



Neural correlates of real-world route learning

Victor R. Schinazi*, Russell A. Epstein

Department of Psychology, Center for Cognitive Neuroscience, University of Pennsylvania, Philadelphia, PA 19104, USA

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ABSTRACT

Classical theories of spatial microgenesis (Siegel and White, 1975) posit that information about landmarks and the paths between them is acquired prior to the establishment of more holistic survey-level representations. To test this idea, we examined the neural and behavioral correlates of landmark and path encoding during a real-world route learning episode. Subjects were taught a novel 3 km route around the University of Pennsylvania campus and then brought to the laboratory where they performed a recognition task that required them to discriminate between on-route and off-route buildings. Each building was preceded by a masked prime, which could either be the building that immediately preceded the target building along the route or immediately succeeded it. Consistent with previous reports using a similar paradigm in a virtual environment (Janzen and Weststeijn, 2007), buildings at navigational decision points (DPs) were more easily recognized than non-DP buildings and recognition was facilitated by in-route vs. against-route primes. Functional magnetic resonance imaging (fMRI) data collected during the recognition task revealed two effects of interest: first, greater response to DP vs. non-DP buildings in a wide network of brain regions previously implicated in spatial processing; second, a significant interaction between building location (DP vs. non-DP) and route direction (in-route vs. against-route) in a retrosplenial/parietal-occipital sulcus region previously labeled the retrosplenial complex (RSC). These results indicate that newly learned real-world routes are coded in terms of paths between decision points and suggest that the RSC may be a critical locus for integrating landmark and path information.

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Introduction

A strategy for successful navigation in large-scale environments is to follow routes defined by landmarks and the spatial relationships between them. Such a strategy is likely to be especially useful for urban navigation where landmarks are plentiful and the space is generally too large to be perceived in its entirety from any one vantage point. Siegel and White (1975) proposed that spatial knowledge develops in a series of stages where landmark and route knowledge are the precursors of survey knowledge; a scheme that has been labeled the dominant framework (Montello, 1998). Neuroscientific work on spatial navigation, on the other hand, has often focused on the systems that support flexible route generation using cognitive maps, or the following of “well-worn” routes that are coded in terms of stimulus-response contingencies, leaving the neural systems that encode newly learned routes, which are not yet well-worn or incorporated into a cognitive map, relatively unexplored. Here we address this lacuna by examining fMRI activity related to the coding of landmarks and spatial relationships between landmarks along a newly learned route.

Subjects were trained on a 3.8 km route through the University of Pennsylvania campus and the surrounding territory and later scanned while viewing photographs of buildings from the route. Our design is a real-world adaptation of a paradigm previously employed by Janzen and Weststeijn (2007) to study route learning in a virtual (i.e. videogame) environment. Using a masked prime recognition task, these authors found behavioral and neural evidence that individuals distinguish between objects at navigational decision points (i.e. locations such as intersections where there is possibility for a change in direction) and other objects; furthermore, the direction of travel is specifically encoded at decision points. fMRI results revealed that the posterior parahippocampal gyrus responded preferentially to objects at decision points and that the superior parietal lobe, anterior cingulate and right caudate nucleus were sensitive to the direction of travel at these locations (Janzen and van Turenout, 2004; Janzen and Weststeijn, 2007). Although we expected to replicate the behavioral results from this earlier study, we anticipated the possibility that different neural systems would be involved in route learning under natural learning conditions, where real-world routes are populated with ecologically valid landmarks (i.e. buildings rather than small objects on tabletops) and are too complex to be learned through stimulus-response contingencies.

We were especially interested in determining the involvement of the parahippocampal place area (PPA) (Epstein and Kanwisher, 1998) and retrosplenial complex (RSC) in landmark and route learning. The

* Corresponding author. Department of Psychology, University of Pennsylvania, 3720 Walnut Street, Philadelphia, PA 19104, USA. Fax: +1 215 898 1892.

E-mail address: schinazi@sas.upenn.edu (V.R. Schinazi).

PPA and RSC respond preferentially to stimuli of potential navigational relevance, such landscapes, cityscapes and rooms, and are critical nodes of the larger network of regions that are typically activated during navigation tasks (Aguirre et al., 1996; Ghaem et al., 1997; Maguire et al., 1998; Hartley et al., 2003; Rosenbaum et al., 2004; Spiers and Maguire, 2007). Previous work suggests that the PPA plays a particularly important role in the coding of scenes and buildings (Epstein et al., 1999); furthermore, insofar as the PPA is coterminous with the posterior parahippocampal gyrus, the previous work on decision points suggests that its response to even nonscene/non-building objects can be modulated by the navigational relevance of these objects (Janzen and van Turennout, 2004; Janzen and Weststeijn, 2007). The RSC, on the other hand, may play a key role in the coding of directional information that allows us to understand the spatial relationship between different locations (Sato et al., 2006; Byrne et al., 2007; Epstein, 2008). Thus, we predicted that PPA should respond strongly to buildings from the path, and we set out to determine if this response would be modulated by the position of buildings at decision points. We also set out to substantiate a possible role for RSC in the coding of path direction. To anticipate, both these predicted functions were supported and elaborated by the data.

Materials and methods

Subjects

Two experiments were performed. Sixteen subjects (4 right-handed males, 1 left-handed male, 11 RH females, median age 23 years, range 19–28) with normal or corrected-to-normal vision participated in Experiment 1 and 16 subjects meeting the same criteria (7 RH males, 1 LH male, 7 RH females, 1 LH female, median age 21 years, range 19–31) participated in Experiment 2. All subjects were recruited from the University of Pennsylvania community and had lived on campus for at least 1 year. Written informed consent was obtained according to the provisions set by the local institutional review board.

Materials

The study area consisted of a 3.8 km circuitous route around the University of Pennsylvania campus and surrounding area. A total of 180 buildings were located directly on the route (Fig. 1a). Of these, 85 were located at decision points (DPs) which were intersections where there was a possibility for a change in direction, while 95 were located at non-decision points (NDPs). Ninety additional buildings not directly on the route but located within the general vicinity were selected as foils. A digital camera was used to obtain color photographs (768 × 768 pixels) of all 270 buildings for use as stimuli. Visual masks (90 total) were constructed by scrambling route and foil images in a 30 × 30 grid and then randomly combining fragments across scrambled images.

Design and procedure

Both experiments began with a study phase during which subjects were guided along a preset route and asked to remember both the route and all the buildings located directly along it. They were told that they were being trained to become future tour guides for the University and that this was the route they would show visitors and prospective students. They were also told that there would be many buildings along the route and that they should pay close attention and do their best to remember as many of them as possible. Upon completing a circuit, subjects were asked to reproduce the route by guiding the experimenter. If subjects wandered off course, they were stopped by the experimenter who explained the error and put them back on track. Subjects were very accurate in reproducing the route

with only 1 subject committing a small deviation in the West portion of the route. The learning phase lasted for 90 min (45 min for each circuit).

The testing phase began immediately after subjects completed the second pass through the circuit. In Experiment 1, subjects were brought to the laboratory where behavioral data was obtained. In Experiment 2, subjects were brought directly to the MRI scanner located at the University of Pennsylvania Hospital where both behavioral and fMRI data were obtained. Subjects were not informed of the major hypotheses at any point during the experiment.

Experiment 1 (behavioral)

Subjects were tested using a masked prime recognition task similar to the one implemented by Janzen and colleagues (Janzen, 2006; Janzen and Weststeijn, 2007). On each trial subjects viewed a photograph of a building and used the keyboard to indicate whether it was directly on the route or not. Each target building was preceded by a masked prime, which could either be a building that immediately preceded or followed the target along the route (Fig. 2). More specifically, each trial began with a fixation cross centered on the screen (100 ms); followed by a mask (150 ms), the prime building (40 ms), and then a second mask (60 ms). After a brief interval (100 ms), the target building appeared on the screen and remained visible for 5000 ms or until the subject responded. The next trial began immediately afterwards. Subjects were instructed to respond as quickly as possible while maintaining accuracy. Post-hoc questioning revealed that subjects were not consciously aware of the masked primes.

The 180 on-route buildings allowed for a total of 90 prime-target pairs. These were assigned to four conditions taking into account the order in which buildings appeared along the route (in-route vs. against-route) and whether the target building was located at a decision point or not (Fig. 1b). In the *in-route decision point* and the *in-route non-decision point* conditions (45 pairs in all) the prime building was the building immediately preceding the target building on the same side of the street. In the *against-route decision point* and *against-route non-decision point* conditions (45 pairs in all) the prime building was the building immediately following the target building on the same side of the street. These conditions were counterbalanced across subjects so that each building appeared equally often as an in-route prime, in-route target, against-route prime and against-route target. Decision points could either involve turns or straight continuation; turns vs. non-turns. These were closely balanced in number (DP turn = 42; DP straight = 43). In addition to these 90 prime-target trials, 45 foil trials were created by randomly pairing images of the 90 buildings that were not directly on the route. Event order was randomized for each subject.

After the main experiment, subjects were asked to rate their familiarity with each individual building along the route. Subjects viewed photographs of the 180 buildings presented on a desktop computer and rated their pre-experimental familiarity with each building on a scale from 1 to 5, with 1 being “not familiar” to 5 being “very familiar.”

Experiment 2 (fMRI)

The experiment was essentially the same as Experiment 1 but performed in the fMRI scanner. In particular, the task, stimuli, and presentation parameters were identical, except for the fact that target buildings in Experiment 2 remained on the screen for a fixed interval of 2000 ms rather than disappearing after the subject made a response. This ensured that fMRI response differences between conditions could not be attributed to differences in the length of the physical stimulation. The next trial then began after a 3550 ms fixation interval, making each trial 6 s long.

The experiment consisted of three experimental scans followed by two functional localizer scans. Experimental scans ranged from 6 min

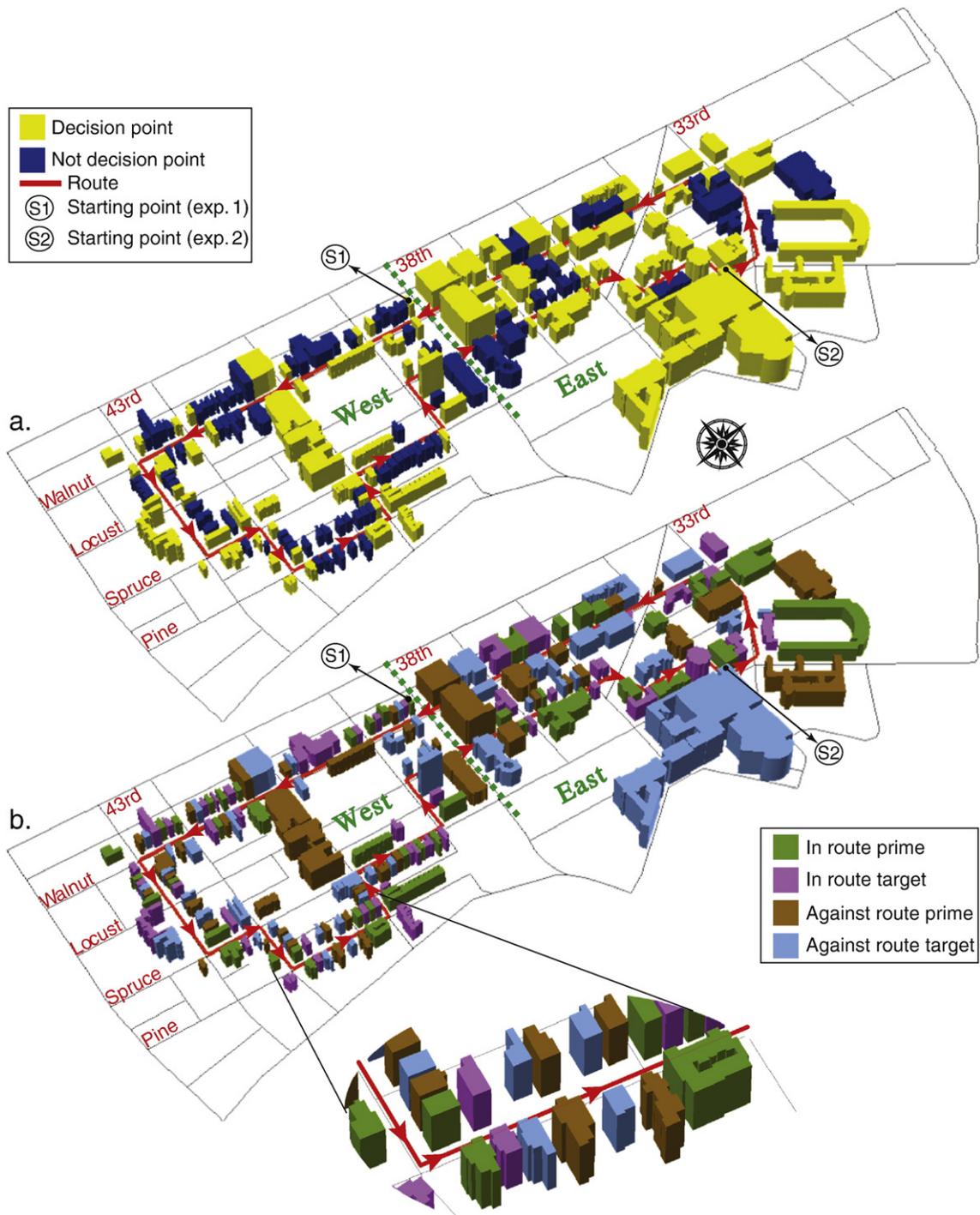


Fig. 1. Study area for experiments 1 and 2. (a) A total of 180 buildings were located directly along the 3.8 km route. Of these, 85 were located at decision points (yellow), while 95 were at non-decision point locations (blue). (b) The 180 buildings were assigned conditions taking into account the order they appeared along the route. In the *in-route decision point* and the *in-route non-decision point* conditions the prime building was the building immediately preceding the target building on the same side of the street (green buildings primes pink building). In the *against-route decision point* and *against-route non-decision point* conditions the prime building was the building immediately following the target building on the same side of the street (brown building primes blue building).

21 s to 6 min 45 s in length and included 28–32 experimental trials drawn approximately equally from the four main condition of interest (in-route DP, in-route-NDP, against-route DP, against-route NDP) along with 15 foil trials with the same time structure and 30 “null” trials (3 s of fixation) which served to jitter the interstimulus interval. In total, 90 trials containing buildings from the route and 45 foil trials were shown in the experimental scans.

During functional localizer scans (8 min 15 s each), subjects viewed color photographs of scenes, objects and other stimuli at a

rate of 1.33 pictures/s presented in 15-s block as described previously (see Epstein et al., 2005).

Scanning took place at the Hospital of the University of Pennsylvania on a 3-T Siemens Trio equipped with an 8-channel multiple array Nova Medical head coil. T_2^* -weighted images sensitive to blood oxygenation level-dependent contrast were acquired using a gradient-echo echo-planar pulse sequence (time repetition [TR]= 3000 ms, time echo [TE]= 30 ms, voxel size = $3 \times 3 \times 3$ mm, matrix size $64 \times 64 \times 45$). A 3D magnetization prepared rapid gradient-echo pulse sequence

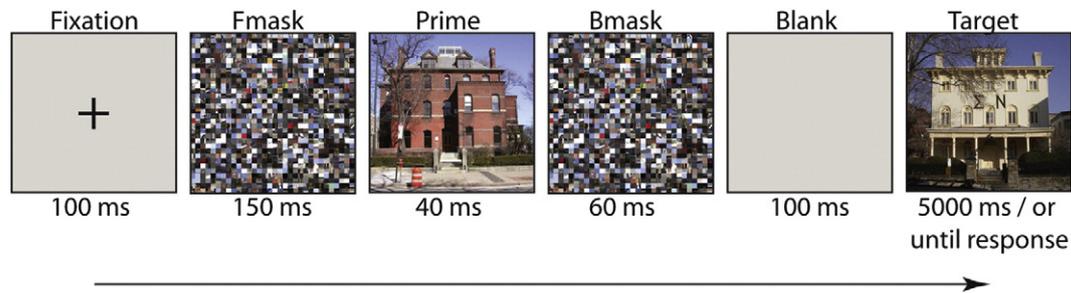


Fig. 2. Experimental procedure for Experiment 1. On each trial, subjects viewed a photograph of a building and reported whether it was on the route or not. Each target building was preceded by a masked prime, which could either be a building that immediately preceded or succeeded the target along the route. Procedure for Experiment 2 was similar except that the target building remained on the screen for a set interval of 2 s followed by a 3.55 s fixation period.

(TR = 1620 ms, TE = 3 ms, time to inversion = 950 ms, voxel size = $0.9766 \times 0.9766 \times 1$ mm, matrix size = $192 \times 256 \times 160$) was used to acquire structural T_1 -weighted images for anatomical localization. Visual stimuli were rear projected into a Mylar screen at the head of the scanner with an Epson 8100 3-LCD projector equipped with a Buhl long-throw lens and viewed through a mirror mounted to the head coil. Behavioral responses during the fMRI session were recorded using a 4-button fiber optic response pad.

fMRI data analysis

fMRI data were corrected for differences in slice timing by resampling the slices in time to match the first slice of each volume, realigned with respect to the first image acquired during a scanning session, spatially normalized to the Montreal Neurological Institute template, and then spatially smoothed with a 6 mm full-width half-maximum (FWHM) Gaussian filter. Analyses were conducted using the general linear model as implemented in VoxBo (www.voxbo.org), including an empirically defined $1/f$ noise model, filters that removed high and low temporal frequencies, regressors that accounted for global signal variations and nuisance regressors that accounted for between-scan differences. The five different trial types (in-route DP, in-route NDP, against-route DP, against-route NDP, foil) were modeled as 6-s long events and convolved with a canonical hemodynamic response function. Both whole-brain and region of interest analysis were performed.

For whole-brain analyses, subject specific beta maps were calculated for the contrast of interest. In order to facilitate between-subject averaging, these were additionally smoothed to 10 mm FWHM prior to entry into a random-effects analysis. Monte-Carlo simulations involving sign permutation were used to estimate the true false-positive rate and establish significance levels corresponding to $p < 0.05$, corrected for multiple comparisons across voxels.

For region of interest analysis, regions previously implicated in building and scene-related processing were defined for each subject using data from functional localizer scans. These consisted of the set of contiguous voxels that responded more strongly ($t > 3.5$) to scenes than to common objects in the posterior parahippocampal/collateral sulcus region (PPA) and retrosplenial/parietal-occipital sulcus region (RSC). Using this criterion, we were able to localize the PPA and RSC bilaterally in all 16 subjects. The hippocampus (HIP) was anatomically defined from T1 structural images for each subject with itk-SNAP (www.itk-snap.org/pmwiki/pmwiki.php) and the Duvernoy and Bourgouin (1999) brain atlas as a guideline. The mean sizes of these ROIs were as follows: left PPA, 2.4 ± 1.4 cm³; right PPA, 3.5 ± 2.0 cm³; left RSC, 2.7 ± 2.0 cm³; right RSC, 3.8 ± 2.5 cm³; left HIP, 3.85 ± 0.78 cm³; right HIP, 3.88 ± 0.75 cm³ (errors are 1 SD). The time course of the fMRI response during the main experimental scans was then extracted from each ROI (averaging over all voxels) and entered into the general linear model in order to calculate parameter estimates (beta values) for each condition. These were used as the

dependent variables in a second level random-effects analysis of variance. There was no evidence of a difference in the pattern of response between the left and right hemisphere for the PPA, RSC or hippocampus, so data from the two hemispheres were averaged before second level analyses.

Results

Our analyses focused on three interrelated questions. First, are buildings at decision points processed differently than buildings at non-decision points? Second, can we observe effects of route direction, and if so, are these effects especially strong at decision points? Third, how does familiarity with the various buildings along the route affect the encoding of decision point and route direction? We examined these questions using both behavioral (Experiments 1 and 2) and neuroimaging (Experiment 2) measures.

Experiment 1

Results are summarized in Table 1. All subjects performed above chance on the on-route/off-route discrimination task (hit rate for on-route target = 0.78 ± 0.02 , correct rejection rate for off-route foils = 0.71 ± 0.02 , mean accuracy over all trials = 0.76 ± 0.01). Results of a 2×2 repeated measures ANOVA with building location (decision point vs. non-decision point) and route direction (in-route vs. against-route) as factors revealed a main effect of location ($F_{(1,15)} = 16.5$, $p = 0.001$) with subjects being significantly more accurate when recognizing buildings at decision points than when recognizing buildings at non-decision points. There was no effect of route direction ($p = 0.91$, NS) nor was there an interaction between building location and route direction ($p = 0.44$, NS). No difference in recognition accuracy was observed between decision points at which the route turned (left or right) and decision points at which the route kept going straight (t -test; $p = 0.83$).

Reaction times were analyzed for trials for which subjects responded correctly. A 2×2 repeated measures ANOVA found no main effect of building location ($p = 0.175$, NS). However, there was a significant main effect of route direction ($F_{(1,15)} = 4.7$, $p = 0.047$) reflecting the fact that subjects responded more quickly for in-route trials than for against-route trials. Furthermore, there was a significant interaction between building location and route direction

Table 1

Behavioral results (accuracy and reaction times) for Experiment 1. Mean and SEM for each condition are shown. Reaction times are for correct trials only.

	Accuracy (% correct)	Reaction time (ms)
In-route DP	82.8 ± 1.7	1544.13 ± 72.23
Against-route DP	81.8 ± 3.0	1704.42 ± 101.35
In-route NDP	72.0 ± 3.0	1549.73 ± 86.84
Against-route NDP	73.3 ± 3.0	1560.37 ± 76.80

($F_{(1,15)}=5.0$, $p=0.04$) insofar as the route direction effect was stronger at decision points than at non-decision points. Indeed, t -tests revealed that the route-direction effect was only significant at decision points (in-route vs. against-route $t=3.2$, $p=0.006$ at DPs, $t=0.2$, $P=0.844$, NS, at NDPs). No difference in reaction time was observed between decision points at which the route turned and decision points at which the route kept going straight (t -test; $p=0.33$).

In sum, the accuracy data indicate that DP buildings were better remembered than NDP buildings. The reaction time data complement this finding by indicating that responses are faster when buildings appear in the same order in a trial as they appeared along the route; however, this facilitation is found only for target buildings located at decision points. Thus, we observed evidence for special processing of buildings at decision point and coding of route direction at these locations.

Experiment 2

This experiment was almost identical to Experiment 1, except that behavioral and neural data were obtained in the fMRI scanner. We focus first on the fMRI data before turning to the behavioral data, which largely replicate the results of Experiment 1 (with some exceptions; see Behavioral data section). We performed two sets of analyses on the fMRI data: one incorporated data from the entire route, and the other divided the route into two parts which were examined separately. This division reflects the fact that the route transversed two very different regions of the campus, one highly familiar and one much less familiar. Thus, by comparing fMRI responses obtained from the two halves of the route, we were able to gain insight into how routes are encoded in more familiar versus less familiar environments.

Our primary concern in these analyses was to identify cortical regions that might be involved in representing information about landmarks at decision points or representing route direction at these points. We predicted that regions that represent information about decision points should respond more strongly to DP buildings than to NDP buildings. We further predicted that regions that represent path direction should respond differentially to in-route vs. against-route trials, and we expected that this effect might be larger at decision points than non-decision points in some of these regions. Based on previous work, we expected the PPA to be especially involved in the coding of decision points, and we expected RSC to be especially involved in the coding of route direction at these points. However, we had no prior reason to believe that these regions would be the only brain areas involved in the encoding or retrieval of these spatial quantities, so both whole-brain and targeted region of interest (ROI) analyses were performed.

Whole-brain analyses

The results of the first set of whole-brain analyses (involving data from the entire route) are summarized in Table 2. We investigated memory for decision points by contrasting activity for buildings at these locations to other target buildings along the route (DP>NDP). Several regions responded more strongly to DP buildings. Most notable is a set of medial parietal regions extending from the superior parietal lobe/precuneus through the parietal-occipital sulcus (POS) into the retrosplenial/anterior calcarine region, which bracket and partially overlap the previously described retrosplenial complex (RSC). Also of interest are the strong activations in the middle occipital gyrus (MOG), supplementary motor area (SMA), and along the superior frontal sulcus (SFS) near the junction with the frontal eye fields (FEF). Interestingly, we did not observe activity in the posterior parahippocampal gyrus proper at a corrected significance level, although activation was observed in an immediately adjoining locus in the superior lingual gyrus. Consistent with behavioral data, an

Table 2

Results of random-effects group analysis for Experiment 2 (data from entire route). Regions listed exhibited significant effects at $p<0.05$, corrected for multiple comparisons.

	x	y	z	Size (cm ³)	z-score
<i>Building location effect (decision point>non-decision point)</i>					
R Thalamus	12	-31	1	0.32	4.37
L Thalamus	-17	-33	4	0.27	4.37
R Superior lingual gyrus	11	-46	0	0.46	4.24
R Retrosplenial/anterior calcarine	17	-53	12	0.38	3.92
L Retrosplenial/anterior calcarine	-22	-50	6	1.08	4.26
R Middle occipital gyrus	40	-75	33	1.78	4.57
L Middle occipital gyrus	-46	-74	33	2.30	4.41
R Parietal-occipital sulcus	14	-57	26	0.62	4.60
L Parietal-occipital sulcus	-21	-63	26	1.16	4.84
Precuneus	3	-61	59	2.75	4.62
R Precuneus/superior parietal lobule	17	-61	63	2.70	5.11
L Precuneus/superior parietal lobule	-16	-60	63	2.67	4.99
Supplementary motor area (SMA)/Pre-SMA	-6	7	54	1.51	4.30
R Superior frontal sulcus (SFS)	14	6	52	0.41	3.95
L Superior frontal sulcus (SFS)/frontal eye fields (FEF)	-27	1	58	3.67	4.72
<i>Route direction effect (in-route>against-route)</i>					
R Lingual gyrus	2	-66	3	0.38	4.38

additional analysis for the contrast DP turn>DP straight did not reveal any significant activations. Analysis of the route direction effect (in-route>against-route) found an active region in the right posterior lingual gyrus but no region showing the reverse pattern (against-route>in-route). Nor did any brain region exhibit a significant interaction between building location and route direction.

The second set of whole-brain analyses examined response for the eastern and western halves of the route separately. These analyses were motivated by the results of the familiarity survey (Fig. 3), which indicated that subjects were more familiar with the buildings on the eastern portion of the route than on the western portion of the route in both Experiment 1 (East = 3.64 ± 0.75 , West = 2.43 ± 0.62 ; $t_{15} = 8.36$, $p<0.00001$) and Experiment 2 (East 4.13 ± 0.70 , West = 2.84 ± 0.92 ; $t_{15} = 10.45$, $p<0.00001$). These ratings reflect the fact that the eastern half of the training route transversed the most familiar portion of the campus, which included many offices, classrooms, and prominent buildings. The western half of the route, on the other hand, transversed a residential neighborhood that was less well-known to students and included smaller, less prominent residential homes. It is possible that in the eastern portion of the environment, subjects learned the novel route by connecting together landmarks and paths segments that were already familiar to them from previous navigational episodes, whereas in the western portion of the environment, subjects learned many of the landmarks and path segments during the training session. Thus, one would expect fMRI effects on the eastern portion of the route to reflect the engagement of mechanisms that support retrieval of long-term spatial knowledge, while one would expect fMRI effects on the western side of the route to reflect the engagement of mechanisms that support retrieval of newly learned spatial knowledge.

Analyses performed on the responses to buildings drawn from the eastern (more familiar) half of the route revealed few significant effects (Table 3). In contrast to the many regions that responded more strongly to DP vs. NDP buildings in the previous analysis (for which buildings from both halves of the route were included), only the cerebellum showed a decision-point effect (DP>NDP). No brain region showed differential activity for in-route vs. against-route trials, and an analysis of the interaction between building location and route direction revealed only a small active region exhibiting a reverse contrast (against-route>in-route at decision points) in the right middle cingulum. Although the paucity of strong effects on the East side of campus may at first seem surprising, it is worth keeping in mind that these analyses only identify regions that respond

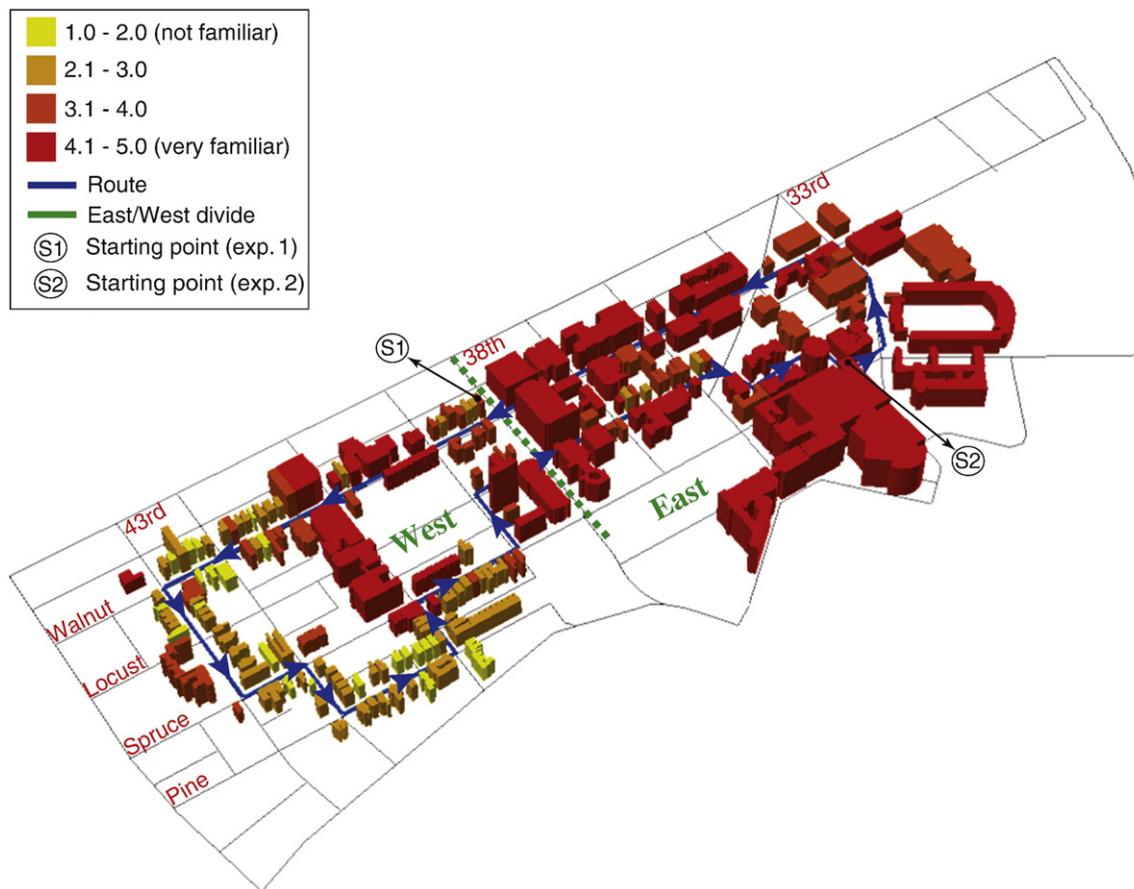


Fig. 3. Results from the familiarity survey. Subjects rated their pre-experimental familiarity with each of the 180 buildings on a scale from 1 (not familiar) to 5 (very familiar). Average building results were then plotted on a map of the study area. A clear division can be noted with subjects showing greater familiarity with buildings east of 38th street. Plotted data are from Experiment 2; results from Experiment 1 were nearly identical.

Table 3

Results of random-effects group analysis for Experiment 2 (data from East and West portions of route analyzed separately). Regions listed exhibited significant effects at $p < 0.05$, corrected for multiple comparisons.

	x	y	z	Size (cm ³)	z-score
<i>Building location effect (decision point > non-decision point)</i>					
East					
R Cerebellum	6	-45	-12	0.19	4.34
L Cerebellum	-15	-47	-18	0.08	4.26
West					
R Retrosplenial/anterior calcarine	18	-50	7	0.38	3.83
L Retrosplenial/anterior calcarine	-22	-51	6	1.92	4.91
R Posterior parahippocampal gyrus (PPA)	21	-43	-1	0.22	3.90
R Middle occipital gyrus	39	-74	33	1.54	4.15
L Middle occipital gyrus	-47	-72	33	0.84	4.12
L Parietal-occipital sulcus	-20	-63	36	0.43	3.91
Precuneus	3	-61	59	1.03	4.65
R Precuneus/superior parietal lobule	14	-61	60	0.92	4.83
L Precuneus/superior parietal lobule	-13	-61	60	2.32	4.54
Supplementary motor area (SMA)/Pre-SMA	-1	9	55	4.29	5.03
R Superior frontal sulcus (SFS)/frontal eye fields (FEF)	33	-3	58	1.13	4.83
L Superior frontal sulcus (SFS)/frontal eye fields (FEF)	-32	0	60	2.48	5.92
<i>Route direction × building location interaction</i>					
East					
R Mid cingulum	7	-36	45	0.11	3.94
West					
R Retrosplenial/parietal-occipital sulcus (RSC)	10	-59	15	0.32	4.37
L Retrosplenial/parietal-occipital sulcus (RSC)	-21	-56	15	0.16	4.43

differentially to DP vs. NDP buildings, and in-route vs. against-route trials. They do not identify regions that respond equally strongly to these paired conditions.

The pattern for the western side of the campus was quite different (Table 3 and Fig. 4). Several regions were activated in the DP vs. NDP contrast, all of which exhibited greater response to decision point buildings compared to non-decision point buildings. These included the superior parietal lobule/precuneus, parietal-occipital sulcus, retrosplenial/anterior calcarine region, middle occipital gyrus, SMA/Pre-SMA and the SFS/FEF. These regions were similar to those identified in the previous analysis involving data from the entire route, suggesting that the previous results were largely driven by differences between DP and NDP buildings on the West side of campus. In addition, we observed a small locus of DP-related activity in the right posterior parahippocampal gyrus. No regions were activated for the in-route vs. against-route contrast. However, analysis of the interaction between decision point and route direction revealed a single region that responded more strongly to in-route vs. against-route trials at decision points: a region near the boundary of retrosplenial cortex and the parietal-occipital sulcus which was largely identical to the RSC region identified by the scene > object contrast in the functional localizer scans (Fig. 5).

These results are consistent with our original hypothesis, insofar as they suggest that the RSC may be involved in coding the direction of travel at locations that are relevant for navigation (a finding that was further substantiated by the region of interest analyses, see ROI analysis section). Furthermore, we observed an effect of decision point, but it was not restricted to parahippocampal cortex—it was found throughout a large set of brain regions distributed throughout the frontal, parietal, and occipital lobes. Notably, these effects were

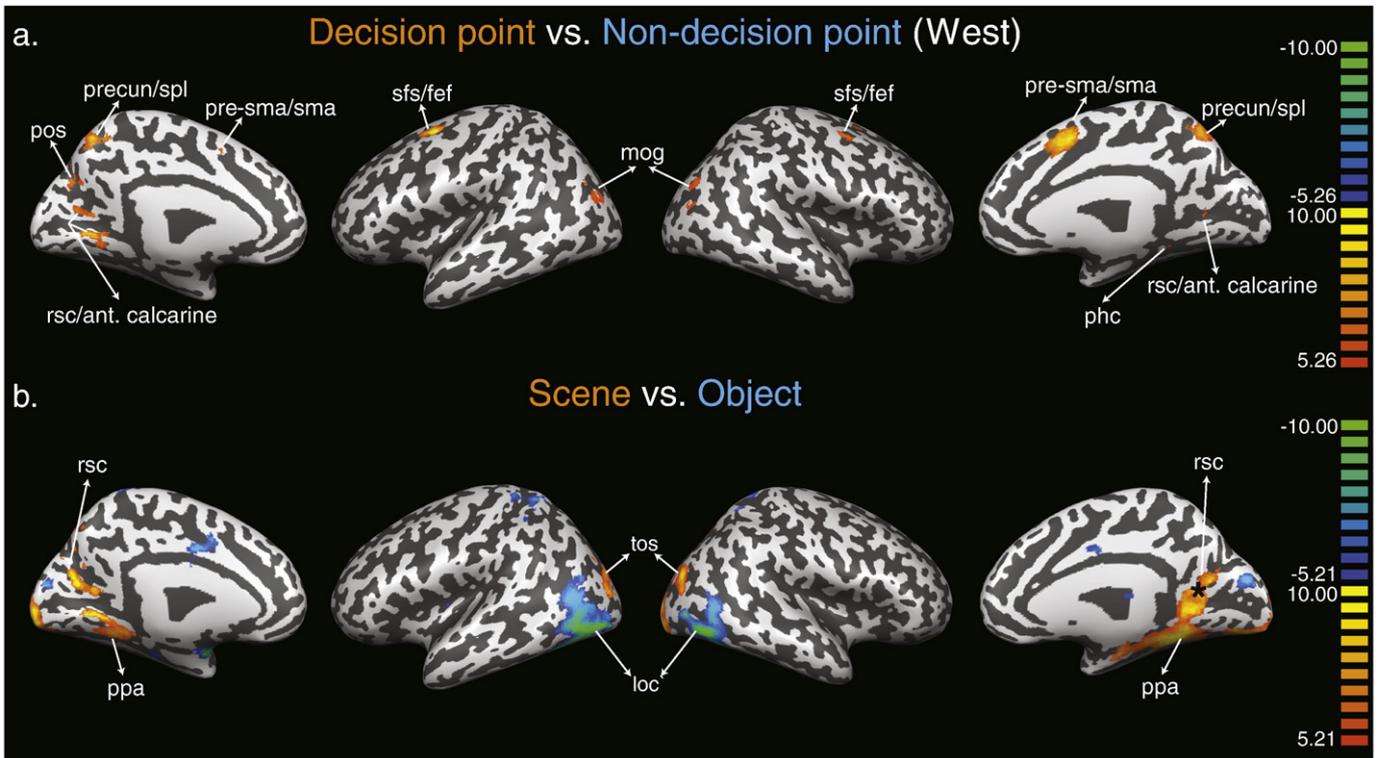


Fig. 4. fMRI results from Experiment 2. (a) Decision point effect for buildings on the west (less familiar) portion of the route. Voxels responding more strongly ($p < 0.05$, corrected) to buildings located at decision points compared to non-decision point buildings are plotted in orange on an inflated version of the cortex. From left to right, the four views depict the left hemisphere (medial surface), left hemisphere (lateral surface), right hemisphere (lateral surface) and right hemisphere (medial surface). Gyri are light gray on the inflated surface, whereas sulci are dark gray. Decision points more strongly recruited a wide network of regions including the superior parietal lobule (spl)/precuneus (precun), parietal-occipital sulcus (pos), retrosplenial cortex (rsc)/anterior calcarine sulcus, middle occipital gyrus (mog), supplementary motor area (sma)/pre-supplementary motor area (pre-sma), superior frontal sulcus (sfs)/frontal eye fields (fef), and parahippocampal cortex (phc). (b) Regions responding differentially to scenes compared to objects in the functional localizer scans. Regions responding more strongly to scenes (orange) include the parahippocampal cortex region previously labeled the parahippocampal place area (ppa), a retrosplenial cortex/parietal-occipital sulcus region previously labeled the retrosplenial complex (rsc), and the transverse occipital sulcus (tos). Regions responding more strongly to objects compared to scenes (blue) include the lateral occipital complex (loc). The PPA and RSC were defined in individual subjects ($t > 3.5$) for the ROI analysis. Note the overlap between the regions showing strong response to scenes (ppa, rsc) and regions exhibiting a decision point effect in panel (a). The asterisk denotes a region within the RSC where the interaction between building location and route direction was significant (see Fig. 5).

most prominent on the unfamiliar, western side of the environment, suggesting that they correspond to coding of novel landmarks and paths. We now turn to the ROI analyses.

ROI analysis

Previous literature implicates certain brain regions in navigation-related processing, including the parahippocampal place area (PPA) and retrosplenial complex (RSC). Because of our pre-existing hypotheses regarding these brain areas, we targeted them using a region of interest (ROI) approach. For each subject, the PPA and RSC were functionally defined based on greater response to scenes than to nonscene objects. We then extracted the MRI response within each ROI and conducted a 2×2 repeated measures ANOVA on these data with buildings location (decision point vs. non-decision point) and route direction (in-route vs. against-route) as factors.

As before, we analyzed the East and West portions of the route separately. Consistent with the results from the whole-brain analyses, a 2×2 repeated measures ANOVA for the more familiar East side of the campus did not reveal any significant main effects or interactions. Specifically, there was no main effect of building location (PPA $p = 0.99$; RSC $p = 0.75$; both NS), route direction (PPA $p = 0.42$; RSC $p = 0.35$; both NS) or location \times route direction interaction (PPA $p = 0.99$; RSC $p = 0.88$; both NS). However, as before, the pattern on the less familiar West portion of the route was quite different (Fig. 6). Greater response to decision point vs. non-decision point buildings was observed in the PPA ($F_{(1,15)} = 30.22$, $p = 0.00006$) and RSC ($F_{(1,15)} = 39.23$, $p = 0.00002$), while a main effect of route direction (in-route $>$ against-route) was observed in the PPA ($F_{(1,15)} = 4.68$, $p = 0.05$)

but not in the RSC ($p = 0.21$, NS). Most critically, the interaction between building location and route direction was significant in the PPA ($F_{(1,15)} = 5.16$, $p = 0.04$) and very strong in RSC ($F_{(1,15)} = 13.28$, $p = 0.002$). Indeed, planned t -tests revealed that the route-direction effect in the PPA and RSC was significant at decision points (PPA $t_{15} = 3.1$, $p = 0.007$; RSC $t_{15} = 2.47$, $p = 0.03$) but not at non-decision points (PPA $t_{15} = 0.005$, $p = 1.00$; RSC $t_{15} = 0.783$, $p = 0.45$; both NS).

A further set of ROI analyses examined the fMRI response in the hippocampus, which was defined anatomically based on the T1 structural scans. Although the hippocampus has been implicated in some navigational tasks, we did not expect to see differential activity between our conditions in the current experiment, because neither landmark nor path direction coding requires retrieval of a cognitive map. Indeed, we observed no significant effects in the hippocampus, on either portion of the route. Specifically, there was no main effect of building location (East $p = 0.41$, West $p = 0.17$, both NS), route direction (East $p = 0.75$, West $p = 0.5$; both NS) or location \times route direction interaction (East $p = 0.22$, West $p = 0.79$, both NS).

Behavioral data

Although it was not the focus of the experiment, behavioral data were collected for subjects in Experiment 2. All subjects performed well above chance level in the recognition task (hit rate for on-route targets = 0.75 ± 0.02 , correct rejection rate for off-route foils = 0.80 ± 0.02 , mean accuracy over all trials = 0.77 ± 0.02). A 2×2 repeated measures ANOVA with building location and route direction as factors revealed a greater accuracy for DP compared to NDP buildings ($F_{(1,15)} = 7.3$, $p = 0.016$) but no main effect of route direction

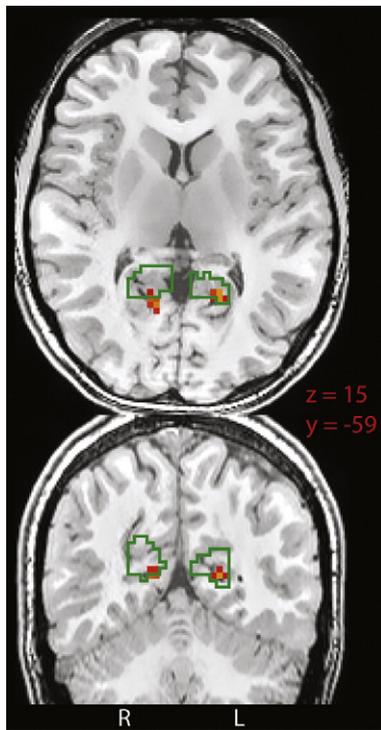


Fig. 5. Whole-brain analysis of the interaction between building location (DP>NDP) and route direction (in-route>against-route) for the West portion of the route ($p < 0.05$, corrected). Results revealed a single region (bilateral) near the boundary of retrosplenial cortex and parietal-occipital sulcus which was largely identical to the RSC region identified by the scene>object contrast in the functional localizer scans (green boundary).

($p = 0.14$, NS) and no interaction between building location and route direction ($p = 0.19$, NS). These results replicate the findings of the first experiment. In contrast, we failed to replicate the route priming effect observed in the reaction time data in the first experiment. A 2×2 repeated measures ANOVA on reaction times from correct trials found no significant effects of building location ($p = 0.56$, NS), route direction ($p = 0.67$, NS), or interaction between location and route direction ($p = 0.39$, NS). No difference in accuracy ($p = 0.69$) or reaction time ($p = 0.14$) were observed between decision points at

which the route turns and decision points at which the route keeps going straight.

It is unclear why Experiment 2 replicated the accuracy effects of Experiment 1 but not the reaction time effects. One possibility is that the reaction time effects were weakened by longer interval between study and test phase. Whereas behavioral testing in Experiment 1 occurred immediately after the study phase, there was a delay in Experiment 2 because it took time to situate subjects in the scanner and perform necessary pre-scan procedures. Alternatively, the reaction time effect might have been affected by the physical aspects of the apparatus (lying on one's back, responding with a button box instead of a keyboard). It is worth noting that Janzen and Weststeijn (2007) also failed to replicate their reaction time results inside the scanner suggesting that these effects are quite fragile and may not directly relate to the route-direction effects observed in the fMRI response.

In a further set of analyses, we explored the effect of environmental familiarity on response accuracy, by adding campus side (East vs. West) as an additional factor to our previous ANOVA. A significant interaction was found for campus side and building location ($F_{(1,15)} = 7.69$, $p = 0.01$). The form of this interaction was quite interesting. Accuracy was equivalent for DP buildings on the East side of campus (0.79 ± 0.05), DP buildings on the West side of campus (0.80 ± 0.03), and NDP buildings on the East side of campus (0.81 ± 0.04). In contrast, accuracy was significantly lower for NDP buildings on the West side of campus (0.69 ± 0.04). It is notable that this pattern is similar to that observed in the fMRI data—the DP vs. NDP effect in both PPA and RSC seems to be driven primarily by reduced response for NDP buildings on the West side of campus. Thus, activity in these regions seems to correspond to retrieval of spatial or episodic information that allows successful completion of the on-route/off-route discrimination task. There were no significant interactions between campus side and route direction ($p = 0.6$, NS).

Photo angle

A final set of analyses addressed a possible confound in our design which would affect the interpretation of our results. When designing the stimuli for the experiment, special care was taken to capture the entire façade of the building as experienced by the subjects when learning the route. This resulted in several buildings being photographed from an oblique (i.e. diagonal) angle instead of from their canonical front. This occurred more often for DP buildings (54 of 85 oblique) than for NDP

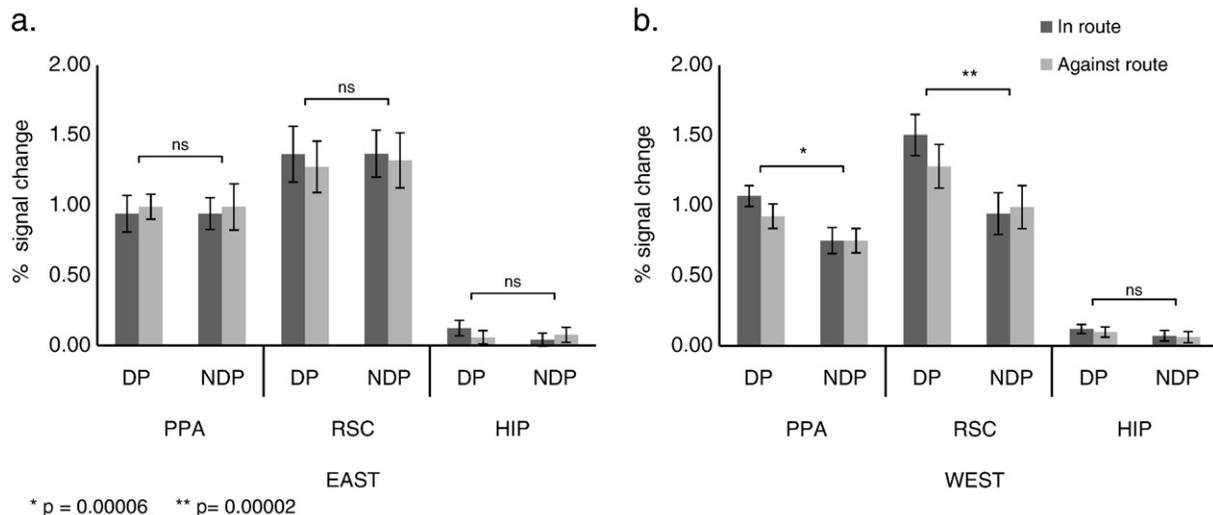


Fig. 6. fMRI response in the PPA, RSC and hippocampus for the East (more familiar) and West (less familiar) portions of the route. Activity was not modulated by building location (decision point vs. non-decision point) or route direction (in-route vs. against-route) on the East portion of the route (a). In contrast, on the West portion of the route, there was a strong effect of building location (decision point>non-decision point) and an interaction between route direction and building location (in-route>against-route at decision points only) in the PPA and RSC (b).

buildings (12 of 95 oblique). In order to control for the possibility that the decision point effect might be driven by the angle the photograph was taken and not the intrinsic navigation value of DP buildings, we examined the effect of photo angle within regions showing a significant building location effect (DP > NDP) on the West side of campus in the whole-brain analysis (listed in Table 3). This was done by submitting activation within these regions to a 2 × 2 repeated measures ANOVA with building location (DP vs. NDP) and photo angle (straight vs. oblique) as factors. For this analysis, data from the left and right hemispheres were combined for regions exhibiting bilateral activation (i.e. the MOG, Retrosplenial/Anterior Calcarine, Precuneus/SPL, and SFS/FEF).

Significant main effects of location (DP > NDP) were observed in all eight regions (all $F_s > 9$, all $ps < 0.01$) which is not surprising given that these regions were chosen on the basis of this difference. More interestingly, a main effect of photo angle (i.e. greater response to oblique compared to straight views) was observed in the parietal-occipital sulcus, SPL, retrosplenial/anterior calcarine, and SFS (all $F_s > 6$, all $ps < 0.05$) but not in the other four regions ($ps > 0.1$, NS). Most importantly, however, was the absence of a significant interaction between building location and photo angle in seven of the eight regions [parietal-occipital sulcus ($F_{(1,15)} = 0.08$, $p = 0.79$, NS), precuneus ($F_{(1,15)} = 1.73$, $p = 0.21$, NS), SPL ($F_{(1,15)} = 2.95$, $p = 0.11$, NS), posterior parahippocampal gyrus ($F_{(1,15)} = 0.33$, $p = 0.58$, NS), retrosplenial/anterior calcarine ($F_{(1,15)} = 0.07$, $p = 0.80$, NS), SFS ($F_{(1,15)} = 0.44$, $p = 0.52$) and SMA ($F_{(1,15)} = 1.71$, $p = 0.21$, NS)] with the sole exception being the middle occipital gyrus ($F_{(1,15)} = 6.17$, $p = 0.03$). In fact, t -tests revealed that the decision point effect was significant for both straight and oblique views in 7 of 8 regions [all $ts > 2$, all $ps \leq 0.05$]. The only exception was posterior parahippocampal gyrus, where the decision point effect was significant for straight views ($t = 4.0$, $p = 0.001$) fell short of significance for oblique views ($t = 1.6$, $p = 0.13$, NS). Thus, the decision point effect cannot be reduced to an effect of photo angle, because it is found for both diagonal and canonical views.

Discussion

We investigated the neural and behavioral correlates of real-world route learning, focusing on the coding of landmark and route direction. Behavioral results indicated that buildings at navigational decision points (i.e. intersections) were more easily recognized compared to other buildings along the route and that route direction was encoded at these decision points. fMRI results revealed greater response to decision point (DP) buildings compared to non-decision points (NDP) buildings in several cortical regions along with route-direction-sensitive activity for decision point buildings in the retrosplenial complex (RSC). Interestingly, these neural effects were observed only for the portion of the route that transversed territory that was initially unfamiliar to the subjects but were not found in the more familiar portion of the environment. These results provide important insights into the neural codes that mediate real-world navigation while providing new evidence on the interaction of landmark and route knowledge that subserve the development of cognitive maps. We will first discuss the coding of decision points and then the coding of route direction before turning to broader implications.

Decision point coding

Our behavioral data confirm and extend results from previous studies indicating that items at decision points act as mnemonic markers that facilitate navigation along newly learned routes (Jansen-Osmann, 2002; Janzen, 2006 for review). These earlier studies used virtual environments or static learning paradigms to demonstrate that subjects are faster (Janzen and van Turennout, 2004) and more accurate (Blades and Medlicott, 1992) when recognizing DP objects

than when recognizing NDP objects; furthermore, they have an easier time giving route descriptions and wayfinding when DP objects are present than when they are absent (Cohen and Schuepfer, 1980). Our study extends these previous findings by demonstrating that DP buildings are better remembered than NDP buildings when encountered during a real-world learning episode.

With regards to the neural correlates of these effects, we were especially interested in the role of the PPA in DP coding. In previous studies examining this issue (Janzen and van Turennout, 2004; Janzen and Weststeijn, 2007) subjects were familiarized with a route through a virtual-reality maze and then scanned with fMRI while they viewed objects that had been placed either at decision points or other maze locations. Increased activity for DP vs. NDP objects was observed almost exclusively in the PPA (i.e. posterior parahippocampal gyrus). Our current experiment adapted this paradigm to the real world using more ecologically plausible landmarks. We replicated the earlier finding that the PPA responds preferentially to items previously encountered at decision points, but showed that this was only reliable on the unfamiliar (West) side of campus. Furthermore, decision-point related activity was also observed in a number of other brain regions. These findings suggest that DP buildings act as powerful cues that elicit the automatic engagement of several different brain regions involved in navigationally relevant processing, not just the PPA.

Some of the regions responding to buildings at decision points (PPA, retrosplenial cortex, parietal-occipital sulcus) were previously identified as responding more strongly to visual scenes than to nonscene objects (Epstein et al., 2005). Importantly, these regions are active not only during the perception of visual scenes (Epstein and Kanwisher, 1998) but also when scenes are cued or brought to mind (O'Craven and Kanwisher, 2000; Hassabis et al., 2007; Epstein and Ward, 2010). Thus, one possible interpretation of these results is that DP buildings are better cues for the retrieval of visuospatial scene information than NDP buildings. When seen removed from their surroundings during the recognition task, buildings at decision points are not visually different than other buildings along the route. During navigation however, the position of these buildings at intersections afford the subject a more comprehensive perspective of the geometric structure and spatial layout of the scene. As a result, scenes associated with DP buildings would have been spatially richer than scenes associated non-DP buildings, leading to greater response if the associated scenes were automatically recalled. This hypothesis could also explain activation in the precuneus, which along with retrosplenial cortex and POS might support a medial parietal processing stream for visuospatial memory retrieval and imagery (Ghaem et al., 1997; Gron et al., 2000; Burgess et al., 2001; Shelton and Gabrieli, 2002; Blanch et al., 2004; Byrne et al., 2007; Epstein et al., 2007a).

The fact that previous studies (Janzen and van Turennout, 2004; Janzen and Weststeijn, 2007) observed DP-related activity in the PPA only whereas here we observe activity in a larger portion of the scene processing network may relate to the scale of the visuospatial scene representations encoded in virtual vs. real-world environments. The PPA is believed to play a critical role in the representation of the spatial structure of the local scene (Epstein and Kanwisher, 1998). In contrast, the retrosplenial/parietal-occipital sulcus region is believed to play an important role in situating the local scene within the broader spatial environment (Epstein et al., 2007a,b; Park et al., 2007), responding strongly only after subjects have learned the locations of the scenes within an larger spatial framework (Wolbers and Buchel, 2005). Thus, DP items might only trigger retrosplenial activity when they are encountered within an extended real-world environment as in the current experiment.

Beyond the scene processing network, DP-related activity was observed in the SFS/FEF pre-SMA/SMA, and superior parietal lobule. It is notable that this is almost identical to the set of frontal and parietal regions that activated during retrieval of familiar spatial information in a previous study from our laboratory (Epstein et al.,

2007a) in which subjects viewed photographs of the Penn campus and reported either location or facing direction. The current study is similar insofar as subjects reported the location of previously encountered buildings relative to a previously learned path. Taken together, the results of the two studies suggest that this set of regions may play a key role in the retrieval and manipulation of spatial information. DP buildings might activate this network more strongly than NDP buildings because their spatial location is better defined in memory. Several lines of previous work are consistent with this claim. For example, frontal regions such as the SFS and SMA are active during the retrieval of spatial information from both working (Courtney et al., 1998; Glahn et al., 2002) and long-term memory (Rosenbaum et al., 2004; Rosenbaum et al., 2007). The SMA has also been found to be active during mental simulation of routes (Ghaem et al., 1997) while the FEF has recently been linked to the shifting, within working memory, from an egocentric to an allocentric reference frame (Wallentin et al., 2008). We believe the role of these frontal-parietal regions in spatial navigation and other spatial tasks deserves further investigation.

In sum, our results support the idea that the routes through unfamiliar environments are learned in part by coding of navigational decision points. The wide range of cortical regions showing a DP vs. NDP effect suggests that many different varieties of spatial information might be linked to these points.

Route direction coding

Effects of route direction were examined by comparing the differential influence of in-route vs. against-route masked primes on behavioral and fMRI response. A route-direction-sensitive behavioral priming effect was observed in Experiment 1 which was significant for DP but not NDP buildings, replicating previous results (Janzen and Weststeijn, 2007). An analogous neural effect—greater response to in-route compared to against-route trials for DP buildings only—was observed in RSC in Experiment 2. It would be incorrect to refer to this as a “priming” effect insofar as response was greater (rather than reduced) for the in-route trials. Rather, these data suggest that RSC encodes path-related representations that are activated when buildings at or adjacent to decision points are viewed in their previously encountered order.

The finding of path direction-related activity in RSC was not entirely unexpected. Neuroimaging data indicate that this region plays an important role in the coding of spatial relationships between locations in large-scale environments (Wolbers and Buchel, 2005; Epstein et al., 2007a). Consistent with these results, a recent neurophysiological study identified “navigation neurons” in a medial parietal region analogous to human RSC that responded selectively to specific combinations of movement and location (i.e., turn left at intersection “x”) when monkeys navigated along several different remembered paths in a virtual environment (Sato et al., 2006). A subset of these neurons behaved in a route-selective manner by distinguishing between paths passing through the same location. Although it is unclear whether the monkey medial parietal region examined by Sato and colleagues is homologous to human RSC, it is notable that patients with retrosplenial damage often report problems pointing to landmarks that are not currently visible (Takahashi et al., 1997), a syndrome known as “heading disorientation” (Aguirre and D’Esposito, 1999). Taken as a whole, these results suggest that RSC might do more than just encode the sequence of buildings along a route; it might also encode a representation of the allocentric bearings between navigationally relevant locations (see Epstein, 2008 for further discussion). Chaining together several of these bearings might be one way to represent a route.

Notably, the retrosplenial/medial parietal region activated in the current study was not identified in previous studies performed in virtual environments (Janzen and Weststeijn, 2007). Rather, these earlier studies revealed route-direction-sensitive activity in the superior

parietal lobe, middle temporal gyrus, caudate and anterior cingulate. It is unclear why we obtained different results. One possibility is that subjects in previous studies using non-immersive environments learned routes through simple sequence learning which did not require RSC engagement.

Implications for topographical learning

Classic theories of the development of spatial knowledge (Shemyakin, 1962; Siegel and White, 1975) propose that individuals first learn landmarks followed by the routes that connect them, eventually integrating these into a more holistic survey-level representation. Our results are generally consistent with this scheme insofar as they demonstrate specific mechanisms involved in the representation of landmarks and path direction at an early stage of spatial learning prior to the development of survey knowledge. However, insofar as our results reveal effects of both landmark and route direction after a relatively short learning episode, they suggest that spatial microgenesis might not always follow a strict stage-like development but rather may proceed in a continuous and integrated fashion (Montello, 1998; Ishikawa and Montello, 2006). Landmarks are not isolated features of the environment but linked to specific actions and directions (i.e. turn right at the gas station) during navigation (Blades, 1991). This reciprocal relationship was emphasized by Gärling et al. (1981) who showed that in some cases route knowledge may actually precede landmark knowledge as it provides spatial-temporal framework for the construction of mental representations during navigation. Our finding of a significant interaction between the coding of decision points and the coding of travel direction provides further support for the idea the route and landmark learning may occur simultaneously.

This type of route learning, in which paths are encoded in terms of landmarks and the travel directions between them, might be just one of several topographical learning systems in the human brain. For example, the landmark and path representations revealed in the current study may complement a more metrical and Euclidean “cognitive map” representation supported by the hippocampus and entorhinal cortex (Gallistel, 1990; Maguire et al., 1998; Hafting et al., 2005). It may also be distinct from the striatal learning system that encodes “well-worn paths” in terms of motor actions performed at specific locations (Hartley et al., 2003). In this vein, it is interesting to note the differences in accuracy and activation in the East and West portion of the route, which suggests that the path and landmark system might only engage in situations where the environment is relatively unfamiliar. In the less familiar West portion of the route, DP buildings were more accurately recognized than NDP buildings and there was a corresponding difference in fMRI response, suggesting that DP buildings played a key role as navigation or wayfinding anchors. In the more familiar eastern portion of the route, on the other hand, a saturation of the DP effect was observed, suggesting that subjects no longer differentiated between DP and NDP building for navigation purposes. It appears that in newly learned environments, where long-term spatial knowledge is unavailable, subjects utilize a route learning strategy in which the bearings between decision points are explicitly encoded at navigationally relevant locations.

Conclusion

Our data suggests that in real-world navigation the direction a route is travelled is encoded at decision points (intersections) where there is a possibility for a change in direction. Neuroimaging results revealed an extensive network of brain regions known to play a role in spatial navigation that responded preferentially to buildings at decision points with the RSC playing a central role in the processing of direction information at landmarks. These effects were particularly prominent in the unfamiliar section of the environment suggesting

the engagement of mechanisms particularly attuned for the coding and retrieval of newly learned spatial knowledge.

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