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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 behavior in mammals[1,2]. These cells increase their firing rates when the animal traverses specific regions of its surroundings, thus providing a context-dependent map of the environment[3,4,5]. Neuroimaging studies implicate the hippocampus and the parahippocampal region in human navigation[6,7,8]. However, these regions also respond selectively to visual stimuli[9,10,11,12,13]. 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. 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 (stores) (Fig. 1 A,B). Before exploring the town, recordings were made while subjects viewed store fronts they would later see during the game (Fig. 1 C-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 were 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 *goal*. An analysis of variance for each cell across these three factors revealed that 42% of cells responded significantly ($p < .05$) 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 percent of cells showed interaction effects only. To ensure that view responses did not simply reflect perception of objects outside their spatial context, we compared neural responses to store fronts viewed prior to navigation. Only 2% of cells (less than the Type-I error rate) responded preferentially to specific store 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% fullfilled the criteria for *bona fide* place selectivity (31 out of 279). Fig. 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 hippocampus were *bona fide* place responsive cells) than in the frontal lobes, the parahippocampal region, and amygdala ($\chi^2(3) = 11.3$, $p < .01$; 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 to the rate outside of the field. As can be seen in representative examples (Fig 2A and *Supplementary Information,*

Fig. 3), place fields usually occurred in regions that were frequently traversed and showed robust increases in firing rate compared to background. To determine whether the place responses of our cells were directionally 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) = .32, $p = .70$) and the distribution (Fig. 2C) did not deviate from normality ($\chi^2(9) = .88$, $p = .99$), suggesting that there was no directional tendency across the population of hippocampal neurons (if the place responses we recorded were uni-directional, the distribution of differences in firing rates would have been different from zero). We further analyzed place-responsive neurons to determine if they were modulated by the subject's goal. Twenty-six percent 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 Store S_C was the goal (Fig. 2D), the cell showed clear place selective responses compared to when Store S_C was not the goal (Fig. 2E). Whereas the cell was strongly modulated by place and goal, the cell was not modulated by view (Fig. 2F).

Eighty-eight percent of view cells (29 out of 33) responded preferentially to a single object during navigation (Fig 3A, e.g. a specific store or passenger). Twenty-four view cells were responsive to a specific store, and among these cells, 14 were location-independent (i.e. they showed no place×view interaction effect and they exhibited a high firing rate in many of the locations where the store was viewed, Fig 3B,C). Location-independent view responsive cells were significantly clustered in the parahippocampal region (Fig 3F, $\chi^2(3) = 11.3$, $p < .01$), where they comprised 7 out of 10 view responsive cells. Fifteen view cells across anatomical regions (only 3 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 stores were viewed from certain spatial locations (Fig. 3D,E). Location-dependent view responsive cells were not clustered by anatomical region.

Twenty-one percent of cells (59 out of 279) responded to subjects' goal (i.e., one of the target stores (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 ($\chi^2(3) = 6.7$, $p = .1$). Goal cells with no main effects of place fired robustly regardless of spatial position (*Supplementary Information, Fig. 2A,B*). Fifteen percent of goal responsive cells also showed view × goal interaction effects. These cells increased their firing rate during viewing depending on whether or not the store was a goal (Fig. 4D and *Supplementary Information, Fig. 2D*); the majority of these view-dependent goal cells (77%) responded to stores 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 ($\chi^2(1) = 10.5$, $p < .005$). This finding, together with 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 from the rat supports the role of the hippocampus in spatial coding, as do studies in humans[8], single unit recordings in the primate 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"[17, 4, 5]. 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 while 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 play 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 6 unlabeled, non-target buildings and 3 labeled, target stores (Fig. 1B). During a single session, subjects made 7 deliveries of passengers to each target store in a random order. Passengers were picked-up by driving near them; text then appeared instructing subjects to which store 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 store (accomplished by driving into it), subjects were instructed whether they

had found the correct store (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. Stores and passengers looked the same from all angles they were viewed; stores were identified by highly visible names.

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 Information, 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-micron 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, Tucson, AZ). Responses of individual cells were isolated based upon the distribution of inter-spike intervals and parameters of the spike waveforms (*Supplementary Information, Fig. 1B*, MClust; A. David Redish and K. Harris). MR scans following placement of electrodes, or post-placement CT scans coregistered to preoperative MR scans, were used to verify the anatomical location of the electrodes (*Supplementary Information, Fig. 1A*; see also[23,24,12]). 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[25], to include pre-and para-subiculum, entorhinal and perirhinal cortices and parahippocampal cortex. Cells with firing rates above 15 Hz were considered 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 overlayed on each virtual town. The *view* factor coded for times when subjects viewed Store S_A, Store S_B, Store 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 Information, Table 2* for ANOVA results).

Periods when the subject remained stationary in the game $>$ 500 msec 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 ANOVA also showed one or more place fields using the spike shuffling method. Areas occupied for less than 5 sec were not considered 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 msec. We included only viewing epochs when more than 70% of an object was visible for at least 500 msec; 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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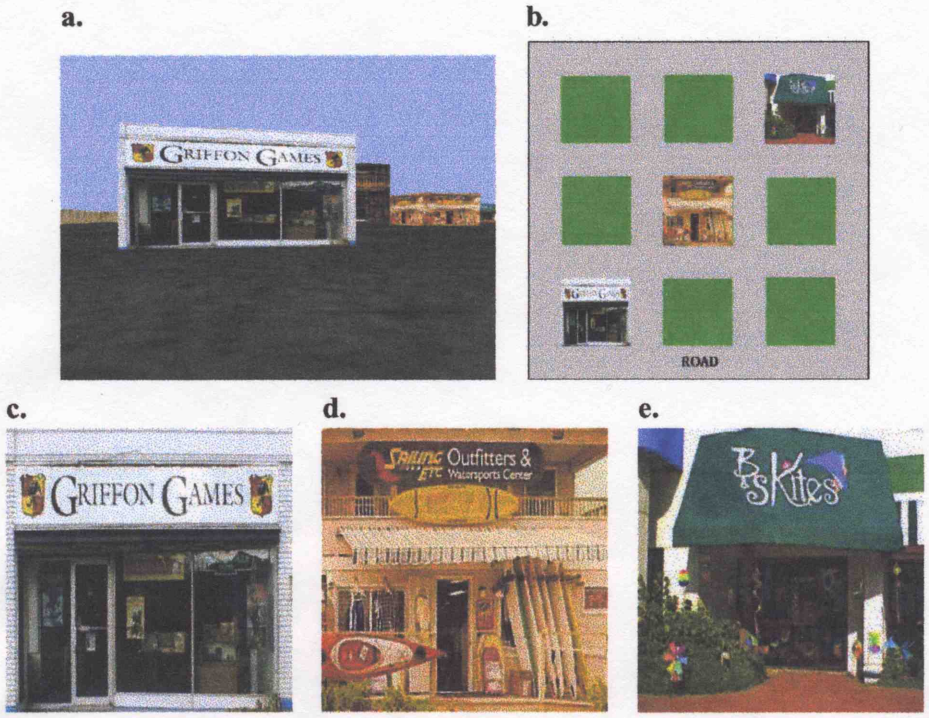

Figure 1: **Taxi-Driver Game. a.** An example of a view seen as a subject navigated through a randomly generated town. Each town contained three labeled, target stores chosen randomly from a pool of 20 possibilities and 6 unlabeled, non-target buildings chosen from a pool of 48 possibilities. **b.**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

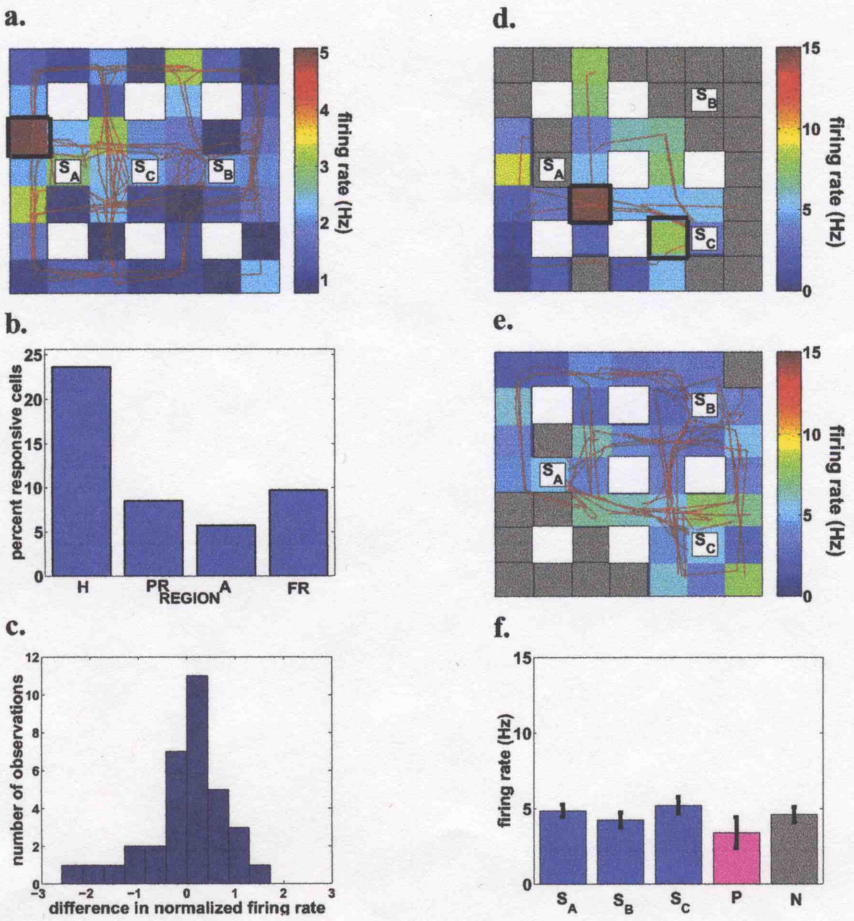

Figure 2: **Place responsive cells. a.** Firing-rate map of a right hippocampal cell showing signifi cant place selectivity. Letters ($\mathcal{S}_A$,$\mathcal{S}_B$,$\mathcal{S}_C$) indicate store locations, white boxes indicate non-target buildings, gray boxes indicate unoccupied areas, red lines indicate the subject's trajectory, and black squares indicate regions of signifi cantly high fi ring rate (all examples, $p < .01$; see Methods). **b.** Place-responsive cells were clustered in the hippocampus (H) compared to amygdala (A), parahippocampal region (PR) and frontal lobes (FR). **c.** Regions of high fi ring included high numbers of traversals in different directions. The distribution of fi ring-rate differences across these traversals was centered on zero and normal. **d.** Firing rate map of a right-hippocampal cell showing signifi cant place selectivity when searching for Store $\mathcal{S}_C$, but no such specifi city when searching for other goals (**e.**; areas with < 2 traversals were excluded). This cell similarly showed no effect of viewing specifi c targets (**f.**; *P* indicates viewing passengers, *N* indicates a control background view.)

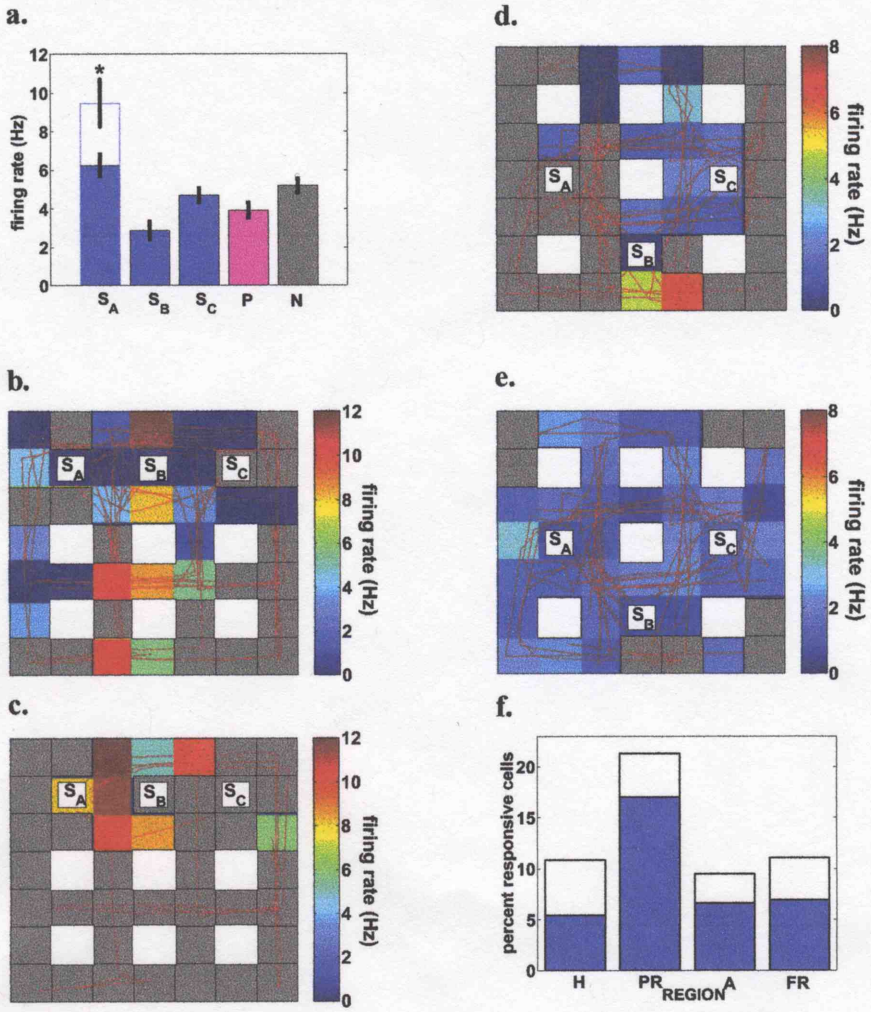

Figure 3: **View responsive cells.** **a.** Mean firing rate for a right parahippocampal cell that responded to viewing $\mathcal{S}_A$ (as compared with other stores, passengers [P] and control views [N]). The firing rate to viewing $\mathcal{S}_A$ (but not other targets) increased significantly when $\mathcal{S}_A$ was the goal (white bar). **b.** Firing rate map shows that this cell responded to viewing $\mathcal{S}_A$ from disparate regions; gray regions indicate that $\mathcal{S}_A$ was not viewed. **c.** When searching for $\mathcal{S}_A$, the firing rate was consistently high whenever it was viewed. **d.** Firing rate map of a view-responsive cell in left amygdala. This cell's activity was modulated by the subject's position; it fired most strongly when $\mathcal{S}_C$ was viewed from the town corner nearest to $\mathcal{S}_B$, but not from other spatial positions, and (**e.**) not when other objects were viewed. **f.** Percent of location-independent view cells across brain regions (blue bars, responses to stores; total bar height, responses to all goals [stores and passengers]).

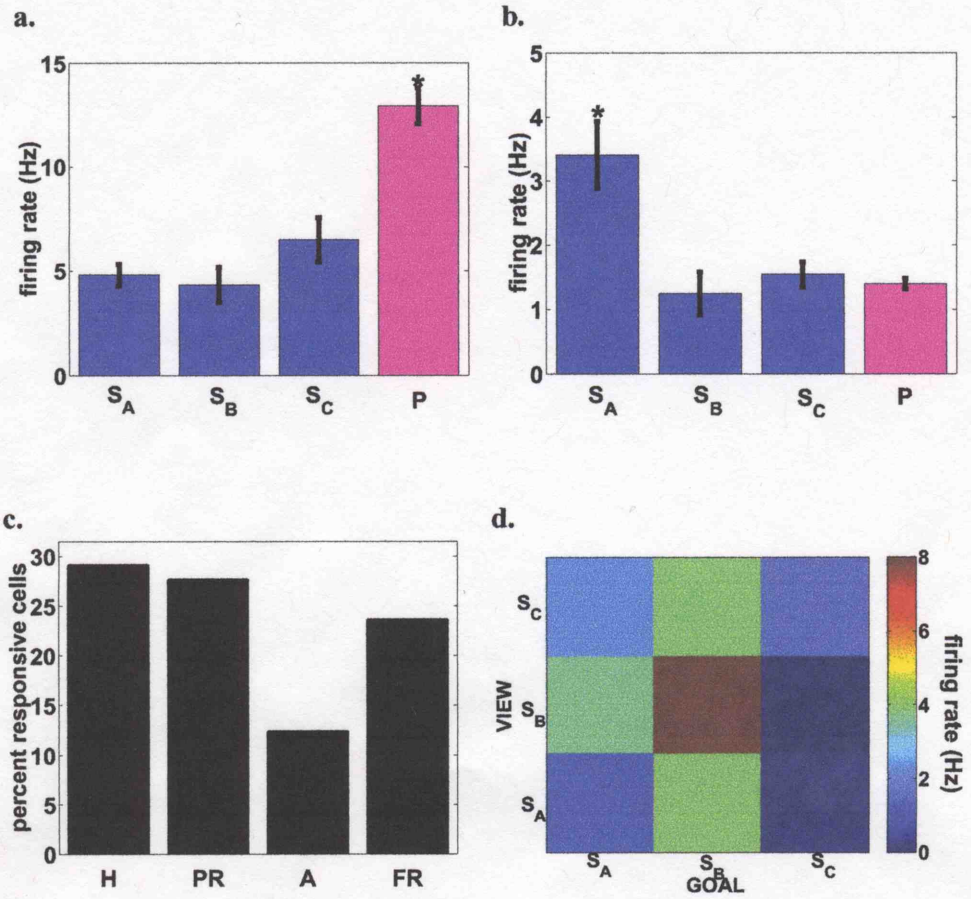

Figure 4: **Goal responsive cells. a.** Mean firing rate for a right hippocampal cell that responded when seeking passengers (P) and **b.** for a different right hippocampal cell that responded when seeking S_A. **c.** Goal responsive cells were not significantly clustered by anatomical region. Some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