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Research report

# Selective role of lingual/parahippocampal gyrus and retrosplenial complex in spatial memory across viewpoint changes relative to the environmental reference frame

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## HIGHLIGHTS

- Lingual/parahippocampal gyrus and retrosplenial complex prefer to encode space within stable frames.
- Retrosplenial complex updates locations across viewpoint changes within stable frames.
- Retrosplenial cortex represents a crucial area in coding one's own position and heading in familiar environments.
- Parieto-frontal regions update locations independently from frame stability.

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## ABSTRACT

Remembering object locations across different views is a fundamental competence for keeping oriented in large-scale space. Here we investigated such ability by comparing encoding and retrieval of locations across viewpoint changes relative to different spatial frames of reference. We acquired functional magnetic resonance images while subjects detected target displacements across consecutive views of a familiar virtual room, reporting changes in the target absolute position in the room (stable environmental frame), changes in its position relative to a set of movable objects (unstable object-based frame), and changes relative to their point of view (control viewer-centered frame). Behavioral costs were higher for the stable environmental frame, and a cortical network including the lingual/parahippocampal gyrus (LPHG) and the retrosplenial complex (RSC) selectively encoded spatial locations relative to this frame. Several regions, including the dorsal fronto-parietal cortex and the LPHG, were modulated by the amount of experienced viewpoint change, but only the RSC was selectively modulated by the amount of viewpoint change relative to the environmental frame, thus showing a special role in coding one's own position and heading in familiar environments.

## 1. Introduction

Human beings have an outstanding capacity to seamlessly recognize scenes and to remember spatial locations despite intervening changes in point of view, such as those occurring when we walk or are passively transported through a familiar environment. This ability, which is fundamental to spatial orientation, can be experimentally measured by asking observers to study a scene from a given viewpoint, and then, after a true, imagined, or virtual self displacement, to detect whether a given object has been moved, or to point to a memorized location [1–17]. In principle, people could simply match the studied and the test view through some process of mental rotation. However, memory across viewpoint changes involves some more specific process: people perform better when they (physically or virtually) move in the environment around a stationary object array, than when they are still and an object array rotates around them [5–7,18–21], although the two situations appear identical from a geometrical standpoint. This and other lines of evidence [22–24] show that comparing different views of a scene involves some form of mental self-rotation, which is distinct from the process of mentally rotating objects.

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In terms of spatial reference frames, mental rotation of objects requires transforming an object-based frame relative to a fixed egocentric reference, while compensating for occurred viewpoint changes requires transforming an egocentric frame relative to an external (i.e., allocentric) reference (a “perspective transformation”: [21]). In principle, any set of objects can be used to establish an allocentric reference frame relative to which to evaluate a viewpoint change, and the operations involved in encoding spatial locations and then in updating memorized locations after a perceived viewpoint change may not depend on the particular set of objects chosen. However, human neuroimaging studies have shown not only that perceptual coding in egocentric and allocentric reference frames have distinguishable neural signatures (reviewed in [25]), but also that two different forms of allocentric representations can be distinguished: object-based reference frames, encoding spatial locations relative to arbitrary objects, and environmental reference frames, encoding spatial locations relative to some fixed features of the environment [21,25]. A particular set of cortical regions are selectively activated when a spatial judgment is referenced to enduring environmental features but not to unstable objects [26]. These regions include portions of the medial temporal cortex and adjacent antero-medial occipital lobe (fusiform, lingual and posterior parahippocampal gyrus), the retrosplenial cortex and the precuneus. Their selectivity for environmental referencing depends on the stability of the spatial location of environmental features over time and not on their perceptual features or orienting value [25]. Intracerebral recordings within the posterior medial temporal lobe recently showed that this kind of allocentric selectivity constitutes a separate, later processing stage relative to early visual scene processing [27].

On the basis of the distinction between environmental and object-based allocentric reference frames, we suggest that perspective transformations may be preferentially associated with the former. Indirect evidence for this idea comes from neuroimaging studies which have shown that the cortical regions selective for environmental reference frames are involved in recognizing a scene across different views (see [28] for a recent review) and in perspective vs. object-based transformations [29]. However, previous studies requiring to memorize and recall object locations across viewpoint changes have used either stable environmental features [16,29] or unstable configurations of objects [18,20]. In the present event-related functional magnetic resonance imaging (fMRI) study, we adapted a viewpoint-change paradigm often used in behavioral research [7,13] and compared perspective transformations relative to object-based vs. environmental reference frames, under the hypothesis that the neural circuit described above is actively exploited either during memory encoding or when updating memorized locations after a viewpoint change, but only if the established reference frame includes stable environmental features.

We asked observers to encode the spatial location of a target object in a virtual room with respect either to stable, familiar features of the scene (room frame), or to an arbitrary, unstable object set (objects frame). Observers then experienced a certain amount of viewpoint change, with “views” defined either relative to the room or to the object set, and asked them to judge whether the target was in the same spatial location as before, with “same” locations again defined relative to either the room or the object set. Importantly, the manipulation of the amount of viewpoint change allowed us to test a further prediction: regions actively involved in perspective transformations relative to the environmental reference frame should be selectively modulated by the amount of experienced viewpoint change, only when this is defined in room-based, but not in object-relative coordinates.

## 2. Materials and methods

### 2.1. Subjects

Fifteen neurologically normal volunteers (all males, mean age 25.4 yrs, s.d. 3.9) participated to the fMRI study. All subjects were right handed, as assessed by the Edinburgh Handedness Inventory ([30]: mean index = 0.65, s.d. 0.19) and had normal or corrected-to-normal vision. The protocol was approved by the ethical committee of Fondazione Santa Lucia, Roma, and written informed consent was obtained from each participant before starting the study.

### 2.2. Stimuli

The virtual environment was designed using 3Dstudio Max 9 (Autodesk Inc., San Rafael, CA, USA), and represented an internal view of a living room, containing both fixed cues on the walls, and unstable cues on a carpet on the floor (Fig. 1**A**). The fixed cues were stable elements of the room such as one door, one fireplace, one spiral staircase, one large French corner window, two small grating windows, and two wide windows. The room was designed with a square plan so that the four walls could be distinguished only on the basis of the layout of these distinctive cues. The unstable cues were five pieces of furniture arranged in different configurations on a circular carpet stably located at the center of the room: one circular table (always placed at the center of the carpet), one stool, one Greek vase, one pouf and one bedside lamp. Note that we selected only view-invariant objects (symmetric with respect to the vertical axis) in order to avoid any facilitation effect induced by the intrinsic orientation of each object. Close to the carpet, a plant (the target object) was added, at different locations, on the room floor to test memory.

During the experiment, the participants were shown different snapshots of the virtual environment. Each snapshot simulated a photograph of the environment taken with a 24-mm lens (74 by 59 deg simulated field of view) from one of eight different viewpoints. Each viewpoint corresponded to the position of a virtual camera (shown in blue and numbered 0–7 in Fig. 1**A**). The different virtual cameras were distributed at 45 deg intervals along a circle whose center corresponded to the center of the virtual room. Each camera was directed toward the center of the room, where the furniture set was placed. Each snapshot also included a plant, used as the target object, which was located outside the carpet but quite close to it, in one of eight possible positions, distributed every 45 deg along a smaller concentric circle (shown in green and numbered 0–7 in Fig. 1**A**). The target was never presented directly in front of the observer or directly behind the carpet (for example, for snapshots obtained from camera 1, the target could be neither in position 1 nor 5), and was presented half of the times on the left and the remaining half on the right of the observer. Each snapshot depicted the virtual room so as to include the whole furniture set on the carpet, the target and some of the fixed cues on the walls.

### 2.3. Experimental paradigm

The complete experimental design was 2 by 3 by 3 factorial, with two *tasks* performed relative to three *spatial reference frames*, with three amounts of *viewpoint change*. Participants alternated two tasks: the *position task*, designed to require encoding and retrieval of spatial locations across viewpoint changes; and the *color task*, designed to control for perceptual, motor, and attentional components of the position task. Both tasks were performed in three variants corresponding to three types of reference frames: the *room frame* (a stable environmental allocentric frame), the *objects frame* (an unstable, object-based allocentric frame), and the *viewer frame* (an egocentric frame). In each trial, participants were shown the letter P or C for 300 ms at the center of the screen, instructing the position or the color task, respectively. Then, they were shown a first view of the room from an unpredictable viewpoint for 4 s (*study phase*: Fig. 1**B**). After either a short (2 s) or a long (6 s) delay, participants were shown a second view of the room, again from an unpredictable viewpoint (*test phase*: Fig. 1**B**). The viewpoint in the test phase could either be the same as in the study phase (no viewpoint change or 0 deg), or be rotated by 45 deg (small viewpoint change or 45 deg) or by 135 deg (large viewpoint change or 135 deg). The following trial started after a variable inter-trial interval (ITI; 2, 4, or 6 s). Such ITIs constituted an independent and common low-level baseline for all scans.

### 2.4. Position task

In the *position task*, participants detected spatial displacements of the target object with respect to either of the three types of reference frames. Participants reported either (a) changes in the absolute spatial location of the target in the room (*room frame*), or (b) changes in its location relative to the furniture set on the central circular carpet (*objects frame*), or (c) changes in its location relative to the viewer (*viewer frame*). Participants pressed the “yes” button with their right index finger if the target was in the same position as in the study phase, or the “no” button with their right middle finger if the target was in a different position, relative to the relevant reference frame. For the room frame, participants judged whether the position of the target in the room was constant; for the objects frame, participants judged whether the position of the target relative to the furniture set was constant. The two frames crucially differed for the use of enduring information about stable features of the environment and volatile information about locations of objects, respectively.

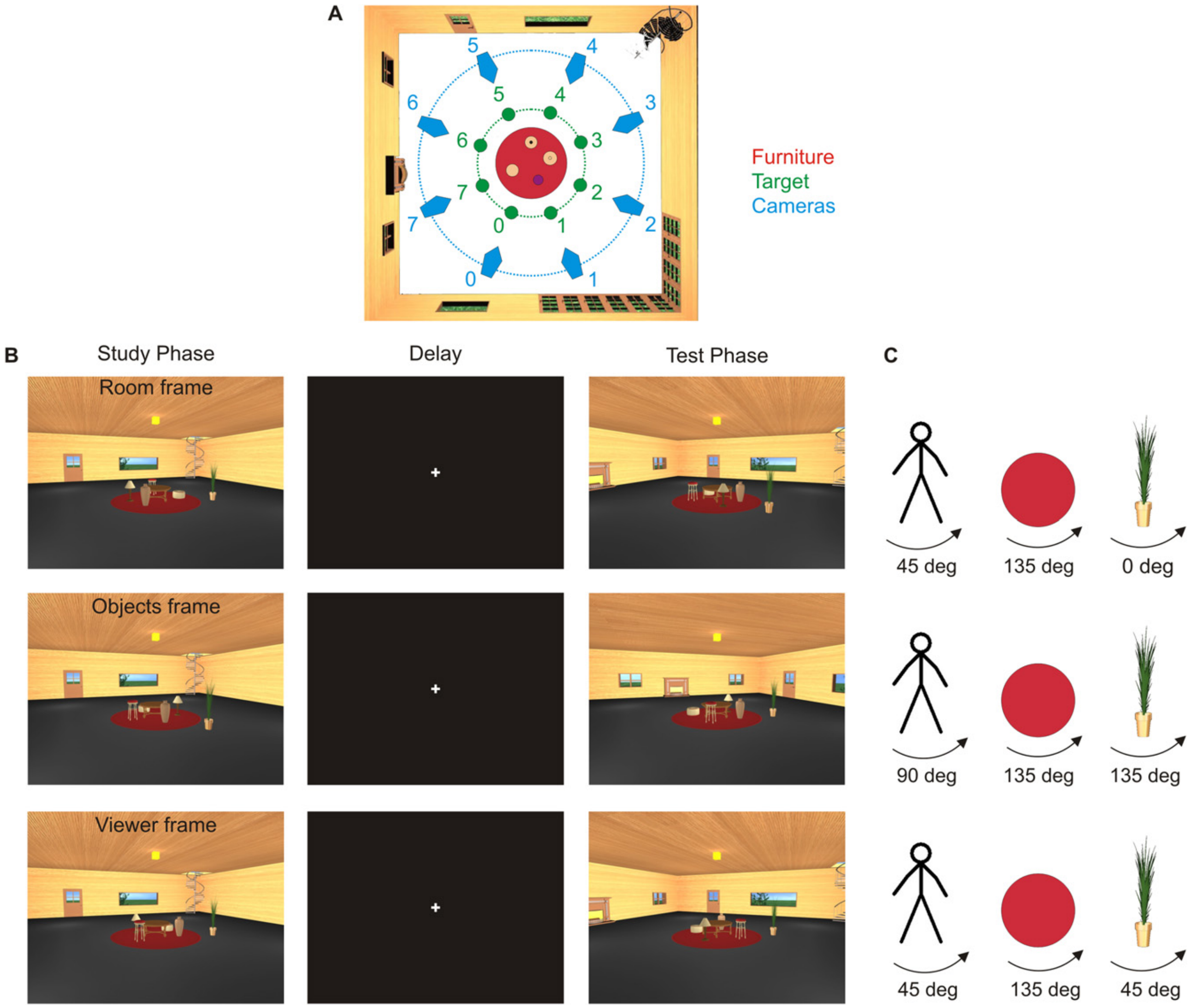

**Fig. 1.** Experimental paradigm: (A) Top view of the virtual environment used in the experiment. Blue numbers mark the possible positions of the virtual cameras used to take the snapshots employed as stimuli, arranged on a circle also shown in blue. Green numbers mark the possible positions of the target object (the plant), arranged on a circle also shown in green. (B) Three examples of trials of the position task, for the room (top row), objects (middle row), and viewer (bottom row) reference frames. The three columns show examples of stimuli for the study, delay and test phases, respectively. (C) Experimental manipulations in the three example trials, in terms of rotation of the observer's point of view (i.e., of the camera) relative to the room (left column), rotation of the objects frame (i.e., of the carpet) relative to the room (middle column), and rotation of the target object (i.e., the plant) relative to the room. Relative to the relevant reference frame, all the examples show a viewpoint change of 45 deg, and in all the examples the plant position remains the same. Note that in the room frame, the carpet is rotated of a different amount with respect to the observer's point of view (45 vs. 135 deg), so that these two reference frames are totally disentangled. In the objects frame, both the carpet and the plant are rotated of an equivalent amount (which is always different from the rotation of the observer's point of view), so that the objects-target relative position remains the same irrespective of the observer's point of view. In the viewer frame, the observer's point of view and the plant position are rotated of an equivalent amount (which is always different from the object array rotation), so that the viewer-centered position of the target remains the same. (For interpretation of references to color in this figure legend, the reader is referred to the web version of this article.)

In both cases the task required to encode the position of the target object in short-term spatial memory, and the position of the target object unpredictably changed across trials; so, we did not manipulate the time scale of the encoding and retrieval process. For the viewer frame, participants encoded the position of the plant relative to their current point of view, i.e., in viewer-centered coordinates. Participants then decided whether the viewer-centered location of the plant was the same or different in the test phase. Although participants again could undergo an unpredictable viewpoint change, this manipulation by design should not produce any effect, because by definition viewer-centered judgments are the same across viewpoint changes.

The experimental design crucially depends on the complete disentanglement between room and objects reference frames. When encoding room-absolute spatial locations, observers can of course rely upon their long-term knowledge of the room layout, and in particular of the position of stable and distal cues such as doors, windows, and staircases. We arranged the position of the pieces of furniture so that this was not possible by design when encoding objects-relative locations. First, in each trial the five pieces of furniture were located in different absolute-room locations on the carpet and in a different relative arrangement. We created eight different furniture sets, where the same five pieces of furniture were arranged in different configurations. Each furniture set could be presented in eight different orientations, in steps of 45 deg, resulting in 64 different layouts, which were randomly assigned to each trial. This ensured that participants could not build up by learning and rely upon any form of enduring spatial representation of the location of each piece of furniture or of the furniture set as a whole. In other words, the objects reference frame was constituted by objects without a stable position and configuration in the environment, thus not being part of the pre-learned room layout.

This manipulation alone, however, would not preclude participants from encoding the room-absolute location of the plant even when they were requested to encode its objects-relative location, or vice versa. Thus we needed a way to further disentangle the two reference frames, so that the objects-relative location of the plant during the test phase could not be predicted based on its room-absolute location in the study phase, and vice versa. This was made by rotating the carpet (and thus the furniture set as a whole) within the room by an unpredictable amount across the two consecutive views of each single trial. The resulting combinations of viewpoint changes relative to the various reference frames are detailed below.

In same viewpoint (0 deg) trials (Supplementary Fig. 1C, left column), the viewpoint remained the same relative to the relevant frame (either room or objects) but changed relative to the other (irrelevant) frame. This was obtained, for the room frame, by rotating the furniture set relative to the room, without moving the camera (Supplementary Fig. 1C, left column, top row), and, for the objects frame, by rotating both the camera and the furniture set by the same amount, thus leaving the spatial relationships between the observer and the furniture set the same, while changing those between the observer and the room (Supplementary Fig. 1C, left column, middle row). In the viewer frame, the viewpoint stayed the same relative to both room and objects frames, i.e., the camera and furniture set did not rotate (Supplementary Fig. 1C, left column, bottom row). Thus, the viewer-0 deg condition was the only one in which the three reference frames were aligned.

In different viewpoint (45 and 135 deg) trials (Supplementary Fig. 1C, middle and right columns), the test camera was always different from the study camera (thus dissociating the room from the viewer frame), the furniture set always rotated in the room (thus dissociating the room from the objects frame), and the amount of rotation of the camera was always inconsistent with that of the furniture set (thus dissociating the objects from the viewer frame). The viewpoint change was computed relative to the room (i.e., camera rotation) for the room and viewer frames, and relative to the furniture set (i.e., as the difference between camera and furniture rotation) for the objects frame. For example, in Supplementary Fig. 1C (middle column, middle row), the furniture set is rotated by 135 deg counterclockwise across the two views and the camera is rotated by 90 deg counterclockwise: thus, the viewpoint change relative to the furniture set is 45 deg.

The target position during the test phase was arranged so that in half of the trials it remained the same as in the study phase, relative to the relevant reference frame. In the remaining half of the trials, the plant underwent a displacement of 135 deg, either in clockwise or counterclockwise direction, with respect to the relevant frame. Importantly, the target never remained in the same location relative to the other two reference frames (except in the viewer-0 deg condition, where the three frames were aligned). Note that these manipulations were explicit and participants were well informed and trained before entering the MR scanner. In this way, using the other reference frame during the study phase was useless, if not impossible.

### 2.5. Color task

The *color task* used modified snapshots of the virtual room (see examples in Supplementary Fig. 2). Both in the study and test phases, the target color was either “normal” (as in the position task) or covered with a blue texture. In the room and objects conditions, the same manipulation was applied to the room walls and to the pieces of furniture, respectively. In half of the trials, the color of the target (and of the room walls or pieces of furniture) remained the same from the study to the test phase. In the other half, there was a change in the color of the target (viewer condition), in the color of the target and/or of the room walls (room condition), or in the color of the target and/or of the pieces of furniture (objects condition). All the possible combinations between a “normal” and a “blue” color were presented. The target position always changed with respect to the relevant frame of reference. This ensured that, for each reference frame, spatial attention was allocated to the same regions and objects in the display as in the position task. Participants reported changes in the color of the plant, rather than in its spatial location, together with the color of the room walls (for the room frame), or the color of the furniture set (for the objects frame), by pressing the “yes” button if all the relevant elements had unchanged colors, or “no” if there was some change in the color.

### 2.6. Apparatus and imaging procedure

Images were acquired using a 3 T Siemens Allegra MR system (Siemens Medical systems, Erlangen, Germany) operating at the Neuroimaging Laboratory, Foundation Santa Lucia, using a standard head coil. Stimuli were generated by a control computer located outside the MR room, running in-house software [31] implemented in MATLAB (The MathWorks Inc., Natick, MA, USA). An LCD video projector with a customized lens was used to project wide-field visual stimuli (69 by 55 deg of visual angle) to a back projection screen mounted inside the MR tube, very close (10–12 cm) to the subject head, and visible through a mirror mounted inside the head coil [32,33]. Presentation timing was controlled and triggered by the acquisition of fMRI images. Responses were given through push buttons connected to the control computer via optic fibers.

Echo-planar functional MR images (TR = 2 s, TE = 30 ms, flip angle = 70 deg, 64 × 64 image matrix, 3 × 3 mm in-plane resolution, 30 slices, 4.5 mm slice thickness with no gap, interleaved excitation order) were acquired in the AC–PC plane using blood-oxygenation level-dependent imaging [34]. From the superior convexity, sampling included all the cerebral cortex, excluding only the ventral portion of the cerebellum. A three-dimensional high resolution anatomical image was also acquired for each subject (Siemens MPRAGE sequence, TR = 2 s, TE = 4.38 ms, flip angle = 8 deg, 512 × 512 image matrix, 0.5 × 0.5 mm in-plane resolution, 176 contiguous 1 mm thick sagittal slices). The first four volumes of each scan were discarded to achieve steady-state T1 weighting, and the experimental tasks started at the beginning of the fifth image.

Before entering the scanner, subjects were familiarized with the room. We presented a 52-s movie consisting of a 360 deg tour of the virtual room, with only the stable landmarks and the carpet but no pieces of furniture. During this period, subjects memorized the global spatial layout of the room before the experiment. They were allowed to watch the movie until they were sure to be able to draw a sketch representing the survey perspective of the room. All subjects observed either one or two virtual tours and reproduced the correct map of the explored room. This was crucial to ensure they had developed a long-term knowledge of the room layout.

Each subject then completed six functional acquisition scans for the main experiment, two for each frame of reference (room, objects, and viewer), in a sequence counterbalanced across subjects. Each scan lasted approximately 8 min (48 trials, 256 functional MR volumes), and within each scan position and color trials were randomly intermixed. Reference frames were studied in separate scans, but the main effect of reference frame did not merely reflect between-scans differences in the overall activity. Such possible confound was indeed prevented by (a) using an independent and common low-level baseline in all scans, i.e., fixation periods between trials and (b) counter-balancing the order of scans across subjects, which means that we should not expect any systematic change between scans in the group analysis. In any case, the reference frame by task interaction did not suffer from this interpretability problem.

Eleven subjects also completed two functional localizer scans for scene-responsive regions in the parahippocampal and medial occipito-parietal cortex [28]. During each scan we acquired 234 functional MR volumes, while participants viewed eight alternating blocks (16 s) of photographs of faces and places/scenes presented for 300 ms every 500 ms, interleaved with fixation periods of 15 s on average [35].

### 2.7. Data analysis

Images were preprocessed and analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Functional time series from each subject were first temporally corrected for slice timing, using the middle slice acquired in time as a reference, and then spatially corrected for head movement, using a least-squares approach and six parameter rigid body spatial transformations. They were then spatially normalized using an automatic nonlinear stereotaxic normalization procedure (final voxel size: 3 mm × 3 mm × 3 mm) and spatially smoothed with a three dimensional Gaussian filter (6 mm full-width-half-maximum). The template image for spatial normalization was based on average data provided by the Montreal Neurological Institute [36] and conforms to a standard coordinate referencing system [37].

Images were analyzed using a standard random-effects procedure. The time series of functional MR images obtained from each participant was analyzed separately. The effects of the experimental paradigm were estimated on a voxel-by-voxel basis, according to the general linear model extended to allow the analysis of fMRI data as a time series. The model included a temporal high-pass filter to remove low-frequency confounds with a period above 128 s. Serial correlation in the fMRI time series were estimated with a restricted maximum likelihood (ReML) algorithm using an autoregressive AR(1) model during parameter estimation, assuming the same correlation structure for each voxel, within each scan. The ReML estimates were then used to whiten the data.

The initial analysis aimed at selecting a set of regions differentially implicated in the position task relative to the color task, without any assumption on the shape of the hemodynamic response or on the time period within a trial (study or test phase) where the difference in the signal arose. We thus employed a deconvolution approach, modeling each trial as a set of finite impulse basis functions [38,39] covering 14 time points every 2 s, starting from the onset of the study snapshot. Separate sets of basis functions were used for short (2 s) and long (6 s) delay trials, for position and color task trials, and for each reference frame. The resulting estimates of individual event-related time courses entered a random-effects group analysis, implementing a repeated-measures factorial analysis of variance (task by reference frame by delay length by time point) with non-sphericity correction. Using an “omnibus” F-contrast, we searched for voxels exhibiting differences in the BOLD signal between the position and the color task, in at least one time point and in at least one combination of reference frame and delay length. The resulting statistical parametric map was thresholded at $F_{84,1176} = 2.05$, corresponding to $p < 0.01$, corrected for multiple comparisons based on family-wise error (*FWE*), and is shown in Fig. 3. Based on this map, we created regions of interest for further analyses (Table 1), by grouping together, for each regional peak, all neighboring voxels at a maximum distance of 8 mm from the peak.

We also used independently defined, theoretically motivated, regions of interest, i.e., the parahippocampal place area (PPA) and the retrosplenial complex (RSC), as defined on separate “localizer” scans. For localizer scans, place/scene and face blocks were modeled as box-car functions, convolved with a canonical hemodynamic response function. The PPA and the RSC were identified in individual analyses as subject-specific regions responding more strongly to places/scenes than to faces in the posterior parahippocampal cortex and in the retrosplenial complex, respectively. The RSC was defined extensively, following [28], to include the posterior cingulate (Brodmann areas 23–31), the retrosplenial cortex proper (Brodmann areas 29–30), and the nearby ventral parietal-occipital sulcus and anterior calcarine sulcus. Individual regions of interest were created by selecting all activated voxels ($p < 0.05$, corrected for multiple comparisons) at a maximum distance of 16 mm from the activation peak.

Since the time courses exhibited distinct activation peaks for the study and test phases, at least for the longest delay length, and a canonical shape for the hemodynamic response, further analyses were conducted by modeling each

**Table 1**

Regions selective for spatial memory across viewpoint changes. Regional peaks (MNI coordinates) and size (number of voxels) of the regions exhibiting differential BOLD time courses during position vs. color trials in at least one reference frame, for either short or long delay trials (see also Fig. 3). pIPS: posterior intraparietal sulcus (pIPS); PTO: parieto-temporal-occipital junction; PC: precuneus; SMG: supramarginal gyrus; FEF: frontal eye fields; LPHG: lingual/parahippocampal gyrus; RSC: retrosplenial complex.

| Region | Hemisphere | MNI coordinates | | | Size (voxels) |
|---|---|---|---|---|---|
| | | x | y | z | |
| pIPS | Left | −15 | −67 | 52 | 179 |
| | Right | 18 | −67 | 52 | 172 |
| PTO | Left | −27 | −79 | 34 | 187 |
| | Right | 36 | −76 | 31 | 255 |
| PC | Left | −9 | −73 | 49 | 138 |
| | Right | 9 | −64 | 58 | 218 |
| SMG | Left | −36 | −49 | 49 | 166 |
| | Right | 45 | −34 | 46 | 248 |
| FEF | Left | −21 | 5 | 55 | 93 |
| | Right | 27 | −1 | 58 | 115 |
| LPHG | Left | −12 | −70 | −5 | 115 |
| | Right | 15 | −67 | −5 | 121 |
| RSC | Left | −18 | −58 | 19 | 65 |
| | Right | 18 | −55 | 19 | 88 |

neural event as a canonical hemodynamic response function, chosen to represent the relationship between neuronal activation and blood flow changes [40]. Assuming a canonical shape for the hemodynamic response function allowed us to model the onset of the study and of the test phase of each trial as two separate events. Separate regressors were included for each combination of task, reference frame, and (for the test phases) viewpoint change. These analyses were conducted on averaged time series created by averaging individual subjects' unsmoothed time series across all voxels in each region of interest. The resulting parameter estimates, representing individual estimated amplitudes of the hemodynamic response in terms of percentage signal change, entered a group random-effects analysis implementing a repeated-measures factorial analysis of variance (task by reference frame, for the study phase; task by reference frame by viewpoint change, for the test phase).

The use of selective analysis of averaged regional signals is motivated here by the complexity of the experimental design, which includes factors with multiple levels, whose interactions are particularly relevant for the experimental questions. The characterization of significant interactions through post hoc tests at the voxel level, although theoretically possible, would be unpractical, would inflate the multiple comparison problem intrinsic to voxel-wise analysis, and would ultimately reduce power. Here we make an exploratory, rather than hypothesis-driven, use of selective analysis [41], with regions of interest defined on the basis of the data themselves. Critical for the validity of this approach and to avoid circularity [42] is the independence between the criterion used for region selection and the hypotheses tested on data obtained from such regions. Here we used one experimental factor (Task) to define regions, and we tested the other main effects and interactions in the factorial design on the resulting data [43].

## 3. Results

### 3.1. Behavior: dissociations in spatial memory across environmental and object-based reference frames

Error rates (Fig. 2A) and response times (Fig. 2B) were analyzed as a function of task (position, color), reference frame (room, objects, viewer), and viewpoint change (0, 45, 135 deg), in a repeated-measures analysis of variance (ANOVA). The analysis on error rates revealed main effects of task ($F_{1,14} = 7.50$; $p < 0.05$), reference frame ($F_{2,28} = 11.67$; $p < 0.001$), and viewpoint change ($F_{2,28} = 13.76$, $p < 0.0001$). Also the task by reference frame ($F_{2,28} = 22.12$; $p < 0.0001$), task by viewpoint change ($F_{2,28} = 11.07$; $p < 0.001$) and reference frame by viewpoint change ($F_{4,56} = 7.041$; $p < 0.001$) interactions were significant.

Importantly, the task by reference frame by viewpoint change interaction was significant ($F_{4,56} = 4.47$; $p < 0.005$). Post hoc analysis of this interaction (Newman–Keuls test, $p < 0.05$) showed that performing the position task within the room frame generated more errors after a large than after a small viewpoint change, and both these conditions generated more errors than all the other combinations of task, reference frame and viewpoint change. We also split errors into misses and false alarms (i.e., errors in different and in same position/color trials): data are reported in Supplementary Table 1 and confirmed the already described pattern.

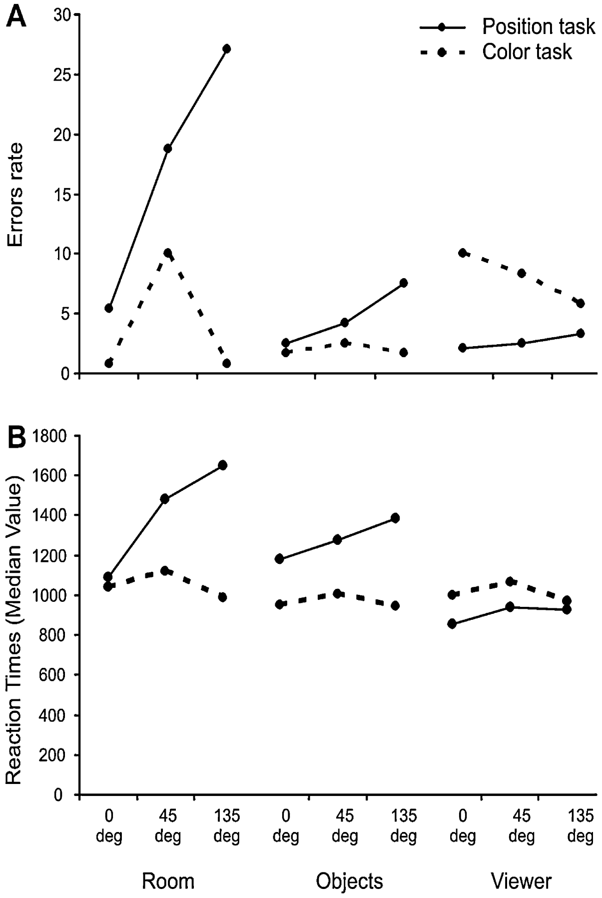

**Fig. 2.** Behavioral results: error rates (A) and response times (B) are shown as a function of task (position, color), reference frame (room, objects, viewer), and viewpoint change (0, 45, 135 deg).

The ANOVA on response times (median value) revealed main effects of task ($F_{1,14} = 79.169$; $p < 0.0001$), reference frame ($F_{2,28} = 57.45$; $p < 0.0001$), and viewpoint change ($F_{2,28} = 44.46$, $p < 0.0001$). Interactions were also all significant: task by reference frame ($F_{2,28} = 65.09$; $p < 0.0001$), task by viewpoint change ($F_{2,28} = 45.48$; $p < 0.0001$), reference frame by viewpoint change ($F_{4,56} = 10.39$; $p < 0.0001$), and task by reference frame by viewpoint change ($F_{4,56} = 18.99$; $p < 0.001$). Post hoc analysis (Newman–Keuls test, $p < 0.05$) revealed a linear effect of the angular displacement ($0 < 45 < 135$) in the position task but not in the color task, for both the room and objects frames but not for the viewer frame, where the difference between a small (45 deg) and a large (135 deg) viewpoint change was not significant. This was expected by design, since for the viewer frame viewpoint changes do not affect the relevant self-to-target spatial computation.

The effect of viewpoint change on the position task was higher for the room than for the objects frame: responses were significantly slower for the room than for the objects frame in the 45 and 135 deg conditions. Comparison across the two tasks showed that the position task took longer to complete than the color task only when there was a (small or large) viewpoint change, and when this viewpoint change was relevant to the task (i.e., for the room and object frames, but not for the viewer frame).

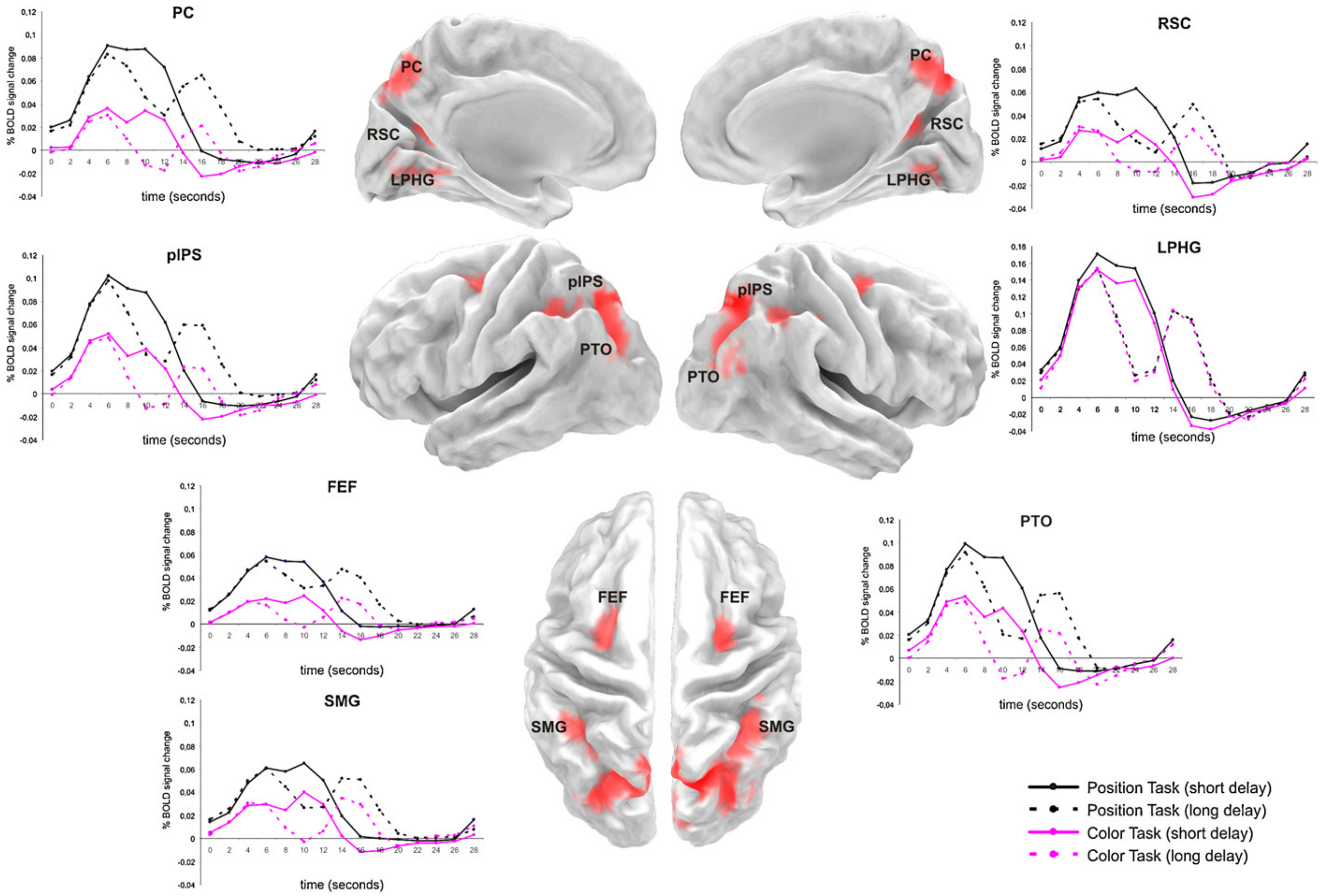

**Fig. 3.** Regions selective for object location memory. Regions exhibiting differential BOLD time courses during position vs. color trials in at least one reference frame, for either short or long delay trials. Note that, even if the reference frames was included in the F-contrast, the plots show the BOLD activation averaged across them. Regions are rendered in red on reconstructions of the medial, lateral, and dorsal surfaces (top, middle, and bottom panels, respectively) of the two cerebral hemispheres of the PALS atlas [73]. The line plots show, for each region, the group averaged event-related BOLD time courses during short- and long-delay trials (solid and dashed lines, respectively) of the position and color tasks (black and pink lines, respectively). BOLD responses are in arbitrary units, with one unit corresponding to 1% of the mean BOLD signal change during the baseline period across all intra-cerebral voxels. The plots show the BOLD activation averaged across hemispheres. pIPS: posterior intraparietal sulcus (pIPS); PTO: parieto-temporal-occipital junction; PC: precuneus; SMG: supramarginal gyrus; FEF: frontal eye fields; LPHG: lingual/parahippocampal gyrus; RSC: retrosplenial complex. (For interpretation of references to color in this figure legend, the reader is referred to the web version of this article.)

These behavioral results on response times and accuracy have at least two important implications for the fMRI study. First, increasing response times (and decreased accuracy) with increasing amounts of viewpoint changes are generally considered as an index of viewpoint-dependent encoding of spatial locations [14,16,44]. If subjects encoded the spatial location of the plant in a true viewpoint-independent form, relative to the room (environmental frame) or to the furniture set (object-based frame), their performance should not depend on the angular difference between the study and the test viewpoint. Thus, response times are compatible with the idea that subjects encode the plant position egocentrically, and at the same time encode their spatial relationship with the room or the furniture set. In the test phase, they would first estimate the amount of viewpoint change by comparing their position relative to the room or the furniture set with that in the study phase, and then update the memorized position of the plant by the estimated viewpoint change. This "offline" updating process would be fundamentally analogous to a mental self-rotation and would require an amount of time proportional to the amount of viewpoint change.

However, response times also suggest a distinction between changing one's viewpoint relative to a set of objects not associated with a stable, enduring position in the room, and changing one's viewpoint relative to the stable, enduring cues on the room wall. The latter updating process produces a higher behavioral cost in terms of response time increases as a function of the amount of viewpoint changes.

### 3.2. *Cortical regions selective for spatial location memory across viewpoint changes*

The analysis of BOLD time courses followed two main stages: a data selection stage, aimed at identifying brain regions involved in the spatial memory experimental paradigm; and a selective analysis stage, aimed at characterizing the response of these areas during the study and test phases and, critically, the differences between the room and the objects reference frames. For the data selection stage, we wanted to include any voxel which was differentially implicated in the position task relative to the color task in at least one reference frame, without any assumption on the shape of the hemodynamic response and on the time period within a trial (study or test phase).

Four main groups of regions showed bilateral significant BOLD response signal differences between the two tasks (Fig. 3; Table 1): the posterior parietal cortex, the superior-posterior frontal lobe, the lingual–parahippocampal gyrus (LPHG), and the parieto-occipital sulcus. The posterior parietal region bilaterally included the posterior part of the intraparietal sulcus (pIPS), and the adjoining superior and inferior parietal lobules, extending posteriorly into the parieto-temporal-occipital junction (PTO). In the right hemisphere, the parieto-temporal-occipital activation extended more anteriorly into the angular gyrus. Bilaterally, the parietal activation extended medially into the precuneus (PC) and anteriorly into the supramarginal gyrus (SMG). The frontal region was bilaterally located at the intersection between the superior frontal and the precentral sulci, and probably corresponds to the human frontal eye fields (FEF). The lingual/parahippocampal activation included the anterior lingual gyrus where it meets the posterior parahippocampal gyrus, nearby the so-called lingual landmark area (LLA: [45] and the parahippocampal place area (PPA: [46]). The region on the anterior bank of the ventral portion of the parieto-occipital sulcus, near the junction with the anterior calcarine sulcus, well corresponds to a scene-responsive region, which is generally referred to as retrosplenial cortex [28,47,48]. Since this region is functionally defined and not necessarily coincides with the anatomically defined retrosplenial cortex (Brodmann areas 29 and 30: [49,50]), we will use the term “retrosplenial complex” (RSC) instead.

For each of these regions, Fig. 3 also shows the averaged BOLD time courses for the position and color tasks, for trials with short (2 s) and long (6 s) study-test delays. These time courses are averaged across voxels, across reference frames, and across subjects. Inspection of these data shows that the differences between the two tasks invariably occur because the signal is higher in the position than in the color task. For short delay trials, a single sustained peak of the BOLD response is observed, encompassing the study and test phases, while for long delay trials two separate peaks, with an equivalent time-to-peak from the start of the study and the test phases, are clearly visible. The overall shape of the response in both cases is compatible with a linear combination of two standard hemodynamic responses to the study and the test image, respectively. For these reasons, further analyses were conducted, by modeling the onsets of the study and the test image as two separate neural events and assuming a standard shape for the BOLD response evoked by both.

The percent BOLD signal change, estimated in each of the cortical regions resulting from the data selection stage and in the independently defined PPA and RSC (see next paragraph), was analyzed separately for the study and test phases, with a 2 by 3 (task by reference frame) and a 2 by 3 by 3 (task by reference frame by viewpoint change) ANOVA, respectively. In the study phase, the viewpoint change did not enter in the analysis because subjects could not predict the amount of viewpoint change which would occur during the test phase.

### 3.3. *Effects of reference frame and viewpoint change on PPA and RSC*

The PPA and RSC are routinely localized in healthy volunteers based on their selectivity for visual scenes [45,51]. To examine whether retrosplenial and lingual/parahippocampal activation resulting in this study corresponded to the scene-selective PPA and RSC defined in most previous studies, we scanned a subgroup of 11 subjects in a separate experimental session, while they passively viewed pictures of scenes and faces in alternating blocks (Fig. 4A). The RSC was functionally localized in 10/11 participants as the region in the retrosplenial cortex and/or parietal-occipital sulcus responding more strongly to scenes than to faces (average MNI coordinates: left −18, −48, 12; right 21, −57, 14). The scene-selective region identified in the localizer session (Fig. 4B, blue patches) anatomically corresponded to the RSC activated in the main experiment (Fig. 4C, red patches). The PPA was functionally localized in 11/11 participants as the region in the lingual–parahippocampal gyrus responding more strongly to scenes than to faces (average MNI coordinates: left −25, −48, −9; right 27, −47, −9). The comparison between the individually defined PPA from the localizer (Fig. 4B, blue patches) and the LPHG activation from the main experiment (Fig. 4C, red patches), revealed only a partial overlap. In the left hemisphere, the anterior part of the LPHG overlapped with the posterior part of the PPA, while in the right hemisphere the LPHG was entirely more posterior than the PPA.

Individual regions of interest resulting from the functional localizers were used to analyze the data of the main experiment. Fig. 4D and E shows the percent BOLD signal change estimated for the study phase (left panel) in PPA and RSC, as a function of task (position, color) and reference frame (room, objects, viewer) and for the test phase (right panel), as a function of task (position, color), reference frame (room, objects, viewer), and viewpoint change (0, 45, 135 deg). The analysis of the RSC data revealed, for the study phase (Fig. 4D, left panel), a significant interaction between task and reference frame in both left and right RSC ($F_{2,18} = 28.26$; $p < 0.0001$; $F_{2,18} = 12.90$; $p < 0.001$), with activation in the position task higher in the room as compared to both objects and viewer frames (post hoc: $p < 0.01$).

To examine more closely the differential impact of the room and objects frames of reference on the RSC activation, we excluded the viewer frame from the ANOVA. A task by reference frame interaction in this analysis points to a differential selectivity for environmental (room-absolute) vs. object-based (objects-relative) reference frames during encoding. We still obtained a significant task by frame interaction in both left and right RSC ($F_{1,9} = 46.98$; $p < 0.001$; $F_{1,9} = 18.09$; $p < 0.01$), confirming the RSC selectivity for the long-term spatial representation since the activation in the position relative to the color task was higher for the room than for the objects frame (post hocs: $p < 0.05$). For the test phase (Fig. 4D, right panel), we again found a significant task by reference frame interaction in both left and right RSC ($F_{2,18} = 17.99$; $p < 0.001$; $F_{2,18} = 38.14$; $p < 0.0001$). The reference frame by viewpoint change interaction resulted to be significant in the left RSC ($F_{4,36} = 2.90$, $p < 0.05$) and marginally significant in the right RSC ($F_{4,36} = 2.18$; $p = 0.09$). The RSC activity increased for the room frame (but not for the other frames) in the presence of a viewpoint change (45 deg and 135 deg respect to 0 deg), during both position and color tasks (post-hocs: $p < 0.05$). As before, after excluding the viewer frame from the analysis, the selective angular trend on the room frame was confirmed by the reference frame by viewpoint change interaction in both left and right RSC ($F_{2,18} = 5.65$; $p < 0.05$; $F_{2,18} = 3.93$; $p < 0.05$), again indicating a viewpoint dependence (45 deg and 135 deg > 0 deg) only on the room frame of reference, regardless of the task demands. The RSC activity could reflect an automatic process that, in presence of a viewpoint change on a stable reference frame, allows people to re-establish one’s own position after disorientation.

For the PPA, results for the study phase (Fig. 4E, left panel) showed a significant task by reference frame interaction in both left ($F_{2,20} = 17.81$; $p < 0.0001$) and right PPA ($F_{2,20} = 4.11$; $p < 0.05$), due to a greater difference between the position and color tasks for the room frame (post hocs: $p < 0.001$). In the right PPA we also observed a significant greater activation in the position relative to the color task for the objects frame ($p = 0.04$). The task by frame interaction, again due to a greater activation in the position relative the color task in the room frame ($p < 0.001$, and only for the right PPA also in the objects frame: $p < 0.05$) was still significant after excluding the viewer frame from the analysis (left PPA: $F_{1,10} = 28.71$ $p < 0.001$; right PPA: $F_{1,10} = 6.28$; $p < 0.05$). For the test phase (Fig. 4E, right panel), the task by frame interaction was again significant in both left ($F_{2,20} = 7.23$, $p < 0.01$) and right PPA ($F_{2,20} = 4.71$, $p < 0.05$). The main effect of viewpoint change (left PPA: $F_{2,20} = 12.25$, $p < 0.001$; right PPA: $F_{2,20} = 6.43$, $p < 0.01$) reflected a higher activation in the presence of a viewpoint rotation (45 and

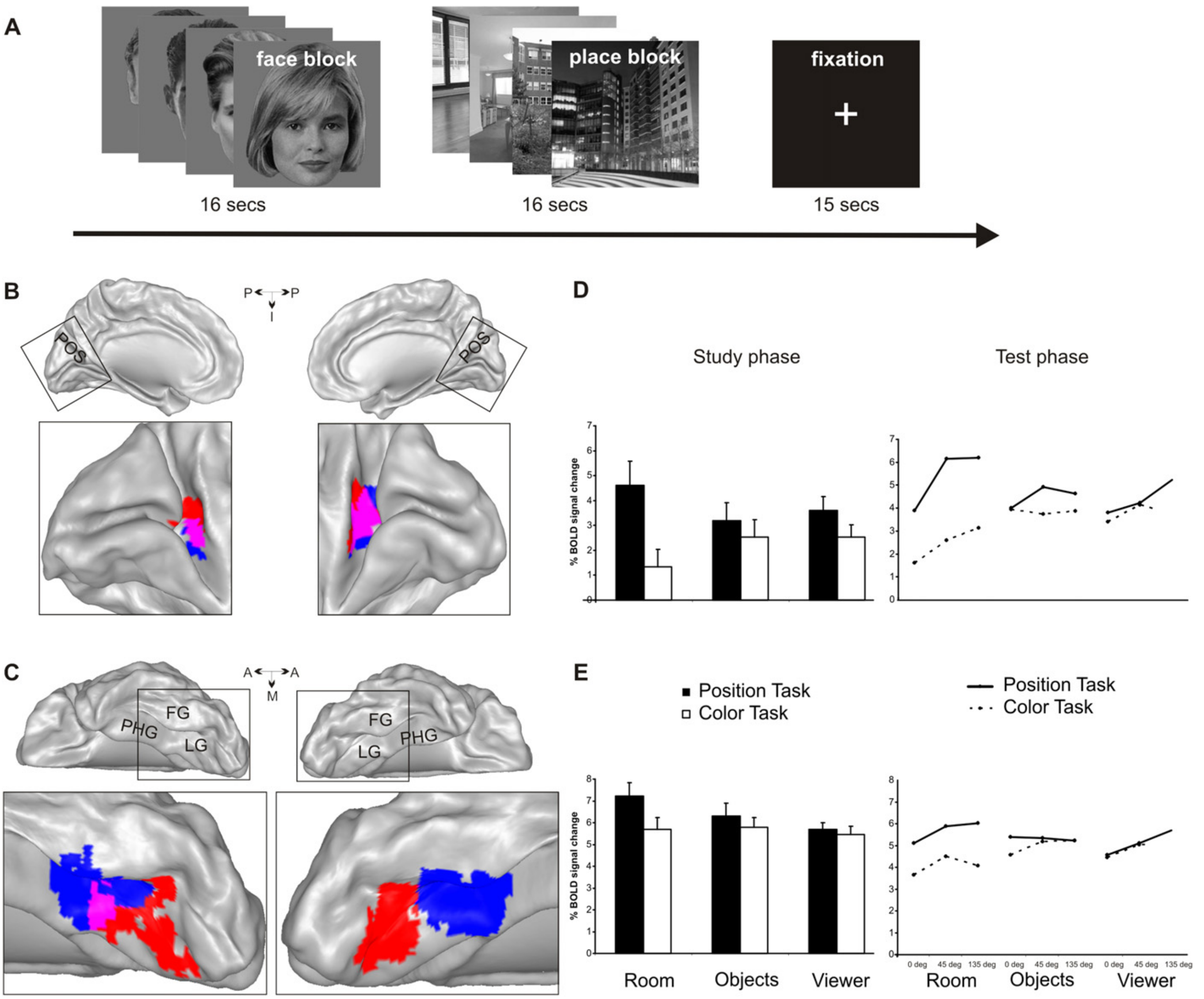

**Fig. 4.** Localizer scan. Independent localization of RSC and PPA. (A) Experimental paradigm used to localize RSC and PPA. (B) Location of RSC as resulting from the group activation of the main experiment (red), and superposition of the individually defined RSCs on the basis of the localizer scans (blue). Medial views of the cortical surface of both left (LH) and right (RH) hemispheres (left and right panel, respectively) are presented. Pink color indicates overlap of the experiment- and localizer-based activations. (C) Location of LPHG as resulting from the group activation of the main experiment (red), and superposition of the individually defined PPAs on the basis of the localizer scans (blue). Medial/inferior views of the cortical surface of both left (LH) and right (RH) hemispheres (left and right panel, respectively) are presented. (D) BOLD signal change, averaged across subjects and hemispheres, in the RSC, as defined from the localizer scan, during the study phase (left panel) and during the test phase (right panel). (E) Same as D but for PPA. (For interpretation of references to color in this figure legend, the reader is referred to the web version of this article.)

135 deg > 0 deg, $p < 0.05$). The absence of a significant reference frame by viewpoint change interaction revealed that the viewpoint rotation effect did not depend on the specific frame of reference. As before, restricting the analysis on the room and objects frames, the ANOVA confirmed the main effect of viewpoint change (left PPA: $F_{2,20} = 4.70$, $p < 0.05$; right PPA: $F_{2,20} = 6.35$, $p < 0.01$) indicating a higher activation in the presence of a viewpoint change (45 and 135 deg > 0 deg, $p < 0.05$), the task by frame interaction (left PPA: $F_{2,20} = 20.05$, $p < 0.01$; right PPA: $F_{2,20} = 9.01$, $p < 0.05$), due to a greater activation in the position vs. color task selectively for the room frame, and the absence of the frame by viewpoint change interaction, suggesting that the viewpoint change effect was not specific for the room neither for the objects frame.

Overall, both PPA and RSC were selective for the environmental frame both in the study and in the test phase, but only the RSC showed a selective increase of activation when the viewpoint changed on the room frame. The functional localizer gave us the opportunity to ensure statistical independence to the results, thus avoiding circularity and invalid statistical inference [42]. Independence of the selective analysis should be further ensured by future studies using split-data analyses, i.e. by dividing data into odd and even runs of the experiment and by performing selection and selective analysis on these independent datasets.

### 3.4. *Study phase: selectivity for encoding locations relative to the environmental frame*

Fig. 5 shows the percent BOLD signal change estimated for the study phase in each of the cortical regions resulting from the data selection stage (3.2), as a function of task (position, color) and reference frame (room, objects, viewer). In all regions, except for the left LPHG, we confirmed the presence of a main effect of task (position > color; $p < 0.05$). Since the analyzed regions were selected on the basis of the presence of an effect of task (either during the

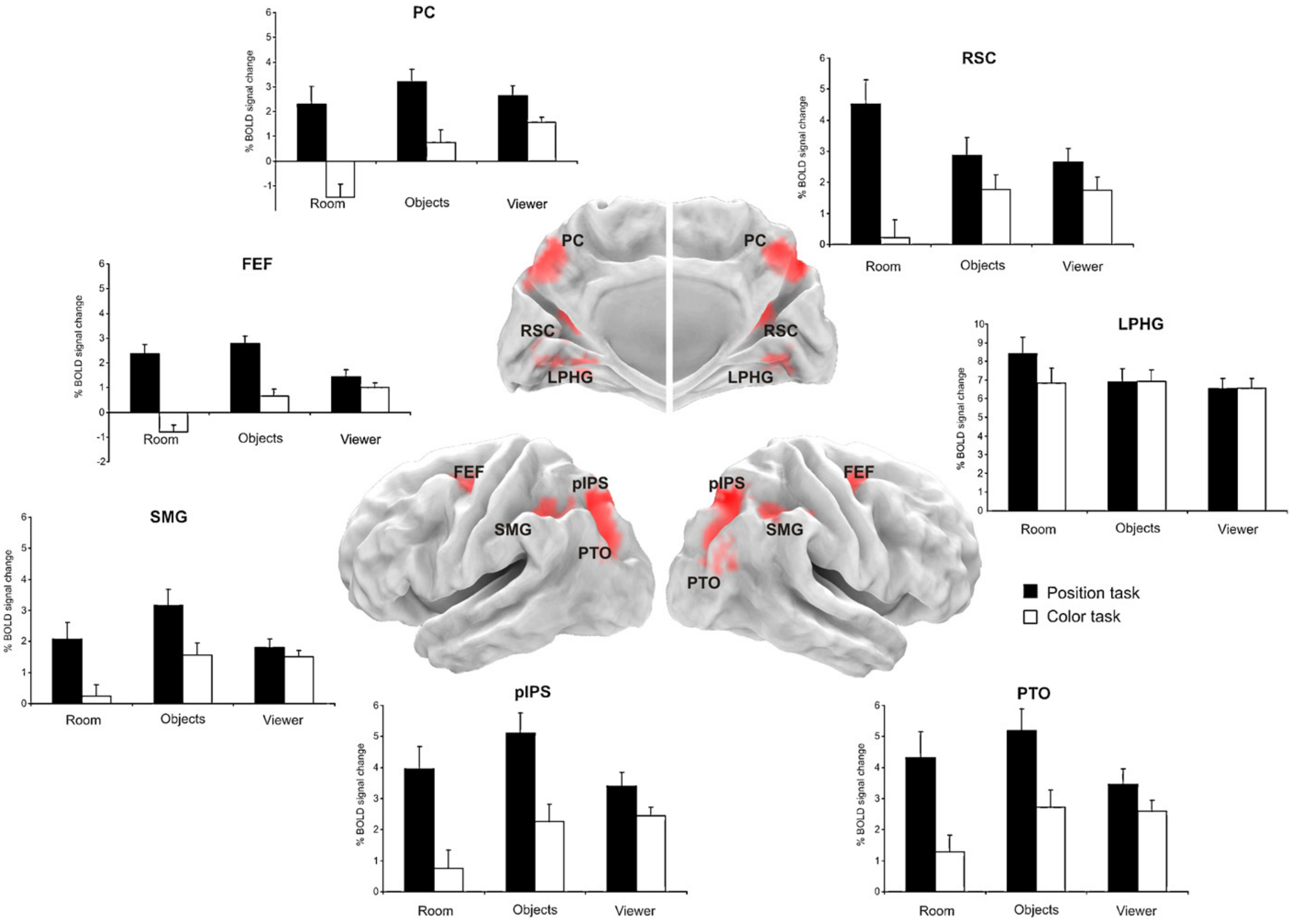

**Fig. 5.** Study phase. Group-averaged estimates of BOLD signal change amplitudes during the study phase in the regions shown in Fig. 3, as a function of task (position task: black; color task: white) and reference frame (room, objects and viewer). The plots show the BOLD activation averaged across the two hemispheres. Note that the regions shown here were selected because of their higher BOLD signal in the position than in the color task. What is relevant to observe in the plots is how the difference between the two tasks is modulated by the reference frame.

study or the test phase), this was hardly surprising. What we were really interested in is how the difference between the two tasks was modulated by the reference frame. A main effect of reference frame (objects > room; $p < 0.05$) was evident in fronto-parietal regions (FEF, SMG, PC, pIPS and PTO). The task by reference frame interaction was significant ($p < 0.01$) in all regions, and could be invariably explained as a smaller or absent difference between the position and color tasks in the viewer frame with respect to the room and objects frames. This was expected by design, since the room and objects frames both require to encode the target spatial location in preparation for a viewpoint change, while for the viewer frame it is enough to encode in viewer-centered coordinates, since the subsequent viewpoint change can be safely ignored. This result implies that subjects do not simply encode spatial locations egocentrically, independently of what they will be asked for in the test phase. Rather, subjects seem to engage additional neurocognitive processes in the preparation for a viewpoint change.

After excluding the viewer frame from the ANOVA, we still obtained a strong interaction in the RSC (left: $F_{1,14} = 56.57$; $p < 0.00001$; right: $F_{1,14} = 31.49$; $p < 0.0001$) and LPHG (left: $F_{1,14} = 74.79$; $p < 0.00001$; right: $F_{1,14} = 42.93$; $p < 0.00001$). In these regions, the activation in the position relative to the color task was higher for the room than for the objects frame, demonstrating a selective involvement in encoding absolute spatial locations in the room, i.e., locations relative to a stable, memorized representation of the room. The interaction was also significant in the FEF (left: $F_{1,14} = 9.40$; $p < 0.01$; right: $F_{1,14} = 6.64$; $p < 0.05$), and in the left PC ($F_{1,14} = 5.03$; $p < 0.05$). However, these regions did not prefer either stable or unstable reference frames to encode locations during the position task: the interaction was due to a lower signal for the room than for the objects frame during the color task. Note that this interaction needs to be cautiously considered because it may reflect differences among reference frames presented in different scans. However, we are interested in the difference between the position and color tasks for each reference frame and it is questionable whether this particular profile exhibited by FEF and PC makes the conclusion about their selectivity for enduring spatial representations less robust. It is worth reminding that we employed separate control (color) tasks for each reference frame, in order to match the requirements of the main spatial memory task for what concerns the allocation of attention on different objects in space (e.g., distal cues for the room frame, more proximal objects for the objects frame, the target alone in the viewer frame). Such attentional differences can well result in a main effect of reference frame but cannot bias the task by reference frame interaction. Thus, differences in the activation in the color task across reference frames are not unexpected and confirm the importance of introducing differential control tasks for each reference frame. What seems directly relevant for our purposes is the amount of difference between the position and color tasks for each reference frame.

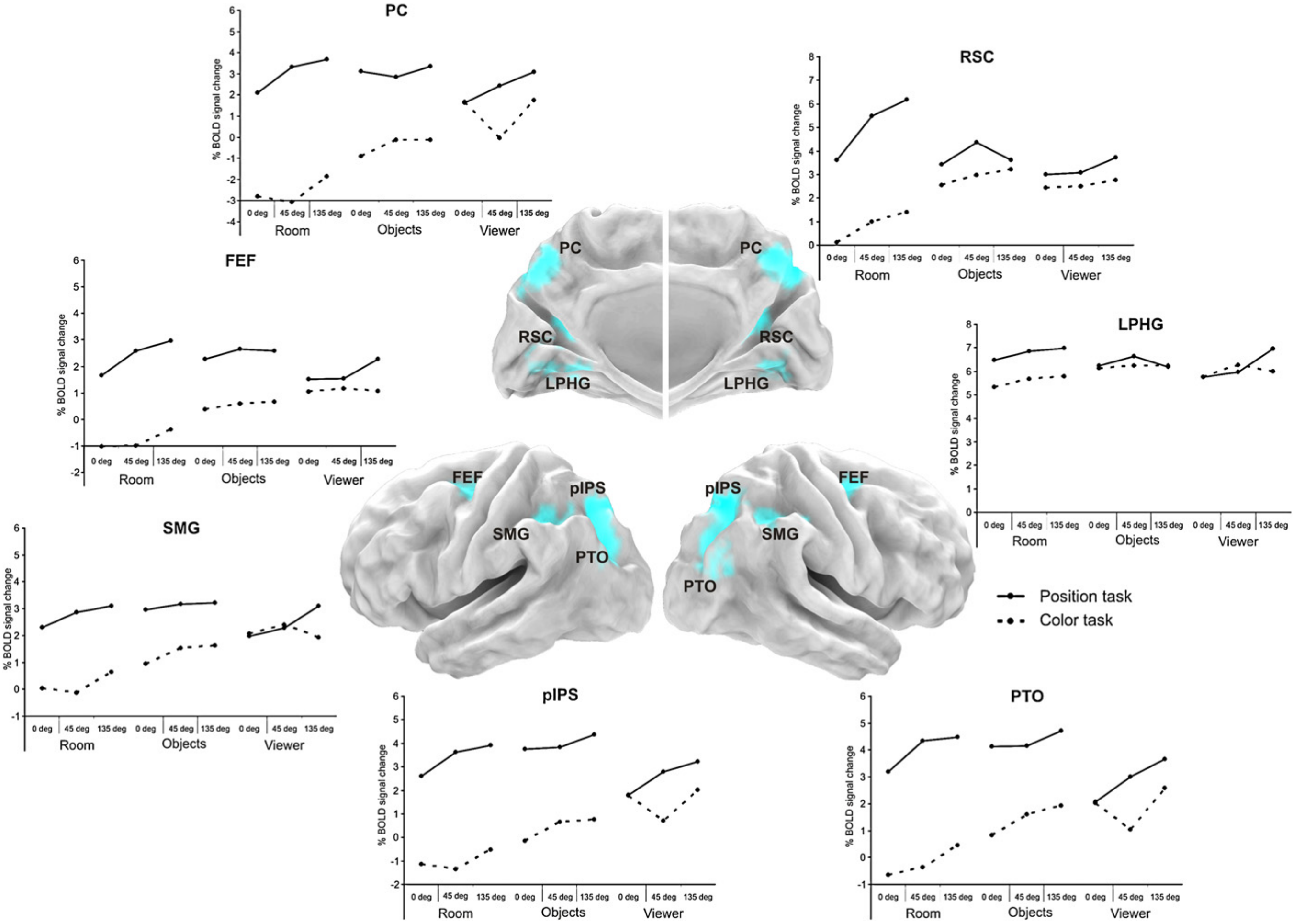

**Fig. 6.** Test phase. Group-averaged estimates of BOLD signal change amplitudes during the test phase in the regions shown in Fig. 3, as a function of task (position task: solid lines; color task: dashed lines), reference frame, and viewpoint change. The plots show the BOLD activation averaged across the two hemispheres. Note that the regions shown here were selected because of their higher BOLD signal in the position than in the color task. What is relevant to observe in the plots is how the difference between the two tasks is modulated by the other two factors.

### *3.5. Test phase: selectivity for updating memorized locations relative to the environmental frame*

Fig. 6 shows the percent BOLD signal change estimated for the test phase in each of the cortical regions resulting from the data selection stage (3.2), as a function of task (position, color), reference frame (room, objects, viewer), and viewpoint change (0, 45, 135 deg). Only trials associated with correct responses were analyzed. In all regions we found a main effect of task (position > color; $p < 0.001$, except for the left and marginally for the right LPHG ($p = 0.051$). Again, this effect is hardly surprising and is not of interest here, since it is the direct result of selecting regions for the presence of a difference between the two tasks. The main effect of viewpoint change (45 > 0 deg and 135 > 0 deg; $p < 0.05$) was observed in bilateral RSC, FEF, and PTO, right pIPS, left PC and LPHG.

The interaction between task and reference frame was significant in all regions ($p < 0.05$) and marginally significant in the right LPHG (p = 0.06), again generally due to a smaller or absent difference between the position and color tasks in the viewer frame with respect to the other frames. The interaction between reference frame and viewpoint change was significant only in the RSC (left: $F_{4,56} = 4.26$; $p < 0.005$; right $F_{4,56} = 3.39$; $p < 0.05$), with activation increasing in the presence of a viewpoint change (45, 135 deg), but only for the room frame. Here, Newman–Keuls post-hocs revealed significant differences between 0 and 45 deg and between 0 and 135 deg of viewpoint rotation in both position and color tasks ($p < 0.01$). In the right hemisphere, we also found a three-way interaction (task by reference frame by viewpoint change) in LPHG and FEF ($F_{4,56} = 4.58$; $p < 0.01$; $F_{4,56} = 3.04$; $p < 0.05$). In the right LPHG, the interaction was due to a higher activation in the position relative to the color task at 45 deg of viewpoint change on the room frame ($p = 0.03$). In the right FEF, the three-way interaction was explained by the viewpoint change effect on the room frame of both tasks and on the viewer frame of the position task. Thus, the increase of activation as a function of viewpoint change was selective for retrieving memorized spatial and perceptual features in environmental coordinates and only spatial information relative to the viewer frame (note that the viewpoint change on the viewer frame, which is irrelevant since the viewer-centered judgments does not change across perspectives, was computed as a viewpoint change on the room and thus again in environmental coordinates). This angular effect on the viewer frame could confirm our hypothesis of an automatic reorientation occurring every time one's viewpoint changed relative to a stable environment, independently of the requested task.

As mentioned before, the viewer frame represents a high level control condition in which the amount of viewpoint change was actually irrelevant for solving the task. After excluding this condition from the analysis, as we did for the study phase, the repeated-measures ANOVA still revealed a significant reference frame by viewpoint change interaction in both left ($F_{2,28} = 5.89$; $p < 0.01$) and right RSC ($F_{2,28} = 6.21$; $p < 0.01$), and in the right FEF ($F_{2,28} = 6421$; $p < 0.05$). As above, this effect was due to a selective effect of viewpoint change on the room frame. In the RSC, the post hoc analysis indeed revealed a significant difference between 0 and 45 deg and between 0 and 135 deg of viewpoint rotation for the room frame ($p < 0.001$). In a similar vein, the right FEF showed a selective effect of viewpoint change ($0 < 45 < 135$ deg; $p < 0.05$) only on the room frame. Thus, the RSC and the right FEF activity increased as a function of the viewpoint change on the room.

Even if the viewpoint change affected only the room frame, only a three-way interaction (task by reference frame by viewpoint change) showing a higher angular effect on the room frame of the position task would allow to conclude for the existence of an "offline" updating process selective for the enduring representation of the stable environment. Interestingly, this three-way interaction was found only in the right RSC ($F_{2,28} = 4.10$; $p < 0.05$), indicating a more evident angular trend in the position than in the color task, of course only for the environmental frame.

### 3.6. *Controlling for task difficulty and time-on-task effects*

The pattern of behavioral and imaging results raises the issue of whether they are due to qualitative differences between tasks and reference frames, or merely quantitative differences related to how strongly or how long a given aspecific process is needed to solve the task. Indeed, the position task showed higher updating costs, i.e., a steeper relationship between viewpoint change and response times, for the environment than for the objects frame, suggesting a possible difference in task difficulty across the two reference frames.

It is highly unlikely that task difficulty per se, i.e., the aspecific amount of cognitive load, has a significant impact on the reported results. We did not observe activation of either the prefrontal cortex, which reflects increasing demands on executive processing [52], or of the anterior cingulum, which is related to cognitive control and effortful task completion [53–55]. Also, the position-environment condition (the most difficult condition, according to behavioral results), did not cause a widespread increase of activation in the posterior parietal and frontal regions, but a selective increase in PPA and RSC relative to the other conditions.

However, it remains possible that an aspecific process of spatial updating across viewpoint changes (not qualitatively different for the environment and the objects frame) determined the activation of RSC and LPHG, which would be modulated according to the difficulty of the updating process and/or to the time needed to perform the process. We empirically tested this hypothesis through two control analyses.

First, if the activation modulation in RSC and LPHG reflects a genuine qualitative difference between the environment and the object reference frames, then the task (position vs. color) by frame (environment vs. objects) interaction should be significant even if only considering the test phase in the 0 deg condition. In this particular condition, no actual updating of the memorized target location takes place (although the subject is prepared to do so). The ANOVA on the BOLD signal change, focused on the 0 deg condition of the room and objects frames, confirmed our prediction, since the task by frame interaction was still significant in both left ($F_{1,14} = 24.70$; $p < 0.001$) and right RSC ($F_{1,14} = 9.86$; $p < 0.01$).

Second, if the effect of the amount of viewpoint change observed in RSC is directly related to the updating cost, modeling the response time as the expected duration of the neural response should control for the time-on-task effect, i.e., for the apparent increase of activation generated by an increased duration of the underlying cognitive and neural process. Thus, we reanalyzed the RSC time courses modeling the duration of the test phase regressors as a function of the response times in individual trials. Our hypothesis of a genuine involvement of RSC in spatial updating of memorized target locations for the environment frame allows to make two specific predictions. First, the reference frame by viewpoint change interaction, which was significant in the main analysis, should disappear, because this effect was supposedly due to the same process (spatial updating) being engaged for a variable amount of time, depending on the amount of viewpoint change. Thus, controlling for the time spent on task should cancel this effect out. Second, the task by reference frame interaction should still be significant, because this interaction was supposedly due to two different processes (spatial updating for the two reference frames) being engaged. Thus, controlling for the time spent on task should not cancel this effect out. These predictions were confirmed for both the left and right RSC (reference frame by viewpoint change interaction: left RSC, $F_{2,28} = 2.41$; $p > 0.05$; right RSC, $F_{2,28} = 1.96$; $p > 0.05$); task by reference frame interaction: left RSC, $F_{1,14} = 51.99$; $p < 0.00001$; right RSC, $F_{1,14} = 41.63$; $p < 0.00001$). Although the former result is based on the absence of a significant effect and thus needs to be considered as only suggestive, the latter result demonstrates that the task by reference frame interaction in RSC does not depend on a time-on-task effect.

## 4. Discussion

Remembering object locations across different views is a fundamental competence for keeping oriented in large-scale space. Compensating for changes in point of view appears to be a specific cognitive ability, relying on a process of mental self-rotation, or perspective transformation, which is distinct from the process of mentally rotating objects. Differently from previous neuroimaging studies which have compared perspective transformations to mental rotation of objects (e.g., [29]), here we compared different kinds of perspective transformations according to the involved spatial reference frame. Based on the distinction between object-relative and environment-absolute frames of reference [25,26], we hypothesized that perspective transformations performed relative to absolute, but not relative, allocentric reference frames would be hard-coded in a neural network known to be involved in scene processing, spatial learning, and navigation.

In the present study, we measured brain activation both during encoding of spatial locations in the preparation for a viewpoint change (study phase), and during updating of memorized locations after the occurrence of the viewpoint change, i.e., during the perspective transformation process (test phase). We manipulated both the spatial reference frame, by comparing an environmental-absolute (*room*), an object-relative (*objects*), and an egocentric (*viewer*) frame, and the amount of experienced viewpoint change. The viewer frame acted as a high-level control condition, since viewpoint changes are irrelevant if a task has to be performed within an egocentric coordinate system. Possible differences in spatial attention and eye movements across the frames of reference were controlled through a task requiring to memorize the color of the target object (instead of its position) together with the color of the relevant frame of reference. Additionally, we used a wide-field stimulation setup which gives subjects the impression to be inside the virtual world, thus allowing to investigate the neural bases of spatial memory processes in a realistic way.

A bilateral dorsal fronto-parietal network, including FEF, PC, SMG, pIPS, and PTO, resulted to be activated both when encoding (study phase) and when updating (test phase) spatial locations in memory, relative to the color control task. These regions have been previously described as involved in spatial coding, navigation and topographical memory [10,16,25,26,56–58]. Two aspects of the results corroborated an involvement of these regions in perspective transformations. First, their activation was higher, both in the study and in the test phase, for the room and objects frames (the two conditions where the viewpoint change was relevant) than for the viewer frame (the condition where the viewpoint change was irrelevant). Second, most fronto-parietal regions showed a main effect of the amount of viewpoint change in the test phase, i.e., more activation when subjects do experience a viewpoint change (and a perspective transformation is actually necessary) than when the image shown in the test phase is from the same viewpoint as in the study phase (so that no perspective transformation is actually necessary). However, all fronto-parietal regions (but the FEF, see below) did not distinguish between the environmental (room) and the objects frame. Thus, fronto-parietal regions are involved in spatial transformations of the egocentric frame, but irrespective of the kind of external frame relative to which the transformation is performed. Given the known specialization of fronto-parietal cortex for egocentric spatial representations [25], in the present context these regions may be involved in preparing and then implementing the update of egocentric coordinates which is needed to compensate for viewpoint changes.

Despite a certain degree of similarity, we found also a clear dissociation between the environmental and the object-based reference frames. For the study phase, we found a significant task by frame interaction in the FEF, left PC, RSC and LPHG. Both FEF and left PC are known to be involved in spatial working memory [16] and mental imagery [59], respectively. Their activation profile, however, seemed to depend more on differences in the color than in the position task across reference frames, so some caution is needed in concluding about their selectivity for the room frame. The RSC and LPHG, instead, clearly showed higher activation in the position vs. the color task for the room than for the objects frame, demonstrating that they are selectively involved in encoding locations relative to the stable elements of the environment. During the test phase, both RSC and LPHG, like most fronto-parietal regions, showed an effect of the amount of viewpoint change, but the RSC showed this effect selectively for the environmental (room) frame. This particular aspect of the results calls for a particular role of the RSC in perspective transformations relative to an environmental reference frame. As extensively discussed in the Results section, the reported effects in RSC and LPHG cannot be merely attributed to differences in task difficulty across the two allocentric reference frames. The RSC indeed maintains its selectivity for the room frame even after taking into account the time needed to perform the perspective transformation, while the viewpoint change effect is apparently accounted for by differences in processing time. Data provided by the control analysis suggested that spatial processes under investigation played a main role, but we cannot entirely rule out the possibility that other aspects of the task which are not indexed by differences in response times might contribute to its difficulty and attentional demands.

The increase of activity as a consequence of an environment-centered viewpoint change is consistent with the idea that RSC may play a pivotal role of interface between body and world centered reference frames, being well-positioned to support spatial conversion from an egocentric frame in the parietal cortex to an allocentric frame in the medial temporal lobe and vice versa [14,60,61]; see also [48] and [62] for recent reviews. The idea of a coordination of egocentric heading and allocentric representations of the environment is supported by several pieces of evidence. First, studies of anatomical connectivity in the monkey [49,50] and resting-state functional connectivity in humans [63,64] show that RSC and posterior cingulate cortex are interconnected with both inferior parietal and medial temporal regions. Second, RSC lesions in humans lead to heading disorientation, a form of topographic disorientation in which patients are unable to derive directional information from landmarks they can recognize [57] and, in some cases, to describe routes through maps of familiar places they can draw [65]. Third, the RSC is active when heading direction is calculated from optic flow [66] and is modulated by learned heading directions [67].

The fact that the RSC response reflects an increase of updating costs whenever the viewpoint changes is also in accordance with the idea that the RSC supports the integration of different views under the same spatial context [68]. Indeed, when viewers need a more expansive representation of the scene beyond what is currently perceived, based on associations among views that are seen before [25,51], the integrative function of the RSC allows to perceive a continuous world from multiple views and supports reorientation mechanisms by situating single scenes within the same broader spatial environment.

Results from the localizer scans showed that RSC well corresponds to the functionally defined scene-responsive region that is strongly active during scene viewing, scene imagery and mental navigation through familiar environments [28]. LPHG instead only partially includes the PPA, another well-known scene-responsive region, in the left hemisphere, while in the right hemisphere it is entirely more posterior than the PPA. Several evidence suggest that the anterior lingual gyrus carries out the buttom-up perceptual analysis of the appearance of a place (necessary for its recognition) whereas the PPA is more involved in encoding new place information. The anterior lingual gyrus indeed contains a building-selective region involved in the recognition of stimuli with orienting value (“lingual landmark area” or LLA: [56]), whose lesion often leads to “landmark agnosia” [57]. PPA instead seems to be more involved in the perception or encoding of the local scene and familiarity weakly affects its activity [28]. Patients with PPA lesions show “pure topographical disorientation” [69], and can find their way around familiar environments but are unable to learn new environments. Thus, the familiar environment exploited in our task could have caused a more extended activation of the lingual rather than the parahippocampal gyrus.

Despite of the anatomical discrepancy between LPHG and PPA, their identical activation profile reflects a selectivity for environment-based memory (main experiment) as well as for scene processing (functional localizer). A similar profile has been recently described during intracerebral recordings from electrodes implanted within the posterior parahippocampal cortex of epileptic patients [27]. Timely separated increases of gamma band amplitude revealed an early scene-selective effect and a late allocentric environment-based effect, within the same cortical site. Future investigations should help clarifying the relationship between functional selectivity and anatomical segregation within the medial occipito-temporal cortex, as assessed with perceptual and memory scene-related processes at the regional and whole brain level.

Recently, Schmidt et al. [16] have used a similar paradigm to explore spatial working memory across different viewpoints. Their main experimental task was nearly identical to our position task performed within an environmental reference frame, but with more levels of viewpoint change, allowing for a parametric analysis of the relationship between viewpoint change and cerebral activation. The authors report activation in nearly all of the regions described in the present paper, with a parahippocampal region (similar to our LPHG) being the only region showing an increase of activation proportional to the amount of experienced viewpoint change. Here we report a main effect of viewpoint change in LPHG, that is compatible with this result. However, we also report similar effects in other regions (such as RSC, FEF, PTO, right pIPS, and left PC). These regions may show signal increases when a viewpoint change occurs, but these changes may be not proportional to the amount of such a change. Furthermore, while Schmidt et al. [16] compared their memory task to a baseline task with no memory demands, the presence in our paradigm of a high-level control task with a study and a test phase (although not requiring spatial location memory) and of multiple frames of reference, allows us to conclude that sensitivity to viewpoint changes in LPHG is not selective for the spatial memory task (no interaction between task and viewpoint change) and for the environmental frame of reference (no interaction between reference frame and viewpoint change). The RSC is instead the only region showing a selective effect of viewpoint change for the environmental frame. Although Schmidt et al. [16] did not explicitly report activation in the RSC, their parieto-occipital focus (peak MNI coordinates: left: −16, −60, 8; right: 12, −52, 12) may include at least part of the RSC (average MNI coordinates: left −18, −48, 12; right 21, −57, 14).

Summarizing, our data suggest that RSC and PPA/LPHG support different mechanisms: PPA/LPHG activity, which is sensitive to the environmental structural features, reflects the perceptual analysis of the local scene [51] that enables it to be remembered and subsequently recognized [28]; RSC activity, which is additionally modulated by the amount of viewpoint change relative to the environmental frame, would support orientation mechanisms within a broader environment and allow the integration of different scenes under the same spatial context [68], thus confirming its pivotal role in updating spatial locations in memory.

Several questions regarding the PPA and RSC role in spatial memory remain to be addressed. Recent reports suggested that familiarity may play a crucial role in driving RSC activity [70,71] and that objects activate the PPA if stably located at decision points along the route [72]. In our experiment, the elements defining the room frame are "stable" for two different reasons: first, they are assumed to be stable based on their structural and functional features, and subjects' previous experience (walls, windows and staircases do not move); second, they are perceived in the same reciprocal configuration throughout the whole experiment. Further studies are needed to disentangle familiarity and/or stability effects, for example by comparing environments with a different degree of familiarity or environmental features expected to be fixed within the environment (e.g., walls and stairs) with objects potentially movable (e.g., furniture) but which are experienced in a constant configuration over time.

## 5. Conclusions

During the complex process of encoding and updating a spatial location across viewpoint changes there are regions (RSC and LPHG/PPA) selectively involved in environment-based computations and regions (fronto-parietal areas) whose activity do not discriminate between environmental and objects-based reference frames. While both RSC and LPHG/PPA are particularly involved in encoding spatial locations relative to fixed landmarks, only the RSC shows a preference for retrieving locations from a new environmental viewpoint, supporting the hypothesis that RSC translates between different viewpoints of the external world, using information about current heading for interfacing viewpoint-dependent and viewpoint-independent representations.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbr.2012.12.031.

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