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Binding of Hippocampal CA1 Neural Activity to Multiple Reference Frames in a Landmark-Based Navigation Task

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The behavioral correlates of rat hippocampal CA1 cells were examined in a spatial navigation task in which two cylindrical landmarks predicted the location of food. The landmarks were maintained at a constant distance from each other but were moved from trial to trial within a large arena surrounded by static background cues. On each trial, the rats were released from a box to which they returned for additional food after locating the goal. The box also was located variably from trial to trial and was moved to a new location while the animals were searching for the goal site. The discharge characteristics of multiple, simultaneously recorded cells were examined with respect to the landmarks, the static background cues, and the box in which each trial started and ended. Three clear categories of cells were observed: (1) cells with location-specific firing (place cells); (2) goal/landmark-related cells that fired in the vicinity of the goal or landmarks, regardless of their location in the arena; and (3) box-related cells that fired either when the rat was in the box or as it was leaving or entering the box, regardless of its location in the arena. Disjunctive cells with separate firing fields in more than one reference frame also were observed. These results suggest that in this task a subpopulation of hippocampal cells encodes location in the fixed spatial frame, whereas other subpopulations encode location with respect to different reference frames associated with the task-relevant, mobile objects.

Key words: spatial navigation; place cells; CA1; rat; computation; population code

The rat hippocampus plays an important role in spatial learning and navigation. Lesion experiments indicate that an intact hippocampus is necessary for learning spatial locations defined by distal cues (O'Keefe and Nadel, 1978; Barnes, 1988; Jarrard, 1993), and many recording studies have documented that hippocampal pyramidal and granule cells often fire in a consistent relation to the location of the animal in space (O'Keefe and Dostrovsky, 1971; O'Keefe and Conway, 1978; Kubie and Ranck, 1983; McNaughton et al., 1983a,b; Muller et al., 1987; Eichenbaum et al., 1989; Wiener et al., 1989; Jung and McNaughton, 1993; Wilson and McNaughton, 1993); however, whether any perceptual or motor invariants are represented by such firing has not been determined.

Presumably, navigation involves encoding location with respect to discrete objects, i.e., landmarks. The behavioral studies of Collett et al. (1986) showed that gerbils incorporate landmarks into their spatial representation by encoding and storing distances and bearings from individual landmarks to a reward location. The role of the hippocampus in navigation, together with the findings of Collett et al. (1986), led us to ask whether landmarks are represented explicitly in the hippocampus. Previous studies have shown that in some situations hippocampal cell activity is insensitive to partial or complete removal of cues (O'Keefe and Conway, 1978; McNaughton et al., 1989; Quirk et al., 1990; Markus et al., 1994). These studies, however, were not designed to reveal explicit landmark representations. The experiments described in this study were intended to fill this gap.

The cognitive-map theory of O'Keefe and Nadel (1978) predicts a stable configuration of place cells relative to fixed spatial cues in an environment, regardless of behavior or reward contingencies; however, recent findings indicate that multiple factors contribute to hippocampal cell activity. For example, Breese et al. (1989) and Fukuda et al. (1992) showed that place fields shift together with shifting reward locations. Also, in some tasks hippocampal cells respond to nonspatial variables, such as sampling of a cue, reward contingencies, etc. (Berger et al., 1983; Eichenbaum et al., 1987; Wiener et al., 1989; Otto and Eichenbaum, 1992; Young et al., 1994). Furthermore, when the task is switched from random foraging to sequential retrieval of food from a few specific locations on the same apparatus, a substantial number of place fields shift location (Markus et al., 1995). Thus, the factors controlling hippocampal cell activity are task-dependent and complex.

The purpose of the present study was to examine the role of landmarks in controlling hippocampal cell activity. In a task modeled after that of Collett et al. (1986), the locations of two landmarks were varied so that their influence could be distinguished from the influence of static background cues. The behavioral demands and the reward contingencies of the task remained unchanged; only the locations at which these behaviors were displayed varied across trials. Our results indicate that several independent aspects of the task, including, but not limited to, spatial location, are represented among subpopulations of CA1 neurons.

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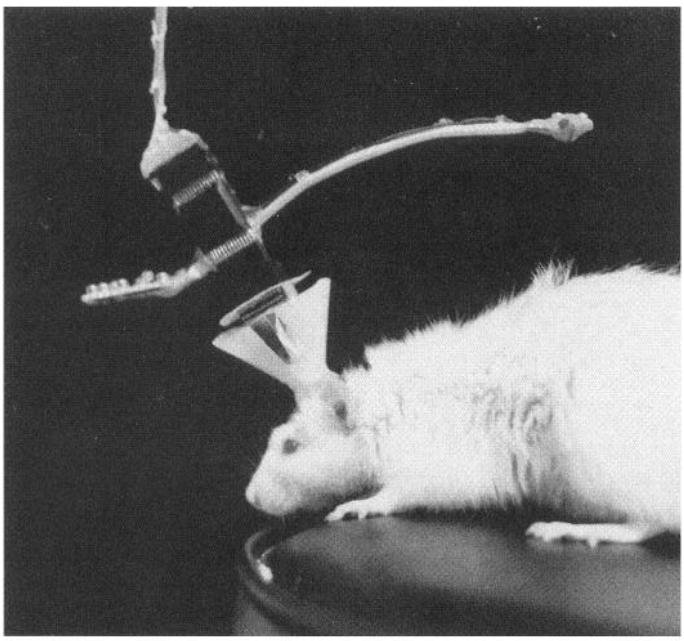

Figure 1. Configuration of microdrive and headstage on the rat's head. The microdrive array of 14 separately movable tetrodes was enclosed within a protective plastic cone. The headstage containing two 24 channel preamplifiers and a multichannel cable was attached to the microdrive via a multipin connector only during recording. A 14 cm bent aluminum rod holding infrared diodes for position and direction monitoring was an integral component of the headstage.

An abstract of this work has been published (Gothard et al., 1994).

MATERIALS AND METHODS

Construction of electrode assembly. Tetrode recording probes were constructed by twisting together four strands of polyimide-coated, 14-μm-diameter nichrome wire (Reid, Neptune, NJ). To obtain adherence and stiffness, the insulation was softened briefly by heating while the wires were under tension and then allowed to cool. The wires were cut flat at the same level, and each tip was gold-plated separately to reduce the impedance of individual electrodes to 400–500 kΩ. The overall diameter of the tetrode was ~40 μm. The tetrode was mounted and glued into two nested polyimide tubes (Hudson International, Trenton, GA), 78 and 110 μm outside diameter, respectively, which then were mounted in a microdrive array.

The multielectrode drive array (Fig. 1) was similar in principle to a prototype developed by Wilson and McNaughton (1993). It consisted of an inverted conical core machined from Delrin (Small Parts, Miami Lakes, FL), which contained an array of fourteen 30 gauge stainless steel guide cannulae (Small Parts). The guide-cannula array, held together with heat-shrink tubing, ended at the apex of the cone (i.e., nearest the brain) so that the electrodes emerged from it into the brain in a parallel configuration. The other ends of the tubes fanned out at an angle of 30° through predrilled, inclined guide holes in the core and emerged from the core as an evenly spaced circle around the base of the cone. A set of 14 drive screws (stainless steel 0–80) was distributed around the top of the drive core, again at 30° angles from the vertical axis. Each of these was coupled via a molded plastic nut to a 23 gauge drive cannula, such that when the screws were turned the drive cannula was directed through the guide hole and over the inclined portion of the 30 gauge guide cannula.

A tetrode assembly was inserted into the drive cannula so that the tetrode tip just protruded from the bottom of the corresponding guide tube. The tetrode was glued to the drive cannula at the top end only. A full turn of the screw advanced the drive cannula and tetrode 320 μm. The tip of the tetrode thus was advanced through the brain, and the guide and drive cannulae prevented the portion of the probe remaining outside the brain from buckling. The total available travel distance was 5–7 mm. The tetrodes emerged from the guide cannula array in a parallel hexagonal lattice with an interprobe spacing of ~250 μm. Two of the tetrodes served as reference or electroencephalogram electrodes or both. The four wires of each of the other 12 tetrodes were connected to separate channels of a multipin connector mounted on the top of the drive core. A ground lead was connected to a jeweler's screw placed in the skull.

Subjects and surgery. Three 9-month-old Fisher 344 male rats were caged separately and maintained on a 12 hr light–dark cycle. Training and recording were done during the dark cycle. Initially, the rats were food-restricted to 85% of their *ad libitum* weight. After the rats had learned the task, their weights were allowed to increase to 90–95% of the *ad libitum* weight. All procedures followed National Institutes of Health guidelines for the use of vertebrate animals.

While the rats were under sodium pentobarbital anesthesia (40 mg/kg body weight), they were placed in a stereotaxic frame and implanted with the microdrive assembly positioned over the dorsal hippocampus of the right hemisphere. After removal of the dura, the tip of the guide-tube array was placed on the brain surface so that subsequent rotation of the drive screws would advance the tetrode probes into the brain, leaving the guide tubes on the surface. The craniotomy surrounding the tube array was filled with melted bone wax to protect the brain and the tetrodes from the dental cement, which anchored the assembly to small, stainless steel screws placed in the skull. The stereotaxic coordinates for the placement of the electrode array were 2.5 mm lateral and 3.8 mm posterior from bregma. During a period of ~1 week after surgery, the tetrodes were lowered gradually to the CA1 layer of the dorsal hippocampus.

Recording equipment. Two unity-gain, miniature, 25 channel FET-preamplifiers (CFP-1020, Multichannel Concepts, Gaithersburg, MD) were attached to the connector pin array on top of the drive assembly. A multiwire cable connected the preamplifiers to a 64 channel commutator (Beila Idea Development, Anaheim, CA) mounted in the ceiling of the recording room. From the commutator, the signal was directed to seven custom-designed, 8 channel amplifier modules with digitally programmable gain and filter settings (Neurolynx, Tucson, AZ). Each amplifier module processed data from two tetrodes and transmitted the corresponding signals to a dedicated 80486 PC. Each computer was equipped with an analog-to-digital converter capable of 32 kHz/channel sampling frequency (DT 2821G, Data Translation, Marlboro, MA), data acquisition software (Discovery, DataWave, Longmont, CO), and a programmable 10 kHz time-stamp clock. One computer served as a master system that synchronized the time-stamp clocks of the six other computers via a parallel 8-bit command cable. A voltage threshold was set independently for each tetrode channel. When the threshold was exceeded on any of the channels, a 1 msec sample of data (32 points/channel) beginning 0.25 msec before the threshold crossing was collected from all four channels and stored on disk.

The position and head orientation of the animal were monitored by tracking two clusters of infrared diodes mounted on the front and rear of a 17 cm lightweight aluminum rod attached to the headstage. The front diodes generated a larger light spot than the back diodes, thus permitting the software to discriminate front from back. The video tracking system (SA-2 Dragon Tracker, Boulder, CO) registered the x,y coordinates of the two sets of diodes with a sampling frequency of 20 Hz and an effective pixel resolution of ~1.5 cm. The total tracking error was estimated to be ~5 cm, in part because of tilt error attributable to the height of the diode array above the rat's head. The location of the front diode array was taken as the location of the rat.

Cell identification. Cells were distinguished primarily via the relative amplitudes of their spikes on the four tetrode wires (McNaughton et al., 1983b; Recce et al., 1991). When the probe tip was located in the CA1 pyramidal layer, as many as 15 cells could be identified and isolated with a technique called "cluster cutting" (McNaughton et al., 1989). The method involved the extraction of a set of spike waveform parameters (mainly spike height and spike width) for each spike from the four tetrode channels and the separation of units on the basis of these parameters using interactive graphics software. Different combinations of parameter pairs were projected as two-dimensional scatter plots. When this was done, points derived from single cells tended to form recognizable clusters. The spikes within a cluster were enclosed in a polygon drawn by using a computer mouse. The data points then were projected into new two-dimensional plots in which the earlier partitions of the data were preserved by color-coding the points lying within the polygon boundaries. This process was repeated until a multidimensional set of boundaries was established that provided the subjectively best separation of spike waveform clusters.

Complex spike cells (i.e., pyramidal cells) were distinguished from

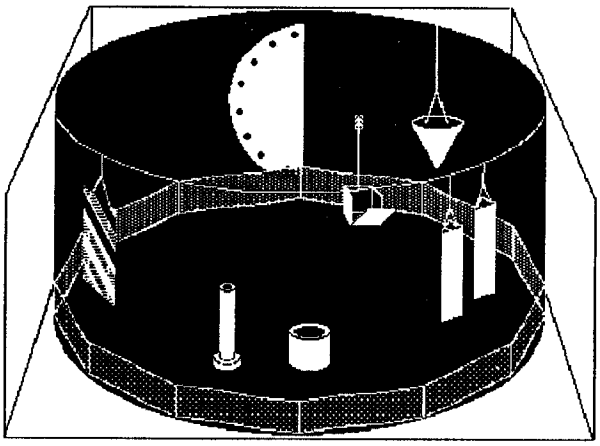

Figure 2. Training and recording environment. The 3.5-m-diameter circular arena had a black floor and was surrounded by black curtains extending from ceiling to floor. At the base of the curtains, a 30-cm-high wall, made of 12 pieces of black-painted plywood, prevented the rats from escaping behind the curtains. Five objects were placed in front of the curtains as static background cues: a 2-m-diameter semicircular panel on the south wall, a 60-cm-high white cone suspended from the ceiling at the southwest, two identical white polyhedra placed 20 cm apart at the northwest, and an 80 × 60 cm^2 striped panel suspended at the northeast. As viewed from the goal, the tall, thin landmark always appeared on the right, whereas the short, thick landmark appeared on the left. The animal was introduced into the environment without disorientation. During training and recording sessions, two experimenters were inside the arena with the rat. One experimenter moved the box and opened and closed the door of the box; the other experimenter relocated the landmarks while the animal was inside the box.

theta cells (interneurons) by a number of criteria (Fox and Ranck, 1981; McNaughton et al., 1983a). To be classified as a complex spike cell, a unit was required to meet the following criteria: (1) to be recorded simultaneously with other complex spike cells (in the CA1 layer); (2) to fire at least a small number of complex spike bursts during the recording session; (3) to have a spike width of at least 300 μsec, as measured from peak to valley of the average action potential waveform; and (4) to have an overall mean rate of <5 Hz during the recording session. To be classified as a theta cell, a unit was required to do the following: (1) to fire no complex spike bursts; (2) to have a spike width of <300 μsec; and (3) to fire with a mean rate of >5 Hz during the recording session (McNaughton et al., 1983a). Only those cells that were active during the behavioral sessions are reported here. Previous studies (Thompson and Best, 1989) have shown that many hippocampal cells that appear on an electrode during sleep become virtually silent in a particular behavioral task. Thus, the proportion of cells with particular behavioral correlates reported here reflects the proportion of cells showing significant activity in these behavioral tasks and likely is smaller than the proportion within the population as a whole.

Selectivity of hippocampal neurons is reduced when the animal is stationary, eating, grooming, or otherwise not engaged in what Vanderwolf et al. (1975) referred to as type I behavior (i.e., active locomotion, orienting, rearing, sniffing, etc.). To minimize this effect, data for which the tracking diode velocity was <15 cm/sec were excluded.

Training and recording environment. The training and recording environment was a 3.5-m-diameter circular arena with black floors, surrounded by black curtains extending from ceiling to floor (Fig. 2). Five large white objects were hung inside the curtains. These constituted static background cues, and they remained at fixed locations throughout training and recording. Two white cylindrical landmarks, a short, thick one (21 cm wide and 43 cm high) and a tall, thin one (6 cm wide and 76 cm high), were moved from trial to trial to new locations inside the arena. The distance between the landmarks always remained the same (60 ± 5 cm). The goal location was defined as the tip of an isosceles triangle, the base of which was the line connecting the two landmarks. The goal was always on the side of the landmarks from which the tall, thin landmark appeared on the right side and the short, thick landmark appeared on the left. The distance from the goal to each landmark was 40 cm. The arena was illuminated by four dim lights mounted symmetrically on the ceiling.

Behavioral training. The task was to find the goal location, which varied from trial to trial. The rat was released from and returned to a 38 × 28 cm^2, 30-cm-high cardboard box with a drawbridge-style door. The landmarks were not visible from inside the box. The box was moved to a new location and baited with a few chocolate "sprinkles" (cake decoration, 2–5 mm long, 1 mm diameter) while the rat was traveling toward the goal, so that each trial ended in a location that was different from its starting location. The goal also was baited with 5–20 chocolate sprinkles placed on the black floor in a 1- to 2-cm-diameter cluster. The goal was not baited on nonrewarded trials, which occurred randomly in one of every six trials. The training was divided into three stages: pretraining, shaping, and task-specific training.

During pretraining, the rats were introduced into the arena and allowed to explore at will. The box and landmarks were placed at arbitrary, fixed locations in the arena. A white plastic cup at the goal location contained half of the daily food ration supplemented with chocolate sprinkles. A similar plastic cup with the other half of the daily food ration was placed in the box. Initially, the rats spent most of the time inside the box; later they started exploring their surroundings and within a week became accustomed to the environment, the presence of the experimenters in the arena, and feeding at the goal and inside the box.

During the shaping stage, the door of the box was closed while the rat was inside, and the food reward, both in the box and at the goal, was shifted gradually from rodent pellets to chocolate sprinkles. The size of the plastic cups was reduced gradually until the cups were eliminated completely. In one session, the rats visited the goal 5–10 times. At the end of this stage (~1 week), the rats were accustomed to the open and closed box and ran toward the goal confidently every time the door of the box was opened.

The final, task-specific phase of training was slightly different for each of the three variants of the task (see below). During the early part of the task-specific stage, the landmarks were shifted only slightly (20–30 cm) between trials; this distance then was increased gradually until the new location was completely random. The rats were not allowed to enter the box until the goal had been located successfully or until the search exceeded 1 min. When the rats ran 30–40 trials in 30 min, they were considered to be ready for electrode implantation. After a recovery period of ~1 week, the rats were retrained and rapidly regained their previous levels of performance. During recording sessions, the duration of a trial rarely exceeded 1 min. The sessions were terminated when the rat began to slow down because of satiety or fatigue.

Two experimenters were present in the arena with the rat, one opening and closing the box, the other repositioning the landmarks between trials. Possible biases in the behavior of the animals attributable to the presence of the two experimenters were minimized by requiring one experimenter always to stand behind the box and the other to take random positions at the periphery of the arena.

Three different versions of the task were used.

In the *rotated* version of the task, the landmarks could be placed anywhere in the arena, as long as the line connecting the landmarks was aligned on an east–west axis or rotated and aligned on a north–south axis. The rat was released from the box anywhere along the periphery of the arena; after the rat found the goal, the box was brought to the vicinity of the landmarks. The rat then entered the box and was carried to a new start location (Fig. 3).

In the *translated* version of the task, the landmarks were translated to random locations in the northern two-thirds of the arena, with the tall, thin landmark always to the east of the short, thick one, such that the goal was always south of the landmarks. The box was moved to random locations along the south edge of the arena, with the opening always facing north toward the landmarks. The box was repositioned while the rat was near the goal and was not moved while the rat was inside (Fig. 3).

In the *central* version (which was used only as a control for one animal), the tall, thin landmark was always to the east of the short, thick landmark, and the range of movement of the landmarks was restricted to a 120-cm-diameter region in the center of the arena. The box was placed in pseudorandom order at five pre-established locations in the arena, with the opening always facing north. A new set of five locations was selected for each recording session.

Analysis of search behavior. To measure the extent to which the search behavior of the rats was guided by the landmarks, trajectory data for the rats in all nonreinforced trials were superimposed and aligned so that the landmarks and the goal locations overlapped. In these trials, no olfactory or visual cues were available to locate the reward. Therefore, the extent to which the paths taken by the rat were concentrated in the vicinity of the

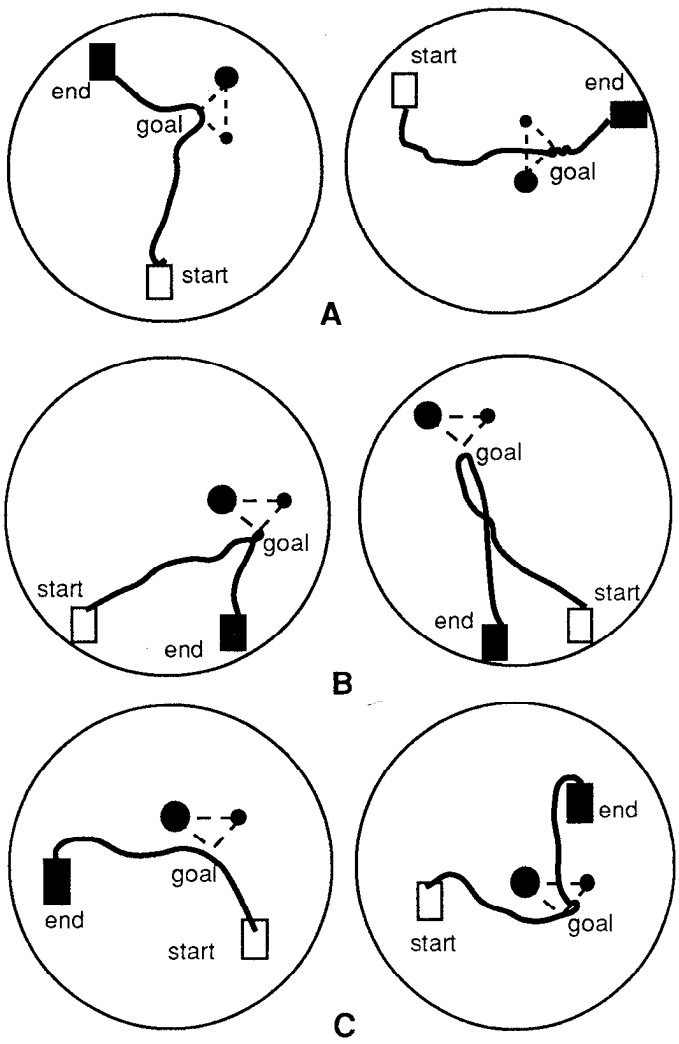

Figure 3. Illustration of the procedures for different versions of the task (not to scale). The trials are depicted in the reference frame of the arena. *A*, Two consecutive trials in the rotated version of the task. The *large solid circles* represent the short, thick landmark, and the *small solid circles* represent the tall, thin landmark. The *dashed lines* show the isosceles triangle of which the vertex was the correct goal location. The goal was always on the side of the landmarks from which the tall, thin landmark appeared on the right side and the short, thick landmark appeared on the left. The *open rectangles* indicate the location of the box at the beginning of the trial. The *solid rectangles* indicate the location of the box at the end of the trial. The *solid lines* indicate the trajectory taken by the rat. Between the two trials, the landmarks were translated and rotated and the box was moved to a new location. *B*, Two consecutive trials in the translated version of the task. In this version of the task, the landmarks maintained their east–west orientation and were only translated, i.e., the goal always remained south of the landmarks. The end location from each trial became the start location for the next trial. *C*, Two consecutive trials in the central version of the task. The tall, thin landmark was always to the east of the short, thick landmark, and the range of movement was restricted to a 120 cm^2 region in the center of the arena. The box was placed in pseudorandom order at five pre-established locations in the arena, with the opening always facing north. Different sets of five locations were used on different days.

goal reflects the precision with which the rats located the goal on the basis of the landmarks.

Measures of binding. The task design permitted the analysis of the data with respect to each of four different reference frames: the static background, the landmark/goal, and the location of the box at the start and at the end of a trial. These analyses were made possible by keyboard entries

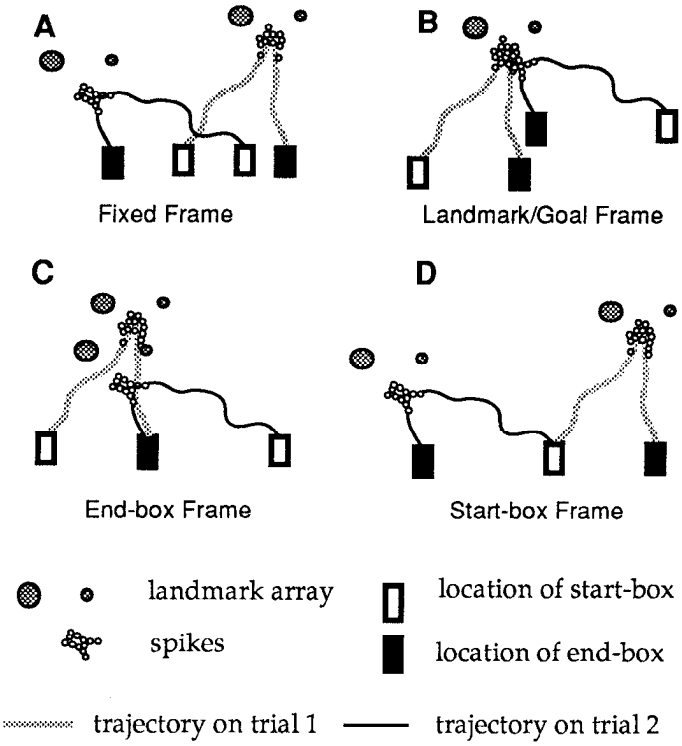

Figure 4. The four reference frames in which spatial information of cell discharge was assessed. In each drawing, two hypothetical trials are shown (*stippled line* and *solid line*). The *small* and *large stippled circles* represent landmark positions. The *open rectangles* depict the position of the box at the start of each trial, the *solid rectangles* depict the position of the box at the end of each trial, and the *small open circles* indicate the spikes fired by the cell. The hypothetical cell depicted in this figure fires a few spikes when the rat is near the goal and is silent in other locations. To establish the binding of this cell to a particular reference frame, the trials are aligned in four different ways: in the fixed (arena) frame (*A*), in the landmark/goal frame (*B*), in the end-box frame (*C*), and in the start-box frame (*D*). In the landmark/goal frame, all of the firing is concentrated in a single area, whereas in the other frames two separate areas of firing appear. Such a cell would have been classified as bound primarily to the landmark/goal frame. Cells were classified on the basis of the alignment that gave the tightest concentration of firing (i.e., largest spatial information per spike).

of "event flags" in the data files at the moment when the rat entered or exited the box and when it arrived at the goal.

If the firing of a cell bears a constant relationship to a particular feature of the environment or task, then a map of spatial firing rates, obtained by superimposing the maps for each trial aligned on that feature, should reveal a localized peak of firing. For example, if a cell is bound to the landmarks, then a shift in the location of the landmarks should induce a corresponding shift in the location at which the cell fires. A firing-rate map obtained by superimposing all of the trials, aligned on the landmarks, should reveal concentrated firing, whereas a firing-rate map aligned with respect to the arena or box reference frames should show broadly dispersed firing (Fig. 4).

To quantify the degree to which firing is spatially related to a feature, the spatial information per spike was calculated (Skaggs et al., 1993). This measure quantifies the amount of information that the occurrence of a single spike conveys regarding the location of the rat and is given by the formula:

$$I = \sum_i p_i \frac{\lambda_i}{\lambda} \log_2\left(\frac{\lambda_i}{\lambda}\right),$$

where I is the information, measured in bits per spike, i is the index of the bin representing the location where the spike occurred, p_i is the probability of the rat being at location i, λ_i is the mean firing rate of the cell

when the rat is at location i, and $\lambda = \Sigma\lambda_i p_i$ is the overall mean firing rate of the cell.

High information content per spike signifies that a single spike is a strong predictor of the location of the rat. For each cell, the spatial information per spike was examined relative to each of four different reference frames: (1) the arena frame, (2) the landmark/goal frame, (3) the start-location frame, and (4) the end-location frame.

A nonparametric test then was used to determine whether the spatial tuning in the reference frame giving the largest information per spike value was statistically significant. This test was to recalculate the information per spike value with the spike sequence of the cell time-shifted with respect to the position sequence of the rat. The information per spike was calculated for 100 different time shifts, each a random fraction of the total duration of the session (but never <1 min). A cell was considered to show significant ($p < 0.01$) location-specific firing if the value of the information per spike on the actual data was larger than the value of the same measure on any of the 100 randomly time-shifted data sets. This test is rather conservative and does not depend on any assumptions regarding the spatiotemporal distribution of firing.

For the analyses reported in this paper, the information per spike was calculated separately with the position and spike data collapsed onto either the x or the y axis, i.e., using either the x or y coordinate of the rat to represent its spatial location. This was done because the position sampling was often quite irregular across the two-dimensional region of the arena; the sampling was much better when the data were collapsed onto a single dimension. (The formula for information per spike requires only that the position of the rat be represented by a bin index i; there is no reason that i cannot represent the x or y coordinate rather than the fully specified two-dimensional position.)

To be classified as having an identifiable behavioral correlate, a cell had to meet three criteria: (1) it had to fire at least 100 spikes during the course of the session (otherwise the sample was considered inadequate); (2) it required a significant ($p < 0.01$) information per spike in at least one of the four reference frames; and (3) the maximal information per spike had to occur in the same reference frame when the data were collapsed on the x axis as when the data were collapsed on the y axis (otherwise the correlate was considered ambiguous).

It was possible for the activity of a cell to be related to more than one feature of the environment or task. This could happen in at least two ways. First, a cell could be related independently to at least two features of the environment (disjunctive correlate). An example of a disjunctive correlate would be a cell that fired whenever the rat was leaving the box and also when the rat was at the goal location. Second, a cell could display significant activity only when two or more features are combined in a particular way (conjunctive correlate). For example, a cell might have a strong relation to the landmarks, but only when the landmarks are located in a particular portion of the arena.

It was not possible to classify all cells in these terms statistically, however, because the behavioral sampling was not sufficient (the recording environment was large, the rats did not run more than 30–35 trials in one session, and the rats covered a variable and relatively small proportion of the environment on a given trial). Although complex properties were apparent on visual inspection of the data in a number of cases in which a cell was classified as bound to a certain feature, no firm claim is intended regarding whether the cell was bound independently, conjunctively, disjunctively, or otherwise; our only claim is that the activity of the cell bears a stronger relation to that feature than to any of the others considered in the analysis. Statistical verification of the precise nature of the relations would require a different experimental design in which the spatial sampling is uniform in all alignments.

RESULTS

Hippocampal CA1 pyramidal cells from three rats were recorded. Cells from one rat were recorded only in the rotated version of the task (42 cells), cells from the second rat were recorded in the rotated (95 cells) and translated (296 cells) versions, and cells from the third rat were recorded in the translated (25 cells) and central versions (26 cells).

The behavior was controlled by the landmarks

After ~200 training trials distributed over ~20 d, the rats learned to exit the box, orient to the landmarks, locate the goal, eat the reward, orient back to the box, and return to it. In the initial stages of training, all three rats showed a strong tendency to return to the goal location from the previous trial, ignoring the landmarks. Without specific tests, it was impossible to determine which cues the rats used to locate the goal. Comparison of the search pattern on rewarded and nonrewarded trials, however, failed to reveal any significant differences in path length, latency, or pattern of deviation from the direct path (data not shown). This suggests that the rats were guided more by the learned spatial relationship between the landmarks and the goal and less by the sensory qualities of the reward. Careful observation of the behavior indicated that the rats changed search strategy when they reached the vicinity of the goal. At ~10 cm from the goal, they typically slowed down and explored by casting about and vigorously moving their vibrissae, which suggests that they expected to find the reward by using visual, olfactory, or tactile cues. Although these sensory cues were readily available on all rewarded trials, the rats sometimes ran over the chocolate sprinkles without noticing them and occasionally missed the goal by passing within a few centimeters of it.

The rats used the landmarks to find the goal, as shown by the concentration of their search within the distance between the landmarks and the goal. Figure 5 shows a plot of the mean density of search (in $\text{sec} \cdot \text{cm}^{-2} \cdot \text{trial}^{-1}$) as a function of distance from the goal for all of the nonrewarded trials. The peak search density was at the goal location and not in the immediate vicinity of the landmarks, which indicates that the rats used the landmarks as spatial cues rather than as beacons, at least from close range.

In the rotated version of the task, the rats needed to discriminate between the two landmarks to determine on which side of the landmarks the goal was located (see Fig. 3*A*). When the rat was at the correct goal location, the tall landmark appeared on the right and the short landmark appeared on the left. Viewed from the opposite side, the landmarks were reversed. The rats often searched on whichever side they reached first, but only when they were the correct distance from the landmarks, which indicates that they learned the spatial relationships between the landmarks and the goal, but they did not learn to discriminate between the correct and reversed landmark configurations.

Cells were bound to the static background cues, the landmarks, and the box

Four major categories of cells were observed (see Fig. 6): (1) place cells with stable place fields relative to the static background cues; (2) goal/landmark-related cells that were bound to the landmarks independent of their location in the arena; (3) box-related cells that fired either inside the box or as the animal was leaving or returning to the box (with few exceptions, the box-inward and box-outward cells fired for either inward or outward motion, but not both); and (4) cells with compound response profiles.

Of the 484 recorded cells, 121 cells were eliminated from analysis either because they fired <100 spikes (61 cells) or because the nonparametric test for information content did not reach significance ($p < 0.01$) in any reference frame (60 cells). Most of the latter showed variations in firing rate as a function of location in one or more reference frames, but these variations were neither large nor consistent enough to permit the cells to be classified. Of the 363 cells that were included in the analysis, 227 cells (62%) had an identifiable behavioral correlate. For the 136 remaining cells, the behavioral correlate could not be interpreted unequivocally. These cells showed significant ($p < 0.01$) location-specific firing, but with the current classification criteria it was impossible to establish the reference frames to which these cells were bound. [Recall that the information per spike measure was

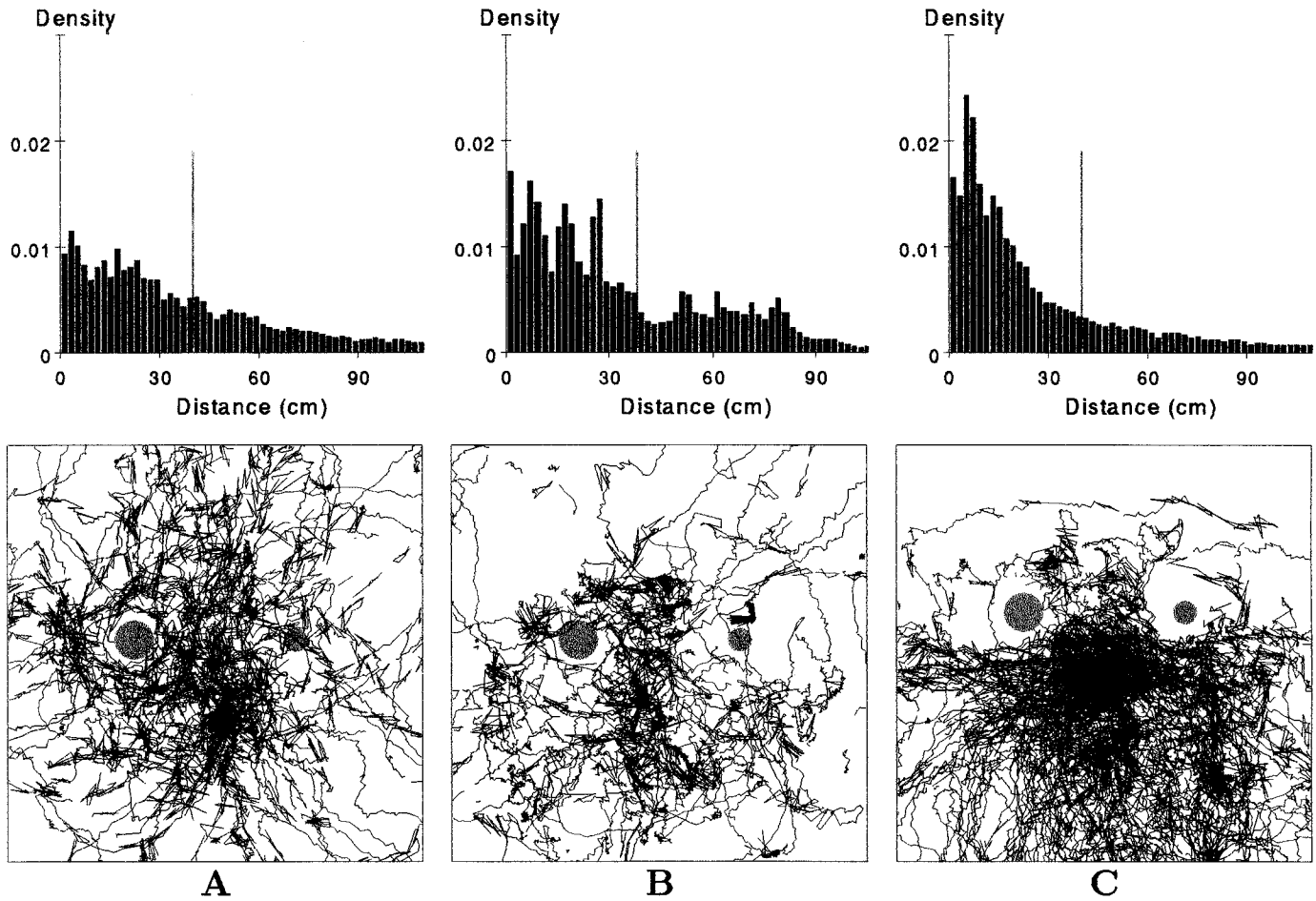

Figure 5. Search behavior on the nonrewarded trials. The *top* shows plots of the density of search (in $sec \cdot cm^{-2} \cdot trial^{-1}$) as a function of distance from the goal on nonrewarded trials. Under each plot a corresponding map is shown, representing all of the nonrewarded trials overlaid in the alignment of the landmarks. The *large* and *small gray dots* represent the thick and thin landmarks, respectively. The *lines* represent the overlaid trajectories of the rat. *A*, All nonrewarded trials (14) for rat 2 in the rotated version of the task; *B*, all nonrewarded trials (24) for rat 1 in the rotated version of the task; *C*, all nonrewarded trials (61) for rat 2 in the translated version of the task. Although the search pattern was more accurate in the translated version, in both versions the densest occupancy was concentrated within 30 cm of the goal location, a radius smaller than the distance between the goal and the landmarks, which was 40 cm (indicated by the *thin line*). This figure shows that the rats used the landmarks to guide their search.

obtained by collapsing the data on the x and y axes, and the criterion to establish the binding of a cell to a reference frame was that the cell had maximal information per spike measures on both axes in the same reference frame. For example, if a cell had maximal information per spike on the x and the y axes in the arena frame, it was classified as bound to the arena frame (place cell), but if it had maximal information per spike in the arena frame on the x axis and in the landmark frame on the y axis, then the reference frame to which it was bound could not be established and the cell was eliminated from further analysis.]

Of the 227 cells with an identifiable behavioral correlate, 102 (45%) were place cells, 23 (10%) were landmark/goal-related cells, 46 (20%) were box-outward cells, 38 (16%) were box-inward cells, and 18 cells (8%) were active when the rat was inside the box.

Place cells

A cell was classified as a place cell if it had the highest information content when the trials were aligned in the arena frame. Of the 102 place cells, 77 cells appeared to have a single field and 25 cells had multiple fields. An example of a place cell with a single field is shown in Figure 6*E*. Place fields were scattered more or less homogeneously throughout the arena. Because of sampling irregularities attributable to the behavior of the rat, it was rarely possible to quantify any dependence of firing of place cells on the orientation of the head of the rat while the animal was in the place field. In the translated version of the task, however, there was an apparent tendency for cells with place fields in the southern half of the arena (i.e., within the range of movement of the box) to be more directionally dependent than cells with fields within the range of movement of the landmarks. These cells tended to fire preferentially when the rats were running through their fields in one direction (either to or from the goal). Some cells fired robustly in their fields over a broad range of head orientations.

Landmark/goal-related cells

For 23 cells, the information measure was maximal when the trials were aligned on the landmarks. For all but one of the cells in this category, the firing was concentrated near the goal location, but different cells fired maximally before arrival at the goal, at the goal itself, or after departure from the goal. The exceptional cell had increased firing rates when the rat was passing in front of the large landmark (Fig. 6*A*). These cells could be described as place cells in landmark/goal-centered coordinates. Many cells classified by

the analysis as goal-related had variable rates and were unreliable, sometimes failing altogether to fire at the goal, regardless of its location in the arena. It was not clear whether this variability was related to variation in the exact location of the rat relative to the goal or to some other factor such as the location of the landmarks in the arena. With one exception, goal-related cells fired during nonreinforced trials, indicating that they were not related directly to perception of the reward.

Box-related cells

In a similar manner, cells bound to the box could be considered place cells in box-centered coordinates. Of the 102 cells bound to the box, 18 cells fired when the rat was inside the box, 46 cells fired when the rat was leaving the box (box-outward cells), and 38 cells fired when the rat was entering the box (box-inward cells). Cells that were clearly box-related were found in all versions of the task and, in contrast to goal-related cells, their firing was highly reliable across trials. An example of a box-inward cell is shown in Figure 6*C*; a box-outward cell is shown in Figure 6*D*. For these cells, the information content in the end-box alignment or the start-box alignment was higher than in the arena or landmark/goal alignments, indicating a stronger correlation of the cell discharge with the location of the rat relative to the box than with location in the arena.

Box-inward cells exhibited peak firing at variable distances (20–40 cm) from the box (Fig. 7*B*). These cells fired as the animal approached the box, regardless of whether it was open or closed. Box-outward cells (Fig. 7*A*) also had peak firing at various distances from the box (up to ~40 cm). Some box-outward cells fired for longer portions of the trajectory than others, but all box-outward cells in the sample stopped firing when the rat was farther than ~70 cm from the box. While the rat was inside the box eating the reward and waiting to be released for a new trial, a different set of box-related cells (in-box cells) was active. These cells stopped firing when the box was opened and the rat started outward. Many of these in-box cells appeared to have place fields occupying a fraction of the interior of the box.

A few exceptional box-related cells fired both when the rat was exiting and when it was entering the box. Figure 7*C* shows a box-inward/outward cell from the central version of the task. This example also illustrates the fact that fields classified as box-related actually were bound to the box and were not merely broad directional place fields located at the southern edge of the arena, as might have been inferred from the translated version of the task alone.

Disjunctive and conjunctive cells

Some cells clearly exhibited disjunctive properties. Disjunctive cells showed specific firing related to more than one reference frame in the task. Examples of disjunctions were observed between all combinations of reference frames (Fig. 8). The demonstration of conjunctive firing was much more problematic. Establishment of conjunctions would require multiple sampling for each goal and box location, and the experiments were not designed for this purpose. Only 25–30 trials were available from each recording session, and there were many more landmark and box locations. The clearest example of apparent conjunction was a box-inward cell in the rotated version of the task (see Fig. 8), which fired only when the rat approached the box from north to south (this cell could also be interpreted as one with a place field in box-centered coordinates located to the north of the box). Cells that fired inside the box were never conjunctive, i.e., they fired reliably in all box locations.

Population properties

There was no apparent evidence for a topographical organization of the observed correlates of the cells. Adjacent cells recorded from the same tetrode were not homogenous in terms of their behavioral correlates; nor did adjacent place cells show adjacent place fields. When a cell was recorded multiple times, it showed the same behavioral correlate over days. The relative proportion of cells with different behavioral correlates was constant over time and across animals. Cells with different behavioral correlates were coactive during a recording session, but no clear examples were seen in which cells bound to different reference frames fired at the same time. For example, in one session during which 23 cells were recorded simultaneously, 8 cells had one or more place fields, 1 cell was goal-related, 1 cell was box-inward, 3 cells were box-outward, 1 cell fired only when the animal was inside the box, and 9 cells were unclassifiable. In none of the cases was there evidence for simultaneous activation of multiple reference frames.

Although box-related cells were highly reliable, firing with similar rates on virtually every trial, goal-related cells often failed to fire on some trials. Place cells appeared to be intermediate in reliability; they fired more consistently than goal-related cells and less consistently than box-related cells. With two exceptions, none of the cells ceased firing in accordance with its assigned correlate because of any manipulation. The two exceptions were the putative conjunctive cell shown in Figure 8*A* and a goal-related cell that ceased firing during nonrewarded trials.

DISCUSSION

The main conclusion of the present study is that in a task requiring guidance with respect to variably located objects within an otherwise fixed environment, both the fixed environment and the movable objects define independent spatial reference frames that are encoded by different subsets of hippocampal neurons. The overall results can be summarized in three main points. (1) The rats learned a spatial location predicted by landmarks, the positions of which varied from trial to trial relative to the fixed reference frame. (2) Landmark/goal-related cells and box-related cells fired in fixed spatial relationships to these objects, apparently independently of the location of the objects relative to the fixed frame. (3) Although the static background cues were not directly relevant for the required behavior, 45% of the cells showed the tightest distribution of firing in relation to this frame (i.e., place cells). This fraction does not reflect the 136 of 363 cells with significant spatial information per spike on one or more axes, but in which correlates could not be established unequivocally according to our criteria.

The successful acquisition by the rats of a spatial task based on variably located landmarks is in contrast with the results of Biegler et al. (1993), who emphasized the importance of landmark stability for spatial learning. On the other hand, Collett et al. (1986) and, recently, Biegler and Morris (R. Biegler, personal communication) showed that when two landmarks are stable with respect to each other but unstable with respect to the fixed frame of the environment, rodents can learn to find a location predicted by those landmarks. In our study, however, all rats initially showed a tendency to ignore the landmarks and to return to the previous goal location. Only after ~200 training trials was the behavior guided reliably by the landmarks and not by the fixed background cues. The large proportion of place cells recorded in this task suggests that the rats did not ignore the global spatial frame of the

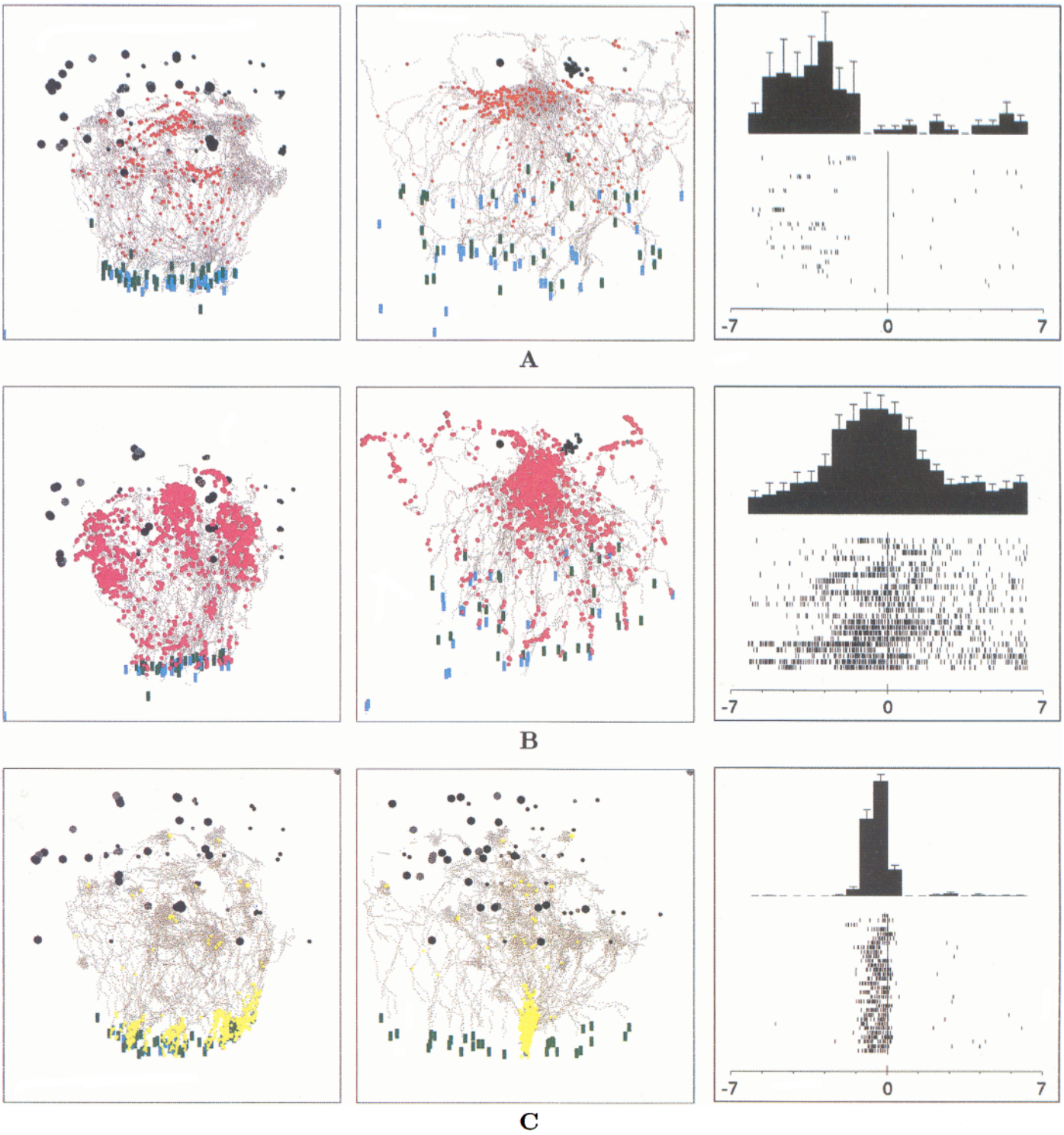

Figure 6. Two examples of each category of cell. For each cell, a firing map in the arena frame is shown on the *left*, the alignment most relevant for the strongest behavioral correlate is shown in the *middle*, and histogram and raster plots for the same cell aligned on the relevant event are shown on the *right*. In each picture, the *small* and *large black dots* indicate the tall, thin landmark and the short, thick landmark, respectively; the *gray lines* depict the superimposed trajectories of the rat; the *small green marks* indicate the position of the box at the start of each trial; the *small blue marks* show the position of the box at the end of each trial; and the *small dots of various colors* each represent a spike fired by the cell. *A*, Landmark/goal-related cell. The firing was more concentrated in the landmark/goal frame (*center*) than in the fixed (arena) frame (*left*). The raster and histogram are aligned on the arrival of the rat at the goal. This cell fired with higher rates when the rat was passing in front of the short, thick landmark. *B*, Landmark/goal-related cell. *Left*, Fixed frame; *center*, landmark/goal frame; *right*, histogram and raster aligned on arrival at goal. This cell exhibited elevated rates of firing near the time of arrival at the goal. *C*, Box-inward cell. *Left*, Fixed frame; *center*, end-box frame; *right*, histogram and raster aligned on arrival at box. This cell fired just before the rat entered the box.

Figure 6. continued *D*, Box-outward cell. *Left*, Fixed frame; *center*, start-box frame; *right*, histogram and raster aligned on departure from box. This cell fired shortly after the rat exited the box. *E*, Place cell. *Left*, Fixed frame; *center*, landmark/goal frame; *right*, histogram and raster aligned on arrival at goal. This cell had a place field near the center of the arena. In the landmark/goal frame, the cell has no significant spatial specificity. *F*, Place cell. *Left*, Fixed frame; *center*, end-box frame; *right*, histogram and raster aligned on arrival at box. This cell had a place field in the southeast region of the arena. Note that the spatial concentration of firing is tighter in the arena frame than in the end-box frame.

arena and that they appeared to update their location within it. Figure 5, which illustrates the density of search as a function of the radius of a circle concentric with the goal, shows that instead of searching near the landmarks, the rats used them to compute the goal location. If they had used the landmarks as beacons, the search would have been more concentrated in the immediate vicinity of the landmarks than at the correct distance from them. This is supported by the fact that the firing of goal-related cells

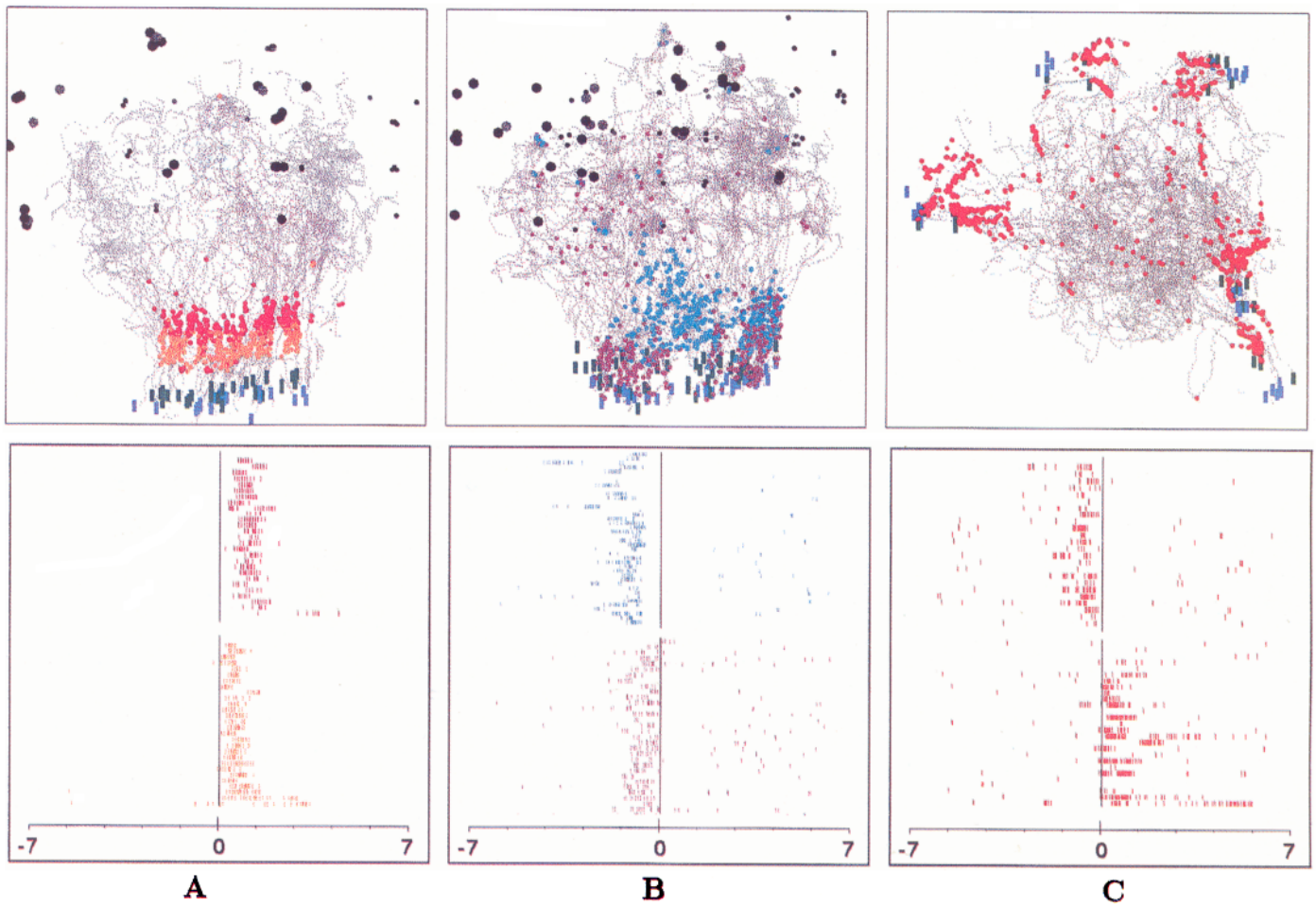

Figure 7. Properties of box-inward and box-outward cells. The *top* shows spatial firing maps in the reference frame of the arena. The *bottom* shows two raster plots for the same cells, with corresponding color code. *A*, Two simultaneously recorded box-outward cells from the translated version of the task, illustrating that different cells fired maximally at different locations within a given reference frame, rather than only in the immediate vicinity of the reference object. The rasters for the two cells (*magenta* and *orange*) are aligned on the moment of departure from the box. *B*, Two simultaneously recorded box-inward cells from the translated version of the task, again illustrating that different cells fired maximally at different locations within a given reference frame. The rasters for the two cells (*teal* and *purple*) are aligned on the moment of arrival at the box. *C*, A box-inward/outward cell recorded in the central version of the task. The five box locations are indicated by the *clusters* of *green* and *blue* marks, which represent the position of the box at the beginning and end of each trial, respectively. The landmark locations are not shown. The *red dots* represent spikes emitted during both box entry and box exit. The firing was independent of the angle at which the rat approached or departed from the box. The top raster is aligned on the arrival at the box; the bottom raster is aligned on the departure from the box.

was clustered near the goal and was located only exceptionally in the vicinity of the landmarks themselves. Moreover, for both box- and goal-related cells, firing fields were distributed at different distances from their respective reference locations and were not centered at a common point. This also supports the idea that these locations served as origins of spatial frames (McNaughton et al., 1991; Wan et al., 1994; McNaughton et al., in press) rather than as beacons. It is likely, however, that the rats used the landmarks as beacons from larger distances and as spatial cues from smaller distances and that along the trajectory between box and goal and return, several changes of reference frame occurred.

O'Keefe and Nadel (1978) suggested a distinction between taxon-based (hippocampal-independent) and locale-based (hippocampal-dependent) problem solving. Our results could be interpreted as indicating that the rats solve this task by treating the landmarks (or box) as a taxon when the rats are distant and switch to a locale-based strategy in the vicinity of the goal or the box. A natural prediction arising from this interpretation is that if animals with hippocampal lesions were trained in this task, they would be able to learn to search in the vicinity of the landmarks, but their search would be distributed over a considerably broader region. This prediction receives some support from the findings of Bingman and Mench (1990), who reported that hippocampal-lesioned homing pigeons were able to fly into the vicinity of their home loft but were impaired in using local landmarks to find the precise location.

To account for the observed interaction between static background cues and a set of controlled spatial cues that were rotated from trial to trial, O'Keefe and Speakman (1987) suggested that their rats acquired separate representations for each configuration of the controlled and static background cues. Although in their study place-cell firing primarily followed the orientation of the controlled cues, they demonstrated significant interactions between the two frameworks. Given that in our experiments >300

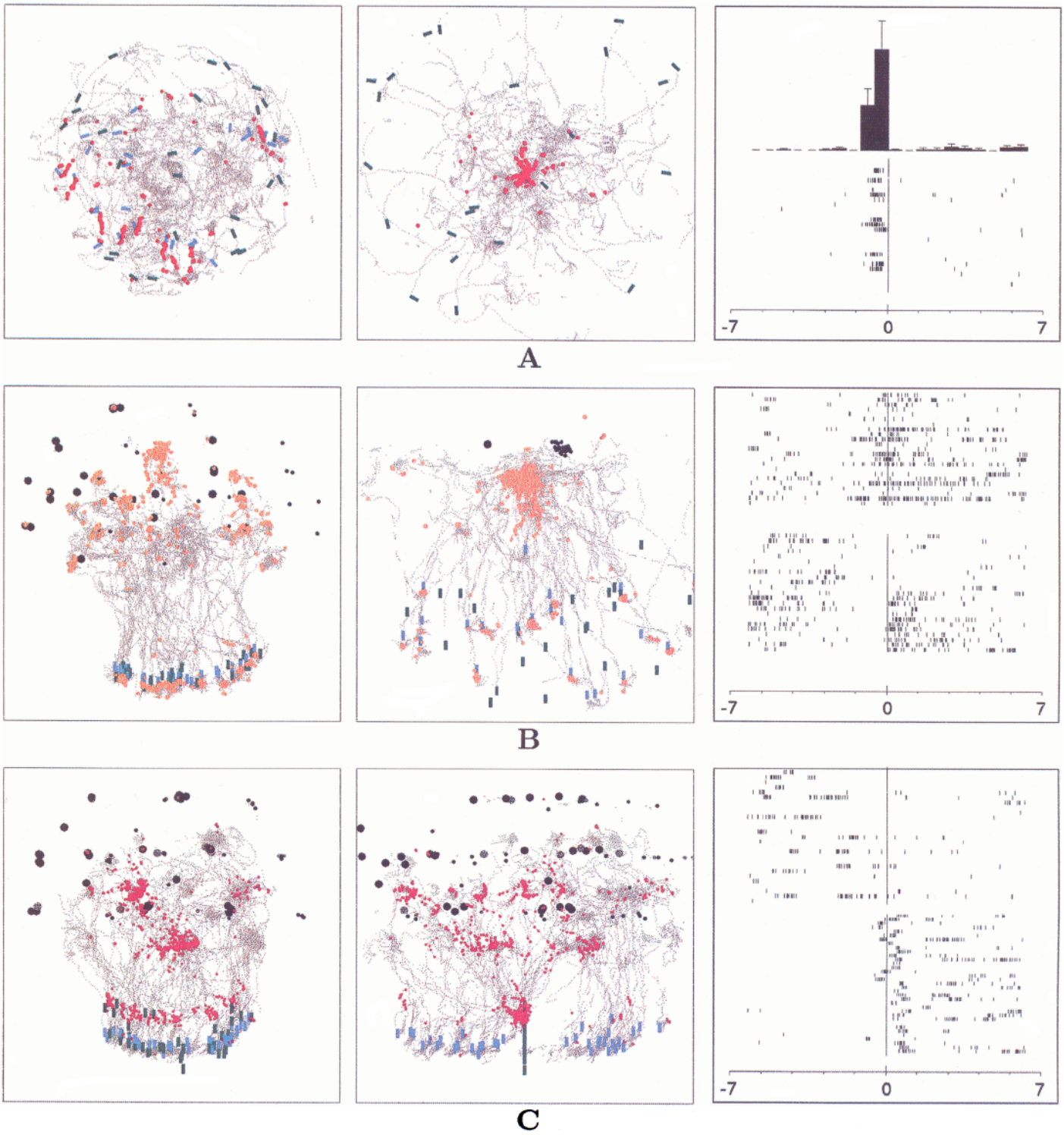

Figure 8. Interactions among reference frames. *A*, Putative conjunctive cell. The *left* shows a box-inward cell from the rotated version of the task. This box-inward cell fired primarily when the box was in the southern region at the arena and, hence, can be considered to be reflecting a conjunction of the fixed and box frames; however, a more accurate description, revealed by detailed trial-by-trial analysis, is that this cell had a directional place field in the box frame, firing only when the rat approached the box from the north. There were no unambiguous examples of conjunctive cells. *B*, Disjunctive cell. This cell fired both at the goal and inside the box. *Left*, Fixed frame; *center*, landmark/goal frame; *right*, upper raster aligned on arrival at goal, lower raster aligned on arrival at box. *C*, Disjunctive cell. This cell fired both during departure from the box and at two specific locations in the arena. *Left*, Fixed frame; *center*, start-box frame; *right*, upper raster aligned on arrival at goal, lower raster aligned on departure from box.

configurations of landmark and box locations were used, it is unlikely that the rats acquired separate representations for each configuration. Our data suggest that the animals solved this task by representing their location separately relative to the global and to the local spatial frames and that these frames largely were independent of one another. Interactions between reference frames (i.e., conjunctive cells) could be neither demonstrated clearly nor ruled out because of the limited sampling of the arena on any given trial. The existence of disjunctive cells, which appear to have place fields in more than one reference frame, is consistent with a large body of previous work indicating that place cells can have fields in more than one environment (O'Keefe and Conway, 1978; Kubie and Ranck, 1983). With this interpretation, "environment" and "reference frame" may be synonymous, at least from a functional perspective. This interpretation suggests, for example, that a box cell in the present context easily could be a place cell in another.

The idea that different groups of cells represent location within different reference frames raises the question of whether more than one reference frame can be represented simultaneously in the hippocampal network. Although the present experiments were not designed to answer this question, it appears that cells bound to different reference frames were not activated simultaneously. For example, in those trials in which the goal location fell within the firing field of a place cell, the place cell appeared to be silent while the rat was at the goal; however, many goal-related cells fired strongly at this time.

No difference was observed among the types and proportions of cells for the different versions of the task, despite the fact that the rats made different kinds of errors in each version. In the translated version, they had a tendency to overshoot the goal when the landmarks were placed very close to the start-box; in the rotated version, they did not discriminate successfully between the correct goal and the "inverted goal" (see Fig. 3).

The existence of landmark- and box-related cells confirms the hypothesis that task-relevant landmarks or locations explicitly control the firing of hippocampal cells, as suggested by McNaughton et al. (1991). None of the landmark- or box-related cells, however, fired at $\gtrsim$70 cm beyond the area in which the corresponding appropriate behavior was required, i.e., searching for the reward or entering or exiting the box. This suggests that behavioral context plays an important role in switching spatial reference frames, a conclusion similar to that of McNaughton et al. (in press) and Markus et al. (1995), who showed that place fields in a fixed environment often shift between tasks requiring different foci of spatial attention and that directional firing of place cells on tasks requiring navigation between two locations (e.g., linear tracks) could be explained in this manner. A similar conclusion, on the basis of the idea of input from a separate path-integration module, was suggested independently by Wan et al. (1994). In any event, the absence of landmark- and box-related firing at greater distances suggests that the landmarks and the box did not constitute global spatial reference frames. This raises the question of whether global spatial reference frames exist at all in the hippocampal representation, because our data do not provide a basis for distinguishing whether the static background frame was unitary or a mosaic of multiple frames (see Worden, 1992) that maintained constant relationships to one another.

Goal-related cells have been described previously in various paradigms as approach-consummate (Ranck, 1973) or goal-approach (Eichenbaum et al., 1987) cells, and other authors have reported shifting or alteration of place fields when reward locations change (Breese et al., 1989; Fukuda et al., 1992). The present findings raise the question of whether these cells should be considered explicitly reward-related, in the appetitive sense, or whether reward locations (among others) define the origins of spatial reference frames. The cells firing on the approach to the box or goal sites certainly are amenable to such an interpretation; however, the observation that different cells had peak firing zones at different distances from the reward sites, and that approximately the same proportions of cells were selective for departure from the goal or box as for the approach, again tends to support the multiple reference frame interpretation.

The idea that hippocampal representations of spatial relationships are partitioned into quasi-independent reference frames has much in common with the view that animals represent locations as bearings and distances (i.e., vectors) from or to landmarks or points of particular behavioral significance (Mittelstaedt and Mittelstaedt, 1980; Collett et al., 1986; McNaughton et al., 1991, 1994; Worden, 1992; Wan et al., 1994), rather than by encoding explicit relationships among groups of landmarks. Although this idea appears to be compatible with the body of experimental literature on hippocampal cells, and although it might account for the long-standing problem of why place cells are directional in some contexts and not in others (McNaughton et al., 1983a,b; Muller et al., 1987, 1994; Markus et al., in press), it leaves open as many questions as it answers. Those questions include the following. What determines the establishment of a reference point? How is the metric for location relative to a reference point encoded? What determines when the system shifts its representation of location from one reference point to another? How might different reference frames be integrated to enable effective long-range navigation?

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