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Prospective and Retrospective Memory Coding in the Hippocampus

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Summary

The effect of memory on hippocampal neuronal activity was assessed as rats performed a spatial task that was impaired by fornix lesions. The influences of current location, recently entered places, and places about to be entered were compared. Three new findings emerged. (1) Current, retrospective, and prospective coding were common and recorded simultaneously in neural ensembles. (2) The origin of journeys influenced firing even when rats made detours, showing that recent memory could modulate neuronal activity more than spatial trajectory. (3) Diminished retrospective coding and, more markedly, reduced prospective coding in error trials suggested that the neuronal signal was important for task performance. The population of hippocampal neurons thus encoded information about the recent past, the present, and the imminent future, consistent with a neuronal mechanism for episodic memory.

Introduction

Human memory is sensitive to and organized by cognitive structure, exemplified verbally by narratives that contain linked series of events with a well-defined beginning, middle, and end (Tulving, 1972; Tulving and Markowitsch, 1998) and in overt actions by journeys typically undertaken to accomplish a particular purpose. Recollecting such experiences, people can "travel through time" by representing sequences in episodic memory (Tulving, 1972) and thereby anticipate the likely outcome of familiar situations. The hippocampus is crucial for the rapid acquisition and persistence of such memories (Vargha-Khadem et al., 1997). Nonverbal animals may possess a form of episodic memory (Morris, 2001), defined operationally in tasks that require knowing *what, when*, and *where* (Clayton et al., 2001; Clayton and Dickinson, 1998). In rats, damage to the hippocampus causes profound and enduring deficits in memory for places, social interactions, and odor sequences (reviewed in Eichenbaum et al., 1999). Each of these tasks requires rats to know either *what, when*, or *where*, and performance in tasks that require simultaneous integration of all three elements are especially sensitive to hippocampal damage (C. Ergorul and H.B. Eichenbaum, personal communication).

The neuronal code for episodic memory remains unclear, and the causal relationship between hippocampal neuronal activity and memory performance remains unknown, in part because relatively few experiments record neuronal activity in hippocampus-dependent tasks that explicitly vary memory demands while holding constant other aspects of behavior. Hippocampal neurons in behaving rodents have long been thought to encode "where" via *place fields*, local regions of an environment that selectively elicit high firing rates, regardless of whether or not the behavior requires hippocampus-dependent memory (O'Keefe and Dostrovsky, 1971; Muller et al., 1987; O'Keefe and Burgess, 1996). Place fields have been interpreted as evidence that the hippocampus represents a spatial map and guides navigation (O'Keefe and Nadel, 1978). Alternatively, hippocampal neurons may contribute to memory more broadly by rapidly encoding the cognitive, perceptual, and behavioral structure of experience (Eichenbaum et al., 1999). From this view, the hippocampal representation includes *what* and *when* in addition to *where* and encodes events within an episodic context.

Behavioral context has been reported to alter hippocampal neuronal responses, so that place field activity was modulated by either recent or impending behavior (Frank et al., 2000; Wood et al., 2000). The crucial mnemonic and behavioral variables that influence hippocampal activity, however, remain controversial (Lenck-Santini et al., 2001). Contextual modulation of place fields was found in continuous spatial alternation tasks in which rats were trained to move through a common spatial path on the way to different goal locations (Frank et al., 2000; Wood et al., 2000). Neither experiment verified that task performance required hippocampal function, and although spatial alternation tasks typically do, continuous alternation tasks can also be solved by alternate strategies that depend on other brain systems (e.g., Tonkiss et al., 1990). Neither experiment distinguished the influence of memory context from that of spatial *trajectory*, the particular sequence of entered locations. Finally, neither experiment used a paradigm that clearly marked the beginning and end of a journey, the fundamental elements in structuring an experience as an episode. In one study (Wood et al., 2000), the rat followed a "figure 8" trajectory, so that the influence of the recent past on neuronal firing (*retrospective coding*) could not be distinguished from a predictive signal (*prospective coding*). In the other study (Frank et al., 2000), retrospective and prospective coding were distinguished, but the same location served alternately as both the start and the end of every journey, rendering the cognitive significance of the location ambiguous and the meaning of correlated neuronal activity unclear.

The present experiment was designed to directly compare the influence of recent and impending events on hippocampal neuronal activity in a task that required a functional hippocampal system (Figure 1B). To dissociate memory demand from spatial location and movement trajectory, rats were trained to go from two opposite start arms to two opposite goal arms in a + maze (Figure 1A). In each trial, the rat was placed in a start arm and required to select a correct goal arm to obtain food; between trials it was kept on a waiting platform. The start arm was varied in pseudorandom order, and the goal arm was kept constant until the rat performed reliably, then the opposite goal arm was rewarded. The

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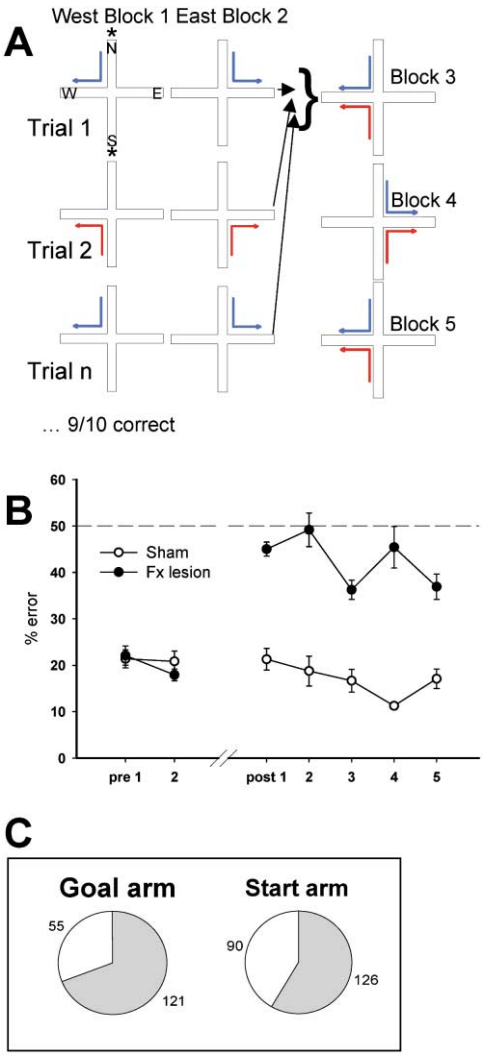

Figure 1. A Spatial Task that Required Memory for Temporal Context Was Impaired by Fornix Lesions and Revealed Prospective, Place, and Retrospective Coding in the Hippocampus

(A) In a discrete trial, spatial win-stay task with serial reversals, rats were placed at the end of a start arm (N or S) and were trained to find food at the end of a goal arm (E or W). The start arm varied in a pseudorandom sequence within each block of trials so that equivalent numbers of journeys began in each arm (arrows). Only one goal arm contained food during a block of trials (e.g., West Block 1). After a rat enter the correct goal arm in 9/10 consecutive trials, the reward contingency was reversed, and food was put into the other goal arm for the next block of trials (e.g., East Block 2). Placing the rat in front of the baited food cup in the new goal signaled the start of the new block. Rats performed the task for 40 to 60 trials each day, which entailed four to six blocks and three to five reversals.
(B) Fornix lesions impaired + maze performance. Rats were trained until they attained a criterion of four reversals in 60 trials for two consecutive days and were given either sham or fornix lesions. Sham lesions did not alter performance (open circles), whereas fornix lesions reduced performance to near chance (filled circles). The vertical axis shows the percent of incorrect arm entries (higher is worse performance); the horizontal axis shows days of testing.
(C) Proportion of journey-dependent (gray) and independent (white) fields in goal (left) and start (right) arms defined by place field analysis. "True" place fields as well as those showing either prospective or retrospective coding were common. Place fields in the goal arms were more likely to be journey dependent than those in the start arm [χ^2 (1) = 4.5, $p < 0.05$].

rat thus made one of four *journeys* in each trial: from north to east (NE), from north to west (NW), from south to east (SE), and from south to west (SW). Here we distinguish journeys from spatial trajectories. A *journey* entails traveling from a starting point to a goal and can be accomplished via different routes; a *trajectory* is one particular route or path of many that can be used to complete a journey. Thus, a rat could go directly from a start arm to the end of the goal arm in an L trajectory or first enter the unrewarded arm on the way to the same goal in an indirect trajectory. Entry with all four paws into the unrewarded arm defined an *error*, which the rat was allowed to correct.

The experimental design ensured that each time a rat traversed an arm of the maze, it was guided by identifiable and dissociable memory demands. In the start arms, memory for the trial block guided the prospective behavioral discrimination. In the goal arms, memory for the start arm provided additional retrospective information. A place field that varied in different journeys through the same arm was *journey dependent*, whereas a field that did not show such discriminative activity was *journey independent*. We operationally define journey-dependent activity in the start and goal arms as *prospective* and *retrospective coding*, respectively.

The experiment thereby directly investigated *current* (or place), *trajectory, retrospective*, and *prospective* coding. If the hippocampus encoded only the current location of the rat, then all place fields should be journey independent. If the hippocampus encoded only specific spatial trajectories (Frank et al., 2000), then journey-dependent activity should disappear when rats made detours between a start and a goal. If the hippocampus encoded only recent memory, then all place fields should depend solely on the recent history of the rat's experience and encode only *retrospective* information. Indeed, Frank et al. (2000) reported that 13/81 (16%) place fields in CA1 showed retrospective coding and only 3/83 (4%) showed prospective coding. A corresponding result in the present experiment would reveal journey-dependent fields in the goal but rarely in the start arms. Finally, if the hippocampus represents current location, recent history, and imminent behavior, then the population of hippocampal neurons active in either start or goal arm should include significant proportions of neurons that encode current, retrospective, and prospective information. Such was the case. Each journey included fields that were influenced by recent, present, and imminent events, providing a representation of both place and memory context. The hippocampus thereby provides a temporally extended representation of situations: event sequences that include information about the past, present, and future. Such a code dovetails with the requirements of a neuronal mechanism for episodic memory.

Results

Fornix Lesions Impaired + Maze Performance

To determine if the + maze task required the hippocampal system, a set of rats was trained, assigned to two groups with matched performance (Figure 1B), and

given either fornix lesions or sham surgery. After 1 week of recovery, the rats were tested, and then their brains were processed for histology. Lesion completeness was assessed by immunohistochemical visualization of cholinergic fibers in the hippocampus using an antibody to vesicular acetylcholine transporter (VAChT; Weihe et al., 1996; see the Supplemental Data at http://www.neuron.org/cgi/content/full/40/6/1227/DC1). The animals with sham lesions performed well after surgery, and their performance continued to improve. In contrast, although rats with complete fornix lesions remembered the task procedures and entered goal arms readily, their choice accuracy was severely impaired and remained near chance throughout testing (Figure 1B; ANOVA effect of lesion: $F_{1,6} = 73.7$, $p < 0.01$; effect of day: $F_{6,36} = 11.9$ $p < 0.01$; interaction of lesion and day: $F_{6,36} = 20.5$, $p < 0.01$). Thus, accurate performance in this task required a fully functional hippocampal system, even in highly trained animals.

Hippocampal Neurons Encoded Current Location Together with Retrospective and Prospective Information

The activity of hippocampal complex-spike (CS) neurons (Ranck, 1973) was recorded from five rats as they performed the + maze task (Figure 1). Each recording session included between 40 and 60 trials, three to five reversals, and approximately the same number of the four possible journeys (NE, NW, SE, SW). The rat's position, heading, and the action potentials of 15 to 55 well-isolated units (100–450 μV) were recorded simultaneously. Single units recorded from 12 tetrodes were discriminated offline by defining elliptical clusters of 8 to 32 waveform parameters. Histology confirmed that the electrodes traversed the CA1 layer.

Place Fields

Place fields were first identified in each recording session in its entirety. Place fields were observed throughout the maze, but the analysis excluded the choice point region and focused on the start and goal arms, where movement and spatial location were consistent across trials. If a cell had a place field on more than one arm, the analysis excluded the activity in the center point and treated the cell as having individual subfields on each relevant arm.

Qualitative Observations

Because the rats were well trained and the maze arms were narrow (64 mm), the trajectories in each arm usually included similar positions, headings, and running speeds. Observations during recording and inspection of stored journeys offline revealed that many neurons had true, journey-independent place fields (Figure 2A). Many other cells, however, fired in places during specific journeys, e.g., in the north arm only if the rat was about to go west or in the east arm only after the rat left the south (Figures 2B and 3). Other cells encoded more general aspects of journeys, e.g., firing in both the east and the west arms after leaving the south arm but not the north. The importance of journey rather than trajectory or spatial behavior was shown when cells continued to fire in goal arms selectively depending on the start point, even if the rat made a detour and used an alternate trajectory or made a frank error and entered the incorrect arm first (Figure 4). These observations were quantified using place field analysis and standard statistical methods.

To compare journeys, the entire recording session was divided into five *subfiles*, one for each journey type (NE, NW, SE, SW) and one for error trials. The *error trials* included frank behavioral errors (see above) and *alternative trajectories*, when the rat entered the "incorrect" arm before turning immediately and entering the goal arm. Each place field was then compared in the two types of journeys that included the arm with the field. If a place field was found in the east arm in the overall recording session, then the firing in that arm was compared in all NE and SE journeys. Similarly, a place field in the north start arm in the overall recording session was compared in all NE and NW journeys. If a place field was present in both corresponding journeys, then the place field was defined operationally to be journey independent; if the place field appeared in only one of the journeys, it was defined as journey dependent. The distribution of behavior along the length and width of each arm was quantified in an array of 10 to 12 grid units. Direction, running speed, and position (quantified as visits) were compared for all journeys using paired t tests, and data corresponding to journey pairs that differed significantly in any of these measures were eliminated from subsequent place field analyses.

Three hundred and seventy-eight CS units with distinct waveforms and well-defined place fields in the maze arms were assessed; 278 units had a single place field, on either the start (153) or the goal (125) arm. The other 100 cells had subfields on two or three arms; the latter could be considered "off cells" (Olton et al., 1978). Because the subfields belonging to the same cell behaved independently with regard to journey, each subfield was treated as a separate field. In total, 525 fields were analyzed, 240 in the start arm and 285 in the goal arm.

Many hippocampal cells were journey dependent and encoded significant prospective and retrospective information along with current location. Using a strict place field definition, journey-dependent fields were common on both the start (57%, 162/285 fields) and the goal arms (67%, 162/240 fields). Of the 378 cells recorded, 225 (59%) were journey dependent in at least one place field; of the 525 place fields, 324 (62%) were journey dependent. All fields recorded in journeys that differed in direction, running speed, or position were excluded (133 of the 525 identified fields). The remaining 392 fields nonetheless showed prospective or retrospective coding. Many fields in the start (58%, 126/216) and the goal (69%, 121/176) arms were journey dependent (Figure 1C). The distribution of journey-dependent fields revealed more common retrospective than prospective coding [χ^2 (1) = 4.5, $p < 0.05$].

The selected definition of place fields ensured that the activity of the units included in the analysis was reliable across the entire recording session. This strict definition likely increased the number of fields classified as journey dependent by eliminating fields with less robust activity in one type of journey. The place field definition was therefore relaxed so that fields that had appeared journey dependent were now classified as journey independent. Even with these criteria, 35% (75/216) of start arm fields and 56% (99/176) of goal arm

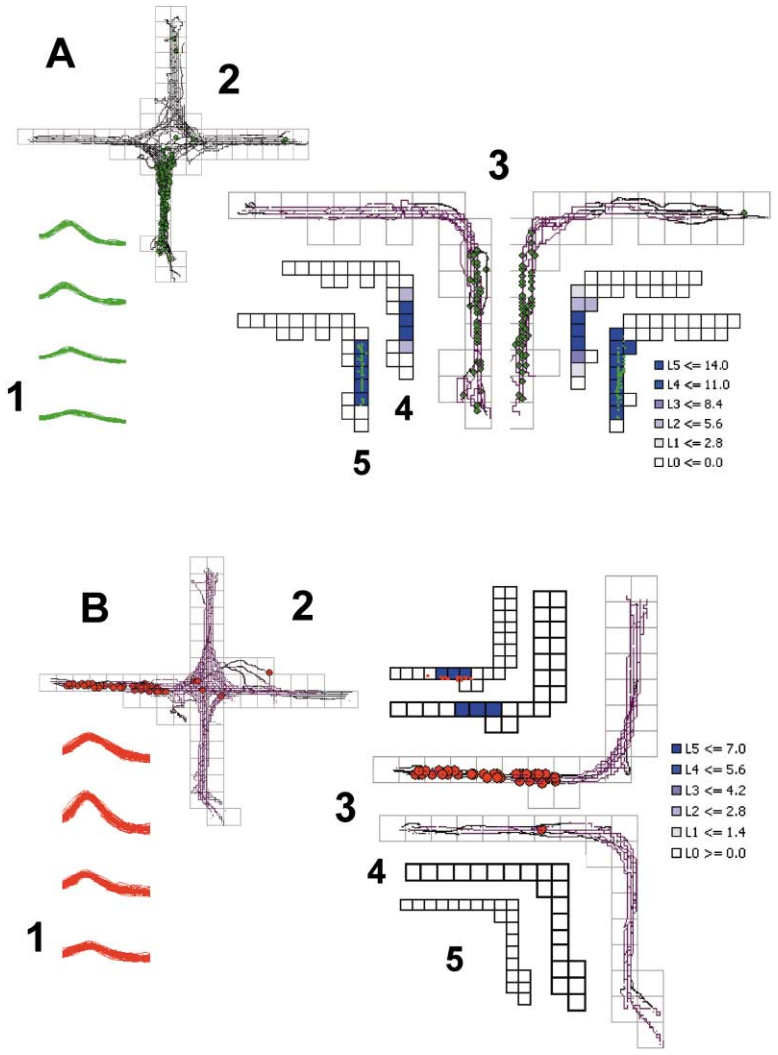

Figure 2. Journey-Independent and Journey-Dependent Place Fields

(A) A journey-independent "true" place field. The waveform (1, waveform max = 150 μV) and place firing plots are shown in all journeys (2) and in separate SE and SW journeys (3). Trajectories shown as lines have spikes overlaid as larger dots. Firing rate (4) and statistically verified subfield maps (5) for each journey type are adjacent. The legend shows spikes/s in the firing rate map (4). Spatial behavior and firing were consistent in both SE and SW journeys.

(B) A journey-dependent place field with retrospective coding. The cell (max = 130 μV) fired reliably in the west arm in NW but not SW journeys.

fields were classified as journey dependent. A complementary analysis tested the effect of journey on the spatial distribution of firing rates using correlations and t tests that were independent of place field definitions; 39% of start arm fields and 78% of goal arm fields differed significantly across journeys (see the Supplemental Data at http://www.neuron.org/cgi/content/full/40/6/1227/DC1). Thus, the significant influence of journey on place fields was revealed by qualitative observations and three quantitative analyses.

Journey-dependent neuronal activity differed between cells with overlapping place fields that were recorded simultaneously (Figure 3). The intersecting region of these overlapping fields shared *identical* motivational, perceptual, and motor behavioral variables, yet spatial firing patterns differed widely, so that one place field was journey dependent and another was not. In all, 194 of 296 (65%) fields that overlapped in at least part of a maze arm were discordant for journey dependence.

Simultaneously recorded ensembles encoded the full range of task-related correlates. Across 60 ensembles of two or more cells, 47 (78%) included both "true" place fields as well as journey-dependent fields. On average, 62% of the cells within these discordant ensembles had journey-dependent fields. The larger ensembles (>7 fields) typically encoded retrospective, place, and prospective information simultaneously. Thus, in this hippocampus-dependent task, the active population of hippocampal neurons encoded a temporally extended representation of journeys that included the present location, recently visited places, and places to be visited imminently.

Journey Influenced Some Place Fields More than Spatial Trajectory

Particular movement sequences through space define spatial trajectories, whereas goal-directed behaviors from one place to another define journeys. In the + maze, a rat could make the same journey from a start to a goal arm via several trajectories, from the most direct path (e.g., north to east) to those that included detours (e.g., north to west to east) (Figure 4). The present task therefore dissociated two potential influences on place fields. If journey-dependent firing was correlated with either a particular trajectory or a combination of a specific view (e.g., from the south) and a particular movement (e.g., a body turn; McNaughton et al., 1996), then discriminative firing should disappear when the rat

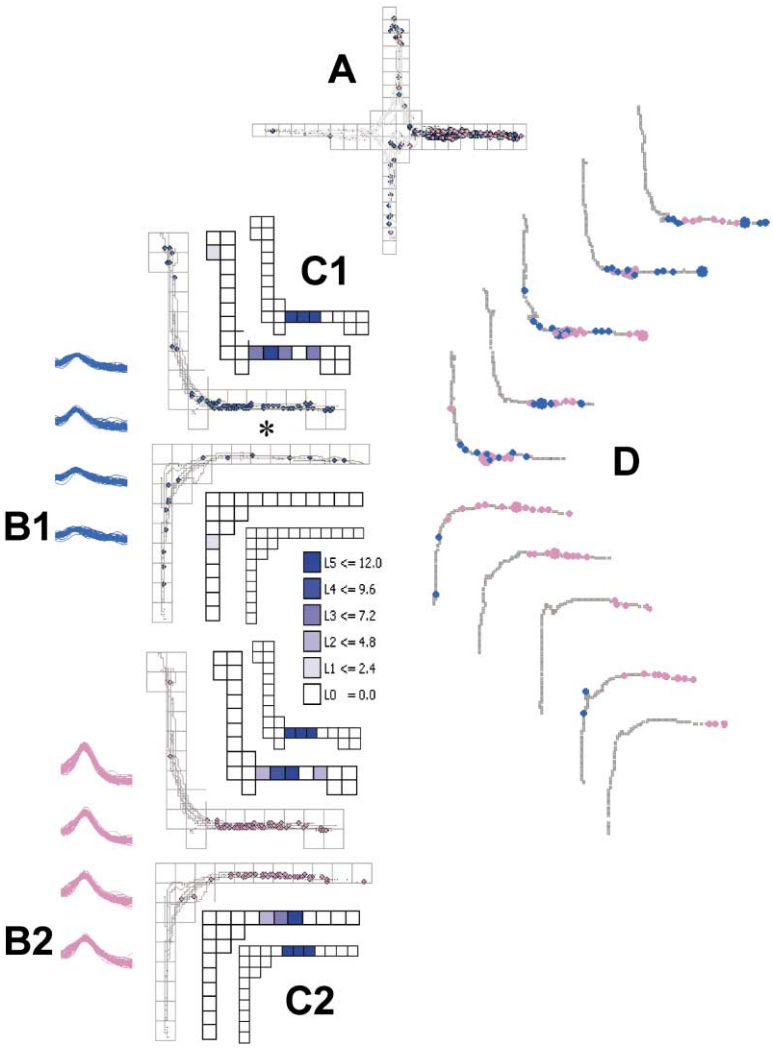

Figure 3. Two Cells Recorded Simultaneously with Overlapping Place Fields that Had Discordant Journey Dependence

(A) All trajectories are shown with both cells' spikes overlaid as blue or pink dots. Both cells had statistically valid place fields in the overall session (data not shown). (B) Waveforms of cells 1 (blue, max = 150 μV) and 2 (pink, max = 300 μV) were clearly discriminated units. Separated NE and SE journeys (C) show individual journeys and place firing plots, mean firing rate maps, and statistically verified subfield maps (left to right; as in Figure 2). Spatial behavior was highly correlated. While cell 2 fired reliably in both types of journeys, cell 1 fired almost exclusively during NE journeys (see *) and thereby revealed retrospective coding. Note that the nearly identical place activity shown by cell 2 was shifted toward the goal end of the arm in SE versus NE journeys. (D) Individual journeys show interleaved firing of cell 1 and 2 in NE journeys (upper traces) and the persistent firing of cell 2 with the near absent firing of cell 1 in SE journeys (lower traces). Spatial trajectory in each journey is shown in gray, and the radius of the colored circle indicates firing rate.

alters its trajectory. This analysis pertained only to fields in the goal arms, because trajectories in the start arms were invariant.

Journeys often influenced place fields more than either spatial trajectory or a combination of views and body turns. Trials that included various detours were replayed to determine if journey-dependent fields in the goal arm had the same pattern of discriminative activity as described in the "correct" trials. Of the 55 journey-dependent fields that could be assessed, 27 (49%) were consistent with the origin of the journey despite varied detours and trajectories (e.g., Figure 4). These cells maintained their fields during journeys from one but not the other start arm, even when the rat entered the incorrect goal arm before the correct one; the fields were maintained through both short and long detours (Figure 4). Thus, during errors, among the fields that maintained journey dependence, none depended on trajectory—the particular movement path. Rather, the activity of these cells coded journeys, actions directed from start to goal locations, rather than sequentially occupied places. Of the 28 remaining fields, 27 lost journey dependence; these cells fired in the goal arm in paths from both start arms. Please note that a neuron that encoded trajectory should stop firing in trials that included indirect paths. Rather, the journey-dependent fields lost selectivity during error trials so that cells fired during both journeys.

Journey-Dependent Activity Declined in Error Trials

The findings described so far show that place field activity in the start arms sometimes predicted subsequent choices and activity in the goal arms often "retrodicted" the start of the journey. If prospective and retrospective coding reflect memory performance, then neuronal activity should also vary with choice accuracy. Journey-dependent firing correlates diminished in error trials, as though the hippocampal representation of the memory demands were compromised (Figures 5–7). Of the 94 journey-dependent place fields that could be assessed during error trials, 56 (59%) lost journey dependence, and the cells fired indiscriminately with regard to journey (Figure 7).

Prospective coding diminished more than retrospective coding in error trials, as would be expected if the signal provided by hippocampal neurons contributed to choice accuracy. Journey dependence was lost in 72%

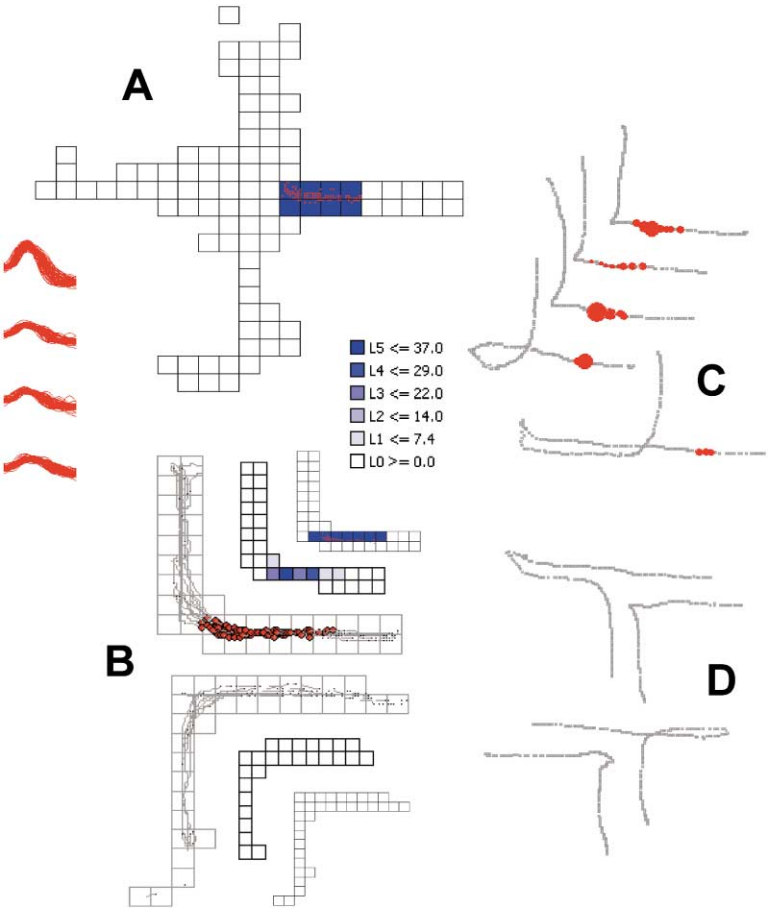

Figure 4. A Journey-Dependent Field with Retrospective Coding that Was Not Controlled by Spatial Trajectory

(A) A prominent place field (waveform max = 160 μV) in the east arm was identified statistically when all trials were considered.

(B) Separated NE and SE journeys show place firing plots and place field maps during all correct trials. Firing in the east arm occurred reliably in NE journeys only.

(C) Individual trials show that the journey-dependent field was preserved during indirect trajectories, in this case even when the rat made a detour and entered the wrong goal arm before entering the correct one.

(D) Incorrect journeys from the south did not evoke firing in the east arm.

(28/39) of journey-dependent fields in the start arms and 51% (28/55) of the fields in the goal arms; the decrease was significantly more common in the start than in the goal arm [χ^2 (1) = 4.1, $p < 0.05$]. Thus, 69% of the fields in the goal arms were journey dependent in correct trials; in assessable error trials, 49% of the fields maintained journey dependence (Figure 7). In contrast, 58% of the fields in the start arms were journey dependent in correct trials, while only 28% of the fields in assessable error trials maintained journey dependence. Note that the "error" trials included those with frank errors and those in which the rat merely took an indirect trajectory to the goal. The observed decrease in journey-dependent fields may therefore underestimate the actual decline in journey-dependent activity associated exclusively with frank errors. The reduction of prospective coding also shows that firing in the start arm did not closely predict the subsequently entered goal arm (Figure 6B), as might be expected if hippocampal neurons were directly engaged in response selection. Together, the data from the error trials suggest, perhaps not surprisingly, that the hippocampal signal was better associated with memory or expectancy than with response selection or motor control.

Discussion

Summary

A spatial memory task that required the hippocampal system revealed that, although some CS neurons encoded only the current location of the rat, many others concurrently encoded either prospective or retrospective information. Fields showing retrospective coding were more common than those showing prospective coding, but both categories were prominent. Journey-dependent firing in the goal arms was often preserved even when rats made detours and followed different spatial paths. Performance errors were associated with an overall reduction in journey selectivity, however, particularly in the start arms, suggesting that the observed firing correlates were related to task performance. Together, the results show that, in a memory task that requires the hippocampal system and emphasizes episodic factors, hippocampal neurons encode a temporally extended representation of journeys. The simultaneous representation of information about the recent past, the present, and the imminent future corresponds with the requirements of a neuronal mechanism for episodic memory.

Animal Models of Episodic Memory

Human neuropsychology suggests that hippocampal function is crucial for remembering the temporal and sequential context of events (Tulving and Markowitsch, 1998). Beyond reminiscence, episodic memory allows detailed expectations to be generated from the context of situations. Nonverbal animals may use an analog to such episodic memory in tasks that require memory for *what, when*, and *where* (e.g., Clayton and Dickinson,

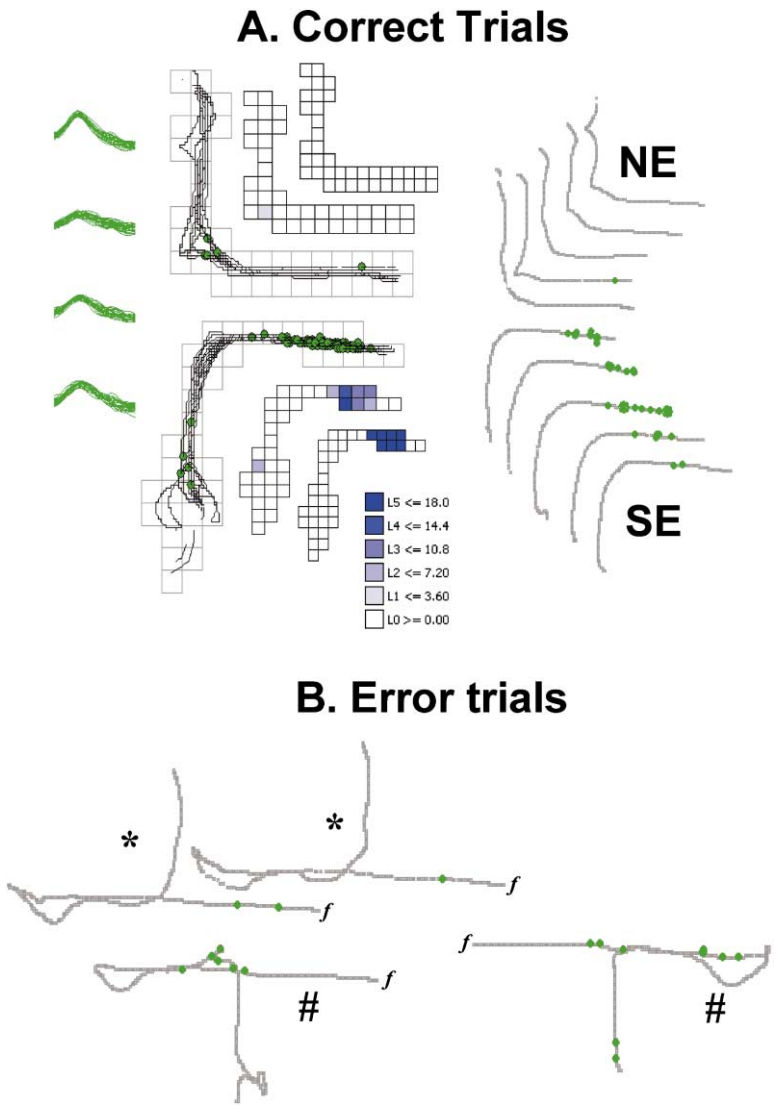

Figure 5. A Journey-Dependent Field with Retrospective Coding that Disappeared during Error Trials

(A) The cell (max = 110 μV) fired reliably during SE but rarely in NE journeys during correct trials, showing retrospective coding.

(B) Unlike the cell in Figure 4, this cell exemplifies one that lost journey dependence during self-corrected error trials; it fired weakly in the east arm during erroneous journeys there from the north (*) and missed firing or fired weakly in erroneous journeys from the south (#). Note that in three trials (left) the food (*f*) was in the east goal, while in the fourth case (right) the food was in the west.

1998; Clayton et al., 2001; Morris, 2001). One category of such tasks has been described as "those in which the animal has to keep changing what it should do in light of what it has just done," (Morris, 2001) such as in the radial maze (Olton and Papas, 1979). Here, the rat was required to remember at the start of a trial which of the two goal arms currently contained food, and then orient itself in a familiar environment to enter the correct arm. Because the food location switched between trial blocks, the rat had to change its response to the same stimuli and remember "where" depending upon "when." Furthermore, the task clearly distinguished the start and the end of a particular trial, so that each journey was unambiguously structured into a time-ordered sequence.

Memory Coding by Hippocampal Neurons

Just as hippocampal function may be essential for the formation of episodic memories (Vargha-Khadem et al., 1997), unit activity reflected the structured memory demands of the task in both prospective and retrospective encoding. The present results verify that structures in the medial temporal lobes are required for and reflect the temporal organization of events (e.g., Agster et al., 2002; Fortin et al., 2002) but contrast with previous work that described relatively rare prospective coding (4%) by hippocampal neurons (which was common in entorhinal cortex; Frank et al., 2000). Different task demands, especially the cognitive and behavioral requirements for discriminating journeys, may help resolve this discrepancy. Frank et al. (2000) assessed prospective and retrospective coding on one central arm that served alternately as both the start and goal of journeys. Coding was thus assessed in one spatial location with ambiguous significance. Moreover, because the task involved continuous alternation, individual trials may have become mnemonically indistinct. Rats can learn continuous alternation tasks as serial patterns using a strategy that does not require hippocampal function (Olton et al., 1984; Tonkiss et al., 1990). In such conditions, some hippocampal neurons may have tracked events in the past, but because their activity was not required to solve the task, few neurons were modulated by impending behavior. In con-

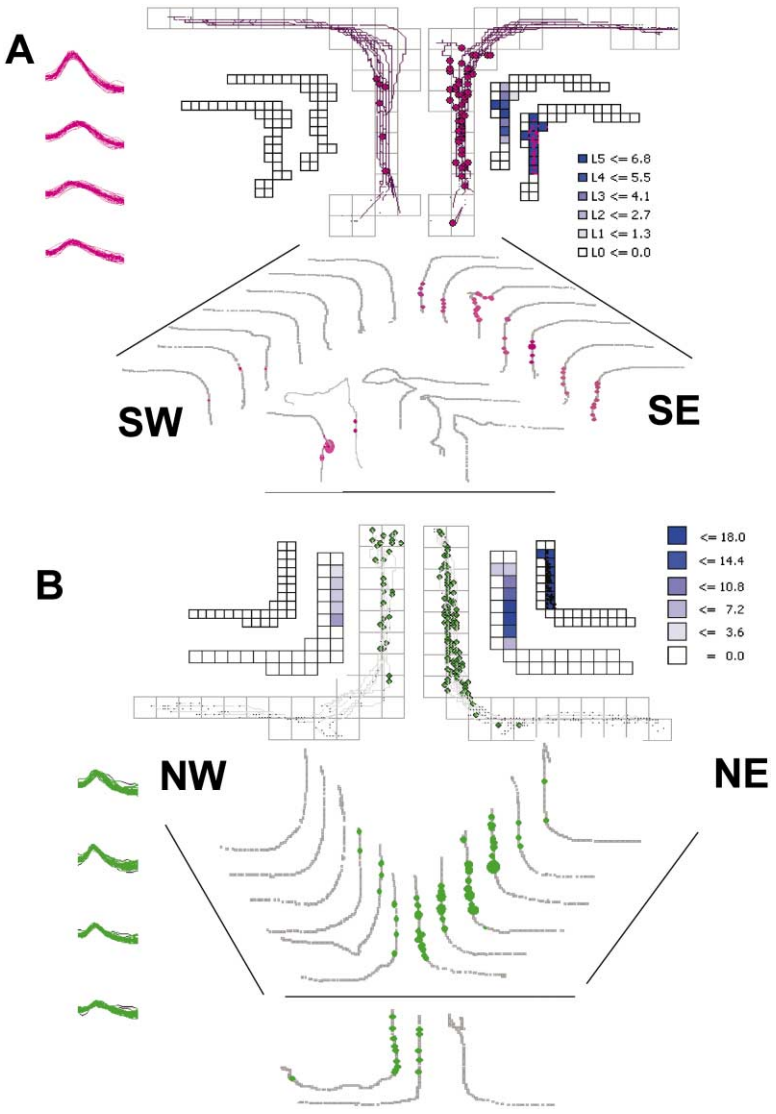

Figure 6. Journey-Dependent Fields Showing Prospective Coding

(A) The cell (max = 230 μV) fired reliably in the south arm during correct SE but rarely during SW journeys. Individual SE and SW correct trials are shown below the diagonal lines. Five error trials (above the horizontal line) show that the cell did not fire in the start arm before the rat incorrectly entered the west arm and turned into the east goal arm (right); it did fire in the start arm when the rat incorrectly entered the west arm (left: in these two error trials, the rat did not correct its choice before the trial ended).

(B) A journey-dependent cell (max = 120 μV) that fired at higher rates during NE than NW journeys and reached the threshold for a place field only in NE journeys. The three error trials below the horizontal line show that the cell activity did not consistently predict the goal arm entered by the rat. In these error trials, as above, the rat did not correct its choice before the trial was ended.

trast, when the meaning of different locations was clearly structured into discrete trials with well-defined beginnings and ends and when the rat had to actively choose "where" depending upon the context of the trial block ("when"), the hippocampal system was both necessary for and actively engaged during task performance (cf. Wible et al., 1986). In this case, the activity of many hippocampal neurons was required to solve the task and was "queried" prior to the choice point to comprise an elevated prospective signal. Thus the hippocampal neural network may function as an episodic memory device, and the entorhinal cortex may then use the hippocampal signal to generalize across experiences (Frank et al., 2000).

Hippocampal neurons may help encode episodes by linking events into temporally extended sequences. This view suggests that hippocampal neurons encode a "memory space," a range of temporally extended representations, from narrowly defined events comprised of the simultaneous conjunctions of percepts and actions, to temporally extensive sequences that bridge events, to "nodes" that link different episodes in a common environment (Eichenbaum et al., 1999). The present results correspond well to this theory. While journey-independent "true" place fields may have exemplified nodal representations of locations, journey-dependent fields were consistent with hypothesized event and sequence representations. From this view, the prominent spatial firing correlates of hippocampal neurons encode, among other things, "journeys to and from important places" (Eichenbaum et al., 1999). The present experiment shows for the first time (to our knowledge) that place fields can be as closely associated with journeys as with trajectories or spatial locations. Sequential activation of the neuronal population encoded distinct representations of each journey from start to goal, despite overlapping locations or varying paths.

The unequal journey dependence in the start and goal arms was not predicted by the memory space view and needs further consideration. Journey-dependent firing in the start arm was less common and may have been influenced only by the context of the trial block, whereas

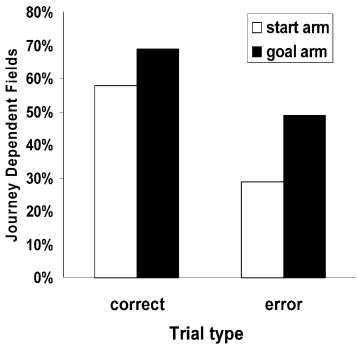

Figure 7. The Proportion of Journey-Dependent Fields Was Higher in Correct Trials, and Both Prospective and Retrospective Coding Diminished in Error Trials

Prospective coding, as reflected by journey-dependent firing in the start arm, declined more than retrospective coding (firing in the goal arm).

firing in the goal arm was more common and may have been activated by both context and recent memory. Beginnings and ends of journeys define two natural boundaries for episodes that are temporally asymmetric. The hippocampus may be more powerfully activated during the encoding of recent events than during the retrieval of imminent ones. From this view, journeys may be encoded when they end or when a reward is obtained (Buzsáki, 1989). Or perhaps memory encoding must occur in "real time" as events unfold, whereas successful memory retrieval can occur with time and information "compressed" into the gist of what is needed, such as when the location of a parked car is remembered only as a brief image that is sufficient to direct subsequent navigation.

Journey-Dependent Firing Weakened during Error Trials

If journey-dependent fields reflect important and relevant aspects of memory representation, then disrupted coding should correlate with memory performance errors. Indeed, journey-selective activity declined in error trials, suggesting that these firing patterns were relevant to task performance. Correlations between hippocampal unit encoding and performance errors have been observed in spatial delayed-matching to sample tasks in rats given amnestic drugs (Hampson et al., 2000). In that case, some errors were typically associated with poor encoding of the sample stimulus, whereas others occurred with long-delay trials. In the present experiment, the "stimulus" was an internal one based on memory and determined by contingency. Because prospective firing in the start arm precedes behavioral discrimination, coding failure there should more closely predict performance errors than in the goal arms, which are entered after the choice. Consistent with this view, prospective coding in the start arm decreased markedly in error trials. Retrospective coding was less affected than prospective coding, which may be expected if the cells in the goal arm are responding to the memory for the recently executed journey. Thus, persistent firing in goal arms could reflect the greater certainty of more recent events (journeys) compared to the interference-prone firing in the start arms.

Multiple Reference Frames and Path Integration

The influence of memory and behavior on hippocampal place fields has spurred the development of new variants of the cognitive map theory of hippocampal function, which was originally intended as a theory of episodic memory: "the representation of experiences within a specific context" (O'Keefe and Nadel, 1978, p. 381). Recent views emphasize that the hippocampal system is specialized for spatial navigation and that its activity reflects path integration (e.g., Gallistel, 1990), so that place field activation can occur either because perceptual input or self-movement cues signal a location. The *multiple reference frames* view further proposes that the hippocampus encodes multiple maps of an environment, called reference frames or charts, with each map anchored to a different landmark or starting point (McNaughton et al., 1996; Redish, 1999). The most recent version of this theory proposes that nonspatial, contextual inputs can activate different charts (Skaggs and McNaughton, 1998).

Trajectory-dependent place fields found in continuous alternation tasks (Wood et al., 2000; Frank et al., 2000) can be explained as reflecting path integration (cf. Markus et al., 1995), wherein different landmarks and self-movements (e.g., body turns) were consistently associated with different trajectories. The present experiment emphasizes the crucial role of nonspatial contextual variables. In each journey, at least two charts would be active concurrently, because ensembles of cells recorded simultaneously had perfectly overlapping fields that differed in journey dependence (Figure 3). Individual neurons would therefore either have to take part in different charts simultaneously or the chart would have to be switched rapidly within each traversal of a place field. Distinguishing between two charts in the start arm would be impossible if the hippocampus derived location exclusively from the starting position, landmarks, and self-movement information, which are identical on the different journeys. The same argument holds for the persistence of journey-dependent firing in the goal arms during error trials. If reference frames guide behavior, then the rat must begin a journey using one reference frame (e.g., NW, see Figure 4) and then switch to another (e.g., from the NW to the NE rather than SE) when food was not found in the first entered arm. The mechanism that directs the switch from one reference frame to another relies on a nonspatial, contextual input to what is otherwise described as a spatial mapping system (Skaggs and McNaughton, 1998).

The episodic memory interpretation of the results is both simpler and more general than the multiple reference frames view (Eichenbaum et al., 1999). From this perspective, hippocampal neurons encode the sequences of perceptions and actions within a behavioral context. This temporally extended representation includes both the invariant and changing features of the environment, including changes based only upon temporal or behavioral context. This framework allows the same stimuli to have different "meaning" and to generate different representations as memory context changes. Context-coded representations can distinguish situations in which the same stimuli require different responses and provide a mechanism for the flexible responding that characterizes spatial and nonspatial

hippocampus-dependent tasks. Previous experiments suggested this possibility but could also be explained straightforwardly by purely spatial path integration; the present results are more definitive.

When Do Place Fields Reflect Memory?

Place fields are observed in tasks that do not require the hippocampus, and even in tasks that do, place field activity does not always correlate with performance (Jeffery et al., 2003). Multiple memory systems provide several strategies for performing almost any task (e.g., White and McDonald, 2002). If distinct memory strategies recruit different neuronal activity patterns among brain systems, then different firing correlates may be observed in similar experiments simply because the rats use a hippocampal-dependent strategy in one lab but not in another. The most powerful strategy to ensure that firing correlates are consistently and causally related to memory performance is to record unit activity in tasks that require the hippocampal system and vary memory demands. This view may help reconcile differences among the experiments that have attempted to assess the influence of memory on place field activity (Wood et al., 2000; Frank et al., 2000; Lenck-Santini et al., 2001). Specific task variables should determine whether or not place fields vary with journeys. (1) The common path must be constrained to include both journeys reliably and to prevent rats from taking separate, parallel paths; this parameter is crucial because if paths differ between journeys (Lenck-Santini et al., 2001, p. 1058) then by definition, journey-selective place fields cannot be assessed. (2) The common path must be taken during clearly dissociable journeys, e.g., with distinct start points and distinct goals, so that the rat discriminates one journey from the other in memory. (3) The rat must use a hippocampus-dependent strategy to discriminate the journeys. If these three requirements are met, then journey-dependent place fields should be commonly observed.

Computational Models of Place Fields

The present results constrain computational models of hippocampal place fields. The strong influence of memory context shown here demonstrates that models based solely on the geometry of environments, local views, spatial trajectory, or path integration (e.g., Burgess et al., 2000; Samsonovich and McNaughton, 1997; Shapiro and Hetherington, 1993; Sharp, 1991) cannot account for the full encoding repertoire of hippocampal neurons. In contrast, the results dovetail with models of hippocampal function that include context (Skaggs and McNaughton, 1998) or sequence processing via recurrent pathways in the dentate gyrus and CA3 (e.g., Hetherington and Shapiro, 1993; Muller et al., 1996; Lisman, 1999; Levy, 1996; Wallenstein et al., 1998). One model simulated the memory property of place fields described by O'Keefe and Speakman (1987) using a recurrent network. The network computed spatial trajectories from arbitrary starting points to one of four designated goal locations using visual input, the recurrent connections among place units, and a goal signal. In this model, the simulated place "units [were] silent…in one or more goal condition [but] had place fields in other goal conditions" (Hetherington and Shapiro, 1993). Thus, the goal provided contextual input that directed recurrent circuits to compute spatial paths via journey-specific place unit activation. The simulation suggests that contextual input to the recurrent circuitry of the hippocampus may be, in principle, sufficient to generate journey-specific place field activity.

Conclusions

Hippocampal neurons showed prospective, place, and retrospective coding. Neuronal activity distinguished between journeys begun in the same place that were aimed toward different goals and discriminated journeys that ended in the same place after starting from different points. Some of these journey-dependent place fields maintained discriminative activity during detours and were thus more influenced by the start and end of a journey than the trajectory of spatial movements. The journey dependence of the overall population diminished, however, when memory failed and rats made performance errors. The neurons therefore appeared to encode memory demands rather than a location or a particular sequence of movements through space. The activity of hippocampal neurons may thus provide a crucial signal for distinguishing among events that occur in the same place at different times and, by simultaneously encoding the recent past, the present, and the imminent future, contribute to a mechanism for episodic memory.

Experimental Procedures

Subjects

Sixteen male Long-Evans rats (400–600 g, 4- to 6-month-old, Charles River Labs) were housed singly (12 hr light cycle) and food deprived to 85% body weight before behavioral training.

Apparatus

The + maze was made of wood, painted gray, and elevated 81.3 cm from the floor of a room that contained several visual cues, including computer racks, chairs, a bulletin board, posters, a window covered with a white blind, and two standing lamps located in the NE and NW corners. Each of four arms was 59.7 cm long and 6.4 cm wide. Two opposing arms were designated as goal arms; the other two arms were designated as start arms. A gray wooden block (29.2 cm high, 6.2 cm wide, 22 cm deep) was used to block the start arm that was unused during a trial. An octagonal waiting platform (16.5 cm/side, painted black) was next to the maze.

Behavioral Training and Testing

The north and south arms of the maze were designated as start arms; the west and east were goal arms. At the start of each trial, half of a Froot Loop was put at the end of one goal arm, the wood block was put into the unused start arm, and the rat was placed at the distal end of the other start arm facing the choice point. Each rat was trained to walk to the food and was allowed to self-correct if it first entered the wrong arm. The start arm was selected from a pseudorandom sequence of 60 trials with $\leq$3 consecutive repetitions. The alternating start arm sequence was intended to discourage the rat from using a body turn strategy to find the food (e.g., Packard and McGaugh, 1996; Restle, 1957). After the rat reached the goal and ate the Froot Loop, it was placed on the waiting platform for 10–15 s while the correct arm was baited and the block was put in the appropriate start arm. After the rat entered the correct goal arm in 9/10 consecutive trials, the other goal arm was baited, and a new block of trials began. The start of each new block was signaled: the rat was put into the correct goal arm where it ate half of

a Froot Loop. Alternating blocks continued throughout each daily session and included as many as 60 trials.

Rats intended for unit recording were trained to a criterion of 70%–80% correct, implanted with recording electrodes, and trained to 90% correct after surgery. Rats intended for the lesion experiment were trained to a criterion of 80% correct over four reversals for two consecutive days, ranked by percent correct within the criterion session, and assigned to either a sham or fornix lesion group to equate the performance of the two groups.

Electrodes and Surgery

Each rat was tranquilized (0.1 mg xylazine and 0.02 mg acepromazine, i.p.), anaesthetized with isoflurane, and placed in a stereotaxic apparatus.

Fornix Lesions

Fornix lesions were made by radiofrequency current; rats in the sham group were anaesthetized, incised, and sutured. Testing resumed 1 week after surgery. All surgical procedures followed approved IACUC guidelines.

Hyperdrive Implant

Twelve tetrodes (Gray et al., 1995) made from four twisted wires (Ni-Cr wire, Rediohm-800, 12.7 μ, Kanthal, Palm Coast, FL) and two reference wires were loaded into a 14-drive assembly (Neurohyperdrive; Kopf Instruments, Tujunga, CA) that allowed independent vertical movement of each drive. The electrode assembly was mounted on the skull with dental cement and bone screws that connected ground wires. The tip of the assembly was lowered to the cortical surface (AP -3.8 mm ML -2 mm from Bregma), and at the end of surgery the tetrodes were driven 1.25 mm into the brain. Testing resumed 1 week after surgery.

Recording Methods

The hyperdrive assembly was mated to a headstage with 54 unity gain, source following amplifiers and ten color LEDs for position tracking. Unit signals were differentially amplified (1000–5000$\times$), band-pass filtered (600–6000 Hz), digitized (32 points/waveform, 1 ms sample, 1 μs resolution), and stored with LED positions by computer (Cheetah 64 Data Acquisition System, Neuralynx, Inc., Tucson, AZ). Waveforms were displayed on a computer screen and played through two audio speakers while the rat was on the hexagonal platform. When stable and isolable CS units were found (Fox and Ranck, 1981; O'Keefe, 1979; Ranck et al., 1982), a recording session ensued that lasted as long as 90 min. Otherwise the electrodes were advanced 20–30 μm and at least 4 hr elapsed before recording to allow the brain tissue to stabilize. Units with spike amplitudes $>$100 μV and twice the mean noise were discriminated offline by identifying clusters defined by waveform parameters (Gray et al., 1995): 1 to 15 waveforms were separated per tetrode. Because the tetrodes may have shifted overnight even when they were not advanced at the end of the recording session, every distinct and isolated waveform was operationally defined as a different unit. Note that because cells were recorded extracellularly and the same neurons may have generated different waveforms over days, the precise number of recorded neurons cannot be known definitively (Knierim, 2002). Behavioral measures of speed, distance, and direction of movement were calculated from the tracked position of the color LEDs.

Data Analysis

Place Field Definition and Statistics

The LED positions (640 $\times$ 480 camera pixels, 16.7 ms/sample) were smoothed using a moving average of five to ten sequentially collected points that occurred within a maximum of 1 s and 10–20 camera pixels of one another. To define place fields, the maze arena was divided into a 28 $\times$ 28 array of 6.35 cm^2 grid units. Firing rate was calculated by dividing the total number of spikes by the total amount of time spent in each grid unit. Place activity was analyzed if the grid unit was visited for a total visit duration $\geq$300 ms and $\geq$5 times. Firing rates were calculated only if the rat was moving faster than 2 cm/s. For each cell, a place field was defined as an area $\geq$2 adjacent grid units with mean firing rate $>$1 spike/s with $\geq$5 spikes per subfield visit. Noncontiguous patches with firing above threshold were defined at "subfields." The spatial distribution of unit activity was analyzed using the one just described based on place fields and another based on the statistical distribution of firing rates using Student's t tests and Pearson's r (see the Supplemental Data at http://www.neuron.org/cgi/content/full/40/6/1227/DC1).

Trial Separation and Journey Analyses

Event flags, generated online, categorized maze locations (e.g., start of north arm, maze center, end of west arm), marked the beginning and end of each trial, and signaled the entry into the correct goal arm or the occurrence of an error. The event flags identified and sorted each trial into one of five subfiles containing only one of the four types of journeys (e.g., NE, SW, etc.) or error trials. To assess the influence of individual journeys, including error trials, on firing, each trial from every recording session was replayed offline and visually inspected. This method ensured that each subfile contained only one type of journey.

Spatial behavior was quantified by calculating the visit locations, movement speed, and the direction of movement in each of the eight cardinal compass point headings for each subfile containing one journey type. Each maze arm was represented by a 2 $\times$ 5 (start arm) or 2 $\times$ 6 (goal arm) array of grid units (6.35 cm^2). The start arm array was shorter than the goal arm array by 1 grid unit to account for the rat's starting orientation facing the choice point in the start arm. Each measure of spatial behavior was calculated for every grid unit, so that one array described the spatial distribution of one parameter across the length and width of each arm with a resolution that approximated the size of the rat's head stage. The array included the length ($\sim$40 cm) of each arm but excluded the area of the choice point, where body turns occurred, and the food cup area, where behavior changed markedly. The array divided the 6.4 cm width of each arm in two and included regions where the rat's head could extend past the edge of the arm. Paired t tests assessed whether spatial behavior was equivalent in each pair of corresponding journeys. For example, the north arm visit array during NE trials was compared to the corresponding array for NW trials. A significant difference ($p < 0.05$) in any of the behavioral measures excluded the associated place fields from further consideration. Replaying every journey showed that this quantification was rather conservative.

Subfields

Well-discriminated single hippocampal neurons can have multiple place fields (*subfields*) (O'Keefe and Burgess, 1996). Because extracellular recording methods cannot determine unequivocally that a waveform is produced by only one neuron, units with two or three subfields were examined across journeys and compared to units with single fields. By the place field analysis, the journey dependence of one subfield was not related to that of the others of the same cell [χ^2 (1) = 0.04, p = 0.84]. Furthermore, the subfields of multifield cells were indistinguishable from the place fields of single field cells. A one-way ANOVA compared the firing rate distribution of cells with one field to cells with multiple subfields; the subfields of multiple field cells behaved independently and did not differ from those of cells with one field ($F_{2,522} = 1.35$, p = 0.26). Because the responses of units with single and multiple fields could not be distinguished, all fields were considered independent, as though they were from separate cells, and were pooled for subsequent analyses.

Error Trials

For a field to be considered in the error analysis, the rat had to make $\geq$2 incorrect trajectories through the region that included the journey-dependent place field. A journey type (e.g., NE) that included a journey-dependent place field was designated as the field's *preferred* journey; the corresponding journey that had no place field (e.g., NW) was designated *nonpreferred*. A field was considered *assessable* if it included $\geq$4 error trials (mean = 7): all but three cells had $>$2 trials in both the preferred and nonpreferred journeys. Assessable fields were categorized as those that lost or maintained selectivity during error trials. If the unit was significantly active in $\geq$2 trials (and $\geq$50% of the incorrect trajectories) during nonpreferred journeys, then the field was categorized as *losing selectivity*. Three fields were also classified as losing selectivity because the units stopped firing altogether during preferred but erroneous journeys. A field was categorized as *maintaining* selectivity during errors if it was active in $\geq$1 of $\geq$2 preferred journeys and in $\leq$1 of $\geq$4 nonpreferred journeys. Most (73/94) of the assessable fields had all-or-none activity patterns during correct and incorrect journeys. The place fields that distinguished journeys by different mean firing rates

(21 of 94 fields) were assessed as above by comparing relative firing rates during error and correct trials.

Fornix Lesions

Normal rats and those with complete fornix lesions (see the Supplemental Data at http://www.neuron.org/cgi/content/full/40/6/1227/DC1) were included in the behavior analysis. Percent performance error was calculated for each rat during each day of testing. The groups were compared across days by two-way ANOVA and post hoc REGWQ tests (SAS Institute, Inc., NY).

Histology

Each rat was overdosed with sodium pentobarbital (100 mg/kg, i.p.) and perfused transcardially with normal saline then 10% formalin. Coronal sections (40 μm) were cut on a freezing-sliding microtome and stained with formol-thionin to highlight cell layers and fiber tracts (Donovick, 1974). Brains obtained from rats with fornix lesions were cut into two blocks. The region around the fornix was stained with formol-thionin to assess the damage to the fiber pathways. The hippocampus was immunostained with VAChT antibody to reveal acetylcholinergic vesicles (Immunostar, dilution 1/50,000). Complete lesions obliterated VAChT-positive fibers in the hippocampus (see the Supplemental Data at http://www.neuron.org/cgi/content/full/40/6/1227/DC1). Electrode tracks traversed the CA1 and CA3 layers.

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