

Hippocampal Neurons Encode Information about Different Types of Memory Episodes Occurring in the Same Location

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Summary

Firing patterns of hippocampal complex-spike neurons were examined for the capacity to encode information important to the memory demands of a task even when the overt behavior and location of the animal are held constant. Neuronal activity was recorded as rats continuously alternated left and right turns from the central stem of a modified T maze. Two-thirds of the cells fired differentially as the rat traversed the common stem on left-turn and right-turn trials, even when potentially confounding variations in running speed, heading, and position on the stem were taken into account. Other cells fired differentially on the two trial types in combination with behavioral and spatial factors or appeared to fire similarly on both trial types. This pattern of results suggests that hippocampal representations encode some of the information necessary for representing specific memory episodes.

Introduction

Multiple lines of research have recently converged on a critical role for the hippocampus in episodic memory, the ability to remember specific personal experiences (Tulving, 1983). Humans with selective hippocampal damage exhibit deficits in episodic memory, sometimes with relative sparing of the ability to acquire general factual knowledge, or semantic memory (Vargha-Khadem et al., 1997). Complementary brain imaging investigations have described selective activation of the hippocampus during learning or recall of episodic memories (Tulving et al., 1994; Gabrieli et al., 1997; Henke et al., 1997). In studies on animals, hippocampal damage results in severe impairments in remembering a recent unique experience in a familiar environment (Steele and Morris, 1999). Correspondingly, hippocampal neurons encode sequential events and places occupied as animals perform a variety of learning and memory tasks, leading several investigators to suggest that the hippocampus represents sequences of events that compose episodic memories (Levy, 1996; Wallenstein et al., 1998; Eichenbaum et al. 1999; Lisman, 1999).

Several characterizations of the firing properties of hippocampal neurons are consistent with the coding of

episodic information. For example, individual hippocampal neurons encode combinations of stimuli, behaviors, and places that are common to particular types of trials as rats perform an olfactory memory task (Wood et al., 1999). In addition, hippocampal cells have been observed to fire differentially associated with an animal's behavior and location depending on the phase of an ongoing task (Wible et al., 1986; Deadwyler et al., 1996; Wiebe and Staubli, 1999). Also, hippocampal firing patterns can change dramatically when animals have distinctive experiences in the same environment, suggesting separate representations for different types of experience within the same spatial context ("mis-place" cells of O'Keefe, 1976; Wiener et al., 1989, Markus et al., 1995; Hampson et al., 1996). However, in each of these studies the distinctive experiences within a given spatial context also differ with respect to the ongoing behavior, the available stimuli, or the specific location or orientation of the animal within the environment (reviewed by Eichenbaum et al., 1999). No study so far has offered unambiguous evidence that hippocampal neurons encode information from distinct experiences independent of potentially confounding behavioral or spatial factors.

In the present study, we characterized the firing patterns of hippocampal neurons under conditions in which the animal performed two distinct types of memory test trials while its overt behavior and the locations occupied were held constant. We employed a version of delayed spatial alternation, a protocol that requires animals to traverse the "stem" of a T maze on each trial and then, at the end of the stem, alternately turn left or right onto choice arms to obtain rewards (Figure 1A). The critical memory demand of this task is to distinguish left-turn and right-turn episodes, and on each trial to remember the last episode and turn in the opposite direction. Rats with hippocampal damage are severely impaired on spatial alternation and other spatial tasks with similar "episodic" memory demands (Olton, 1986).

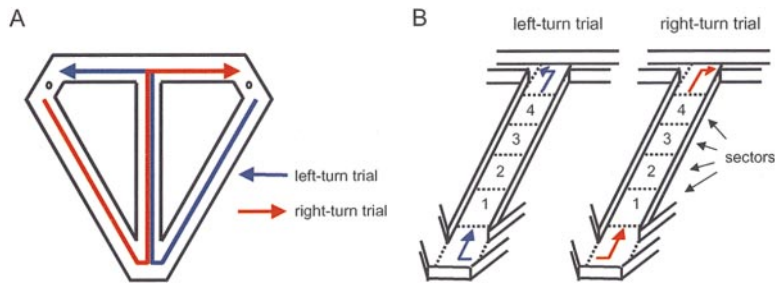
We recorded from CA1 pyramidal cells as rats performed this task, and compared the spatial firing patterns of these cells as rats performed left-turn and right-turn trials. We focused on cells that fired when the rats were on the central portion of the stem of the maze, because this area was traversed as a part of both left-turn and right-turn trials, and the rat's overt behavior, including the direction and speed of running, was similar on both trial types. To the extent that the hippocampal network forms separate representations for left- and right-turn episodes, we expected to observe cells that fired differentially depending on the trial type, even when the rat was on the common stem. Conversely, to the extent that hippocampal cells simply encode the animal's location, or its location in combination with its direction of movement or running behavior in that location, we expected identical firing patterns on both kinds of episodes. The results indicate that different hippocampal cells show each of these patterns. The majority distinguish between the two types of trial, whereas a small subset fire similarly on both trial types. These findings are consistent with our proposal that the hippocampal network contains both representations that are

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firing patterns, left-turn (blue arrow) and right-turn (red arrow) trials were distinguished. Only trials that involved correct responses were included in the analyses.

(B) Schematic of the stem of the T maze indicating divisions of the central portion of the stem into the four sectors used in the data analyses (see Experimental Procedures).

Figure 1. Schematic View of the Modified T Maze

(A) Rats performed a continuous alternation task in which they traversed the central stem of the apparatus on each trial and then alternated between left and right turns at the T junction. Rewards for correct alternations were provided at water ports (small circles) on the end of each choice arm. The rat returned to the base of the stem via connecting arms, and then traversed the central stem again on the next trial. For analysis of neural

specific to particular types of episodes and representations of common events and places that could link episodic representations into a large memory network (Eichenbaum et al., 1999).

Results

Recording and Selection of Cells

Hippocampal complex-spike cells were recorded as animals alternated continuously on a T maze apparatus modified as depicted in Figure 1A (see Experimental Procedures for details). Recording sessions consisted of 30–50 trials composed of an equal number of left-turn and right-turn trials. While hippocampal cells exhibited location-specific activity throughout the apparatus, the focus of the current analysis was on those cells with place fields on the central portion of the stem of the T maze (Figure 1B) that animals traversed on every trial.

Only a subset of the cells encountered—those with place fields on the central stem of the maze—were of interest. Therefore, to maximize the yield of cells, we intentionally chose to use stereotrodes composed of relatively large-diameter wires. This electrode configuration results in the recording of two relatively small action potential waveforms, rather than four larger waveforms, increasing the difficulty of single unit isolation. We used multiple measures of the spike waveforms to isolate cells and employed analyses of refractory periods to increase confidence in the successful isolation of cells that fired at around the same time (i.e., had overlapping place fields). As can be seen in the examples shown in Figure 2, these methods separated units from the background of other recorded activity, and the waveform patterns were unique for each cell and reliable between the two trial types. Nevertheless, it is quite possible that at least some of our recordings involved multicell clusters rather than single cells. To the extent that this is the case, our conclusions reflect properties of small groups of neighboring neurons that may possibly have similar functional characteristics. Conversely, a failure to isolate cells with different functional properties—e.g., separate place fields—would only have obscured trial type-selective firing patterns such as those reported here (see Discussion).

Eighty-two cells with characteristics of complex-spike neurons having place fields on the apparatus were recorded from the CA1 pyramidal cell layer in four rats. Of these, a preliminary assessment that used a conventional analysis for location-specific activity identified 33

cells with distinct place fields on the central stem portion of the T maze (see Experimental Procedures for details). For each of these 33 cells, in a second stage of analysis, the firing rate was calculated on every trial for each of four central sectors of the stem (see Figure 1B). Differences in firing rates associated with left-turn and right-turn trials and with different stem locations (sectors 1–4) were analyzed using a two-way ANOVA. The firing rates of 31 of the 33 cells with place fields on the central stem differed significantly between left- and right-turn trials ($p < 0.05$), or between trial types as a function of sector (trial-type \times sector interaction, $p < 0.05$). The firing rates of the remaining two cells differed significantly among the four sectors ($p < 0.05$) but not between trial types or between trial types as a function of sector ($p > 0.05$).

One possible explanation for this pattern of results is that the differences in firing rates between trial types are secondary to slight but reliable variations during left-turn and right-turn trials in the animal's running speed, its heading direction, or its lateral position on the stem. The activity of hippocampal place cells has been shown previously to be influenced by running speed and head or movement direction (McNaughton et al., 1983; Wiener et al., 1989; Muller et al., 1994; Czurko et al., 1999). Other studies have suggested that even small differences in location on a maze arm can strongly influence their firing rates (Muller et al., 1994). In the present experiment, we attempted to minimize these factors by analyzing the data only for the central portion of the stem, where the animals' direction appeared highly consistent. Also, this part of the stem was made quite narrow to restrict variations in lateral position. To account quantitatively for any remaining effects of these potentially confounding factors, an additional set of analyses was employed for each of the 31 cells that differentiated left-turn and right-turn trials. In these analyses, a two-way ANCOVA was performed on each cell. This comprised essentially the same analysis used to compare firing rates across the four sectors on left-turn and right-turn trials as that described above. However, running speed, heading, and lateral position were included as covariates in the ANCOVA model. Each of these factors assumes one degree of freedom and an associated fraction of the overall variance in the firing rates of the cell. Further post hoc tests on each sector were subsequently performed on cells that had significant effects of trial type ($p < 0.05$) or a significant interaction between trial type and sector ($p < 0.05$) in the ANCOVA. These tests compared firing rates on left-turn and right-turn trials for

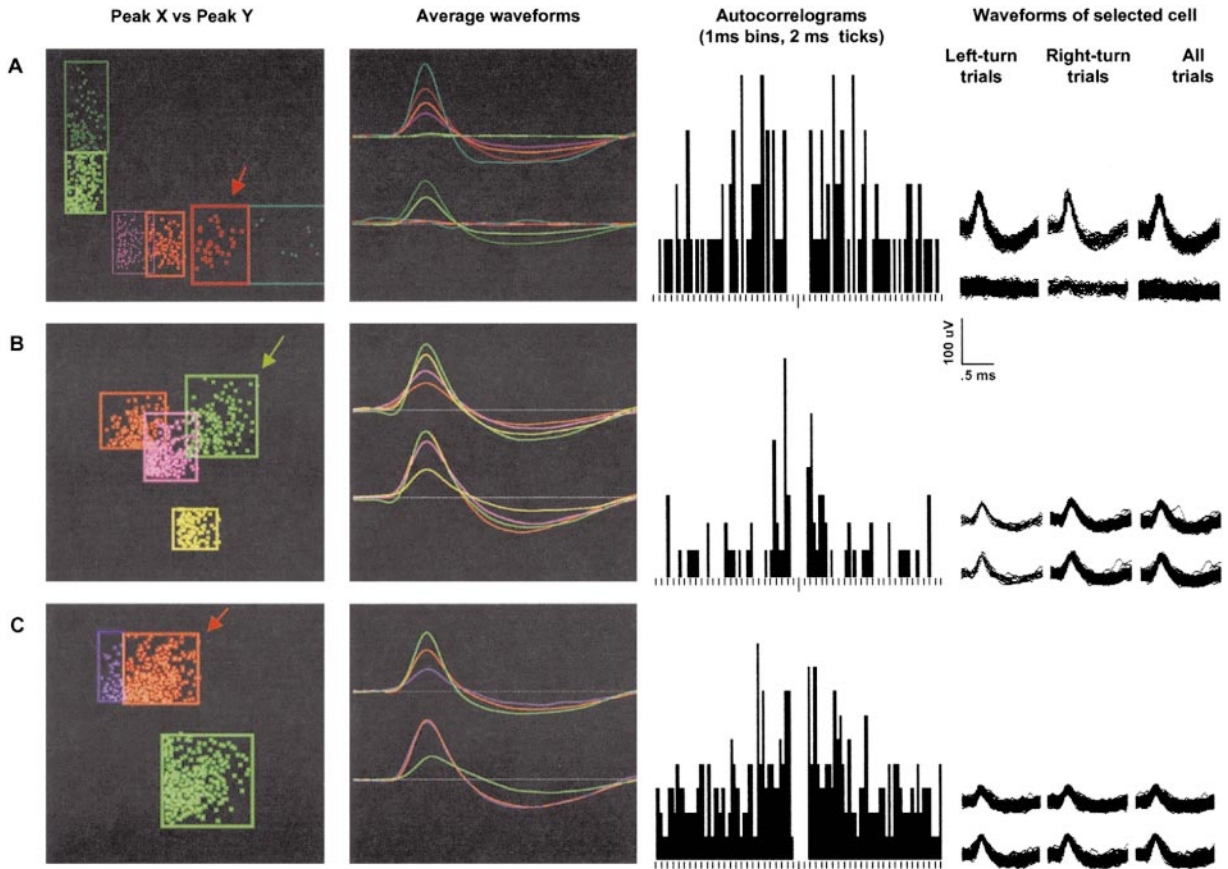


Figure 2. Examples of Isolation Illustrating Common Variations in the Range of Cells Recorded

Cell A is the one whose firing patterns are illustrated in Figure 3A; cell B the one in Figure 3B; and cell C the one in Figure 4A. For each cell, the first column shows the clusters of spikes categorized by the peak magnitudes of the action potentials recorded on each wire (X and Y) of the stereotrode. An arrow indicates the cell selected for further analyses. This was the principal variable combination used in the separation, but in most cells other parameters were also used to gain further separation (see Experimental Procedures). The second column shows the average waveform of each cell that fired when the rat was on the stem and was used in subsequent analyses, as well as average waveforms of the other cells that appear in the cluster cuts to the left. The third column shows the autocorrelogram for each selected cell showing zero incidence of spikes within the refractory period, indicating likely isolation from other units that had overlapping place fields. The fourth column provides waveforms of each selected cell recorded during left-turn trials, right-turn trials, and all trials, respectively, showing the consistency of the waveform patterns across both trial types.

each sector individually, again using running speed, heading, and lateral position as covariates.

The results of these analyses confirmed previous reports that the activity of many hippocampal cells is at least to some extent influenced by the animal's direction of travel and speed as well as by small variations in its lateral position. However, the results indicated that two-thirds (22/33) of the cells with place fields on the central stem fired at significantly different rates on left-turn and right-turn episodes, even when all of these factors were taken into account. There were several variations in the pattern of this differential firing, with some cells activated almost exclusively on one trial type and others activated to a different extent or associated with different areas of the stem on the two trial types. For a further nine cells, the analyses failed to reach significance when the covariates were included. In these cases the variance in firing rates could not be accounted for by the type of trial independent of the influences of the other factors. Examples showing the range of our observations follow.

Cells that Fired Almost Exclusively on Either Left-Turn or Right-Turn Trials

Three examples of cells that were robustly activated on one trial type, but exhibited little activity when the animal traversed the same locations while performing the other trial type, are shown in Figure 3. The cell illustrated in Figure 3A fired robustly as the rat traversed the top three sectors of the central stem on left-turn trials but showed very little activity as the rat traversed the same region on right-turn trials (see also a videoclip of this cell at <http://www.neuron.org/cgi/content/full/27/3/623/DC1>). Inspection of the paths taken by the rat on left-turn and right-turn trials (shown at the left in Figure 3A) reveal largely overlapping movement patterns in sectors 2 and 3, and partially overlapping paths in sector 4. The statistical analyses revealed that the firing rates differed significantly between trial types ($F_{1,144} = 272.07, p < 0.001$), between stem sectors ($F_{3,144} = 55.19, p < 0.001$), and between trial types as a function of sector ($F_{3,144} = 49.16, p < 0.001$). A similar pattern emerged when running speed, heading, and lateral position were included as

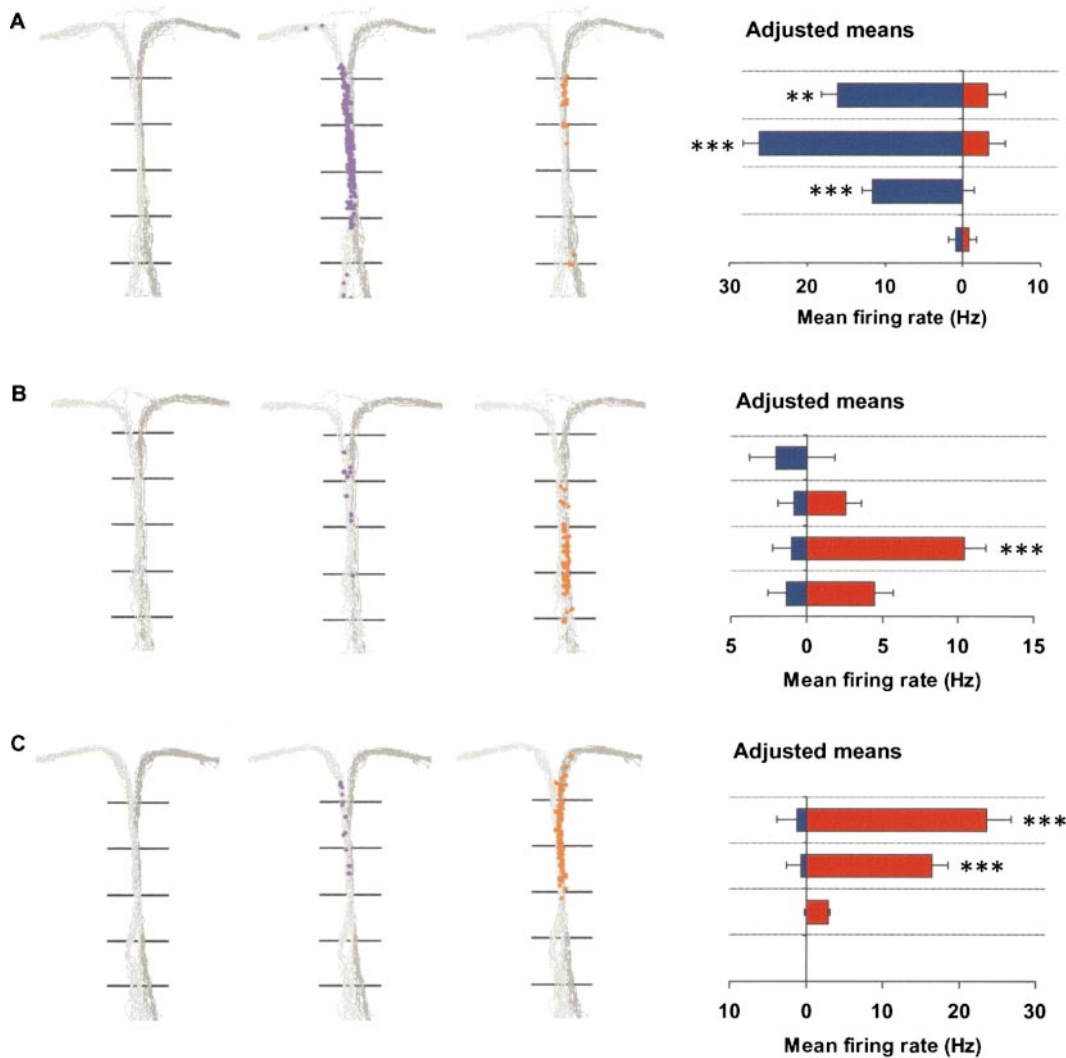


Figure 3. Examples of Hippocampal Cells that Are Active When the Rat Is Traversing the Central Stem

These cells fire almost exclusively during either left-turn or right-turn trials. In each example, the paths taken by the animals on the central stem are plotted in the left panel (light gray, left-turn trial; dark gray, right-turn trial). In the middle panels, the location of the rat when individual spikes occurred is indicated separately for left-turn trials (blue dots) and right-turn trials (red dots). In the right panel, the mean firing rate of the cell for each sector, adjusted for variations in firing associated with covariates (see Results), is shown separately for left-turn trials (blue) and right-turn trials (red).

(A) A cell that fired almost exclusively on left-turn trials as the rat traversed later sectors of the stem.

(B) A cell that fired almost exclusively on right-turn trials as the rat traversed early sectors of the stem.

(C) A cell that fired almost exclusively on right-turn trials as the rat traversed later sectors of the stem.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

covariates in the analysis of variance, with significant differences between trial types ($F_{1,141} = 69.14$, $p < 0.001$), between stem sectors ($F_{3,141} = 26.76$, $p < 0.001$), and between trial types as a function of sector ($F_{3,141} = 28.03$, $p < 0.001$). The post hoc comparison of firing rates between the two trial types at each sector, taking into account the covariates, revealed that the cell's firing rate differed significantly in sectors 2 ($F_{1,33} = 27.30$, $p < 0.001$), 3 ($F_{1,33} = 39.77$, $p < 0.001$), and 4 ($F_{1,33} = 10.45$, $p < 0.01$) but not in sector 1 ($F_{1,33} = 0.003$, $p > 0.95$). This is shown in the right panel of Figure 3A, which plots the means adjusted to subtract the variance in the firing rates contributed by the covariates.

Figure 3B illustrates a cell that fired robustly as the

rat traversed the early portion of the stem on right-turn trials but hardly fired on left-turn trials. Firing rates differed significantly between the two trial types ($F_{1,116} = 38.35$, $p < 0.001$), among the stem sectors ($F_{3,116} = 10.78$, $p < 0.001$), and between trial types as a function of sector ($F_{3,116} = 18.77$, $p < 0.001$). When the covariates were included in the analyses, these significant differences were maintained, although the F values for the main effects were substantially reduced (trial type $F_{1,113} = 6.59$, $p < 0.05$; stem sector $F_{3,113} = 5.28$, $p < 0.01$; trial type \times sector interaction $F_{3,113} = 17.60$, $p < 0.001$). Post hoc analyses showed that the significant difference in firing rate for this cell was restricted to sector 2 ($F_{1,26} = 18.87$, $p < 0.001$) when the covariates were taken into account.

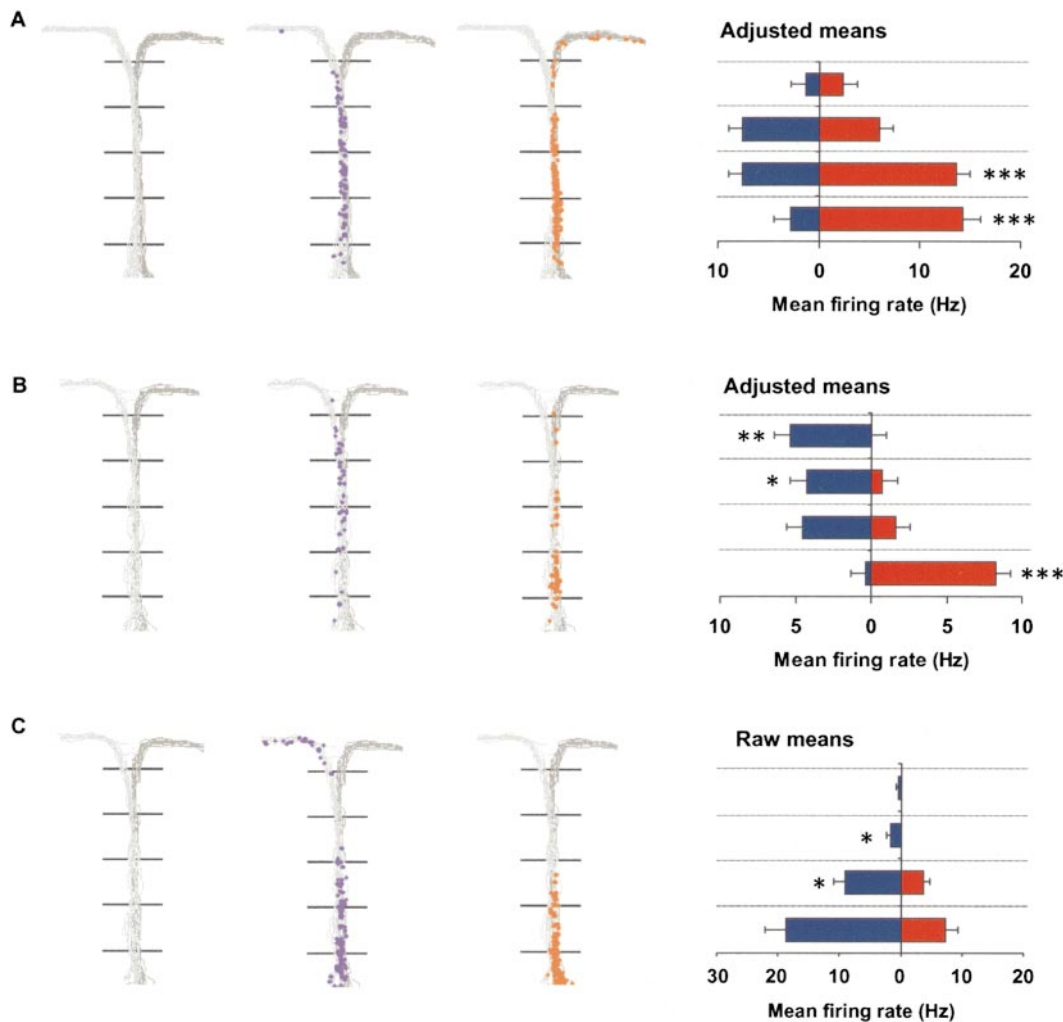


Figure 4. Examples of Hippocampal Cells that Show Different Patterns of Activity as the Rat Is Traversing the Central Stem on Left-Turn and Right-Turn Trials

See Figure 3 legend for general information.

(A) A cell that fired at a higher rate as the rat traversed early sectors of the stem on right-turn trials but also fired substantially associated with the same locations on left-turn trials.

(B) A cell that fired at a higher rate as the rat traversed the first sector on right-turn trials and at a higher rate as the rat traversed the later sectors of the stem on left-turn trials.

(C) A cell that fired substantially as the rat initiated its traversal of the stem on both trial types but fired at a significantly higher rate on left-turn trials.

** $p < 0.01$, *** $p < 0.001$.

The cell depicted in Figure 3C also fired almost exclusively on right-turn trials, with its highest firing rates at the top of the central stem. Firing rates differed significantly between the two trial types ($F_{1,159} = 140.73$, $p < 0.001$), among the stem sectors ($F_{3,159} = 58.45$, $p < 0.001$), and between trial types as a function of sector ($F_{3,159} = 48.02$, $p < 0.001$). A similar pattern was maintained when the covariates were included in the analyses (trial type $F_{1,156} = 63.66$, $p < 0.001$; stem sector $F_{3,156} = 23.82$, $p < 0.001$; trial type \times sector interaction $F_{3,156} = 26.00$, $p < 0.001$). Post hoc tests taking the covariates into account revealed that the firing rate of this cell differed significantly in sectors 3 ($F_{1,37} = 30.62$, $p < 0.001$) and 4 ($F_{1,36} = 13.83$, $p < 0.001$) but not in sectors 1 and 2, where there was little or no activity.

Cells that Fired on Both Left-Turn and Right-Turn Trials, but at Different Rates, or in Different Locations on the Central Stem

Figure 4A illustrates a cell that showed substantial firing when the animal was performing both types of trials, but fired at a significantly higher rate when the rat traversed the stem on one trial type. Figure 4a (left) shows that the animal's paths on the two trial types overlapped, and the middle two images show that the cell was active on both trial types. However, the analyses of this cell revealed that the firing rate differed significantly between the two trial types ($F_{1,168} = 41.95$, $p < 0.001$), among sectors ($F_{3,168} = 22.39$, $p < 0.001$), and between trial types as a function of sector ($F_{3,168} = 17.73$, $p < 0.001$). When the influence of running speed, heading,

and lateral position were considered, the cell's firing rate also differed significantly between the two trial types ($F_{1,165} = 6.80, p < 0.01$), among sectors ($F_{3,165} = 3.42, p < 0.05$), and between trial types as a function of sector ($F_{3,165} = 12.13, p < 0.001$). Post hoc tests on the firing rates in each sector taking the covariates into account revealed significant differences in firing rate between left-turn and right-turn trials associated with sectors 1 ($F_{1,39} = 14.94, p < 0.001$) and 2 ($F_{1,39} = 8.19, p < 0.01$) but not 3 ($F_{1,39} = 0.56, p > 0.46$) and 4 ($F_{1,39} = 0.15, p > 0.70$). Thus, as the rat traversed the early parts of the central stem, the cell fired at a higher rate on right-turn trials than on left-turn trials.

The cell depicted in Figure 4B also fired on the central stem during both types of trial, but the cell fired maximally when the rat was at different locations on the stem during left-turn and right-turn trials. The cell fired toward the top of the stem on left-turn trials, with very little activity at the base of the stem. In contrast, on right-turn trials, the cell was preferentially active nearer the base of the stem. Figure 4B (left) illustrates that the animal's paths on left-turn and right-turn trials overlapped in both regions in which the cell fired. Analyses of this cell revealed that the firing rate did not differ significantly between the two trial types ($F_{1,108} = 0.11, p > 0.73$), confirming that the overall firing rate across the central stem was equivalent on left-turn and right-turn trials. However, the firing rate differed significantly among sectors ($F_{3,108} = 2.72, p < 0.05$), and between trial types as a function of sector ($F_{3,108} = 15.52, p < 0.001$). When the influence of running speed, heading, and lateral position were taken into account, the firing rate did not differ significantly between the two trial types ($F_{1,105} = 0.30, p > 0.58$), or among the four stem sectors ($F_{3,105} = 2.14, p > 0.09$). However, it continued to differ significantly between trial types as a function of sector ($F_{3,105} = 13.76, p < 0.001$). Post hoc analyses including these variables as covariates showed that the cell's firing rate differed significantly between trial types associated with sectors 1 ($F_{1,24} = 30.66, p < 0.001$), 3 ($F_{1,24} = 4.40, p < 0.05$), and 4 ($F_{1,24} = 13.02, p < 0.01$) but not with sector 2 ($F_{1,24} = 3.54, p > 0.07$).

Figure 4C illustrates a cell recorded from the same rat, during the same session as that depicted in Figure 4B. This cell fired robustly when the rat was at the base of the central stem on both left-turn and right-turn trials. However, the analyses revealed that the cell fired at significantly different rates during the two types of trial ($F_{1,108} = 6.52, p < 0.05$). As expected, there were significant differences in firing rate among the stem sectors ($F_{3,108} = 26.35, p < 0.001$), but the firing rate did not differ significantly between trial types as a function of sector ($F_{3,108} = 1.11, p > 0.349$). The difference in firing rates between trial types was accentuated when running speed, heading, and lateral position were included as covariates, ($F_{1,105} = 34.81, p < 0.001$). Again, the firing rate differed significantly among the stem sectors ($F_{3,105} = 19.25, p < 0.001$), but not between trial types as a function of sector ($F_{3,105} = 1.59, p > 0.19$). In order to provide the most conservative estimate of the degree to which firing rate may have differed between the trial types for this cell, and for other cases where the F ratio was lower when the covariates were not considered, the post hoc analyses were performed without including the covariates. These post hoc analyses showed differences in firing rate between trial types in sectors 2 ($F_{1,27} = 5.29, p < 0.05$) and 3 ($F_{1,27} = 5.56, p < 0.05$) but not in sectors

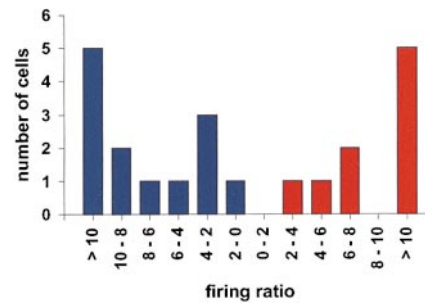


Figure 5. Frequency Distribution of Cells that Fired Preferentially Associated with Left-Turn or Right-Turn Trials

The magnitude of selectivity for cells preferring left-turn (blue) or right-turn (red) trials is expressed as the ratio of firing rates associated with the sector where the firing rate was greatest.

1 and 4. To reflect the analyses used for this cell, the mean firing rates for each sector on left- and right-turn trials depicted in the bar graph in the right panel of Figure 4C are not adjusted to subtract the contribution of the covariates.

Cells Whose Differential Activity Could Not Be Related to Trial Type-Specific Information Independent of Running Speed, Heading, and Lateral Position

As indicated above, approximately one-third (9/31) of the cells that fired differentially on the stem of the T maze no longer showed differences when the animals' running speed, heading direction, or lateral position on the stem were included as covariates in the ANOVA. These results indicate that for a subset of the cells, differences in firing rate may have been attributable to these variables that reflect the animal's behavior within the place field.

Cells that Fired Similarly on Both Trial Types

Surprisingly, only 2/31 cells (each from a different animal) showed no differences in firing on the stem of the T maze between right-turn and left-turn trials. For both of these cells, the firing field was located at the base of the stem, with the center of the firing field below the first sector.

Distribution of Selectivities for Left-Turn and Right-Turn Trials

For each of the 22 cells that fired differentially when the rat was on the central stem, we calculated the ratio of the firing rates on right-turn trials versus left-turn trials in the sector for which that cell had the maximum difference in firing rates. As shown in Figure 5, the distribution of cells preferring left-turn and right-turn trials is approximately even. Notably, the selectivity for trial type was quite robust, such that nearly half of the cells (10/22) had a firing ratio of over 10:1 for the preferred trial type, and almost all of the cells (21/22) had firing ratios of at least 2:1.

Discussion

As rats performed a continuous spatial alternation task, the majority of hippocampal cells fired differentially on left-turn and right-turn trials, even during portions of the

trials when the animal's overt behavior and paths were identical. Some of these cells fired robustly on one type of trial and hardly fired on the other trial type as rats traversed the central stem of the maze that was common to all trials. Others fired at different rates or at different locations on the central stem associated with left-turn and right-turn trials. For most of the cells that differentiated between left-turn and right-turn trials (22/31), the differences in firing rate could not be explained by variations in behavior known to affect place cell activity, including running speed and heading, and were not attributable to small differences in the rats' lateral position on the stem, suggesting that they encode information specific to one kind of trial episode. For the remaining cells that differentiated between left-turn and right-turn trials (9/31), differences in firing rate associated with the type of trial were attributable to some combination of the animal's speed, direction of movement, and location on the maze arm. Only a small minority of hippocampal cells (2/33) fired similarly during both trial types. These cells may have encoded the animal's location, or its location in combination with the direction of movement, running behavior, or other aspects of the task common to both trial types.

In interpreting the present results, it is important to consider the possibility that at least some of our recordings involved multicell clusters rather than single cells. Specifically, would a failure to isolate single neurons have led to false conclusions about the functional properties of the units? For those cells that clearly distinguish the two trial types (e.g., the cases shown in Figure 3), if two (or more) cells were included in a cluster then it must be that each of the cells distinguished the trial types. Similarly, for those cells that fire at different locations on the stem during the two trial types (e.g., Figure 4B), to the extent that these data really are from multiple cells then each is fully selective to one trial type. In cases where the cell appears to fire at different rates on the two trial types (e.g., Figures 4A and 4C), to the extent that multiple cells are confused, then it is possible that some cells have the same firing pattern on the two trial types, while others are selective. The one possible major interpretive error regards the cells that appear to fire with the same pattern on both trial types—if the analysis confused multiple cells with overlapping fields, it is possible that each cell actually fires on only one type of trial. Combining these possibilities, to the extent that we have failed to isolate single neurons from one another, the consequence is that we may have been too conservative in our counting of cells that distinguish the two trial types.

Another potential limitation associated with the relatively small action potential waveforms recorded in many of our cells comes from the observation that the amplitude of hippocampal neuronal spikes can vary systematically. Quirk and Wilson (1999) reported that some hippocampal cells generate different amplitude spikes when rats traverse different portions of a place field. If we were recording from a cell for which smaller amplitude spikes were buried in the background noise, and there was a systematic difference in waveform amplitudes associated with left-turn and right-turn trials, then it is possible that spikes would be preferentially detected on one type of trial. In this scenario, we might be overestimating the magnitude of trial type selectivity in firing rate, or the cell would be better characterized as selective in its waveform rather than in its firing rate. However,

the opposite bias associated with the varying spike amplitudes is a more likely scenario. Quirk and Wilson (1999) described firing rate as the major factor governing systematic differences in spike amplitude, such that the magnitude of the waveform tends to decrease when the cell is firing at higher rates. This factor would not differentially bias the spike counts on different trial types for cells that actually fire at the same rate on both trial types. But, for cells that fire at a higher rate on one trial type, we might differentially miss spikes that fall into the noise, leading to an underestimation of the magnitude of the firing rate differences reported here.

The present findings are consistent with many observations of location-specific activity of hippocampal neurons (O'Keefe, 1976; Muller et al., 1987; Muller, 1996). At the same time, these results add to a growing body of evidence indicating that hippocampal cells encode more than purely spatial information (Hampson et al., 1999; Wiebe and Staubli, 1999; Wood et al., 1999). In particular, consistent with several recent studies, the place-related activity of hippocampal neurons observed here was strongly influenced by the "context" of the ongoing task (e.g., Wiener et al., 1989; Markus et al., 1995; Hampson et al., 1999; reviewed by Eichenbaum et al., 1999). Moreover, the present experiment demonstrates context-specific firing that cannot be explained by readily observable variations in the animal's overt behavior or location.

The observed differences in firing rate on the central stem during the two trial types may reflect the memory demands of the task that the animals were performing. The T maze alternation task involves the animal remembering where it has been, and knowing which turn it should make at the end of the stem in order to reach the next reward site. It has been shown that the hippocampus is required to solve spatial alternation tasks of this kind (Olton, 1986). Indeed, several studies have reported that rats with hippocampal damage perform well in spatial "reference" memory tasks that require learning a constant path and location, but do poorly even in using the same spatial cues when performance is based on remembering a preceding episode (Jarrard, 1986; Olton, 1986). Thus, representations that include trial-specific information about recent events and places, as well as plans for succeeding events and places, would clearly be useful in the context of performing this task. Consistent with this notion, Frank et al. (2000) recently reported that the activity of cells in the hippocampus and entorhinal cortex is influenced both by recent past and immediate future locations and reflects similar segments of different trajectories. Combined with the present results, these observations suggest that hippocampal network activity reflects a fundamental coding of the animal's position and behavior within a sequence of repeated events and places. In the present study, we could not determine whether the differential activity of individual cells was more closely related to where the animal had just come from or where it was just about to go, because the animals seldom made errors that would have allowed us to dissociate past and future locations.

The present observation that hippocampal cells encode more than the animal's place is also consistent with the common finding that location-specific activity of hippocampal cells is highly dependent on the direction of movement, and on the animal's distance from important landmarks, when rats perform tasks in which

their behavior involves approaching specific targets in the environment (Wiener et al., 1989; Muller et al., 1994; Gothard et al., 1996a, 1996b). It has previously been suggested that the apparent directionality and shifting of place fields with important targets in space are due to the existence of multiple spatial maps that employ different "reference frames" (McNaughton et al., 1996; Touretsky and Redish, 1996). Applied to the current findings, this view would suggest that the animal alternates between a "left-turn reference frame" and a "right-turn reference frame," consistent with a key role of trial-specific information processing within a dynamic organization of spatial representations.

Another interpretation of the current results is that, because the maze used here involved a continuous "figure 8"-like pathway, each consecutive pair of left- and right-turn trials are represented as a single extended journey that begins and ends at a unique locus, e.g. the left reward site. In this view, individual hippocampal neurons that encode a specific point or distance traveled along this journey would thus fire on one pass down the central stem but not on the alternate pass. This account of location-related activity differs from the conventional view of hippocampal spatial firing as governed by configurations of external stimuli, as the external stimuli experienced on the central stem during left- and right-turn trials are equivalent. However, it is consistent with the observation that place cells can code distance from a moveable starting box on a linear track (Gothard et al., 1996b). This view accommodates the notion that hippocampal cell activity can reflect the integration of self-motion information (McNaughton et al., 1996). However, even under such a path integration scheme, it is important to note that the integration "resets" each time the rat reaches the unique starting point and repeats on each journey. Thus, the representation parses the continuous training session into a set of repetitive trials.

It is interesting that so many of the cells that fired in the central stem differentiated between the two trial types. In fact, only 2/33 cells fired similarly on both trial types. It is possible that this pattern reflects the fact that the animals had extensive experience with the alternation task and performed it extremely accurately. We might predict that a different pattern would be observed if cells were recorded as animals were learning the spatial alternation task, such that initially many cells would fire similarly when the rat is on the central stem during left-turn and right-turn trials. This observation would parallel previous reports that, when animals are initially exposed to a new environment that is similar to a familiar one, the hippocampal representations are also similar, but after repeated experience the representations diverge (Bostock et al., 1991; Tanila et al., 1997). Unlike previous protocols, if such changes were observed in the present paradigm, they would be attributable not to differences in the environmental cues but to cognitive processes associated with distinguishing the two types of episodes as relevant to solving the task.

Tulving (1983) defined episodic memory as the record of unique personal experiences. The sets of left-turn and right-turn trials examined in the present study are not unique episodes but rather involve repetitions of two types of trial episodes. Thus, the present findings can suggest only that hippocampal representations capture some of the elements that would be necessary for encoding unique episodes. Specifically, the present observations indicate that the hippocampus constructs

distinct representations for behaviors and locations that are differentiated mainly by what occurred earlier and what will occur next within the context of different kinds of repetitive trials. These characteristics are consistent with a role for the hippocampus in representing sequences of events that are common to particular types of memory episodes (Levy, 1996; Wallenstein et al., 1998; Eichenbaum et al., 1999; Lisman, 1999).

Experimental Procedures

Subjects

The subjects were four male Long-Evans rats weighing between 300-350 g at the time of electrode implantation. The rats were allowed ad libitum access to food for the duration of the experiment, but were restricted to 30 min of water per day on the day before each training, testing, and recording session. If no testing or recording was to take place the following day, water was available ad libitum for 24 hr. The rats were housed singly and kept on a 12:12 light:dark cycle. Recording and testing were carried out during the light phase of the cycle, and rats were tested approximately 5 days per week.

Apparatus

The modified T maze apparatus is depicted in Figure 1A. It was constructed of wooden runways 9.4 cm wide with wooden walls 2.0 cm high. Both walls and floor were painted black. The central runway that comprised the stem of the T was 104 cm long, and additional wall strips were added to this portion of the maze to narrow its width to 8.3 cm. A crosspiece 94 cm long formed the choice arms. The distal ends of the choice arms were connected to the base of the stem by additional runways. Small plexiglas wells (6.35 × 6.35 cm square plaques with circular depressions with a radius of 1 cm and maximum depth of 0.5 cm) were recessed into the floor at the end of each choice arm at the points marked on Figure 1a. Water could be delivered to the wells via a cannula (18 gauge) hooked up to a reservoir via tubing and under the control of solenoid valves activated by hand-operated switches. The T maze was elevated 80 cm from the ground on concrete blocks. It was surrounded by black curtains on three sides (the fourth side was partially open to the remainder of the room), and several large, high-contrast, distinctive visual cues were attached to the curtains. The platform and cues remained at the same location relative to each other and to the remainder of the environment throughout the experiment.

Behavioral Training

Before implantation of the recording electrodes, the rats were shaped in multiple stages to perform a continuous spatial alternation task on the modified T maze (similar to Jung et al., 1998). In the first stage, each rat was placed at the base of the central stem of the apparatus, facing the choice arms. Clear plexiglas barriers were placed such that the rat was forced to traverse the central stem and enter one of the choice arms. After it entered one of the arms, a small drop of water was delivered to the well in that arm. The rat was prevented from retracing its route on the choice arm, and so then traversed the connecting arm back to the base of the T. At this point a barrier blocked the entrance to the opposite connecting arm, forcing the animal to traverse the stem of the T again. Another barrier blocked the entrance to the previously entered arm, so the rat was then forced to enter the other choice arm, and water was delivered to the well in this arm. This procedure was repeated, using barriers to direct the animal's traversals over the stem and to alternate entries into the choice arms, until the animals ran the pattern consistently. In the second stage, the use of barriers at the choice point was phased out; each time the rat reached the end of the stem it could enter either arm, but it was rewarded only for alternating arm entries and was not allowed to retrace its steps. In the third stage, the barrier forcing the rat into the stem after returning along the connecting arms was phased out. The animals continued to run in a "figure 8"-like pattern despite no barriers, but they were prevented from retracing their steps at any point.

During each subsequent training and testing session, the rats

were placed on the central stem with no barriers and allowed to run 30–50 continuous trials. The experimenter remained outside the curtained enclosure throughout the session. The animal's behavior was observed via a video monitor connected to the tracking system (see below). On each trial when the rat made a correct (alternating) arm choice, a drop of water was delivered to the well in that arm after the arm entry. On trials when the animal made the incorrect choice, no reward was provided. Furthermore, no reward was provided even if the rat retraced its steps back to the choice point and entered the other choice arm. Instead, following mistakes the rat was required to continue along the connecting arm, reenter the stem, and make the correct choice on the following trial.

Electrodes and Surgery

Stereotrodes were constructed from two 25 or 30 μm formvar-coated nichrome wires (California Fine Wire, Grover City, CA) twisted together in pairs and strengthened with super glue. Five stereotrodes were threaded through a 27-gauge stainless steel cannula (~ 20 mm), and each wire was attached to one pin of a modified 10-pin Augat connector (Newark Electronics, Gaffney, SC). The Augat connector was embedded in an acrylic base and formed part of a microdrive assembly described in detail elsewhere (Kubie, 1984). Three screws attached to the acrylic base allowed the electrode array to be advanced in the dorsoventral plane (Kubie, 1984).

Before implantation, each of the five stereotrodes was cut straight across so that ~ 1.5 mm extended from the tip of the cannula. The electrode array was sterilized with betadine, and the exposed stereotrodes were embedded in a small drop of carbowax, as described previously (Muller et al., 1987). Rats were anesthetized using halothane delivered in a 30:70 oxygen:nitrous oxide mixture and placed in a stereotaxic instrument (Kopf, Tujunga, CA). The skull was exposed, and bregma and lambda were made level. A small hole was drilled over the hippocampus on one side for the placement of the electrode array, and five additional holes were drilled for the placement of skull screws used for electrical grounds and for securing the head stage to the skull. The electrode array was implanted just above the dorsal hippocampus at 3.5 mm posterior to bregma, 2.5 mm lateral to bregma, and 1–1.5 mm below the surface of the brain. The cannula was coated with sterile petroleum jelly. Grip cement (Henry Schein, Melville, NY) was used to secure the bases of the three drive screws of the electrode assembly to the skull, and to cover the exposed skull.

Screening, Testing, and Data Acquisition

Following a 7-day recovery period, daily screening for unit activity was conducted while the rats were in an opaque rectangular box (61.6 cm [long] \times 43.8 cm [wide] \times 40.0 cm [high]) placed on top of the T maze apparatus. If pyramidal cell activity was identified (see below), the animal was placed on the T maze, the screening box was removed, and unit activity was recorded while the animal performed the spatial alternation task as described above. If no pyramidal cell activity was identified during screening, the rats were allowed to run a shortened session consisting of 6–12 trials of the continuous alternation task, and units were not recorded. In both cases, the electrode was advanced 40–80 μm after the session and allowed to settle overnight (at least 16 hr) before the next session.

Neural activity was first passed through a multichannel unity gain source follower field effect transistor (JFET) in the headstage. It was then passed through an overhead commutator (Biela Development), differentially amplified (gain 10,000, Neuralynx digital amplifiers), band-pass filtered (600–6000 Hz), and digitized (28 kHz, Data Translation DT2821) using Enhanced Discovery software (Datawave Technologies) on a Pentium-based personal computer. For each recording session, one of the two wires of the stereotrode with the least neural activity served as the indifferent electrode, and neural activity was recorded on the remaining four stereotrodes.

Preliminary unit isolation was achieved online using the Spike Sort module of the Enhanced Discovery software. Final unit isolation was performed offline, initially using Autocut software (Datawave Technologies), and then refined further by manipulation of the cluster boundaries (see examples in Figure 2). Each waveform was characterized by a cluster of points in eight dimensions (peak and valley magnitudes of the action potential on each stereotrode wire and

the latencies to the peak and valley of the action potential on each wire), and the recordings were considered stable if the cluster remained within the same fixed boundaries throughout the recording session (McNaughton et al., 1983). Autocorrelograms were generated (Autocut) for each cluster to ensure that no spikes occurred within 1.5 ms of any other spike in the same cluster, thus increasing the likelihood that each cluster included spikes from a single neuron. When spikes did occur within this time window, cluster boundaries were altered to exclude them.

The location of the rat was recorded using a video camera tracking system (Datawave Technologies) that tracked an incandescent bulb mounted on the head stage. Location was digitized in the form of x and y coordinate pairs at 60 Hz by an A/D converter and then stored.

Data Analysis

Only cells that exhibited clear place fields on the center stem of the T maze, and that had a spike duration of at least 300 ms (from peak to valley) and a mean firing rate (total spikes divided by recording session time) of less than 2.5 Hz were analyzed. Cells with these characteristics were considered to fit the criteria for being hippocampal pyramidal neurons (Ranck, 1973). Cells that reappeared across daily sessions (that is, cells that appeared on the same electrodes, possessed similar waveforms, and had a similar place field) were counted only once.

The analysis of pyramidal neuron activity proceeded in the following stages.

Stage 1: Location-Related Firing on the Modified T Maze

For each cell, we first determined the spatial distribution of firing rates throughout the entire recording session. This was achieved using software (Field View Analysis, Matthew Shapiro, Montreal) that divided the maze into 1.72×1.72 cm pixels and calculated the firing rate for each pixel as the total number of spikes divided by the total time spent in that pixel across the entire session. Firing rates were calculated only for periods when the rat was moving at least 2 cm/s. Only cells with robust place fields on the apparatus (with an area of at least 8 adjacent pixels each having a firing rate at least three times the mean rate [total number of spikes/total time spent moving at >2 cm/s on the maze]) were considered for further analysis.

Stage 2: Separation and Statistical Comparison of Firing Rates for Cells with Place Fields on the Central Stem for Left-Turn and Right-Turn Trials

In the next stage of analysis, the activity of cells with robust place fields on the central stem of the T maze was separated into correct left-turn trials and correct right-turn trials. Incorrect trials were excluded from these analyses. Because this separation was done after the cell clusters had been cut in the initial file, the two new files contained waveforms that were defined using identical cluster boundaries.

To analyze the activity of cells with place fields in the central stem of the T maze, the central stem was divided into four sectors of equal length (13.5 cm). The four sectors did not include 25 cm at each end of the central stem, as in this area the animals are typically moving in different directions on right-turn and left-turn trials. The following parameters were calculated for each traversal through each of the four sectors (see Figure 1B): (1) *firing rate* was calculated as the number of spikes in the sector divided by the amount of time in the sector; (2) *speed* was measured as the time to traverse the constant length sector; only sectors with a speed of at least 2 cm/s were included; (3) *heading* was calculated as the vector (in radians) from the x-y coordinates of the animal's head as it entered and exited the sector; and (4) *lateral position* was represented by the mean of the x coordinates of the rat within the sector. The camera resolution was such that the x coordinate incremented approximately every 0.48 cm. The central stem was aligned such that it was perpendicular to the x axis determined by the video tracking coordinate frame.

For each cell, a two-way ANOVA was run with trial type (correct left-turn and correct right-turn) and sector (1, 2, 3, and 4) as independent (fixed) variables and firing rate as the dependent measure (SPSS, Chapel Hill, NC). Any cell whose firing rate showed a significant main effect of trial type, or a trial type \times sector interaction,

was identified as potentially differentiating between right-turn and left-turn trials. Any cell with a significant main effect of sector, but no significant main effect of trial type or a trial type \times sector interaction was identified as a conventional place cell, i.e., a location-specific cell that did not differentiate between right-turn and left-turn trials.

For the cells identified as potentially differentiating between trial types, a second analysis was performed to determine whether variations in speed, heading, or lateral position might account for the differences in firing rate between trial types. This was achieved using a two-way ANCOVA for each sector, with trial type and sector as the independent (fixed) variables, firing rate as the dependent measure, and with speed, heading, and lateral position as covariates (SPSS, Chapel Hill, NC). To the extent that these three variables, either alone or in combination, account for the differences in firing rate, including them as covariates in the model decreases the F ratio associated with the trial type. Thus, any cell that continued to show a significant difference in firing rate between right-turn and left-turn trials, or a significant trial type \times sector interaction when the covariates were included in the ANCOVA model, was deemed to reliably distinguish between the two trial types independent of the other variables. Post hoc analyses were run independently for each sector on any cells that distinguished between trial types following the ANCOVA described above. The post hoc tests consisted of an additional ANCOVA for each sector with trial type as the independent variable and firing rate as the dependent variable, with speed, heading, and lateral position included as covariates.

Histology

After completion of recordings, each animal was deeply anesthetized with an overdose (100 mg/kg) of sodium pentobarbital. A 15 mA current was passed through one wire on each stereotrode. The animals were then perfused transcardially with 0.9% phosphate buffered saline, followed by a solution of 10% buffered formalin and 4% potassium ferrocyanide. A Prussian blue reaction resulted, marking the location of the tip of the electrodes through which current had been passed. The brains were removed, stored in formalin for at least 24 hr, sectioned coronally at 50 μ m on a freezing microtome, and then mounted and stained with thionin.

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References

Bostock, E., Muller, R.U., and Kubie, J.L. (1991). Experience-dependent modifications of hippocampal place cell firing. *Hippocampus* 1, 193–206.

Czurko, A., Hirase, H., Csicsvari, J., and Buzsáki, G. (1999). Sustained activation of hippocampal pyramidal cells by “space clamping” in a running wheel. *Eur. J. Neurosci.* 11, 344–352.

Deadwyler, S.A., Bunn, T., and Hampson, R.E. (1996). Hippocampal ensemble activity during spatial delayed-nonmatch-to-sample performance in rats. *J. Neurosci.* 16, 354–372.

Eichenbaum, H., Dudchenko, P., Wood, E.R., Shapiro, M., and Tanila, H. (1999). The hippocampus, place cells, and memory: is it spatial memory or a memory space? *Neuron* 23, 209–226.

Frank, L., Brown, E.N., and Wilson, M. (2000). Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* 27, 169–178.

Gabrieli, J.D.E., Brewer, J.B., Desmond, J.E., and Glover, G.H. (1997). Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science* 276, 264–266.

Gothard, K.M., Skaggs, W.E., Moore, K.M., and McNaughton, B.L. (1996a). Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. *J. Neurosci.* 16, 823–835.

Gothard, K.M., Skaggs, W.E., and McNaughton, B.L. (1996b). Dynamics of mismatch correction in the hippocampal ensemble code

for space: interaction between path integration and environmental cues. *J. Neurosci.* 16, 8027–8040.

Hampson, R.E., Byrd, D.R., Konstantopoulos, J.K., Bunn, T., and Deadwyler, S.A. (1996). Hippocampal place fields: relationship between degree of field overlap and cross-correlations within ensembles of hippocampal neurons. *Hippocampus* 6, 281–293.

Hampson, R.E., Simeral, J.D., and Deadwyler, A. (1999). Distribution of spatial and nonspatial information in dorsal hippocampus. *Nature* 402, 610–614.

Henke, K., Buck, A., Weber, B., and Wieser, H.G. (1997). Human hippocampus establishes associations in memory. *Hippocampus* 7, 249–256.

Jarrard, L. (1986). Selective hippocampal lesions and behavior: Implications for current research and theorizing. In *The Hippocampus, Volume 4*, R.L. Isaacson and K.H. Pribram, eds. (New York: Plenum Press), pp. 93–126.

Jung, M.W., Qin, Y., McNaughton, B.L., and Barnes, C.A. (1998). Firing characteristics of deep layer neurons in prefrontal cortex in rats performing spatial working memory tasks. *Cereb. Cortex* 8, 437–450.

Kubie, J.L. (1984). A driveable bundle of microwires for collecting single-unit data from freely moving rats. *Physiol. Behav.* 32, 115–118.

Levy, W.B. (1996). A sequence predicting CA3 is a flexible associator that learns and uses context to solve hippocampal-like tasks. *Hippocampus* 6, 579–590.

Lisman, J.E. (1999). Relating hippocampal circuitry to function: recall of memory sequences by reciprocal dentate-CA3 interactions. *Neuron* 22, 233–242.

Markus, E.J., Qin, Y.-L., Leonard, B., Skaggs, W.E., McNaughton, B.L., and Barnes, C.A. (1995). Interactions between location and task affect the spatial and directional firing of hippocampal neurons. *J. Neurosci.* 15, 7079–7094.

McNaughton, B.L., Barnes, C.A., and O’Keefe, J. (1983). The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp. Brain Res.* 52, 41–49.

McNaughton, B.L., Barnes, C.A., Gerrard, J.L., Gothard, K., Jung, M.W., Knierim, J.J., Kudrimoti, H., Qin, Y., Skaggs, W.E., Suster, M., and Weaver, K.L. (1996). Deciphering the hippocampal polyglot: the hippocampus as a path integration system. *J. Exp. Biol.* 199, 173–185.

Muller, R.U. (1996). A quarter of a century of place cells. *Neuron* 17, 813–822.

Muller, R.U., Kubie, J.L., and Ranck, J.B., Jr. (1987). Spatial firing patterns of hippocampal complex-spike cells in a fixed environment. *J. Neurosci.* 7, 1935–1950.

Muller, R.U., Bostock, E., Taube, J.S., and Kubie, J.L. (1994). On the directional firing properties of hippocampal place cells. *J. Neurosci.* 14, 7235–7251.

O’Keefe, J.A. (1976). Place units in the hippocampus of the freely moving rat. *Exp. Neurol.* 51, 78–109.

Olton, D.S. (1986). Hippocampal function and memory for temporal context. In *The Hippocampus, Volume 4*, R.L. Isaacson and K.H. Pribram, eds. (New York: Plenum Press), pp. 281–298.

Quirk, M.C., and Wilson, M.A. (1999). Interaction between spike waveform classification and temporal sequence detection. *J. Neurosci. Methods* 94, 41–52.

Ranck, J.B., Jr. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. *Exp. Neurol.* 41, 461–555.

Steele, R.J., and Morris, R.G.M. (1999). Delay dependent impairment in matching-to-place task with chronic and intrahippocampal infusion of the NMDA-antagonist D-AP5. *Hippocampus* 9, 118–136.

Tanila, H., Sipila, P., Shapiro, M., and Eichenbaum, H. (1997). Brain aging: changes in the nature of information coding by the hippocampus. *J. Neurosci.* 17, 5155–5166.

Touretsky, D.S., and Redish, A.D. (1996). Theory of rodent navigation based on interacting representations of space. *Hippocampus* 6, 247–270.

Tulving, E. (1983). *Elements of Episodic Memory* (New York: Oxford University Press).

Tulving, E., Kapur, S., Craik, F.I.M., Moskovitch, M., and Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc. Natl. Acad. Sci. USA* 91, 2016–2020.

Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., and Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 277, 376–380.

Wallenstein, G.V., Eichenbaum, H., and Hasselmo, M.E. (1998). The hippocampus as an associator of discontiguous events. *Trends Neurosci.* 21, 315–365.

Wible, C.G., Findling, R.L., Shapiro, M., Lang, E.J., Crane, S., and Olton, D.S. (1986). Mnemonic correlates of unit activity in the hippocampus. *Brain Res.* 399, 97–110.

Wiebe, S.P., and Staubli, U.V. (1999). Dynamic filtering of recognition memory codes in the hippocampus. *J. Neurosci.* 19, 10562–10574.

Wiener, S.I., Paul, C.A., and Eichenbaum, H. (1989). Spatial and behavioral correlates of hippocampal neuronal activity. *J. Neurosci.* 9, 2737–2763.

Wood, E.R., Dudchenko, P.A., and Eichenbaum, H. (1999). The global record of memory in hippocampal neuronal activity. *Nature* 397, 613–616.