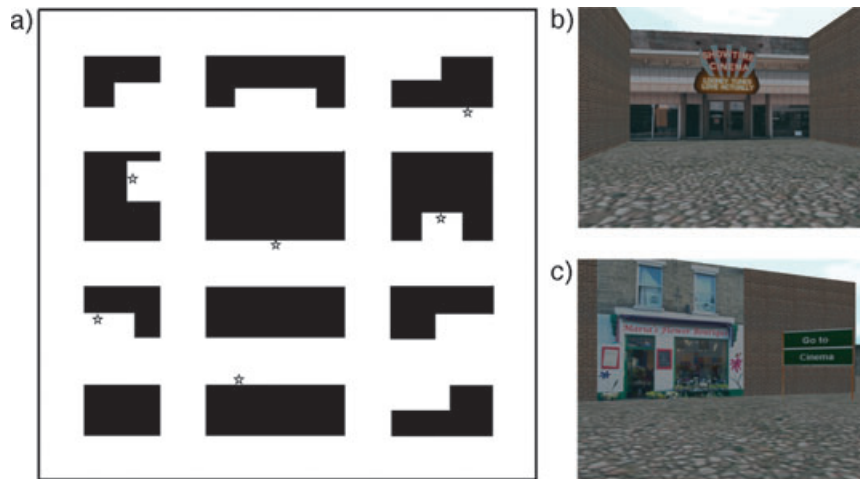


FIG. 1. Views of the virtual environment. (a) Top-view (survey map) of the virtual city including the locations of the six landmarks indicated by stars (not shown to the participants). (b) View of one of the six landmarks as they appear to the participants while learning about the environment. (c) Starting position in one of the 18 trials in which participants were asked to reach specific landmarks: in this example, the subjects were asked to reach the cinema (target location) from the flower shop (starting position).

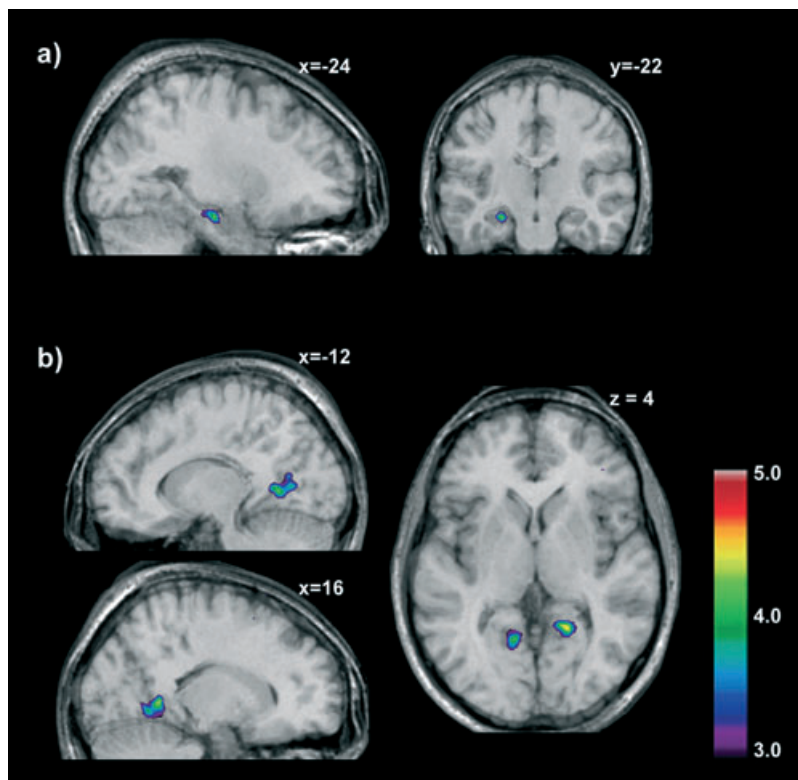


FIG. 2. Brain activity while forming the cognitive map. (a) Increased activity within the left anterior hippocampus (sagittal and coronal views) and (b) the retrosplenial cortex bilaterally (sagittal and horizontal views) while subjects were learning about the environment (i.e. forming the cognitive map). The t maps are superimposed onto the anatomical average of two participants (one female, one male). See Table 1 for the stereotaxic coordinates and the t -values of the peaks of activation.

MRI data acquisition

Functional MRI scanning was carried out with a 1.5-T Siemens Sonata scanner (Siemens AG, Erlangen, Germany). Each scanning session started with the acquisition of high-resolution (1 mm^3) T1-weighted three-dimensional structural images for anatomical localization of the functional data. Functional images were then acquired using blood oxygen level-dependent (BOLD) fMRI, using a T2*-weighted

gradient echo (GE) echo-planar imaging (EPI) sequence (TR, 4500 ms; TE, 50 ms; FA, 90). Two functional runs were carried out, one for the learning and the other for the retrieval condition (both runs included control trials). Each functional run comprised 200 volumes of acquisition. Each acquisition included 32 oblique, contiguous slices (4 mm thickness, positioned in a plane parallel to the hippocampus), covering the entire brain. Tasks were presented via an LCD projector

to a screen placed in front of the scanner, then to the subject via a mirror mounted on the head coil. The subjects performed the tasks by means of an MRI-compatible keypad.

MRI data and statistical analyses

For each functional run, all frames were first realigned to the fourth frame to avoid T1 saturation effects and MRI sensitivity to motion. The images were then spatially smoothed with a 6-mm full-width at half-maximum Gaussian filter to increase the signal-to-noise ratio of the data and the tolerance of the subsequent analysis steps to residual motion in the scans, as well as to minimize resampling artefacts. The motion-corrected data were analysed statistically by using FMRISTAT (Worsley *et al.*, 2002). For both the learning and the retrieval runs, whole brain analyses were carried out by contrasting the learning, the retrieval and the control phases performed during the acquisition scan against each other. Significant BOLD changes were determined at each voxel, based on a linear model with correlated errors. To obtain the average group *t* maps, all individual MRI data were first normalized to the Montreal Neurological Institute (MNI) stereotaxic space constructed from average stereotaxic MRI of 305 normal subjects (Evans *et al.*, 1993) and were then combined using a mixed-effects linear model. The resulting *t* statistic images were thresholded using the minimum given by a Bonferroni correction and random field theory to correct for multiple comparisons (Worsley *et al.*, 1996).

The significance of the activity differences between the compared conditions was determined by the spatial extent of the activated regions (i.e. the cluster of contiguous voxels above a certain threshold). An activation cluster was significant at $P < 0.05$ when it had a volume equal to or greater than 221 mm³ and $t > 3.17$ for all its voxels. Each set of fMRI data was then co-registered to the corresponding anatomical MRI, which was corrected for intensity non-uniformity (Sled *et al.*, 1998), and normalized to the MNI standard stereotaxic space. To examine how brain activity changed over the course of the two experimental conditions, volumes of interest (VOIs) were defined in the hippocampus, the parahippocampal cortex and the retrosplenial cortex by using the activation clusters obtained from the whole brain analysis. Percentage BOLD signal changes in these regions were then calculated at different intervals: every 1-min block for the 13-min learning condition and each trial for the retrieval condition. Repeated-measures analysis of variance was performed to assess differences in BOLD signal changes between VOIs during the entire learning and retrieval phases of scanning.

Results

Behavioural data

During the learning condition, i.e. during the formation of the cognitive map, all subjects exhibited a similar systematic strategy in exploring the environment: each participant defined the northern, southern, western and eastern sides of the city and navigated from one side to the opposite one until all the landmarks were found and all the roads were covered. Some subjects started by moving around the borders of the environment and then explored the city in the methodical fashion described above. When tested for their ability to reproduce the outline of the virtual city, all subjects were able to make a schematic drawing of the environment as viewed from the top, including the correct location of the six landmarks (100% accuracy). Individual reports confirmed the strategies that the subjects had adopted to explore the city (as described above) and the fact that they

had focused on forming a mental representation during the learning condition. In addition, all participants explicitly reported that they could perform easily the retrieval trials because they were able to rely on their mental representation of the environment. During the 18 trials of the retrieval condition, all participants were able to reach the target location by following the shortest pathway (100% accuracy), as assessed, independently, by two experimenters on the remote video-system and the time required by each individual to complete each trial (mean \pm SD: 19.55 \pm 3.96 s).

Imaging data

Whole-brain analysis comparing brain activity during the two experimental conditions (i.e. learning and retrieval) with activity during the control condition revealed significant increases in the frontal and parietal cortex and the hippocampal system. These peaks of increased activity during the learning and retrieval conditions are presented in Table 1. During the learning task (i.e. the formation of the cognitive map), significant increases in brain activity were observed in the left anterior hippocampus (Fig. 2a) and in the retrosplenial cortex, bilaterally (Fig. 2b). The specific changes in the activation pattern during the 13-min learning phase are presented in Fig. 3a. A repeated-measures ANOVA with VOIs (left retrosplenial, right retrosplenial, left anterior hippocampus) and Learning-Phase (minutes 1–13) as independent factors, and BOLD signal change as dependent variable, showed no statistically significant main effect of VOIs ($F_{2,16} = 0.34$; n.s.) or interaction effect of VOIs \times Learning-Phase ($F_{24,192} = 0.22$; n.s.). These findings suggest an equal contribution of the retrosplenial and hippocampal regions during the entire session of learning. There was, however, a statistically significant main effect of Learning-Phase ($F_{12,96} = 4.91$; $P < 0.0001$). *Post-hoc* comparisons (Duncan test) showed that the BOLD signal changes at the beginning (minutes 1, 2 and 3) and the end (minutes 12 and 13) of the learning phase were lower than the BOLD signal changes observed in the middle of the learning session; BOLD signal changes during minutes 4–11 did not differ significantly. This finding indicates an analogous increase in both the retrosplenial and the hippocampal regions during the initial period of learning (minutes 1–3) and a slight decrease at the very end of the learning session (minutes 12 and 13).

With respect to the retrieval condition, which required the use of the cognitive map, significant increases in brain activity were found in the right posterior hippocampus and the parahippocampal cortex, bilaterally (Fig. 4a). Note that the peak of activity in the right hemisphere was located between the hippocampus and the parahippocampal cortex and extended towards both these regions. Activity within the retrosplenial cortex, bilaterally, was found during both the learning and the retrieval conditions (Fig. 4b). To answer the question of whether these brain activities were modulated by performance, time spent by the participants to reach the target locations during the retrieval trials was used as a regressor. There was no significant correlation between time on the task and brain activity. To investigate changes in VOIs that might be dependent on the extent of practice in using the cognitive map, we analysed BOLD signal at three stages of the retrieval condition: initial (first six trials), middle (second six trials) and late (last six trials). A repeated-measures ANOVA with VOIs (left retrosplenial, right retrosplenial, left parahippocampal cortex, right parahippocampal cortex, right posterior hippocampus) and Stage (initial, middle, late) as independent factors and BOLD signal change as dependent variable was carried out. This analysis revealed no statistically significant main effects of VOIs ($F_{4,32} = 0.57$; n.s.), Stage ($F_{2,16} = 0.02$; n.s.) or VOIs \times Stage interaction ($F_{8,64} = 0.71$; n.s.),

TABLE 1. Brain activity peaks for the main effect of acquisition of the cognitive map and using the cognitive map

Anatomical region	Left hemisphere				Right hemisphere			
	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> -value	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> -value
Acquisition of cognitive map (learning vs. control)								
Retrosplenial cortex	-12	-60	6	4.16	20	-54	2	4.75
Hippocampus	-24	-22	-16	4.37				
Premotor cortex (area 6)	-26	6	52	3.89	34	2	50	3.68
Mid-dorsolateral prefrontal cortex (area 9)					12	40	44	3.96
Mid-dorsolateral prefrontal cortex (area 46)	-32	40	22	3.46				
Mid-ventrolateral prefrontal cortex (area 47/12)					40	20	-10	4.11
Middle temporal gyrus (area 21)					56	-40	-2	4.42
					54	8	-20	3.94
Parietal cortex (intraparietal sulcus)	-34	-46	32	3.38	42	-48	30	4.2
Fusiform gyrus					46	-44	-28	4.54
Calcarine sulcus					2	-88	6	4.84
Cerebellum	-8	-54	-18	4.37	4	-72	-10	4.5
Using of cognitive map (retrieval vs. control)								
Restrosplenial cortex	-16	-58	20	5.07	16	-54	14	4.74
Hippocampus/parahippocampal cortex	-24	-38	-12	5.86	24	-38	-6	6.83
Hippocampus					24	-36	-2	5.08
Premotor cortex (area 6)	-26	-10	48	5.0				
Medial superior frontal gyrus (pre SMA)	-6	8	56	4.02				
Mid-dorsolateral prefrontal cortex (area 46)	-34	38	12	5.3	34	30	30	3.2
Mid-dorsolateral prefrontal cortex (area 9/46)	-30	28	32	3.71				
Mid-ventrolateral prefrontal cortex (area 47/12)					28	30	2	4.08
Anterior cingulate cortex	-16	20	32	4.55				
Parietal cortex (intraparietal sulcus)	-32	-38	40	3.93	36	-64	46	5.02
Lingual gyrus	-16	-78	-8	4.41				
Thalamus	-2	-14	-18	4.46	8	-18	20	3.88
Cerebellum	-4	-72	-18	6.6	6	-68	-22	11.71

confirming that, in each trial, the retrosplenial and hippocampal regions (including the parahippocampal cortex) contribute equally to successful performance on the retrieval task; moreover, their contribution was distributed equally during the entire retrieval session without statistically significant increase or decrease in the BOLD signal. The results (trial by trial, from the beginning to the end of the session) are shown in Fig. 3b.

Direct comparisons between the learning and retrieval conditions confirmed the differences in hippocampal and parahippocampal activities during the formation and use of the cognitive map that were revealed from the comparisons with the control activity. In the learning condition minus retrieval condition comparison, a BOLD signal increase was revealed within the left anterior hippocampus, at the exact coordinates of the activity peak shown by the learning task minus control condition comparison. However, the direct comparison learning minus retrieval revealed a signal increase within the right anterior hippocampus that had not been shown in the previous analysis. This additional peak can be explained as follows. In the learning condition vs. the control condition comparison, there was a non-significant decrease in the BOLD signal within the right anterior hippocampus, whereas in the retrieval condition vs. control condition comparison, there was a significant decrease in BOLD signal change in the right anterior hippocampus (and concomitant increased BOLD signal change in the posterior region of the same hippocampus). The direct comparison between these two decreased signal changes resulted in an apparent increase when the two tasks were compared directly. The concomitant increases and decreases in the BOLD signal within the posterior and anterior hippocampus, respectively, agree with findings from other studies that showed a similar effect while individuals navigate within familiar environments (e.g. Maguire *et al.*, 2000, 2006). The above considerations suggest that, in our study,

activity in the right anterior hippocampus was not increased during learning and its signal was significantly decreased during the retrieval phase. By contrast, increased activity was observed in the posterior hippocampal region.

The direct comparison retrieval condition minus learning condition confirmed the previous findings indicating increased BOLD signal within the parahippocampal cortex, bilaterally, and the right posterior hippocampus during retrieval. The dissociation of the hippocampal activity during the learning and retrieval conditions is illustrated in Fig. 5.

Discussion

In this study, we used fMRI combined with a virtual-reality paradigm to investigate the relative contribution of the retrosplenial and hippocampal brain regions in human topographical orientation. The involvement of these brain regions in human navigation had been suggested by neuropsychological (Aguirre & D'Esposito, 1999) and functional neuroimaging studies (for a review, see Maguire, 2001), but the relative contribution of the hippocampus and the retrosplenial cortex to the acquisition as opposed to the use of a cognitive map had not been previously investigated. The present study examined whether these brain regions interact functionally while the subject is building up a cognitive map of the environment and then in using it to navigate within the environment.

During the learning phase, participants were explicitly asked to create a mental representation of the environment: the landmarks and their spatial relationships. During the formation of such a cognitive map there was increased activity mainly involving the parietal, frontal and middle temporal gyri, the retrosplenial cortex bilaterally and the left anterior hippocampus (see Table 1; main effect of learning).

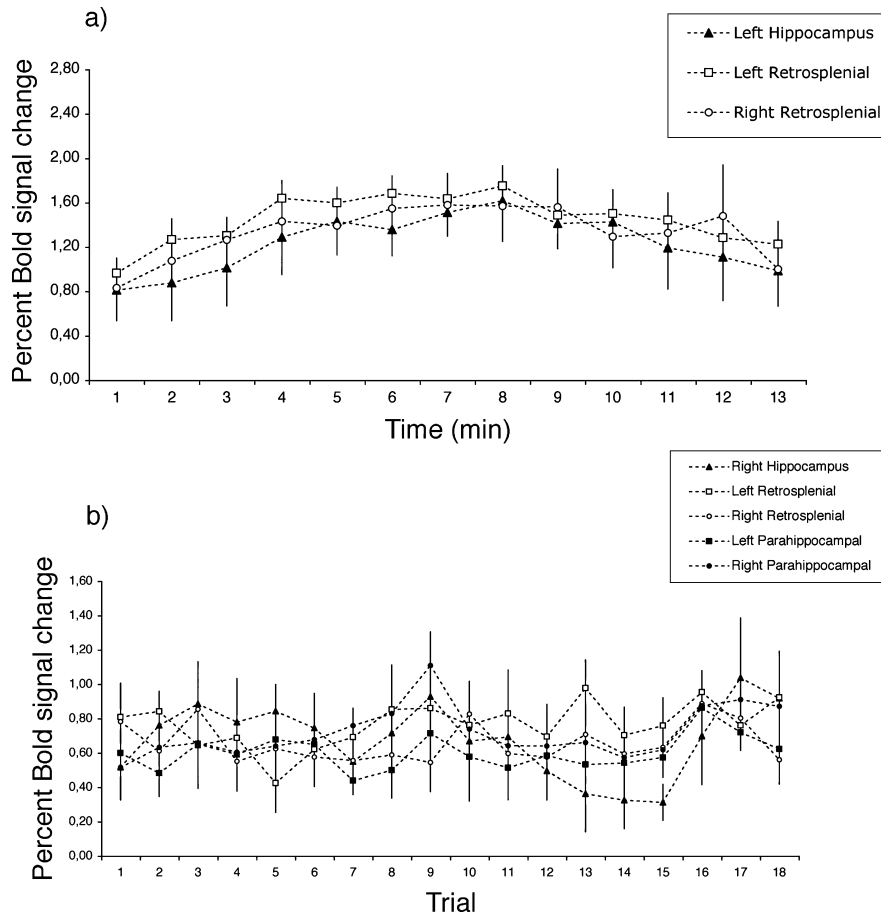


FIG. 3. Brain activity while forming and using the cognitive map. Mean (\pm SEM) percentage BOLD signal changes for the regions of interest are displayed across time (minute 1 to minute 13) during the learning phase (i.e. while forming the cognitive map) (a) and across trials (trial 1 to trial 18) during the retrieval session when participants used the cognitive map for orientation (b).

Importantly, the retrosplenial and hippocampal regions were equally involved during the entire phase of learning. There was an increase in activity within both the retrosplenial and the hippocampal regions during the first few minutes of learning. This activity reached its peak in the middle of the learning phase and decreased during the last few minutes. Note that there were no differences in this pattern of activity between the retrosplenial and hippocampal regions during the entire session of learning.

The use of the cognitive map of the environment that was acquired during the learning phase was tested by asking the subjects to reach different landmarks starting from different places within the environment. During the performance of this task, increased activity was observed in the parietal, frontal, cingulate, retrosplenial and parahippocampal cortex, bilaterally, and the right posterior hippocampus (see Table 1; main effect of retrieval). Again, during performance of this task, the contribution of the retrosplenial and hippocampal regions (including the parahippocampal cortex) was comparable: no differences were found in the BOLD signal between these brain regions across trials for the entire retrieval session. In addition, their contribution was comparable during the entire duration of the scan without any statistically significant increase or decrease in BOLD signal change.

During both the formation and the use of the cognitive map, the subjects were tracking (i.e. monitoring) within their working memory locations that they had already visited in comparison with locations

that still had to be visited. As would be expected, there was increased activity in the mid-dorsolateral prefrontal cortex (areas 46 and 9), which has been shown to be critical for monitoring information in working memory (Petrides, 2005). In addition, there has been increased activity in the mid-ventrolateral prefrontal cortex (area 47/12), which is involved in the active controlled retrieval of information from memory (Petrides, 2005). The parietal cortex was found to be involved in both the learning and the retrieval sessions, consistent with its critical role in spatial perception and movement in space that has been clearly established from work in human subjects (Mesulam, 1981; Posner *et al.*, 1984) and monkeys (Petrides & Iversen, 1979), as well as from functional neuroimaging studies (Ungerleider & Haxby, 1994).

Bilateral parahippocampal activity was confined to the retrieval phase, a result consistent with the role of this region in the processing of viewpoint-specific scenes (Epstein *et al.*, 2005). In our paradigm, environmental scenes were viewpoint-specific only in retrieval trials, i.e. when participants started and reached a target location from a specific point of view. By contrast, during learning, participants approached a particular scene from different angles and there was therefore no viewpoint specificity, resulting in non-significant parahippocampal activity (Epstein *et al.*, 2005). The hippocampal contribution when building up the cognitive map, as opposed to using it, was distinct: while learning, increased activity was confined to the left anterior hippocampus, whereas in retrieval the activity was

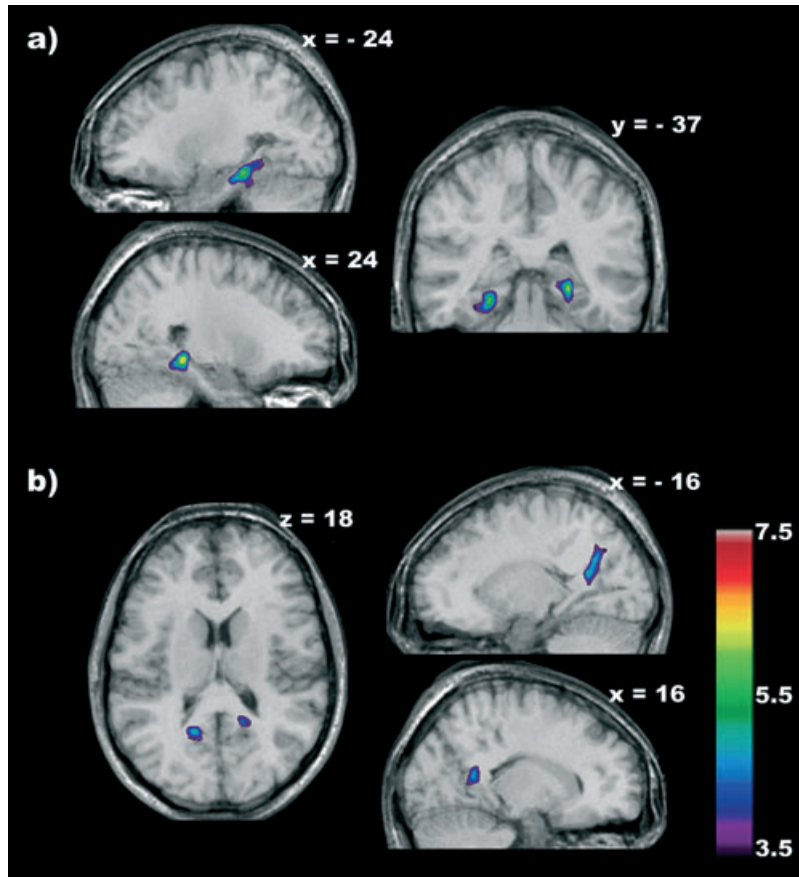


FIG. 4. Brain activity while using the cognitive map. (a) Sagittal and coronal views to display the brain activity within the parahippocampal cortex, bilaterally, and the right posterior hippocampus while participants were reaching different locations within the environment (i.e. using the cognitive map). (b) Sagittal and horizontal views of the brain to show activity within the retrosplenial cortex, bilaterally, while performing the same task. The *t* maps are superimposed onto the anatomical average of two participants (one female, one male). See Table 1 for coordinates and *t*-values of the peaks of activation.

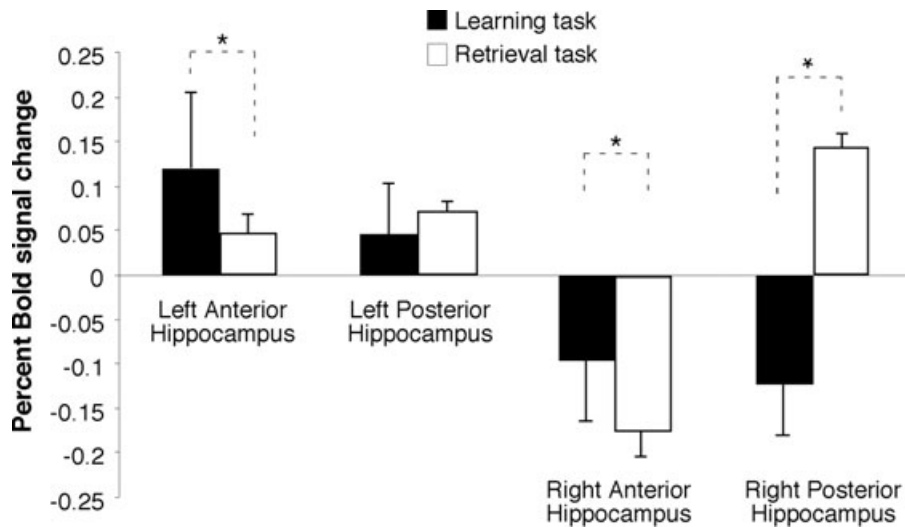


FIG. 5. Hippocampal activity while individuals are forming a cognitive map of the environment (learning) and using it for the purpose of navigation (retrieval). Percentage BOLD signal changes reported in the figure refer to values obtained from comparing the two experimental conditions with the control condition (learning minus control and retrieval minus control). An asterisk indicates statistically significant differences when comparing directly the two tasks (learning vs. retrieval, retrieval vs. learning).

confined to the right posterior hippocampus. The increased activity within the retrosplenial cortex was bilateral during both the formation and the use of the cognitive map.

Based on neuropsychological (Takahashi *et al.*, 1997) and neuroimaging (Maguire, 2001) evidence with human subjects, as well as the presence of head-direction cells in the retrosplenial cortex in rodents

(Taube, 1998; Cho & Sharp, 2001), it has been argued that the retrosplenial cortex may be critical for the transformation of egocentric spatial coordinates, while moving within the environment, to an allocentric representation established within the hippocampus during the formation of the cognitive map (Maguire, 2001; Wolbers & Büchel, 2005). The egocentric coordinates refer to the spatial localization of a landmark in relation to the subject's position, whereas the allocentric representation of the same landmark refers to its relationship with other environmental landmarks independent of the subject's location. The interpretation of the retrosplenial cortex as being critical for the transformation of one kind of information (egocentric) into another (allocentric) is supported by evidence that it processes spatial information in an egocentric frame of reference in humans (Andersen *et al.*, 1997; Galati *et al.*, 2001; Halligan *et al.*, 2003). In this context, our data shed light on the contribution of the retrosplenial cortex in human navigation: (1) the retrosplenial contribution to the transformation of spatial information parallels that of the hippocampus during the establishment of the cognitive map, and (2) such transformations by the retrosplenial cortex are present even when allocentric information needs to be transformed into an egocentric one (i.e. from cognitive map to ground-level perspective). In other words, the specific role of the retrosplenial cortex in topographical orientation may refer to the updating of one type of spatial information into a different one, independently of the direction of the transformation: from the ground-level perspective into the mental representation while forming the cognitive map, and vice versa, from the mental representation into the actual ground-level perspective when the cognitive map is being used for the purpose of navigation.

Although the general role of the hippocampus in human navigation appears well established (Maguire *et al.*, 1998; Ekstrom *et al.*, 2003; Hartley *et al.*, 2003; Iaria *et al.*, 2003), its functional lateralization (left and right hemisphere) and rostral to caudal segregation remain controversial (Grön *et al.*, 2001). Although there is evidence that the left hippocampus may subservise context-dependent episodic memory and the right hippocampus may be related to specific spatial memory demands (Aguirre *et al.*, 1996; Stern *et al.*, 1996; Brewer *et al.*, 1998; Kelley *et al.*, 1998), several neuroimaging studies have reported involvement of the left hippocampus during the performance of spatial memory tasks (Grön *et al.*, 2001; Hartley *et al.*, 2003; Iaria *et al.*, 2003; Incisa della Rocchetta *et al.*, 2004; Wolbers & Büchel, 2005). These results have been interpreted as reflecting verbal contribution during the learning of topographical relations, with engagement of the right hippocampus when the relational information needs to be used (Grön *et al.*, 2001). This interpretation of functional lateralization in the hippocampus in human navigation is in accordance with the known advantage of the left hemisphere in processing categorical spatial relationships and the advantage of the right hemisphere for metric and distance judgements between objects (Kosslyn *et al.*, 1989).

With respect to its anterior/posterior functional segregation, studies in non-human animals (Moser & Moser, 1998) and human patients (Phelps *et al.*, 1991; Corkin *et al.*, 1997), as well as neuroimaging in normal human subjects (Strange *et al.*, 1999; Davachi & Wagner, 2002), indicate that the anterior hippocampus is involved in relational encoding and novelty, whereas the posterior hippocampus may be involved during the retrieval of information (Dolan & Fletcher, 1999) during navigation (Maguire *et al.*, 1998; Hartley *et al.*, 2003; Iaria *et al.*, 2003; Wolbers & Büchel, 2005). In addition, various findings in both human subjects and non-human animals (e.g. Moser *et al.*, 1993; Jung *et al.*, 1994; Colombo *et al.*, 1998; Hock & Bunsey, 1998; Schacter & Wagner, 1999; Lee & Kesner, 2003; Kesner *et al.*, 2004;

Lee *et al.*, 2005; Gogtay *et al.*, 2006; Maguire *et al.*, 2006) suggest that the anterior and posterior hippocampus may rely on distinct processing of memory for objects and spatial scenes, respectively. The dissociation revealed in the present study is in line with both the lateralization and the functional segregation described above: the anterior left hippocampus appears to be involved in the formation of the cognitive map when subjects learn about spatial relationships between the landmarks; in this specific context, individuals engage object-specific processing in order to learn spatial relationships between landmarks. On the other hand, the posterior right hippocampus seems to be more involved when using the cognitive map to reach different locations within the environment; in this case, individuals make use of a more global (mental) scene of the environment, including multiple landmarks and their spatial relationships, to navigate from one place to another. The latter result is also consistent with the reported increased grey matter of the right posterior hippocampus in taxi drivers compared with non-taxi drivers and bus drivers (Maguire *et al.*, 2000, 2006). It could be argued that the increased volume of the right posterior hippocampus in taxi drivers may be explained by the length of time they made use of the cognitive map of the environment which, as we showed here, relies specifically on the right posterior hippocampus.

In a recent fMRI study by Wolbers & Büchel (2005), bilateral activity was observed within the retrosplenial cortex, reflecting learning in terms of accuracy (the better the knowledge of the environment, the greater the retrosplenial activity), as well as activity within the left anterior hippocampus related to the amount of knowledge acquired while learning (the more the novel spatial information that must be processed, the greater the activity within the hippocampus). Based on these results, these investigators suggested a dissociable contribution of the retrosplenial and hippocampal regions during the formation of a cognitive map: the retrosplenial cortex is involved during the entire phase of learning, whereas the hippocampus is more active during the initial phase and less active as performance approaches ceiling, i.e. when no novel information needs to be processed. This conclusion is not consistent with our results, which instead show an equal contribution of both the retrosplenial and the hippocampal regions during the entire learning session. The most parsimonious explanation for these contrasting results may be, as already pointed out by Wolbers & Büchel (2005), that in their study participants may have solved the task, initially, by relying on the environmental landmarks and then, after familiarity with the environment, by acquiring a strategy based on route knowledge. However, previous studies have shown that the use of route knowledge relies on the caudate nucleus, whereas the hippocampus is involved, primarily, when environmental landmarks are used for navigation (Hartley *et al.*, 2003; Iaria *et al.*, 2003). This fact may explain why in the study by Wolbers and Büchel the hippocampus appeared to be involved only in the initial phase of learning without comparable activity in the retrosplenial cortex. By contrast, in our study subjects were aware that they would be required to find different landmark locations starting from different places. This made acquisition of a navigational strategy based on route knowledge unnecessary and resulted (as reported by the subjects) in learning the information most relevant for cognitive map formation. Thus, the hippocampal activity parallels that of the retrosplenial during the entire task.

In summary, the results reported in the present study showed that the retrosplenial and hippocampal regions play a complementary role during both the formation and the use of cognitive maps. The retrosplenial cortex may mediate the transformation from one frame of reference to another, regardless of the direction of this transformation

(i.e. from a ground-level perspective into a mental representation and vice versa). During both learning and retrieval, retrosplenial activity parallels left anterior hippocampal activity involved in forming a cognitive map of the environment and right posterior hippocampal activity when the cognitive map is being used for the purpose of navigation.

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Abbreviations

fMRI, functional magnetic resonance imaging; VOI, volume of interest.

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