the stimulus, which is invariant in its form and motion, or to random eye movements. This leaves the possibility that it reflects a dynamic neural process. When combinations of high- and low-luminance-contrast motion are shown together, as in the examples described here, the motion cues are consistently at variance with the spatial configuration. Unless some form of resolution occurs, the two boundaries might appear to disengage[8]. We propose that the illusory jitter is a visible consequence of this resolution. It has been suggested that reciprocal feedback between, and lateral interactions within, cortical areas can cause synchronous neural spiking with a frequency in the gamma range (20–50 Hz)[17–19]. The characteristic frequency of the illusory jitter described here might similarly reflect the temporal dynamics of recurrent neural processes that mediate the integration of motion-based spatial predictions and subsequent spatial processing. □

Methods

All stimuli used in the conditions represented in Fig. 2a–f were displayed on a 19-inch Sony Trinitron Multiscan 400PS monitor, with a refresh rate of 100 Hz, driven by a VSG 2/5 visual stimulus generator (Cambridge Research Systems). The standard configuration consisted of a large red dot (Commission Internationale d'Éclairage (CIE) 1931 chromaticity chart: $x = 0.60$, $y = 0.34$) with a diameter subtending 1.5° of visual angle, and a smaller superimposed green dot (CIE 1931: $x = 0.28$, $y = 0.595$) with a diameter subtending 0.5°. In the configurations represented in Fig. 2a, b, d–f, the rotating peripheral bull's-eyes were centred 2.25° of visual angle away from a central fixation point, and in Fig. 2f the additional locations were 3.75° eccentric. In the configuration represented in Fig. 2c, two green squares with a width and height of 1.4° were centred 2° above and below a central static fixation point. The central region had a height of 1.4° and a width of 0.25°. These stimuli were viewed in the dark from a distance of 57 cm with the head placed in a chin rest.

For all configurations, other than those depicted in Fig. 2c, g, the physical direction of motion could be clockwise or anti-clockwise, determined at random from trial to trial. During each trial in conditions Fig. 2a–f, the stimulus remained until the observer reported whether jitter was visible or not by pressing one of two levers. In these conditions, during a run of trials, seven luminance levels of the target stimulus were sampled ten times. Each data point in Fig. 3 and in Fig. 4a–f is the mean of four runs.

In the flicker-matching experiment illustrated in Fig. 2f, observers adjusted the luminance flicker frequency of peripheral dots in 5 Hz steps. Note that this sine-wave luminance function was sampled at the monitor refresh rate, 100 Hz. The physical stimulus depicted in Fig. 2g contained four red dots, with a diameter subtending 2° centred 2.25° of visual angle away from a central fixation point. Equiluminant green bars, with a height of 1.25° and a width of 0.25°, were centred within the red dots. The direction of rotation was clockwise and the orientation of the bars was orthogonal to the direction of rotation. LEDs were placed 3.75° eccentrically to the left and right of the central fixation point. Before the peripheral LEDs were shown, it was confirmed that each observer could see illusory jitter of the green bars at each of three physical speeds of rotation. Observers adjusted the rate of sine-wave flicker of the LEDs by adjusting an analogue control on a pulse generator until the rate of flicker seemed to match the rate of the illusory spatial jitter. This was done ten times for each of three stimulus velocities by each observer.

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Cellular networks underlying human spatial navigation

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Place cells of the rodent hippocampus constitute one of the most striking examples of a correlation between neuronal activity and complex behaviour in mammals[1,2]. These cells increase their firing rates when the animal traverses specific regions of its surroundings, providing a context-dependent map of the environment[3–5]. Neuroimaging studies implicate the hippocampus and the parahippocampal region in human navigation[6–8]. However, these regions also respond selectively to visual stimuli[9–13]. It thus remains unclear whether rodent place coding has a homologue in humans or whether human navigation is driven by a different, visually based neural mechanism. We directly recorded from 317 neurons in the human medial temporal and frontal lobes while subjects explored and navigated a virtual town. Here we present evidence for a neural code of human spatial navigation based on cells that respond at specific spatial locations and cells that respond to views of landmarks. The former are present primarily in the hippocampus, and the latter in the parahippocampal region. Cells throughout the frontal and temporal lobes responded to the subjects' navigational goals and to conjunctions of place, goal and view.

Responses of single neurons were recorded in seven subjects who were patients with pharmacologically intractable epilepsy undergoing invasive monitoring with intracranial electrodes to identify the seizure focus for potential surgical treatment (see Methods). Subjects played a taxi driver computer game in which they explored a virtual town, searching for passengers who appeared in random spatial locations and delivering them to fixed target locations (shops, Fig. 1a, b). Before exploring the town, recordings were

made while subjects viewed shop fronts they would later see during the game (Fig. 1c–e). This provided a control for any cellular responses that might be observed based solely on object perception (see Methods).

We recorded from 317 neurons: 67 cells in the hippocampus, 54 in the parahippocampal region, 111 in the amygdala, and 85 in the frontal lobes (see Methods). To determine the nature of cellular responses during spatial navigation, we compared spike rates as a function of the subject's location in the virtual town (place), the object they viewed (view), and their shop or passenger goal. An analysis of variance for each cell across these three factors revealed that 42% of cells responded significantly ($P < 0.05$) to some aspect of the spatial environment, as revealed by a main effect of one or more of the three factors: 26% responded to place, 12% responded to view, and 21% responded to goal. Sixteen per cent of cells showed interaction effects only. To ensure that view responses did not simply reflect perception of objects outside their spatial context, we compared the neural responses to shop fronts viewed prior to navigation. Only 2% of cells (less than the Type I error rate) responded preferentially to specific shop images, suggesting that these responses could not account for the effect of view on firing rate during spatial navigation.

The observation that cells can respond to both place and view raises the question of whether place-responsive cells are in fact coding for place itself, or whether these cells are responding to a subject's view of a given region in our virtual town. The existence of bona fide place cells would require, at a minimum, that these cells do not also respond to view or to conjunctions of place and view. We therefore asked whether the number of cells responding to place but not view were present above the Type I error rate and in what regions these responses were clustered.

Among all cells recorded, 11% fulfilled the criteria for bona fide place selectivity (31 out of 279). Figure 2a illustrates this place selectivity for a cell in the right hippocampus. Place-responsive cells were significantly more prevalent in the hippocampus (24% of cells in the hippocampus were bona fide place responsive cells) than in the frontal lobes, the parahippocampal region and the amygdala ($\chi^2(3) = 11.3$, $P < 0.01$; Fig. 2b). The locations of place fields in place-responsive cells were determined using a spike-shuffling method to locate regions of high firing rate that exceeded background. Place-responsive cells had a mean of 1.7 non-contiguous place fields, and place fields showed a mean increase in firing rate of 74% compared with the rate outside of the field. As can be seen in representative examples (Fig. 2a and Supplementary Fig. 3), place fields usually occurred in regions that were frequently traversed and showed robust increases in firing rate compared with background.

To determine whether the place responses of our cells were direction-dependent, we compared the normalized firing rate in place fields that were traversed in one direction with the opposite direction across all 33 hippocampal place fields (traversals were selected based on the highest numbers of crossings). The mean of the distribution of firing-rate differences did not differ from zero ($t(32) = 0.32$, $P = 0.70$) and the distribution (Fig. 2c) did not deviate from normality ($\chi^2(9) = 0.88$, $P = 0.99$), suggesting that there was no directional tendency across the population of hippocampal neurons (if the place responses we recorded were unidirectional, the distribution of differences in firing rates would have been different from zero). We further analysed place-responsive neurons to determine whether they were modulated by the subject's

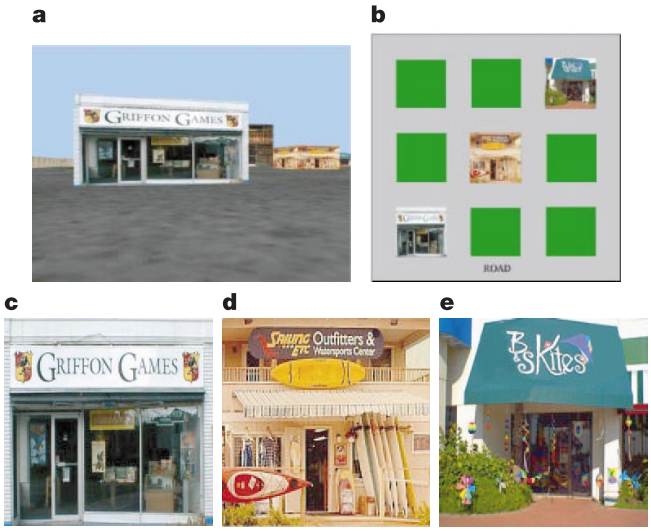

Figure 1 Taxi driver game. **a**, An example of a view seen as a subject navigated through a randomly generated town. Each town contained three labelled, target shops chosen randomly from a pool of 20 possibilities, and 6 unlabelled, non-target buildings chosen from a pool of 48 possibilities. **b**, An example of one particular spatial layout is shown with the corresponding shops (**c**–**e**) searched for during navigation.

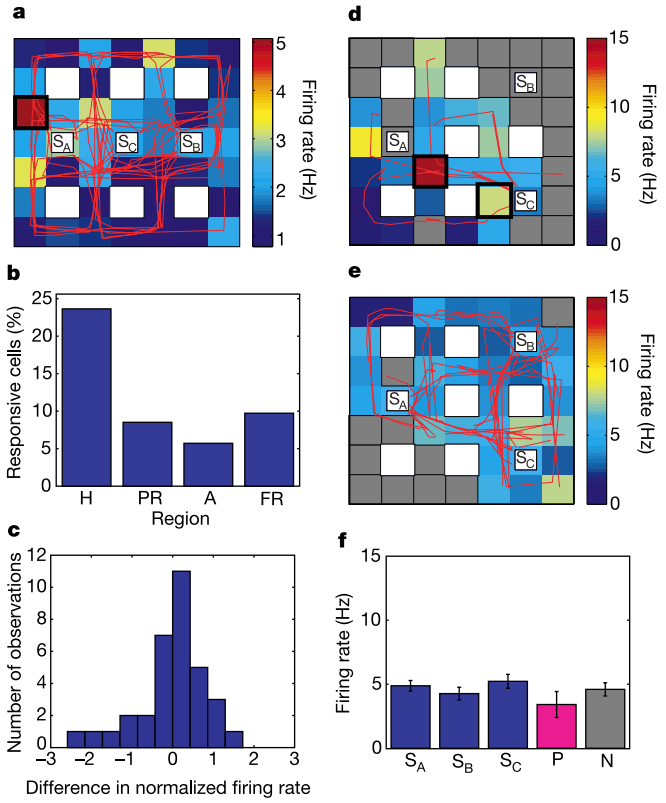

Figure 2 Place-responsive cells. **a**, Firing-rate map of a right hippocampal cell showing significant place selectivity. Letters (S_A,S_B,S_C) indicate shop locations, white boxes indicate non-target buildings, grey boxes indicate unoccupied areas, red lines indicate the subject's trajectory, and black squares indicate regions of significantly high firing rate (all examples, $P < 0.01$; see Methods). **b**, Place-responsive cells were clustered in the hippocampus (H) compared with amygdala (A), parahippocampal region (PR) and frontal lobes (FR). **c**, Regions of high firing included high numbers of traversals in different directions. The distribution of firing-rate differences across these traversals was centred on zero and normal. **d**, Firing-rate map of a right hippocampal cell showing significant place selectivity when searching for shop S_C, but no such specificity when searching for other goals (**e**, areas with <2 traversals were excluded). **f**, This cell similarly showed no effect of viewing specific targets (P indicates viewing passengers; N indicates a control background view).

goal. Twenty-six per cent of place-responsive cells had place × goal interaction effects (8 of 31 cells) and fired in different spatial locations depending on the subject's goal; Fig. 2d, e illustrates the response of a goal-modulated place cell recorded from the right hippocampus. When shop S_C was the goal (Fig. 2d), the cell showed clear place-selective responses compared with when shop S_C was not the goal (Fig. 2e). Whereas the cell was strongly modulated by place and goal, it was not modulated by view (Fig. 2f).

Eighty-eight per cent of view cells (29 out of 33) responded preferentially to a single object during navigation (such as a specific shop or passenger, Fig. 3a). Twenty-four view cells were responsive to a specific shop, and among these cells, 14 were location-independent (that is, they showed no place × view interaction effect and they exhibited a high firing rate in many of the locations where the shop was viewed, Fig. 3b, c). Location-independent view-responsive cells were significantly clustered in the parahippocampal region (Fig. 3f, $\chi^2(3) = 11.3$, $P < 0.01$), where they comprised 7 out of 10 view-responsive cells. Fifteen view cells across anatomical regions (only three of which were in the parahippocampal region) also exhibited place × view interaction effects. These location-dependent view-responsive cells increased their firing rate when specific shops were viewed from certain spatial locations (Fig. 3d, e).

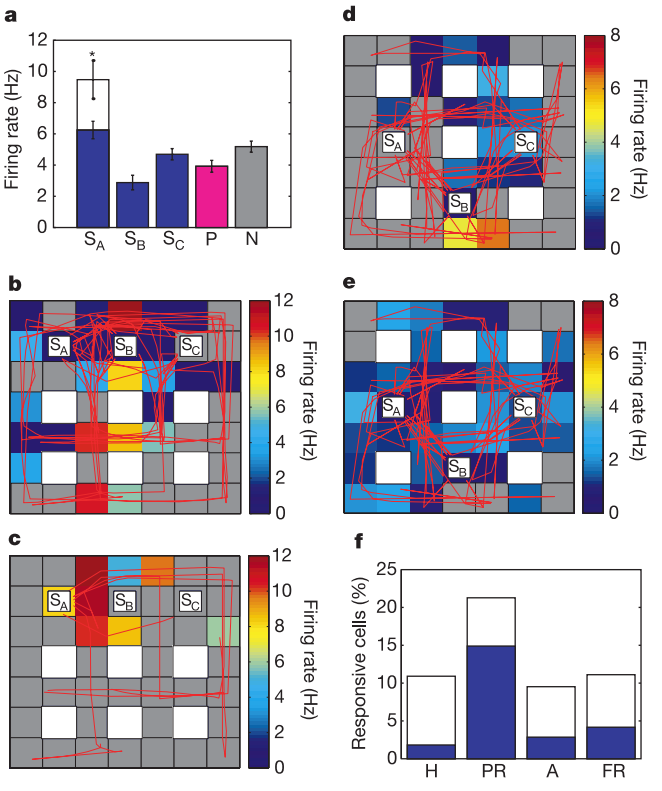

Figure 3 View-responsive cells. **a**, Mean firing rate for a right parahippocampal cell that responded to viewing S_A (as compared with other shops, passengers and control views). The firing rate to viewing S_A (but not other targets) increased significantly when S_A was the goal (white bar). **b**, Firing-rate map shows that this cell responded to viewing S_A from disparate regions; grey regions indicate that S_A was not viewed. **c**, When searching for S_A, the firing rate was consistently high whenever it was viewed. **d**, Firing-rate map of a view-responsive cell in the left amygdala. This cell's activity was modulated by the subject's position; it fired most strongly when S_C was viewed from the town corner nearest to S_B, but not from other spatial positions, and **e**, not when other objects were viewed. **f**, Per cent of location-independent view cells across brain regions. Blue bars, responses to shops; total bar height, responses to all goals (shops and passengers).

Location-dependent view-responsive cells were not clustered by anatomical region.

Twenty-one per cent of cells (59 out of 279) responded to the subjects' goal (that is, one of the target shops (Fig. 4a) or passengers (Fig. 4b)). Although we recorded a smaller percentage of goal-responsive cells in the amygdala than in other regions, this effect was not statistically significant ($\chi^2(3) = 6.7$, $P = 0.1$). Goal cells with no main effects of place fired robustly regardless of spatial position (Supplementary Fig. 2a, b). Fifteen per cent of goal-responsive cells also showed view × goal interaction effects. These cells increased their firing rate during viewing depending on whether or not the shop was a goal (Fig. 4d and Supplementary Fig. 2d); the majority of these view-dependent goal cells (77%) responded to shops and not to passengers.

The anatomical distribution of place- and view-responsive cells reveal a dissociation between the hippocampus and the parahippocampal region, with the hippocampus specialized for place and the parahippocampal region specialized for view ($\chi^2(1) = 10.5$, $P < 0.005$). This finding, together with functional magnetic resonance imaging (fMRI) studies showing that viewing spatial layouts preferentially activates the parahippocampal region[9], suggests that the hippocampus and parahippocampal region perform complementary functions during navigation. Although an extensive literature for the rat supports the role of the hippocampus in spatial coding, as do studies in humans[8], single-unit recordings in primates suggest that the hippocampus responds to spatial views during navigation[14] while the parahippocampal region responds to head direction[15]. Because of our experimental design, we are unable to adequately address bearing responses (see Methods), although we note that hippocampal responses to spatial locations have also been observed in primates during virtual and real spatial translocations[16].

The presence of place–goal conjunctive cells in the hippocampus may indicate its role in associating goal-related contextual inputs with place, as has been noted in rats during spatial "remapping"[4,5,17].

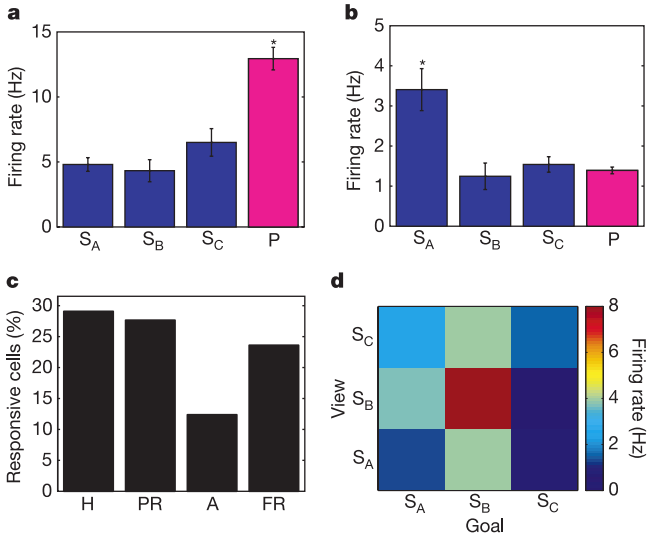

Figure 4 Goal-responsive cells. **a**, Mean firing rate for a right hippocampal cell that responded when seeking passengers (P) and **b**, for a different right hippocampal cell that responded when seeking S_A. **c**, Goal-responsive cells were not significantly clustered by anatomical region. Some goal-responsive cells modulated their firing rate based on what was being viewed, such as this cell in the right amygdala (**d**), which responded preferentially when the goal (shop S_B) was in view. This panel shows firing rates for all combinations of shop being viewed and shop being sought; view × goal conjunctive cells were not clustered by anatomical region.

Location-dependent and goal-dependent view responses, in contrast, may support navigational strategies that require view-dependent, egocentric representations of space. Goal-dependent view responses may provide information on the progress and success in locating a goal, whereas location-dependent view responses could be useful in planning trajectories to visible goals. We observed some location-dependent view-responsive cells in the parahippocampal region (30% of view cells), although a greater number were location-independent (70% of view cells).

It is intriguing to consider the possibility that projections from the hippocampus to the parahippocampal region may have a role in producing view-independent representations of landmarks in spatial scenes[9,10]. Our dissociation of parahippocampal and hippocampal function, together with the data discussed above, provide cellular evidence for an emerging model[18] of the physiological basis of human spatial navigation. In this model, the parahippocampal region extracts allocentric spatial information primarily from salient visual landmarks to form a coarse representation of space[19,20]. The hippocampus combines visual and spatial features, possibly via inputs from the parahippocampal region, with context to compute the flexible map-like representations of space underlying navigation[21,22]. □

Methods

Behavioral methods

Subjects navigated using the arrow keys on a computer keyboard; when moving, velocity was constant. Virtual towns consisted of six unlabelled, non-target buildings and three labelled, target shops (Fig. 1b). During a single session, subjects made seven deliveries of passengers to each target shop in a random order. Passengers were 'picked up' by driving near them; text then appeared instructing subjects as to which shop the passenger should be delivered. A small box of text in the corner of the screen reminded the subject of their goal. Each delivery began from the random position where the passenger was picked up. Upon delivery of the passenger to a fixed-location shop (accomplished by driving into it), subjects were told whether they had found the correct shop (subjects also received 'virtual' payment for delivering passengers). A text instructed subjects to find another passenger, and subjects explored the city until they located another passenger, at which point the cycle began again. Shops and passengers looked the same from all viewing angles; shops were identified by highly visible names (see ref. 23 for further details concerning the taxi driver game).

Patient data and electrophysiology

Six (of seven) patients were right-handed, two were female; one patient had right temporal-lobe epilepsy, one had left frontal-lobe epilepsy; all others had left temporal-lobe epilepsy (Supplementary Table 1). Each patient had between 6 and 14 depth electrodes implanted bilaterally from a lateral orthogonal approach (surgeries were performed by I.F.). Each of these clinical electrodes terminated with a set of nine 40-μm platinum–iridium microwires. Signals from these microwires were recorded at 28 kHz and bandpass-filtered between 0.6 and 6 kHz using a 64-channel acquisition system (Neuralynx). Responses of individual cells were isolated based upon the distribution of inter-spike intervals and parameters of the spike waveforms (Supplementary Fig. 1, MClust, developed by A. D. Redish and K. Harris, http://www.cbc.umn.edu/~redish/mclust). MRI scans following placement of electrodes, or post-placement computed tomography scans coregistered to preoperative MRI scans, were used to verify the anatomical location of the electrodes (Supplementary Fig. 1a; see also refs 12, 24, 25). All patients provided informed consent. All studies conformed with the guidelines of the Medical Institutional Review Board at UCLA.

The 85 cells in the frontal lobes consisted of cells in anterior cingulate, orbital frontal cortex and in supplementary motor cortex. We use the term 'parahippocampal region', as defined by Witter[26], to include pre- and para-subiculum, entorhinal and perirhinal cortices and parahippocampal cortex. Cells with firing rates above 15 Hz were considered to be interneurons and were excluded (6); cells with less than 0.1 Hz firing rate were similarly excluded (32); this left a total of 279 cells for analysis.

Data analysis

Spike counts during different epochs of the taxi driver game were compared using a place (49) × view (5) × goal (4) analysis of variance. The place factor could take on one of 49 values representing a 7 × 7 grid overlaid on each virtual town. The view factor coded for times when subjects viewed shops S_A, S_B or S_C, passenger (P), or background (N). The goal factor coded for times when subjects searched for S_A, S_B, S_C, P (see Supplementary Table 2 for analysis of variance results).

Periods when the subject remained stationary in the game for >500 ms were excluded. Spike-by-position plots were determined by dividing the number of spikes that occurred in a spatial region by the total time spent in that region[2]. Significant 'place fields' were identified by shuffling the spike train randomly and locating firing rates that exceeded 95% of all shuffled spike train firing rates for that region[26]; all cells identified as place-responsive in our analysis also showed one or more place fields using the spike-shuffling method. Areas occupied for less than 5 s were not considered, and nor were areas with less than two passes. The view analysis was performed by calculating what the subject was viewing (S_A, S_B, S_C, P,N) every 30 ms. We included only viewing epochs when more than 70% of an object was visible for at least 500 ms; no other objects could be simultaneously visible. The spike train was then restricted to these times to calculate the firing rate while viewing objects during navigation.

To ensure that cellular responses during navigation were not the result of seizure activity, the responses and firing rates of neurons were compared after excluding all cells from areas of seizure focus: this did not affect cellular responses to place, view and goal ($\chi^2(1) = 2.5$, $P > 0.1$), nor firing rate ($\chi^2(1) = 0.1$, $P > 0.1$).

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