from low to medium frequencies of occurrence, and from four to nine letters in length.

ERPs (sampling rate 6 ms per point, epoch length 1,536 ms, prestimulus baseline 102 ms) produced in response to different classes of test word were obtained from 25 scalp sites as described[23]. ERPs were quantified by measuring the mean amplitude of two latency regions, 300–500 and 500–800 ms after the onset of stimulus. Amplitude differences were assessed by analysis of variance (ANOVA) (degrees of freedom (d.f.) corrected for non-sphericity[24]). Differences in scalp topography were assessed by d.f.-corrected ANOVA of the data from all 25 electrodes after rescaling[25].

Semantic judgement task. Two groups of young adults ($n = 16$) were used in each experiment. For experiment 3, the subjects were the same individuals as those used in experiment 1. A new sample was used in experiment 4.

Experimental items were drawn from the same word pool used to construct the lists for experiments 1 and 2. For experiment 3, two study test blocks identical in structure to those used in experiment 1, although using different items, were administered. The only difference in procedure from experiment 1 was that subjects were required during the test to classify each test word as animate or inanimate. The procedure for experiment 4 was identical to that for experiment 3 except that the depth of processing manipulation at study was blocked. Stimulus display parameters and electroencephalogram recording for these experiments were as for experiment 1. As the differences between old and new words in the two experiments were very similar, and there were no block effects in experiment 4, the data are reported collapsed across experiments.

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A cortical representation of the local visual environment

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Medial temporal brain regions such as the hippocampal formation and parahippocampal cortex have been generally implicated in navigation[1–6] and visual memory[7–9]. However, the specific function of each of these regions is not yet clear. Here we present evidence that a particular area within human parahippocampal cortex is involved in a critical component of navigation: perceiving the local visual environment. This region, which we name the 'parahippocampal place area' (PPA), responds selectively and automatically in functional magnetic resonance imaging (fMRI) to passively viewed scenes, but only weakly to single objects and not at all to faces. The critical factor for this activation appears to be the presence in the stimulus of information about the layout of local space. The response in the PPA to scenes with spatial layout but no discrete objects (empty rooms) is as strong as the response to complex meaningful scenes containing multiple objects (the same rooms furnished) and over twice as strong as the response to arrays of multiple objects without three-dimensional spatial context (the furniture from these rooms on a blank background). This response is reduced if the surfaces in the scene are rearranged so that they no longer define a coherent space. We propose that the PPA represents places by encoding the geometry of the local environment.

In the first experiment, nine right-handed students were scanned with fMRI while viewing 5.5-min videotapes in which scrambled and intact versions of black and white photographs of faces, common objects, houses and scenes were presented in separate epochs (Fig. 1a). Subjects either viewed the photographs passively, or performed a 'one-back' repetition detection task on the same stimuli (see Methods) which obliged them to attend to all stimuli irrespective of inherent interest. In all nine subjects, significantly greater activation was found during presentation of intact scenes than during presentation of intact faces and objects in the PPA, a bilateral region of parahippocampal cortex straddling the collateral sulcus (including the posterior tip of the parahippocampal gyrus and adjacent regions of the fusiform gyrus; Fig. 2). This region does not include the hippocampus proper.

For each subject individually, we used an independent data set from the same scanning session functionally to define a region of interest in the PPA (see Methods). We then extracted the time course of the per cent signal change relative to a fixation baseline within each subject's PPA over the period of the scan. To distinguish changes in activation resulting from high-level differences between the stimulus types from changes in activation resulting from low-level feature differences between the stimulus types, we subtracted the per cent signal change for the scrambled photographs from that for the intact photographs for each stimulus type before comparing the response across stimulus types. Analysis of variance found this activation difference between intact and scrambled photographs to be significantly greater for scenes than for houses ($F(1, 8) = 35.4$, $P < 0.001$), but not significantly greater for houses than for objects ($F(1, 8) = 3.4$, $P = 0.1$). Although the 1-back task was more difficult for scrambled than intact images, the pattern of the PPA response did not differ between the two tasks ($F < 1$), so the greater response to scenes is unlikely to be due to differences in attention or perceptual effort. These results demonstrate that the PPA responds selectively to visually presented scenes even when the response to some of the low-level features (such as local texture and average

luminance) of the stimuli has been subtracted out, and even when subjects merely view the stimuli passively with no task requirement.

The preference of the PPA for photographs of scenes over faces, objects and houses is suggestive, but does not in itself demonstrate that the PPA encodes spatial layout. If the PPA is involved in representing the shape of the local environment, then it should be strongly activated by scenes even when they depict only bare spatial layouts without discrete objects. On the other hand, if the PPA is involved in an analysis of the identities, meanings, or relative locations of the objects in the scenes, then it should be more active for arrays containing multiple objects (without any three-dimensional spatial context) than for bare spatial layouts. To assess these and other possibilities, six subjects were run in a second experiment in which they viewed (Fig. 3a) photographs of (1) unfamiliar indoor scenes of rooms with furniture, plants, and so on: (2) the same rooms photographed from the same angle after all of the objects had been removed; (3) arrays, each of which contained all of the objects from one of the furnished rooms cut out from the original background and rearranged in a random configuration; (4) faces; (5) single objects; (6) familiar outdoor scenes (of the MIT campus); (7) outdoor scenes of unfamiliar natural environments containing few discrete objects; and (8) familiar landmarks (mostly buildings) from the MIT campus cut out from their original backgrounds.

Strikingly, the PPA responded much more strongly to scenes depicting bare spatial layout (empty rooms and landscapes) than it did to faces, objects or multiple object arrays (Fig. 3). The response in the PPA to empty rooms was as strong as the response to the same rooms furnished ($F < 1.3$), and over twice as strong as the response to arrays of multiple objects without spatial context ($F(1, 8) = 24.13$, $P < 0.01$). Further, the response to multiple object arrays was not significantly greater than to single objects ($F < 1$). Finally, the response to empty landscapes with few discrete objects was comparable to the response to empty rooms ($F < 1$). These results demonstrate that the presence of multiple objects is neither sufficient nor necessary for activation of the PPA. On the other hand, scenes depicting the shape of the local environment activate the PPA even if they are bare and uninteresting.

The response to landmarks cut out from their background was significantly higher than the response to objects ($F(1, 8) = 28.0$, $P < 0.01$). The landmarks were mostly buildings, so this result is

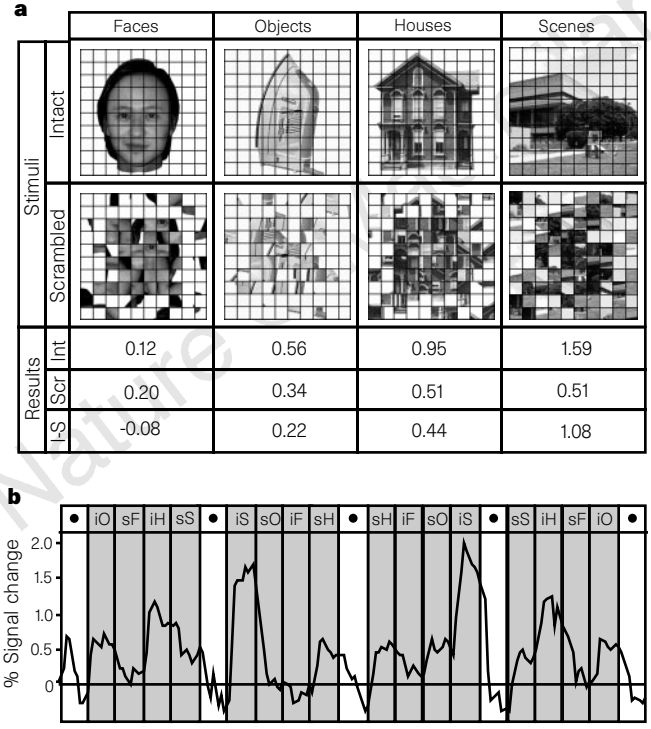

Figure 1 Results of experiment 1, demonstrating that the PPA responds selectively to scenes. **a**, Examples of intact and scrambled versions of the four different types of stumli (top), and the average per cent signal change for each stimulus type in the PPA averaged over all subjects (bottom). The difference between intact and scrambled versions of each picture is a measure of the response in the PPA to each stimulus type partially unconfounded from the response to its low-level visual features. Half of the scenes were outdoor scenes of the MIT campus, and half were indoor scenes of unfamiliar locations. **b**, The time course of the per cent change in MR signal intensity in the PPA over the period of the scan. Per cent signal change was calculated individually for each subject using that subject's fixation activation as baseline and then averaging across subjects (black dot indicates fixation epochs). i, Intact; s, scrambled; S, scenes; F, faces; O, objects; H, houses.

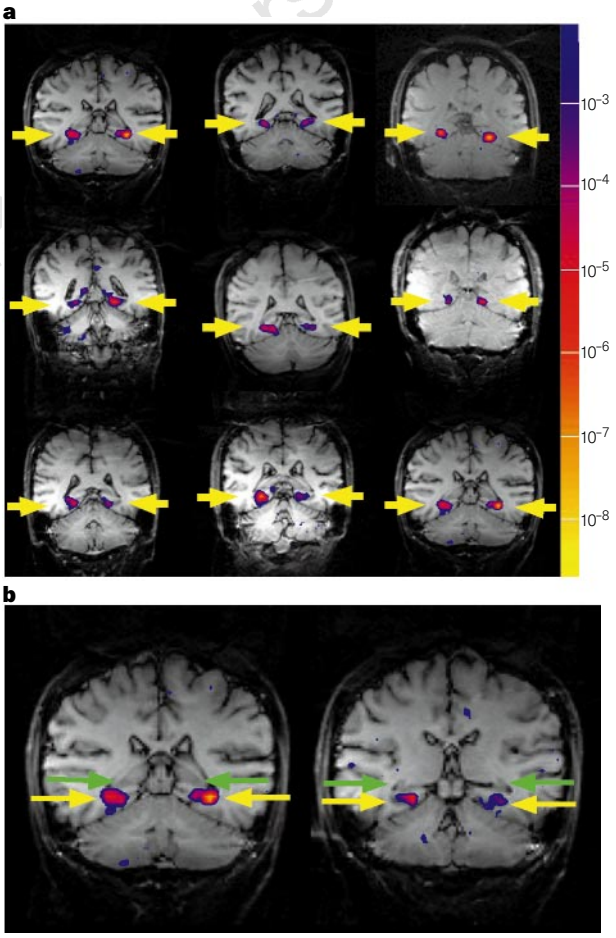

Figure 2 Anatomical location of the PPA. **a**, A single slice from each of the nine subjects in experiment 1 showing the PPA; functional data from this experiment is overlaid on a high-resolution T1-weighted anatomical image of the same slice. Right hemisphere appears on the left. Significance levels reflect the results of a Kolmogorov–Smirnov test comparing the MR signal intensity during viewing of intact scenes to signal intensity during viewing of intact objects and faces. Note that the location of the PPA (indicated with yellow arrows) is strikingly consistent across subjects. The activated region (contiguous voxels reaching the $P < 10^{-4}$ statistical criterion) was larger ($t(8) = 3.21$, $P < 0.01$) in the right hemisphere (average, 1.1 c.c.) than the left hemisphere (0.69 c.c.). Significant activation was also found in the anterior calcarine sulcus, but because of the proximity of this region to retinotopic cortex, this activation is not discussed here. **b**, Two adjacent slices from a single subject demonstrating that the PPA (yellow arrows) does not overlap with the posterior part of the hippocampus (green arrows). Posterior slice appears on the left. Talairach coordinates of PPA activation for this subject are –6, 18, –39 and –6, –34, 30 (S-I, M-L, A-P).

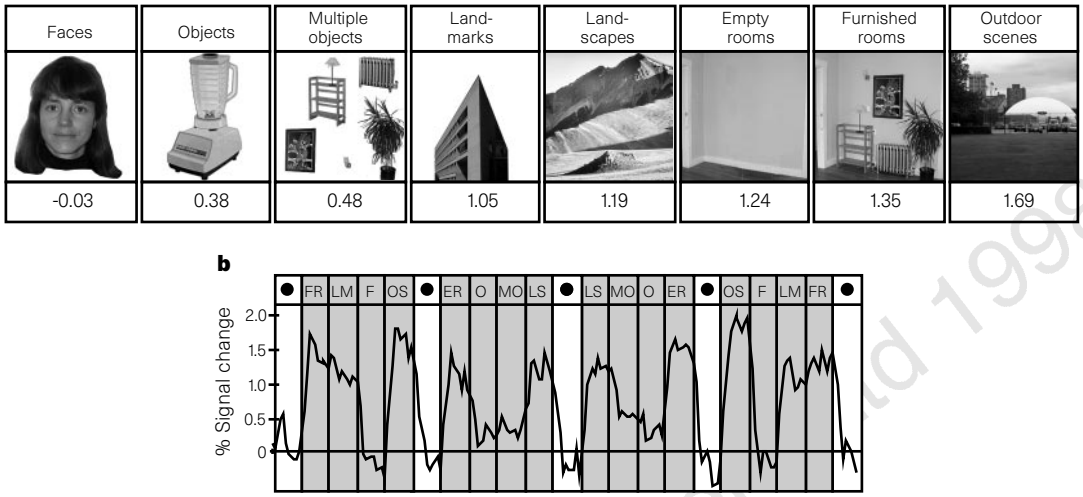

Figure 3 Results of experiment 2. **a**, Examples of the 8 different stimulus types with average per cent signal change in the PPA for each. **b**, Time course of the raw per cent change in MR signal averaged over all subjects. F, faces; O, objects; MO, multiple-object arrays; LM, landmarks; LS, landscapes; ER, empty rooms; FR, furnished rooms; OS, MIT outdoor scenes.

Figure 4 Results of experiment 3, showing the 5 different stimulus types with average per cent signal change in the PPA for each. (Subjects also viewed three other stimulus conditions designed to test other hypotheses; these are not reported here.)

consistent with previous work showing that buildings without background can evince a large response in cortical regions near the collateral sulcus[10,11]. This result could reflect the fact that buildings are large stable structures that define the geometry of local space, or the fact that the subjects were familiar with the spatial context of the landmarks.

In a final test of the spatial-layout hypothesis, we investigated whether the response in the PPA would be reduced if the surfaces in the stimulus did not define a coherent space. Five subjects viewed images of a new set of empty rooms which were 'fractured' into their component surfaces (Fig. 4). In one stimulus condition (fractured rooms), the relative positions of the resulting surfaces were preserved. In another stimulus condition (fractured + rearranged), the relative positions of the resulting surfaces were rearranged so that they no longer defined a space. Subjects also viewed the original unfractured photographs of the rooms (intact rooms), single objects and faces.

The results showed a striking confirmation of the hypothesis: the PPA responded more strongly to both the intact ($F(1,4) = 8.8$, $P < 0.05$) and the fractured rooms ($F(1,4) = 19.5$, $P = 0.01$) than to the fractured + rearranged rooms, whereas the response to the fractured rooms was not significantly different from the response to the intact rooms ($F(1,4) = 2.9$, $P > 0.15$). As both the fractured and the fractured + rearranged stimuli contained the same image components, the difference in response must reflect the fact that the fractured rooms defined a coherent space, whereas the fractured + rearranged rooms did not. Interestingly, even the jumbled surfaces in the fractured + rearranged rooms activated the PPA more than single objects ($F(1,4) = 20.8$, $P = 0.01$); however, the response was clearly greater when these surfaces defined a space.

These experiments show that (1) there is a region of parahippocampal cortex that responds selectively to visual scenes depicting places; (2) activation in this region occurs automatically even when no explicit cognitive test is required; (3) this response is found even if there are no discrete objects in the scene; and (4) the critical factor in this response is the presence in the stimulus of information about the layout of local space. Our findings dovetail with two other lines of research. First, behavioural studies have shown that disorientated human infants[12,13] and rats[14–16] reorientate themselves solely on the basis of the geometry of the local visual environment, ignoring non-spatial cues unless these have been proven by experience to be stable over time[17,18]. Some of the results[12–16] have been taken as evidence for a phylogenetically and developmentally primitive 'geometric module'[19] which uses the shape of the surroundings to determine current location. Second, neuropsychological studies have shown that patients with damage to parahippocampal cortex often experience great difficulty finding their way around novel environments[20–23]. Together with our results, these findings suggest that the PPA performs an analysis of the shape of the local environment that is critical to our ability to determine where we are. □

Methods

Subjects. Ten right-handed students from the Massachusetts Institute of Technology (MIT) performed both experiment 1 and experiment 2. One subject was omitted because of excessive head motion. Because the experimental protocol for experiment 2 was changed after the first three subjects were run, data from these subjects were not included in the analysis of experiment 2. Six right-handed students (from MIT or Harvard) performed experiment 3. One subject was omitted because of excessive head motion.

Materials. Stimuli were digitized black-and-white photographs. Scrambled pictures were created by dividing intact pictures into 100 square sections and then randomizing locations of squares within three concentric rings around fixation.

Procedure. The procedure for all experiments was as follows. Each subject was run on 2–3 scans for both the passive and 1-back tasks for each experiment. For the 1-back task, subjects were instructed to press a button whenever they saw two identical pictures in a row; this task was designed to ensure that subjects attended at least as much to uninteresting stimulus sets (for example, scrambled images) as to the more interesting sets (for example, faces and scenes). Each scan lasted 5 min and 36 s and consisted of sixteen 16-s epochs with fixation periods interleaved as shown in Figs 1b, 3b. During each epoch, 20 different photographs of the same type were shown (with 1 or 2 consecutive repetitions per epoch in the 1-back task). Each photograph was presented for 300 ms followed by a blank interval of 500 ms. There were two epochs for each of the eight stimulus types within each scan; order was counterbalanced over

two versions of each experiment (ABCD-EFGH-HGFE-DCBA for version 1 and HGFE-DCBA-ABCD-EFGH for version 2). The raw data from version 1 were rearranged so that the time courses from the two versions were compatible and could be averaged together.

MRI acquisition. Scanning was done on the 1.5 T (experiments 1 and 2) and 3 T (experiment 3) scanners at the MGH-NMR Center in Charlestown, Massachusetts, using a bite bar to minimize head motion and a bilateral surface coil which provided a high signal-to-noise ratio in posterior brain regions. Standard imaging procedures were used (TR, 2 s; TE, 70 ms; flip angle, 90°; 180° offset, 25 ms) and have been described[24]. Twelve 6-mm-thick near-coronal slices were orientated parallel to the brainstem and covered the occipital lobe as well as the posterior portions of the temporal and parietal lobes; 168 functional images were collected for each slice in each scan.

Data analysis. For each subject, data from all the runs in each experiment were averaged together. The time course of MR signal intensity was extracted from each subject's PPA (averaging over all voxels within the ROI). The data from experiment 2 were used to define the regions of interest (ROIs) for experiment 1, the data from experiment 1 were used to define the ROIs for experiment 2, and the data from an additional experiment not reported here were used to define the ROIs for experiment 3. ROIs included all contiguous voxels in the collateral sulcus region for which a Kolmogorov–Smirnov test revealed higher levels of activation at the significance level of $P < 10^{-4}$ for scenes compared to the average response to faces and objects. The per cent signal change in the PPA ROI was calculated for each subject, experiment, stimulus condition, and task (incorporating an estimated 6-s haemodynamic lag and 4-s interepoch buffer of data which was omitted from the analysis), using the average signal intensity during fixation epochs for the same subject, experiment and task as a baseline[24]. ANOVAs across subjects were run on the average per cent signal change in each of the conditions in each experiment. Because data were analysed within independently defined ROIs, no correction for multiple voxelwise comparisons was made. An analysis of possible laterality effects using separate left versus right hemisphere ROIs for experiment 2 found no main effect of laterality or interaction with any other variable (all F values were <1); therefore laterality was excluded as a factor from all other analyses.

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Altered synaptic physiology and reduced susceptibility to kainate-induced seizures in GluR6-deficient mice

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L-glutamate, the neurotransmitter of the majority of excitatory synapses in the brain, acts on three classes of ionotropic receptors: NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate receptors. Little is known about the physiological role of kainate receptors because in many experimental situations it is not possible to distinguish them from AMPA receptors[1,2]. Mice with disrupted kainate receptor genes enable the study of the specific role of kainate receptors in synaptic transmission as well as in the neurotoxic effects of kainate. We have now generated mutant mice lacking the kainate-receptor subunit GluR6. The hippocampal neurons in the CA3 region of these mutant mice are much less sensitive to kainate. In addition, a postsynaptic kainate current evoked in CA3 neurons by a train of stimulation of the mossy fibre system is absent in the mutant[3,4]. We find that GluR6-deficient mice are less susceptible to systemic administration of kainate, as judged by onset of seizures and by the activation of immediate early genes in the hippocampus. Our results indicate that kainate receptors containing the GluR6 subunit are important in synaptic transmission as well as in the epileptogenic effects of kainate.

We disrupted the GluR6 (or *Grik2*) gene[5] by homologous recombination (Fig. 1a, b). GluR6$^{-/-}$ mice did not differ from their littermates in breeding and general health status, except for a slight reduction in body weight (GluR6$^{+/+}$: 29.3 ± 0.8 g, $n = 10$; GluR6$^{-/-}$: 26.2 ± 0.6 g, $n = 16$, $P < 0.05$). In regions known to express the GluR6 gene, that is, the granule cell layer of the cerebellum or CA3 and dentate gyrus of the hippocampus, no GluR6 messenger RNA could be detected by *in situ* hybridization using a probe recognizing the 3′-end of the mRNA (Fig. 2a). Immunoblot analysis using an anti-GluR6/7 antibody[6] on membrane extracts from wild-type hippocampus showed a strong band corresponding to a relative molecular mass of 115,000 (M_r 115K)

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