Hippocampus

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Abstract

Finding our way in a previously learned, ecologically valid environment concurrently involves spatial and contextual cognitive operations. The former process accesses a cognitive map representing the spatial interactions between all paths in the environment. The latter accesses stored associations between landmark objects and their milieu. Here, we aimed at dissociating their neural basis in the context of memory-based virtual navigation. To do so, subjects freely explored a virtual town during one hour then were scanned using fMRI while retrieving their way between two locations, under four navigation conditions designed to probe separately or jointly the spatial and contextual memory components. Besides prominent commonalities found in a large hippocampo-neocortical network classically involved in topographical navigation, results yield evidence for a partial dissociation between the brain areas supporting spatial and contextual components of memory-based navigation. Performance-related analyses indicate that hippocampal activity mostly supports the spatial component, whereas parahippocampal activity primarily supports the contextual component. Additionally, the recruitment of contextual memory during navigation was associated with higher frontal, posterior parietal and lateral temporal activity. These results provide evidence for a partial segregation of the neural substrates of two crucial memory components in human navigation, whose combined involvement eventually leads to efficient navigation behavior within a learned environment.

Introduction

Route retrieval and way finding in a previously learned environment are critical prerequisites to successfully carry out most of our daily activities. These cognitive abilities involve the creation of a cognitive map of the environment, where are coded its landmarks, paths and their spatial relationships (Maguire et al., 1998a; Berthoz, 2001; Pazzaglia and De Beni, 2001). Neuroimaging studies have revealed that navigation in a virtual environment involves an extended neural network, mostly including hippocampal and parahippocampal areas, frontal, posterior parietal and occipital cortices as well as the caudate nucleus (Aguirre et al., 1996; Ekstrom et al., 2003; Maguire et al., 1998b; Hartley et al., 2003; Voermans et al., 2004; Peigneux et al., 2004; Orban et al., 2006). Within these areas, spatial memory-based navigation prominently relies upon activity in the hippocampal formation (e.g. Burgess et al., 2002; Maguire et al., 1998b), also crucially involved in episodic memory. In contrast, procedural memory-based navigation (i.e., moving along a well-known pathway in a kind of automatic fashion) is rather contingent upon activity in the striatal complex (e.g. Packard and Knowlton, 2002; Hartley et al., 2003; Iaria et al., 2003; Orban et al., 2006). Additional experiments have indicated a role for the parahippocampal gyrus in the storage of object location as a part of the neural mechanisms underlying successful navigation (Janzen and van Turennout, 2004) and retrieval of objects' spatial context (Burgess et al., 2001). Recently, promising attempts have been made to track the neural correlates of spontaneous mentalizing and behaviors during virtual navigation (Spiers and Maguire, 2006a, 2006b).

In the present study, we have focused on another possible dissociation between cognitive processes engaged in route retrieval and way-finding, considering that these actions are supported by manifold memory processes in which two prominent

cognitive components may be identified. The first one, spatial representation memory, involves creation of and/or access to a cognitive map of the environment, where are specified the spatial relationships between the streets independently of the salient features of the environment. For instance, when attempting to reach the school from the church, one can keep in mind an "abstract" map-like representation indicating the appropriate direction to follow at each crossroad, independently of specific environmental cues along the way. Besides this "streets configuration" component, a second, complementary process can be used. It refers to a contextual representation memory (or "landmarks memory") where are stored specific associations between salient landmark objects and their milieu. For instance, one may remember that from church to school, there is a right turn just after the library and then a left turn in front of the red telephone box close to the grocery store. In most cases though, both memory constituents are engaged simultaneously during route retrieval or way finding in a previously learned environment, in that navigation involves the creation of a cognitive map coding both the relationships between paths and between landmarks in episodic memory (Maguire et al., 1998a; Berthoz, 2001; Pazzaglia and De Beni, 2001).

Using functional magnetic resonance imaging (fMRI), we investigated the neural bases of spatial (map-like streets configuration) and contextual (milieu-related landmarks) components of navigation memory. To do so, 16 volunteers were scanned under four complementary memory conditions during route retrieval. Before testing, they freely explored during one hour a complex 3D virtual town, composed of three different surroundings in the same city, with distinctive wall and ground features, and landmark objects (Peigneux et al., 2004, 2006; Orban et al., 2006). In the *Natural* testing condition, they were positioned in the same environment as during the training

period and asked to reach target locations from various starting points. This classical

testing condition (e.g., Maguire et al., 1998b; Peigneux et al., 2004, 2006; Orban et

al., 2006) actually does not dissociate the spatial and contextual components of

memory-based navigation since circulating in such an enriched environment may rely

on either or both, or even rely on a stimulus-response associations strategy mediated

by the striatum (Iaria et al., 2003; Voermans et al., 2004; Bohbot et al., 2004; Orban et

al., 2006). Thus, to engage subjects using more specifically the spatial memory

component of navigation, they had, in the *Impoverished* testing condition, to reach

target locations in this same environment after removal of all landmark objects and

after that the walls and ground were made uniform. In this spatial condition indeed,

subjects must rely on their abstract knowledge of the spatial relationships of the

streets to find a way towards the target. Likewise in the *Alternate* condition, the scene

was the same as in the Natural task but the optimal path between the starting location

and the designated target was blocked by an impassable barrier. In this case,

previously identified landmark objects and other contextual features become less

relevant for navigation: subjects should rather rely on a more spatial, less

contextualized representation of the navigation space to build an alternate route. Thus,

this condition further allowed investigating the spatial component by promoting

alternative route-finding strategies. And finally, to specifically assess the contextual

component of memory in navigation, subjects were asked in the Recognition

condition to follow the same pathways while paying particular attention to the

potential changes made to the town's scenery. To minimize the requirements for

spatial information, they had to follow color dots positioned on the ground all along

the pathway. Additionally, a forced-choice recognition task was proposed after each

walk to reveal *a posteriori* the presence or absence of subjects' awareness of

contextual changes. Besides targeted differences, it should be mentioned that all these conditions involve episodic memory, although additional contribution of procedural memory cannot be excluded.

The analysis of brain imaging data aimed at unraveling the specificity of the spatial and contextual memory components of memory-based navigation, by conducting between-tasks comparisons. Additionally, correlation analyses between functional imaging data and behavioral performance aimed at evidencing the brain structures whose activity differentiates efficient from poor navigation at the within-subject level, and good from bad navigators, at the between-subject level, across the various experimental conditions. We hypothesized that although all tasks would elicit grossly similar activity in the neural network classically engaged in navigation (Aguirre et al., 1996; Maguire et al., 1998b; Burgess, 2002; Hartley et al., 2003; Peigneux et al., 2004), those conditions relying more on the spatial memory component should induce higher activity in the hippocampal/parahippocampal region as well as posterior cortical areas. In contrast, tasks more based on the contextual memory component should rather rely upon frontal (Ranganath and Knight, 2003) and lateral temporal (Ojemann et al., 2002) cortices activity, as well as the parahippocampal gyrus known to be involved in visual recognition memory (Meunier et al., 1993; Rauchs et al., 2006).

Materials and Methods

Subjects

Sixteen healthy right-handed volunteers (8 females, 8 males; mean age of the group: 22.1 years; range: 18-30 years) gave their informed, written consent to participate in this experiment approved by the Ethics Committee of the University of Liège. They

were free of neurological or psychiatric disease and had a normal structural MRI brain scan on visual inspection.

Navigation task

Subjects were trained in a virtual environment developed and validated in our laboratory (Peigneux et al., 2004, 2006; Orban et al., 2006), adapted from a commercially available computer game (Duke Nukem 3D, 3D Realms Entertainment, Apogee Software Ltd., Garland TX) using the editor provided (Build, Ken Silverman, Realms Entertainment). The environment was a complex town composed of three districts (Far West, Urban and English) that were made distinct from each other by different visual backgrounds and objects along the streets. Each of these districts contained a target location identified by a rotating medallion (Fig. 1). The virtual town also contained 10 starting points that were each 35 virtual units apart (optimal path) from their associated target location. Subjects navigated at a constant speed within the environment at the ground level using a four-direction keypad with their right hand. During training, the virtual environment was presented on a desktop 800-MHz Pentium-III PC (screen size, 17'). For testing in the scanner, a mirror allowed the participants to see the display of the virtual town projected on a screen.

  Learning phase: Participants were trained outside of the scanner during four 15-minute exploration periods. They were explicitly instructed to learn the layout of streets, districts and target locations by moving freely within the environment. During the entire training session, pictures of the three target locations and their associated names were continuously available to the subject.

Test conditions: At the end of the training session, subjects were scanned using fMRI while performing four different tasks that aimed at assessing spatial and contextual components involved in memory-based navigation (Fig. 2a).

In the Natural, Impoverished and Alternate conditions, subjects had to retrieve, as fast as possible and in no more than 35 s, the route between two locations in the learned environment. In the Impoverished condition, the environment was made plainly uniform by removing all wall/ground features and objects. In the Natural and Alternate conditions, the environment was identical as during the exploration. In the Alternate condition however, optimal pathways between starting and target points were blocked by an impassable barrier to promote alternative route-finding strategies and to prevent from using a routine navigation behavior. Thus, the Impoverished condition allows to assess the spatial memory component and the Natural condition allows the investigation of both memory processes (spatial and contextual). The Alternate condition was designed to assess spatial memory since, in this task, previously identified landmark objects and contextual features become less relevant for navigation. Indeed, subjects should rather rely on a more spatial, less contextualized representation of the navigation space to build an alternate route. For each of these three tasks, the fMRI scanning session consisted of 10 blocks of tests, each lasting for 35 s, that alternated with 10 blocks of rest, during which a black screen was displayed for a duration randomly lasting from 10 to 17 s. During rest periods, subjects were instructed not to think to anything in particular and to relax as the study is long and demanding. Within the last two seconds of the rest period preceding each test, the target location for the test was indicated orally through MR compatible headphones. After test time elapsed, a quantitative measure of route retrieval performance was determined as the distance remaining between the subject's

actual location and the target to reach, proportional to the length of the optimal path between the starting point and the target. Although various indicators of performance can be computed (e.g. success, walked distance, effective navigation speed, crossroads, dead end errors, …), the distance remaining to target was selected as the main behavioral measure of navigation, in reference to previous studies in our group (Peigneux et al., 2004, 2006) in which the remaining distance (or conversely the distance towards destination) was shown the most sensitive measure of navigation ability. At variance with the Impoverished and Natural conditions in which all targets were 35 virtual units apart from the starting point, the use of barriers in the Alternate condition makes that the average optimal distance was 52 virtual units (SD = 5.8, range 39-58). Therefore, to render performance in the Alternate condition comparable with those in the two other conditions, performance was measured as the distance remaining between the subject's actual location and the position located at 35 virtual units from the starting point on the shortest path towards the target. For the Impoverished, Natural and Alternate conditions, the same 10 tests were administered in a counterbalanced order, both at the between- and within-subjects levels.

In the Recognition condition, subjects had to pay attention to the environmental features of the town during 35s while following colored dots on the ground that signaled the path to follow between the starting and target points. They were instructed to determine whether and where environmental changes were made as compared to the town explored during the learning phase. All changes were easily detectable and did not necessitate stopping along the walk. At the end of each 35-s walk, they were presented with a four-choice panel composed of three pictures taken along the route just previously followed, and a white square (Supplementary Fig. 1). Using a keypad with their left hand, they had to indicate in no more than 10 s the

modified image, or to select the white square if they thought that no modification was made. For the Recognition condition, 22 tests were administered in a pseudo-randomized order (4 possible lists), and alternated with short blocks of rest during which a black screen was displayed for 10-17 seconds. Behavioral performance was measured as the number of correct recognitions. This measure was used to associate a performance index with brain imaging data obtained during the walk between the starting and target points, here deemed as a contextual recognition task as subjects were actively engaged in the detection of potential modifications in the learned environment.

For all subjects, the four tasks were proposed in the following fixed order: Impoverished, Recognition, Natural then Alternate. Although administrating the various tasks in a randomized order would have ruled out the possibility of decreased medial temporal lobe activation as the pathways become familiar (Nyberg, 2005), it was much more important for the purpose of the present study to avoid as much as possible interference between the four tasks. Thus, to minimize re-learning of the contextual details of the environment or of the spatial layout of the routes, the Impoverished and Recognition conditions were administered before the Natural navigation condition. Additionally, although only optimal paths were blocked in the Alternate condition, some subjects never discovered these during the initial exploration period and actually learned an alternate route in which they perseverated. Therefore, we analyzed our subjects' data in the Alternate condition based on the pathways (either optimal or not) followed by them in the immediately preceding Natural condition. Two strategies were differentiated in this condition: true alternate way finding and routine strategy (see Brain Imaging and Results sections for details).

fMRI data acquisition.

Brain imaging data were obtained using a 3 Tesla head-only MRI system (Allegra, Siemens, Erlangen, Germany) equipped with an actively shielded gradient coil system (max gradient amplitude 40 mT/m). For each testing session, the functional multi-slice T2*-weighted images were obtained using a blood oxygen level dependent (BOLD) sensitive single-shot echo planar (EPI) sequence (TR = 2130 ms; TE = 40 ms; flip angle = 90°; FoV = 220x220 mm²; matrix size = 64x64x32) covering the whole brain (128 mm high). Each functional volume consisted of 32 slices, with a thickness of 3 mm (inter-slice gap = 1 mm) and a voxel size of 3.4x3.4x3 mm³. The four initial scans of each session were discarded to control for magnetic saturation effects.

A high-resolution structural MRI scan was also acquired for each subject using a standard three-dimensional T1-weighted sequence (TR = 1960 ms; TE = 4.43 ms; flip angle = 8°; 176 slices; FOV = 230x173 mm²; matrix size = 256x192x176; voxel size = 0.9x0.9x0.9 mm³). The mean and individual MR images were used for a precise identification of loci of activation.

fMRI data analysis.

Functional volumes were pre-processed and analysed using the Statistical Parametric Mapping software SPM2 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/spm2) implemented in MATLAB (Mathworks Inc., Sherbom, MA). For each subject, spatial preprocessing included realignment and adjustment for movement related effects, co-registration of functional and anatomical data, spatial normalization into standard stereotactic MNI space, and spatial smoothing using a Gaussian kernel of 6 mm full width at half maximum (FWHM).

Data were analyzed using a mixed-effects model, aimed at showing stereotypical effect in the population from which the subjects are drawn (Penny and Holmes, 2003). This procedure was implemented in two processing steps accounting respectively for fixed and random effects. For each subject, changes in BOLD responses were estimated in a first-level intra-individual analysis using a general linear model at each voxel. For each experimental condition, the regressors of interest were built using boxcar functions corresponding to each block of navigation convolved with the canonical hemodynamic response function. In the Impoverished, Natural and Alternate conditions, the 10 pre-test 2-s periods during which subjects were orally indicated the name of the target to reach were modeled explicitly. In the Recognition condition, the time during which subjects were presented the four-choice response panel and made their response was also modeled explicitly.

Additionally, the strategy used by the subjects in the Alternate condition was modeled in the design matrix as follows. For each test in this condition, if a subject had followed the optimal path in the Natural condition, its brain activity was analyzed separately for the time spent in the detour portion of the walk, outside of its usual pathway. Otherwise if the subject had followed a non-optimal path during the Natural condition for a given test, and did not encounter the barrier in the Alternate condition for the same test, its brain activity during this period of time was not taken as a detour-related activity. It was rather analyzed as a routine-related navigation activity if the pathway was the one previously followed by the subject or explicitly modeled as a "lost" condition when the subject appeared to be completely disoriented in the environment as compared to his/her behaviour in the Natural condition (i.e., going round in circles, going in a totally wrong direction, entering already known dead

ends…). Only the results of comparisons between detour and routine strategies are of interest here.

Furthermore, in order to test whether modifications of neuronal activity in navigation–related areas were linked to behavioral performance (navigation accuracy or recognition performance), performance regressors were added to the model. This allowed computing at the within-subject level the correlation between navigation (and recognition) performance and the navigation-related regional BOLD response. Hence, within-subjects' correlation analyses looked for cerebral structures in which BOLD response during tests of place finding (or during the recognition task) correlated with subject's trial-to-trial variations in performance.

In all individual analyses, movement parameters derived from realignment of the functional volumes (translations in x, y and z directions and rotations around x, y and z axes) were included as covariates of no interest in the design matrix. High-pass filtering was implemented in the matrix design using a cut-off period of 128 seconds to remove low frequency drifts from the time series. Serial correlations in fMRI signal were estimated with a restricted maximum likelihood (ReML) algorithm, using an intrinsic autoregressive model during parameter estimation. The effects of interest (i.e., main effects of condition, direct comparisons between the four tasks and intra-individual modulations by performance) were then tested by linear contrasts, generating statistical parametric maps [SPM(T)]. Since no inference was made at this fixed effects level of analysis, individual summary statistic images were thresholded at p<0.95 *(uncorrected).*

The individual summary statistics images resulting from these contrasts were then further spatially smoothed (6 mm FWHM Gaussian kernel) and entered in a second-level analysis, corresponding to a random effects (RFX) model in which

subjects are considered random variables. A global null analysis (Friston et al., 2005) computed at the RFX level aimed at highlighting the brain areas commonly engaged during navigation in the four experimental conditions. Restricted maximum likelihood estimates of variance components were used to allow possible departure from the sphericity assumptions in conjunction analyses (Friston et al., 2002). It should be noted that a significant conjunction does not mean all contrasts were individually significant (i.e., conjunction of significance), but rather means that the contrasts were consistently and jointly significant (Friston et al., 2005). Additionally, we investigated the neural activity that differentiated good navigators from bad ones in our population. To do so, correlations were computed at the RFX level between each subject's individual contrast image of the main effect of navigation and its average behavioral performance for this condition.

The resulting set of voxel values for each contrast constituted a map of the t statistic [SPM(T)], thresholded at p<0.001 (uncorrected for multiple comparisons). Statistical inferences were then obtained after corrections at the voxel level using Gaussian random field theory (Worsley et al., 1996), either p^{corr}<0.05 (FWE) corrected for multiple comparisons in the whole brain volume, or $p^{svc(10mm)}$ <0.05, corrected in a small spherical volume (radius 10 mm) around a priori locations of activation in structures of interest, taken from the literature (Table 1, Supplemental Data). Uncorrected values at p < .001 are reported descriptively only.

Finally, posterior probability maps enabled conditional or Bayesian inferences about regionally specific effects, allowing us to ensure that a lack of significant statistical effect in a given contrast was not merely due to a failure to detect this effect using classical inferences (Friston and Penny, 2003).

For all activated voxels, anatomical localization was determined based both on stereotactic coordinates using the co-planar stereotactic atlas of the human brain (Talairach and Tournoux, 1988) after coordinates conversion using M. Brett's set of linear transformations (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) and an automatic algorithm labelling (AAL toolbox; Tzourio-Mazoyer et al., 2002). Confirmation of precise anatomical localization was made based on individuals' and mean structural MR images.

Results

Behavioral performance

In the Impoverished, Natural and Alternate conditions, subjects were required to reach within 35 s a given target from a designated starting point. A quantitative estimate of navigational performance was given by the distance remaining between the subject's actual location at the end of testing and the target, relative to the total length of the shortest possible route. Thus, a value comprised between 0 and 1 indicates that the subject moved towards the target on the optimal path and the smaller the value the closest the subject was from the target. In contrast, a value >1 indicates a displacement in the direction opposite to the target.

As expected given the absence of contextual cues during route retrieval, performance in the Impoverished condition was weaker than in the Natural condition (Table 1a, p<0.001). In order to render performance comparable in the Alternate condition with the index obtained in the other tasks, we measured not only the absolute performance (mean distance remaining to the target relative to the total length of the path = 0.40; SD = 0.16) but also a corrected index relative to an imaginary point located 35 units apart from the starting point on the new optimal path.

This latter measure allows a direct comparison of the subjects' efficiency to find their way between the Alternate and the other conditions. Note that both measures were correlated at the within-subject level (r = 0.78, p<0.001). Results indicate that corrected performance in the Alternate condition was better than in the Impoverished (p<0.001) but did not differ from the Natural (p>0.6) condition (see Table 1a). This result indicates that the Impoverished condition was harder than the two other conditions. In contrast, forcing subjects to find an alternative route to a given target does not reduce their navigation efficiency as performance, when expressed relative to the same path length, did not differ in the Alternate and Natural conditions.

Additionally, we found that performance in the Natural condition was correlated with performance in the Recognition memory task (i.e. number of correct recognitions; p<0.01) and in the Impoverished condition (p<0.01; see Table 1b). Performance in the Impoverished condition was also correlated with performance in the Alternate condition (p<0.05; see Table 1b). These results indicate that both spatial and contextual memory components contribute to accurate navigation in the Natural condition. It also suggests that performance in the Alternate condition, where subjects had to devise an unfamiliar path to reach the target, relies more on the capacity to elaborate an accurate cognitive map of the town, likewise in the Impoverished condition.

Brain imaging data

Navigation-related activations

A conjunction analysis across the Natural, Impoverished, Alternate and Recognition conditions revealed an increase in navigation-related blood oxygen level dependent (BOLD) responses in an extended hippocampo-neocortical network, including the

hippocampus bilaterally as well as occipital, parietal and frontal areas ($p^{corr}<0.05$; Table 2; see Fig. 2b for navigation effects in separate conditions).

Besides these commonalities, differences in navigation-related brain activity were found between the four conditions. There was higher activity in the Natural than in the Impoverished condition in the left fusiform gyrus ($p^{svc}<0.05$), right superior temporal gyrus and cuneus ($p<0.001$; Table 3). The reverse comparison was non significant. As compared to the Natural condition, there was higher activity in the left parahippocampal gyrus ($p^{svc}<0.05$), the bilateral frontal areas (anterior cingulate and superior, inferior and middle frontal gyri) and in the caudate nuclei ($p^{svc}<0.05$) in the Alternate condition. The reverse comparison was non significant. As compared to the Impoverished condition, there was higher activity mainly in the bilateral fusiform gyri ($p^{corr}< 0.05$; Table 3) in the Alternate condition, but also in the lateral temporal and frontal areas ($p<0.001$, uncorrected). The reverse comparison did not yield any significant activation. Finally, navigation in the Recognition condition was associated with higher activity than in the three other conditions in frontal areas, lateral temporal cortex (superior and middle temporal gyri), precuneus, retrosplenial and posterior parietal cortices ($p<0.001$, uncorrected, see Table 4).

In the Alternate condition, the regional cerebral activity was analyzed separately as a function of the subjects' behavior during navigation. The underlying hypothesis was that finding an alternative to the pathway previously learned as optimal by the subject should engage more actively the hippocampus and parahippocampal area than navigating along a well-known route. We also speculated that navigating along the subject's usual path could possibly rely on a response-based (habit) navigation strategy associated with caudate activity (Iaria et al., 2003; Orban et al., 2006). Therefore, the regional cerebral activity associated with navigation in the

known portion of the route (i.e. corresponding to the portion of the route taken by the subject in the immediately preceding Natural condition) was contrasted within each trial with the activity associated with the portion of the route that corresponded to a detour. This analysis revealed higher activity in the detour than in the well-known part of the route bilaterally in the left ([-30 –50 -6], Z score = 4.38, p^{corr}<0.05) and right ([30 –42 -10] Z score = 4.13, p^{svc}< .05; Fig. 3) parahippocampal gyrus, as well as in fusiform and frontal, parietal and occipital areas (p<0.001 uncorrected; Table 5). In contrast, the analysis failed to evidence differential activation in the caudate nucleus between routine and detour behaviors. Posterior probability maps (Friston and Penny, 2003) indicated a low probability to disclose a caudate activation in the detour part of the road (all P < 0.27, range 0.05-0.27).

Performance-related activations

Next, to evidence the brain areas where activity varies from trial to trial according to navigation efficiency within an individual, we looked at the correlation between BOLD response during navigation and the performance measure at each trial within each condition (i.e., performance was the distance remaining to target in the Natural, Impoverished and Alternate conditions; the correct recognition score in the Recognition condition). This analysis highlighted correlation profiles between performance and activity in medial temporal areas (Fig. 4): left hippocampal activity was correlated with navigation performance in the Impoverished and Natural conditions, whereas bilateral parahippocampal activity was associated with performance in the Recognition and Alternate conditions. Additionally, performance was correlated with left parietal activity in the Natural condition, with right or bilateral parietal activity in the Recognition and Alternate conditions respectively, and

with predominant left frontal activity in the Recognition condition (Table 6). Finally, an interaction analysis revealed that activity in the left hippocampus, parahippocampal gyri, parietal lobe (mainly on the right side), frontal areas, precuneus and caudate nuclei correlated more with navigation performance in the Alternate than in the Natural condition (Table 7).

In a second step, we determined the brain areas where activity varies between subjects according to their global navigation efficiency, i.e. the brain regions that differentiate good from poor navigators. At the between-subjects level, we evidenced correlations between subjects' average performance score and their navigation-related BOLD response within each condition. Positive correlations indicate brain areas that activated more in good than poor navigators. Results are summarized in Table 8 and illustrated in Fig. 4. Positive correlations with hippocampal activity were found only in the Impoverished condition ($p^{svc} < 0.05$). At variance, performance was positively correlated with activity in the right lateral temporal cortex in all conditions, and with activity in the precuneus, inferior parietal lobule and frontal areas in the Impoverished, Natural and Alternate conditions.

Discussion

The present study aimed at unravelling the neural substrates of spatial and contextual components of spatial memory-based navigation during route retrieval in an ecologically valid environment. Besides prominent commonalities found in a large hippocampo-neocortical network known to be involved in topographical learning in humans (Aguirre et al., 1996; Maguire et al., 1998b; Burgess et al., 2002; Hartley et al., 2003; Voermans et al., 2004; Peigneux et al., 2004, 2006; Orban et al., 2006; Spiers and Maguire, 2006a), our results yield evidence for a partial dissociation

between the brain areas that sustain these primary memory components, eventually leading to efficient navigation within a newly learned environment.

Between-tasks comparisons revealed subtle differences in navigation-related brain activity that may relate to various cognitive processes. We interpret the higher fusiform, superior temporal and cuneus activity in the Natural than in the Impoverished condition (also found for the fusiform gyrus in the comparison between Alternate and Impoverished conditions) as being induced by the profuseness of visual details (objects, colors, textures, …) in the former case, in line with Maguire et al. (1998a) who found increased activation in fusiform and parahippocampal regions when the navigated environment was visually enriched. Better performance in the Natural than in the Impoverished condition is also in accordance with rodent studies having demonstrated that exposure to an enriched environment enhances memory performance in spatial tasks (Rosenzweig and Bennett, 1996; Frick et al., 2003). In the Alternate condition, in which subjects had to find a new way to reach the target, higher activity was observed in the left parahippocampal gyrus and frontal areas than in the Natural condition. Since the degree of enrichment was similar between those conditions, we propose that higher parahippocampal activity in the Alternate condition reflects an increased dependency upon map-like representations of the environment to find an alternative route near the target. At variance, higher prefrontal involvement may be explained by increased requirements for strategy switching in the presence of obstacles, a reading consistent with prior studies having used tasks with similar cognitive demands (Maguire et al., 1998b; Rosenbaum et al., 2004; Spiers and Maguire, 2006a). Frontal activations are also in line with a role for these areas in planning (Shallice, 1982) and decision making (Fellows, 2004 for review) in the

Alternate condition, and increased working memory demands when updating topographical information (Gron et al., 2000).

In the Recognition task, cerebral activity was consistently higher than in the three other conditions in a large set of brain areas encompassing the precuneus, retrosplenial and posterior parietal cortices, and frontal and lateral temporal cortices. Frontal areas are well known to be involved in contextual and source memory tasks (Ranganath and Knight, 2003). Their involvement in the Recognition condition could therefore reflect the effortful process associated with retrieving the environmental information acquired during the exploration period, in order to ascertain possible differences with the actual scene when following the track. Also, fMRI studies have highlighted a role for the precuneus and posterior parietal cortex in source memory tasks (Lundstrom et al., 2003, 2005; Cavanna and Trimble, 2006), and activations in these regions, extending to posterior cingulate and retrosplenial cortices as well as to the inferior parietal lobule, have been consistently linked to episodic retrieval processes (Wagner et al., 2005). Finally, higher activity in the lateral temporal cortex in the Recognition condition is in line with the results of intracerebral recording in superior, middle and temporal regions in patients performing a series of memory tasks (Ojemann et al., 2002). The authors observed significant changes of neural activity during a recognition task mainly in the superior temporal gyrus and the superior part of the middle temporal gyrus, confirming the role of lateral temporal cortex in memory.

It is worth noticing that activation of the hippocampus *per se* was not different between the four navigation conditions. Beyond its well-known role in human navigation, numerous studies indicate that the hippocampus is also involved in relational memory (Davachi, 2006, for review; Tendolkar et al., 2007). Such a double

role could explain why hippocampal activity is observed in all memory tasks, even if they were designed to tap selectively spatial or associative (contextual) memory processes. A lack of differential involvement of the hippocampus across tasks could also be due to the fixed order in which we administered the tasks. Indeed, such an order constraint, that limits interference between conditions, could have masked hippocampal activation since neural activity in this region is known to decrease as stimuli become more familiar (Nyberg, 2005). Nevertheless, even if the same pathways were presented several times, objects were presented in an unexpected context in the Recognition condition. Detection of contextual novelty also implies the hippocampus (Nyberg, 2005) and may have compensated, at least in part, for the repetition of pathways. Furthermore, in the Alternate condition, the fact that we added barriers along the road created another form of novelty, and may have compensated for the fact that this condition was the last administered. Though, a comparable hippocampal involvement both in spatial and contextual memory is consistent with the report of independent codes for spatial and episodic memory within this same region (Leutgeb et al., 2005). Independent encoding patterns may enable a simultaneous representation of spatial and episodic information, giving additional ground for these two cognitive components to be generally both involved in navigation. However, when brain activity in the Alternate condition was analyzed separately as a function of the subjects' behavior, we found that the hippocampus/parahippocampal area and the fusiform gyrus were more activated in the detour than in well-known part of the route. This result can not be attributed solely to a novelty effect as the alternate routes to reach the target are, for the most part, known by the subjects. This confirms that two different navigation strategies were embedded in the Alternate condition, that must be segregated to find out the neural correlates of

the spatial component. Indeed, it is mostly in the detour portion of the test trial that subjects actually need to rely more heavily on a mental map of the environment to find an alternative route to reach the target, and therefore activate more regions known to be involved in spatial memory. Notwithstanding, an alternative interpretation could be that differences in brain activity between these two conditions relate to behavioral or attentional processing differences, as subjects might have attended more to particular aspects of the environment during the detour than in the routine segments. These results also confirm those reported by Rosenbaum et al. (2004) but depart from those of Spiers and Maguire (2006a), who disclosed an involvement of the retrosplenial cortex in planning new routes, i.e. when topographical representations need to be updated, whereas we did not. However, this apparent discrepancy could be resolved considering that the retrosplenial cortex is always activated throughout the navigation process, as acknowledged by these authors themselves. Therefore, a direct comparison between navigation conditions would be unable to evidence a retrosplenial activity-related behavior. Finally, when comparing brain activity associated with routine and detour behavior within the Alternate condition, no differential activation of the caudate nucleus was evidenced (although caudate activity was globally higher than in the Natural condition). Prior studies indicate that navigation-related caudate activity is present when the environment is well-learned (Packard and Knowlton, 2002; Hartley et al., 2003) and/or consolidated for the long-term after sleep (Orban et al., 2006). Therefore, a lack of differential caudate activation between routine and detour strategies suggests an incomplete consolidation of the town's knowledge at the time of testing.

Although the hippocampus is involved in all navigation conditions, hints for a dedicated association of the hippocampus with the spatial memory component come

from correlation analyses in which we seek the brain areas associated with variations in behavioral performance. At the within-subject level, trial-by-trial variations in place-finding efficiency was correlated with hippocampal activity in the Impoverished and Natural conditions, in line with prior studies indicating that the hippocampus is involved in accurate navigation (e.g., Maguire et al., 1998b; Hartley et al., 2003; Peigneux et al., 2004). Similarly at the between-subjects level, we found greater hippocampal activation in accurate than in poor navigators, like Maguire et al. (1998b) and Orban et al. (2006), but only in the Impoverished condition. This latter correlation, exclusively disclosed in the most difficult task, suggests that only those subjects who were truly able to create a hippocampus-related spatial representation of the town during the exploration period have been able to rely successfully on this map-like representation at the time of testing in a non-enriched, un-contextualised environment. As a whole, these findings concur with the idea that hippocampus activity sustains accurate way-finding in man (Hartley et al., 2003). Contrary to our expectations however, no correlation was found with hippocampal activity in the Alternate condition, also designed to probe the spatial memory component. A potential explanation for this lack of effect could be due to the fact that this condition came last in the protocol, which may have contributed to the reduction in individual performance variability (SD = .13) as compared to the other conditions (SD > .2), decreasing the power of correlation.

At variance in the Recognition condition, correlations between navigation-related cerebral activity and trial-by-trial variations in correct recognition scores were found in the parahippocampal area, noticeably in the perirhinal cortex (Brodmann areas 35 and 36) known to be a key region for visual recognition memory (Meunier et al., 1993; Rauchs et al., 2006). The parahippocampal cortex, and notably the

parahippocampal place area, is also known to selectively respond to and identify individual visual scenes (Epstein and Higgins, 2007) and encode the geometry of the local environment (Epstein and Kanwisher, 1998). Still, this role cannot solely explain the correlations found in the contextual condition, in which subjects had to recognize landmarks in their specific context. In contrast, our results are consistent with the idea that the parahippocampal cortex is also involved in binding processes, mediating contextual associations between spatial and non-spatial stimuli (Aminoff et al., 2007). Such a function has already been aforementioned for the hippocampus. Nevertheless, it appears that a clear-cut dissociation between the contribution of the hippocampus and parahippocampal cortex to memory is not so obvious (see for example Gold et al., 2006). However, Bohbot et al. (1998) found that some patients with hippocampal lesions were still able to retain information over half an hour in a human adaptation of the Morris water maze task, whereas other patients with parahippocampal areas damage were not, suggesting implication of the parahippocampal cortex itself in spatial memory. Aminoff et al. (2007) additionally provided evidence for a functional dissociation within the parahippocampal cortex, with its anterior part involved in associations of non-spatial elements, and its posterior part (overlapping with the parahippocampal place area) mediating associations of spatial stimuli. In our study, correlations were observed in the perirhinal cortex (i.e., the anterior part of the parahippocampal gyrus) in a condition in which subjects had to associate landmarks and their specific context. In the framework of the dissociation proposed by Aminoff et al. (2007), this suggests that performance in the contextual condition was indeed achieved with minimal requirements for the spatial memory component.

Beside segregated correlations between hippocampal (respectively parahippocampal) activity and spatial (respectively contextual) memory, we found

that trial-by-trial, within-individual variations in navigation efficiency also correlate with cerebral activity in a set of neocortical regions essentially encompassing the inferior parietal lobe (IPL) and the left frontal cortex. Activity in the left IPL was correlated with performance in the Natural, Recognition and Alternate conditions, confirming the role of this brain area in episodic retrieval and retrieval success (Wagner et al., 2005). Since IPL activity was linked to behavioral indexes both in the Alternate, Recognition and Natural conditions, it suggests that this area integrates spatial and contextual information to enable accurate navigation. Conversely, performance in the Recognition task was correlated with left frontal activity, which confirms the crucial role of the left frontal cortex in retrieval success (Cabeza and Nyberg, 2000; Konishi et al., 2000), and the involvement of frontal areas in recognition or source memory tasks, as evidenced using fMRI (Fan et al., 2003). Finally, activity in bilateral parietal cortices was correlated with navigation performance in the Alternate condition. Recruitment of the right hemisphere and more particularly of the right infero-posterior parietal cortex, known to be involved in spatial processes (e.g., Woelbers et al., 2004), is compatible with increased reliance upon a spatial map when forced to find an alternative route to reach the target after a barrier has prevented using the optimal path. Note however that correlations between performance and activity in the parahippocampal gyrus were found both in the Recognition and Alternate conditions. These data suggest that besides a crucial involvement of the spatial component in the Alternate condition, concurrent processing and remembering of contextual information is not to be excluded.

Finally, correlation analyses conducted at the between-subject level aimed at evidencing the neural structures whose activity differentiates good from poor navigators, based on their average measure of performance in each condition. Our

study essentially confirms the results obtained by Hartley et al. (2003) who made a comparison between navigation-related activity in novel versus well-learned routes. Here, we have additionally extended these observations to other navigation-related behaviors or strategies. As previously reported (Hartley et al., 2003), there was a significant association between lateral temporal activity and performance in all experimental conditions. Furthermore, in all experimental conditions except the Recognition one, navigation performance was correlated with BOLD responses in a network including the frontal areas bilaterally, the precuneus and the parietal areas notably including the inferior parietal lobule. An association between performance levels and activity in frontal areas may reflect the successful involvement of executive functions in planning routes (Maguire et al., 1998b; Hartley et al., 2003), whereas posterior parietal activations are consistent with a role for this area in visuospatial attention (Grefkes and Fink, 2005) and in mental imagery (Cavanna and Trimbles, 2006). One may speculate that the most accurate navigators are those individuals who, besides higher hippocampal involvement, more efficiently allocate their visuospatial attention and executive functioning resources to the task.

To sum up, the present study provides evidence for a partial segregation of the neural bases of two primary memory processes usually embedded during active navigation in humans. Although these memory components primarily rely on the integrity of a large hippocampo-neocortical network during navigation, behavior-based analyses suggest that activity in the hippocampus mostly sustains spatial memory, whereas parahippocampal activity preponderantly supports contextual memory. Their combined action eventually leads to successful route retrieval in an ecologically valid, virtual environment. Further investigations should assess whether dissociation between the spatial and contextual memory components may be observed

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in patients with circumscribed hippocampal lesions, and how compensatory cognitive mechanisms may be promoted to help them coping with their memory impairment in everyday navigation.

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Figure legends:

Figure 1: Virtual environment.

The map depicts an aerial view of the 3D virtual town in which subjects navigated at the ground level. Snapshots show the three locations used as target for testing during the fMRI sessions. The 10 starting points are represented by letters (from A to J) with associated symbols indicating the target location to reach.

Figure 2:

a. Navigation conditions. The four images illustrate the same location in the environment as viewed by the subject in the four experimental conditions. In the Impoverished condition, subjects were placed in the same environment as during the exploration period, but uniformly deprived of all objects, wall and ground features. In the Natural and Alternate conditions, the environment was exactly the same as in the exploration but in the Alternate condition a barrier blocked the direct, optimal pathway between the starting point and its associated target. In the Recognition task, subjects had to follow a route marked with red or green dots on the floor while paying attention to the environment. They had then to determine using a multiple-choice panel (see Supplementary Figure) if and where was any contextual modification as compared to the town explored during learning.

b. Navigation-related cerebral activity. Each image shows areas where BOLD response is greater than the mean (baseline) activity at the population level, during navigation blocks within the experimental condition illustrated above. Contrasts are displayed at p^{corr} <0.05 superimposed on the MNI template. The blue crosshair locates the hippocampus. The colour bar indicates the t statistic associated with each voxel.

Figure 3: Detour-related activation in the hippocampus. Left panel illustrates brain areas where activity was higher in the detour than in the well-known portion of the route in the Alternate condition. Contrasts are displayed at p<0.001 (uncorrected). The image shows the main peak of activation, located in the left parahippocampal gyrus ([-30 –50 –6], $p^{svc(10mm)}$ <0.05) superimposed on the MNI template. Detour-related activation are also reported in the right parahippocampal gyrus, left insula, left frontal and parietal cortices, cuneus bilaterally and right superior and inferior temporal gyri (p<0.001(uncorrected), Table 5). The color bar indicates the t statistic associated with each voxel. Right panel illustrates the size of effect for each behavior (D: detour, K: well-known) in the right and left hippocampus and parahippocampal gyrus. Error bars are standard deviations.

Figure 4: Brain-behavior correlations. Within-individual between-trials (left panel) and between-subjects (right panel) correlations of brain activity with navigation performance in the four experimental conditions. Images are displayed at p<0.001 (uncorrected). The color bar indicates the t statistic associated with each voxel.

Figure in Supplemental Data:

Figure 1: Choice panel of the recognition task. At the end of each 35-s walk, subjects were presented a four-choice panel composed of three pictures taken along the road just previously followed and a white square. Using the keypad, they had to indicate in no more than 10 s the modified image, or to select the white square if they thought that no modification was made. Once their choice made, the selected image appears surrounded by a yellow rectangle.
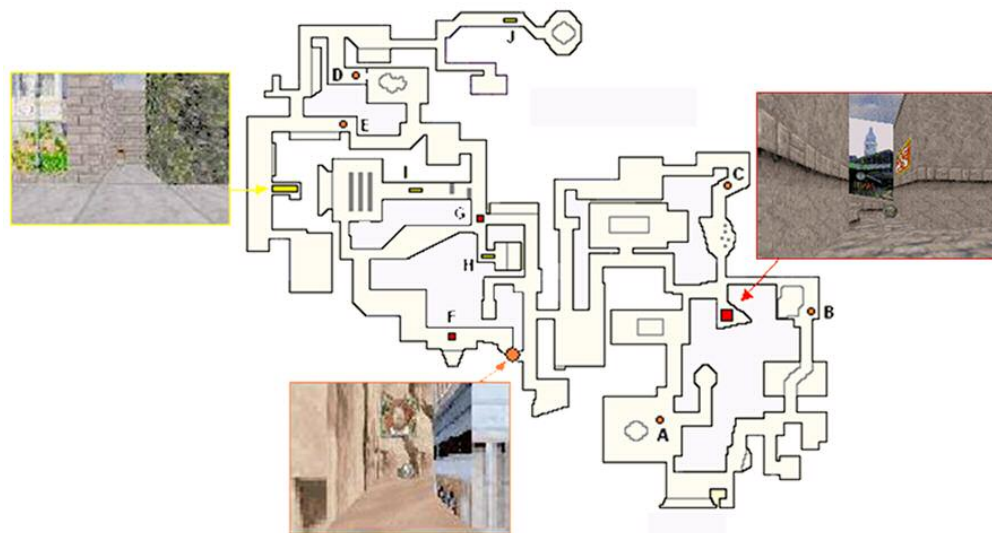
Figure 1: Virtual environment. The map depicts an aerial view of the 3D virtual town in which subjects navigated at the ground level. Snapshots show the three locations used as target for testing during the fMRI sessions. The 10 starting points are represented by letters (from A to J) with associated symbols indicating the target location to reach.
75x52mm (300 x 300 DPI)

Figure 2: a. Navigation conditions. The four images illustrate the same location in the environment as viewed by the subject in the four experimental conditions. In the Impoverished condition, subjects were placed in the same environment as during the exploration period, but uniformly deprived of all objects, wall and ground features. In the Natural and Alternate conditions, the environment was exactly the same as in the exploration but in the Alternate condition a barrier blocked the direct, optimal pathway between the starting point and its associated target. In the Recognition task, subjects had to follow a route marked with red or green dots on the floor while paying attention to the environment. They had then to determine using a multiple-choice panel (see Supplementary Figure) if and where was any contextual modification as compared to the town explored during learning. b. Navigation-related cerebral activity. Each image shows areas where BOLD response is greater than the mean (baseline) activity at the population level, during navigation blocks within the experimental condition illustrated above. Contrasts are displayed at pcorr <0.05 superimposed on the MNI template. The blue crosshair locates the hippocampus. The colour bar indicates the t statistic associated with each voxel.
254x190mm (300 x 300 DPI)

Figure 3: Detour-related activation in the hippocampus. Left panel illustrates brain areas where activity was higher in the detour than in the well-known portion of the route in the Alternate condition. Contrasts are displayed at p<0.001 (uncorrected). The image shows the main peak of activation, located in the left parahippocampal gyrus ([-30   50   6], psvc(10mm) <0.05) superimposed on the MNI template. Detour-related activation are also reported in the right parahippocampal gyrus, left insula, left frontal and parietal cortices, cuneus bilaterally and right superior and inferior temporal gyri (p<0.001(uncorrected), Table 5). The color bar indicates the t statistic associated with each voxel. Right panel illustrates the size of effect for each behavior (D: detour, K: well-known) in the right and left hippocampus and parahippocampal gyrus. Error bars are standard deviations.

Figure 4

	Within subjects	Between subjects

Impoverished condition

Natural condition

Recognition condition

Alternate condition

Figure 4: Brain-behavior correlations. Within-individual between-trials (left panel) and between-subjects (right panel) correlations of brain activity with navigation performance in the four experimental conditions. Images are displayed at p<0.001 (uncorrected). The color bar indicates the t statistic associated with each voxel.
190x254mm (300 x 300 DPI)

Table 1: a. Behavioral performance

Condition	Mean performance ± SD (arbitrary units)	p
Natural	0.29 ± 0.24	<0.001 (a)
Impoverished	0.61 ± 0.22	<0.001 (a)
Alternate (corrected performance)	0.24 ± 0.13	<0.001 (b)

	Mean percentage of correct recognitions ± SD
Recognition	64.1 ± 13.9 %

(a): in comparison to the Impoverished or Natural condition; (b): in comparison to the Impoverished condition.

b. Correlation analyses

	Natural	Alternate
Impoverished	r = 0.61 (p<0.01)	r = 0.56 (p<0.05)
Recognition	r = -0.61 (p<0.01)	ns

ns: non significant.

Table 2: Common navigation-related network.

Region		Cluster size (no. of voxels)	x	y	z	Z	p FWE-corr
R	lingual gyurs	8269	10	-90	-4	7.15	0.000
	middle occipital gyrus		20	-94	6	7.01	0.000
	cuneus		22	-92	20	6.63	0.000
L	middle occipital gyrus	280	-46	-76	2	6.36	0.000
R	middle / superior frontal gyrus	114	26	2	56	6.10	0.000
L	cerebelum	260	-32	-64	-32	6.10	0.000
R	hippocampus	74	24	-28	-4	5.94	0.000
L	precentral gyrus	128	-28	-4	54	5.77	0.001
L	calcarine sulcus	75	-18	-58	14	5.66	0.002
R	calcarine sulcus	135	22	-58	16	5.65	0.002
L	middle cingulate gyrus	19	-14	-18	44	5.56	0.003
L	postcentral gyrus	72	-42	-28	44	5.54	0.003
	Vermis	435	0	-74	-32	5.52	0.004
R	cerebelum		8	-68	-42	5.35	0.009
L	hippocampus	4	-22	-28	-8	5.11	0.025
L	superior parietal gyrus	7	-18	-64	66	5.10	0.025
R	inferior parietal lobule	7	34	-46	50	5.10	0.026

Conjunction analysis of navigation-related effects in the four conditions. All listed regions are statistically significant at the $p^{corr} < 0.05$ level. The coordinates (x, y, z) refer to the strongest activation within a given region. L: left; R: right.

Table 3: Direct comparisons between navigaiton-related activity in the Natural, Impoverished and Alternate conditions.

Region		Cluster size (no. of voxels)	x	y	z	Z
Natural > Impoverished						
L	fusiform gyrus	49	-26	-48	-16	3.78*
R	superior temporal gyrus	78	38	16	-28	3.62
R	cuneus	144	4	-90	34	3.60
Alternate > Natural						
L	middle frontal gyrus	151	-34	52	-4	4.46
L	anterior cingulate gyrus	44	-10	22	46	4.20*
R	middle cingulate gyrus		8	26	40	3.88
L	superior frontal gyrus		-2	38	40	3.12
R	middle frontal gyrus	297	46	38	26	4.13
R	inferior frontal gyrus		42	26	26	3.41
R	cerebelum	161	12	-82	-28	4.00
L	inferior frontal gyrus	144	-38	28	22	3.89
L	parahippocampal gyrus	28	-22	-48	-10	3.76*
R	precentral gyrus	222	50	10	34	3.71
R	caudate nucleus	19	12	10	16	3.70*
L	inferior temporal gyrus	38	-60	-58	-14	3.61
L	lingual gyrus	18	-16	-76	2	3.60
R	angular gyrus	57	54	-50	34	3.59
R	thalamus	204	6	-10	-6	3.58
R	superior frontal gyrus	29	26	64	10	3.57
L	cuneus	15	-6	-66	24	3.57
L	precuneus	92	-4	-68	62	3.57
R	precuneus		4	-66	62	3.45
R	calcarine sulcus	78	20	-56	6	3.55
R	cerebelum	23	14	-60	-32	3.45
L	caudate nucleus	22	-10	6	16	3.40*
R	lingual gyrus	56	20	-76	-2	3.39
R	fusiform gyrus		28	-66	-8	3.27
R	inferior temporal gyrus	26	66	-28	-18	3.34
R	superior parietal gyrus	12	20	-60	54	3.29*
L	middle temporal gyrus	15	-60	-36	-12	3.29
L	inferior parietal lobule	17	-36	-74	48	3.25
Alternate > Impoverished						
L	fusiform gyrus	2483	-22	-48	-14	6.01#
R	fusiform gyrus	1866	30	-50	-16	4.80#
R	inferior temporal gyrus	147	48	42	-16	4.18
L	superior frontal gyrus	52	-22	50	42	3.90
R	superior temporal gyrus	146	34	16	-26	3.82
L	middle frontal gyrus	89	-50	34	30	3.79
R	pulvinar	132	12	-26	2	3.73
R	inferior frontal gyrus	78	44	28	20	3.65
L	precuneus	109	-2	-66	56	3.51
R	superior frontal gyrus	45	24	16	64	3.46
R	supramarginal gyrus	55	54	-52	36	3.33
L	medial part, superior frontal gyrus	16	-6	46	32	3.23
L	posterior cingulate gyrus	15	-14	-58	12	3.19
R	middle temporal gyrus	7	50	-72	24	3.15

* : $p^{svc} < 0.05$; # : $p^{corr} < 0.05$

Table 4: Comparisons between navigation-related activity in the Recognition as compared to the 3 ot

Recognition vs.	Impoverished	Natural
Superior frontal gyrus	[2 48 -14], 4.42; [-8 60 26], 5.33[#]	[10 46 48], 4.09; [-12 58 28], 3.85
Middle frontal gyrus	[-36 20 50], 3.71	[34 32 48], 3.80; [-36 24 36], 4.55
Inferior frontal gyrus	[56 30 0], 3.96; [-60 20 8], 4.23	[62 26 12], 3.96; [-36 28 24], 5.01[#]
Middle cingulate gyrus		[-8 -22 36], 3.25
Precentral gyrus	[-36 6 46], 3.99	[42 -10 50], 4.16 ; [-50 -6 44], 3.71
Postcentral gyrus		[62 -8 38], 3.59; [-36 -20 36], 3.55
Supramarginal gyrus	[68 -40 24], 3.86	[66 -30 36], 3.26; [-54 -40 36], 4.30
Angular gyrus	[60 -54 34], 3.67	[-44 -66 42], 3.44
SMA	[6 14 70], 3.59; [-4 10 66], 3.31	
Superior parietal lobule		[22 -58 54], 3.41*
Inferior parietal lobule		[-36 -62 52], 3.55
Paracentral lobule	[-18 -28 66], 4.17	
Superior temporal gyrus	[56 -8 -12], 4.39; [-66 -22 6], 4.95	[48 -36 12], 4.91; [-64 44 16], 4.51
Middle temporal gyrus	[60 -34 4], 4.76; [-52 0 -28], 5.01	[50 -12 -16], 4.60; [-30 10 -34], 3.70
Inferior temporal gyrus	[-28 -4 -42], 3.50	[48 -48 -26], 3.29; [-52 -56 -20], 3.82
Amygdala	[-30 6 -18], 3.40	
Hippocampus	[30 -12 -14], 3.45*	
Parahippocampal gyrus	[26 -38 -10], 3.16*	
Fusiform gyrus	[32 -48 -16], 3.34*; [-34 -82 -18], 4.69	
Lingual gyrus	[-26 -62 -4], 3.71	
Retrosplenial cortex	[0 -42 26], 4.49	[0 -48 24], 4.90
Posterior cingulate cortex		
Precuneus	[4 -58 32], 3.71	[2 -58 48], 4.14*
Cuneus	[8 -90 36], 3.54; [-2 -88 38], 3.79	
Insula	[-36 6 -12], 3.44	
Caudate nucleus		[-6 2 10], 4.11
Putamen	[20 8 -6], 3.97; [-18 4 -10], 4.94	
Thalamus	[12 -24 4], 3.80; [-14 -24 0], 3.79	[-14 -24 2], 3.40
Cerebellum	[-50 -64 -22], 4.18	[6 -30 -50], 3.79; [-50 -64 -20], 3.43

All activations are reported at p<0.001 (uncorrected) except * : $p^{svc} < 0.05$ and [#] : $p^{corr} < 0.05$.
Results are displayed as follows: [coordinates in MNI template], z score.
SMA: supplementary motor area.

her conditions.

Alternate

[54 30 -2], 3.94
[-4 -22 42], 3.57*
[50 0 40], 3.85; [-22 -22 60], 3.96
[22 -36 64], 3.84
[-64 -48 24] 4.81
[-48 66 30], 3.85

[60 -6 -4], 5.36[#]
[-52 -20 -4], 4.91[#]

[0 -46 28], 4.41
[16 -44 30], 3.71
[4 -46 20], 4.12

[-34 -26 20], 3.68

Table 5: Brain areas significantly more activated in the detour and well-known part of the route (Alternate condition).

Region	Cluster size (voxels)	x	y	z	Z
1) Detour > Well-known part of the route					
L parahippocampal gyrus	918	-30	-50	-6	5.12[#]
L thalamus		-20	-32	4	4.10
L fusiform gyrus		-34	-46	-20	3.92
L insula	148	-32	-2	18	4.58
L inferior frontal operculum		-34	6	20	4.16
L superior parietal gyrus	721	-14	-84	50	4.47
L middle occipital gyrus		-28	-86	12	3.96
L cuneus		-20	-86	26	3.45
R cuneus	1305	14	-90	32	4.34
R superior temporal gyrus	203	46	-78	26	4.26
R parahippocampal gyrus	188	30	-42	-10	4.13*
R inferior temporal gyrus	22	50	-56	-8	3.53
L superior frontal gyrus	43	-20	-4	56	3.52
2) Well-known part of the route > Detour					
R superior temporal gyrus	42	34	14	-44	3.70
L supramarginal gyrus	34	-60	-58	32	3.22

[#]: $p^{corr} < 0.05$; *: $p^{svc} < 0.05$.

Table 6: Performance effects: within subjects correlations.

Region	Impoverished	Natural	Recognition	Alternate
		Condition		
1) Medial temporal areas				
Hippocampus	L: -14 -8 -16	L: -26 -12 -24		
Parahippocampal gyrus			L: -30 2 -40	L: -26 8 -22
			R: 38 -44 -12	R: 34 -34 -12
			L: -30 -46 -12	
Fusiform gyrus		L: -58 -10 -30	L: -50 -64 -18	
2) Lateral temporal areas				
Middle temporal gyrus		L: -36 -64 18	L: -58 -34 -4	L: -62 -54 6
Inferior temporal gyrus				R: 68 -22 -20
3) Parietal areas				
Inferior parietal lobule		L: -54 -48 52	R: 36 -62 44	L: -36 -32 44
Post-central gyrus		L: -32 -28 38		L: -48 -28 38
Supramarginal gyrus				L: -48 -46 32
				R: 60 -48 34
Lateral sulcus				R: 16 10 -12
Angular gyrus			R: 44 -70 34	
Paracentral lobule				R: 10 -34 70
4) Occipital areas				
Precuneus			L: -3 -72 50	
Middle occipital gyrus			R: 28 -94 0	
5) Frontal areas				
Superior frontal gyrus			L: -30 64 2	R: 8 66 20
				L: -2 -30 58
Middle frontal gyrus				L: -38 58 -4
				R: 28 -32 40
Inferior frontal gyrus			L: -48 28 18	
Anterior cingulate gyrus				R: 4 40 8
6) Other structures				
Middle cingulate gyrus				L: -2 -6 36
Posterior cingulate gyrus			L: -2 -34 40	L: -14 -44 32
Putamen		L: -28 -16 -8		
Pulvinar				L: -10 -26 6
				R: 12 -24 8
Amygdala				L: -24 -4 -18
Cerebellum			R: 44 -72 -40	R: 14 -62 -50

All regions listed are statistically significant at the $p<0.001$ level. For brevity, each region that correlated with performance is listed only once; when several peaks were observed in the same region, the coordinates (x, y, z) refer to the strongest activation. L: left; R: right.

Table 7: Brain areas whose activity correlated more with performance in the Alternate than in the Natural condition, at the within-subject level (p<0.001, uncorrected).

Region	Cluster size (voxels)	x	y	z	Z
R/L precuneus	1595	16	-58	30	4.69
		-14	-60	24	4.53
L middle frontal gyrus	72	-38	60	-2	4.51
R inferior parietal lobule	462	58	-46	40	4.28
R middle temporal gyrus	108	66	-20	-18	4.16
L superior temporal gyrus	39	-58	-20	2	4.12
L caudate nucleus	66	-14	2	20	4.11
R caudate nucleus	49	-14	6	16	4.06
L cerebellum	58	-30	-40	-34	4.01
R anterior cingulate gyrus	94	2	46	6	4.01
R cerebellum	200	14	-62	-48	3.92
R middle cingulate gyrus	38	10	-42	36	3.78
R superior frontal gyrus	40	20	10	52	3.73
R superior parietal lobule	95	-24	-68	60	3.63
L hippocampus	34	-20	-36	-4	3.45
L parahippocampal gyrus		-24	-42	-8	3.35
R parahippocampal gyrus	20	30	-42	-8	3.35
R inferior frontal gyrus	17	42	42	8	3.33
R middle frontal gyrus	17	30	60	10	3.28

Table 8: Performance effects: between subjects correlations.

Region	Condition Impoverished	Natural	Recognition	Alternate
1) Lateral temporal areas				
Superior temporal gyrus				R: 58 -4 0
Middle temporal gyrus	L: -60 -36 0 # R: 66 -34 0 #	R: 54 -28 -14		
Inferior temporal gyrus			R: 42 -16 -24	
2)Medial temporal structures				
Hippocampus	L: -22 -14 -24 *			
3) Parietal areas				
Inferior parietal lobule	R: 52 -60 44 #	L: -54 -52 38		R: 52 -64 46
Post-central gyrus				
Supramarginal gyrus		R: 54 -58 36		L: -62 -48 24
4) Occipital areas				
Precuneus	L: -2 -54 32 #	R: 2 -56 34		L: -4 -52 32 R: 20 -50 36
5) Frontal areas				
Superior frontal gyrus	L: -8 58 28 #	L: -16 56 16		L: -12 56 14
Middle frontal gyrus	L: -40 14 48	L: -48 38 -2		
Inferior frontal gyrus	L: -50 30 4 R: 54 30 0	R: 54 30 8		
Precentral gyrus	R: 20 -26 78			R: 22 -26 51
Anterior cingulate gyrus		R: 10 34 8		L: -16 38 4
Insula	L: -36 -14 20	R: 42 -16 8		
6) Other structures				
Cerebellum	L: -26 -88 -38	R: 28 -82 -38	L: -32 -84 -38 R: 30 -86 -40	

All regions listed are statistically significant, at least, at the $p<0.001$ level. For brevity, each region that correlated with performance is listed only once; when several peaks were observed in the same region, the coordinates (x, y, z) refer to the strongest activation.   L: left; R : right; #: $p<0.05$ (FWE corrected); *: $p^{svc}<0.05$.