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Fast Rate Coding in Hippocampal CA3 Cell Ensembles

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ABSTRACT: Environments with overlapping features are represented by distinct patterns of activity in the hippocampus, enabling information to be stored and retrieved with minimal interference. This orthogonalization of correlated inputs is thought to take place within the hippocampus itself. However, the orthogonalization process has been shown to take days to develop in CA1. This prolonged time course is in striking contrast to the fast encoding of behavioral memory by the hippocampus. To explore this apparent paradox, we asked whether orthogonalization depended on the type of remapping exhibited by the hippocampal network. We have previously distinguished two types of remapping, global remapping, which results in the activation of different assemblies of place fields, and rate remapping, which encodes differences between cue constellations by substantial changes in firing rate without a change in the place code. Global remapping has previously been shown to be expressed immediately at novel locations. Here we asked if rate remapping follows a slower time course. Ensemble activity was recorded simultaneously from CA3 and CA1 in rats exposed to two similar, novel environments. It was found that rate changes in response to novel sensory cue configurations can form immediately, just as during global remapping, in particular in CA3. The fast encoding of both spatial and nonspatial information in CA3 is consistent with a role for the autoassociative CA3 circuitry in the acquisition and expression of episodic memories. © **2006 Wiley-Liss, Inc.**

KEY WORDS: remapping; pattern separation; population coding; autoassociative networks; episodic memory

INTRODUCTION

The hippocampal CA3 subfield seems to have a key role in disambiguating sensory input patterns from the neocortex. Using both ensemble recording and gene imaging techniques, investigators have found that partially overlapping sensory inputs are strongly orthogonalized by cell populations in CA3 (Leutgeb et al., 2004; Vazdarjanowa and Guzowski, 2004). Such neuronal pattern separation may support the encoding of new experiences as separate from familiar items in memory, but the process is balanced by pattern completion, which results in stable neuronal activity for small to moderate deviations from previously learned sensory inputs (Nakazawa et al., 2002; Lee and Kesner, 2004; Vazdarjanowa and Guzowski, 2004; Wills et al., 2005). The generalization between inputs by pattern completion is thought to support memory retrieval (Marr, 1971; Treves and Rolls, 1994), but it may not be advantageous for encoding novel inputs as distinct from existing representations. Concurrent retrieval and acquisition would be better supported by network dynamics that allowed for pattern completion and separation to be expressed in parallel or enabled a gradual transition between pattern completion and pattern separation.

Recent studies suggest that hippocampal neuronal populations possess two orthogonal coding schemes to support such parallel responses (Leutgeb et al., 2005a,b). These schemes can be dissociated by manipulating the configuration of input patterns to the hippocampus. Global remapping, expressed as a coherent redistribution of firing locations and firing rates among simultaneously recorded place cells, is nearly always induced when the animal is moved between two distinct locations (Leutgeb et al., 2004, 2005a). Under some circumstances, global remapping can also occur in a constant location, presumably when the features of the local environment are changed rather extensively (Bostock et al., 1991; Kentros et al., 1998). Rate remapping is expressed as a change in the distribution of activity in the population without an accompanying change in the preferred firing locations of the individual neurons. This form of remapping is often induced during selective replacement of cues in an otherwise constant environment (Leutgeb et al., 2005a).

Global remapping and rate remapping may reflect different neuronal computations that follow different time courses. A number of observations indicate that global remapping in the hippocampus is established almost instantaneously, as expected if place cells play a role in encoding differential memories for two locations. When animals are brought from a familiar environment to a similar but novel environment, the place code in CA1 appears to undergo immediate global remapping (Kentros et al., 1998; Hayman et al., 2003; Wills et al., 2005), and the new location-selective firing patterns are stable within minutes after rats are introduced to the novel environment (Wilson and McNaughton, 1993; Frank et al., 2004). Although orthogonalized firing is apparent soon after the animal begins to explore, the emerging place fields continue to develop in CA3 for several minutes after stable CA1 fields have formed (Leutgeb et al., 2004). This dissociation between the two hippocampal cell populations suggests that the fast component in the CA1 cell response is, at least in part, independent of the inputs from CA3 and, therefore, may depend more on direct inputs from the spatial map in the medial entorhinal cortex (Brun et al., 2002; Nakazawa et al., 2003; Fyhn et al., 2004; Hafting et al.,

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2005). The time course of rate remapping has not been determined. Rate remapping may be based to a larger extent on converging place and event information, which could initially be stored in the associative networks of CA3 and later be transferred to CA1 (Leutgeb et al., 2005a,b,c). If this is the case, remapping should first appear in CA3, and CA1 place fields might, under some conditions, express a slower component of rate remapping on top of the fast component. This possibility receives some support from studies showing that when remapping is induced by changing the geometric shape of a box with flexible walls in an otherwise constant environment, representations in CA1 may change slowly, often over the course of several days or weeks (Lever et al., 2002). Unfortunately, since the dissociation between global remapping and rate remapping is not as clear in CA1 as in CA3 (Leutgeb et al., 2005a), the type of remapping cannot be inferred directly from the data in the study by Lever et al. (2002).

If rate remapping always followed a slow time-course, taking days or weeks to reach an asymptotic level, it may not be able to support encoding of new information at the time scale of behavioral learning. Several widely used hippocampal-dependent memory tasks, such as passive avoidance, context conditioning, and delayed-matching and nonmatching to sample tasks, are learned within seconds or minutes, or in a single trial (e.g., Isaacson and Wickelgren, 1962; Izquierdo et al., 1992; Phillips and LeDoux, 1992; Maren et al., 1997; Steele and Morris, 1999). Behavioral evidence supports a role of CA3 (Lee and Kesner, 2004) and, in particular, of synaptic plasticity in CA3 (Lee and Kesner, 2002; Nakazawa et al., 2003), in the fast acquisition of such tasks. If memory is supported by distinct patterns of neuronal activity in CA3, these should be expressed right from the beginning as an animal is exposed to the new information. Thus, to determine whether rate remapping follows a time course that might support the encoding of new information and to establish whether rate remapping has a different time course in CA3 than in CA1, we recorded simultaneously from cells in these hippocampal subfields in a novel environment, using a color-reversal task that previously has been shown to induce robust rate remapping in CA3 during testing in familiar environments (Leutgeb et al., 2005a).

MATERIALS AND METHODS

Subjects

Four male Long Evans rats were housed individually in transparent Plexiglass cages ($45 \times 30 \times 35$ cm^3). The rats were kept at 85–90% of free-feeding body weight. All rats were maintained on a 12-h light/12-h dark schedule. Testing occurred in the dark phase. At the time of surgery, the rats were anesthetized with Equithesin (1 ml/250 g, i.p.) and a hyperdrive with 14 independently movable tetrodes was implanted above the right hippocampus (AP 3.8, ML 3.0, DV 1.5).

Recording Procedures

Tetrodes were constructed from 17 μm polyimide-coated platinum-iridium (90–10%) wire. Electrode tips were plated with platinum to lower electrode impedances to between 200 and 300 kΩ at 1 kHz. The tetrodes were moved either toward CA3c or toward the central part of CA1 (Fig. 1A). Two tetrodes were used to record a reference signal from the corpus callosum and an EEG signal from the stratum lacunosum-moleculare. Five to eight of the tetrodes were lowered toward CA3c, and the remaining tetrodes were lowered toward CA1 while screening for hippocampal spike activity. The rat rested on a pedestal during the screening. On the day of recording, the electrodes were not moved at all or only <20 μm, so as to maintain stable recordings. Spikes were recorded simultaneously from CA3 and CA1 in all experiments.

During screening and recording, the hyperdrive was connected to a multichannel, impedance matching, unity gain headstage. The output of the headstage was conducted via a lightweight multiwire tether and a Neuralynx 82-channel slip-ring commutator to a data acquisition system with 64 digitally programmable amplifiers. Unit activity was amplified by a factor of 3,000–5,000 and band-pass filtered at 600 Hz–6 kHz. Spike waveforms above a threshold of 55 μV were time-stamped and digitized at 32 kHz for 1 μs. Light emitting diodes on the headstage were tracked at 50 Hz. EEG from stratum lacunosum-moleculare was recorded continuously in the 1–450 Hz band.

Behavioral Procedures

Both the recording room and the white and black square recording box were, on recording day 1, new to the animal. All previous training and testing had been done in a different room and box. Two animals had been pretrained for 1 week in a gray cylinder (90 cm in diameter). The other two animals were tested in the new room after 5–6 weeks of training and testing in a gray morph box (Leutgeb et al., 2005b).

The recording rooms were rectangular, with the recording equipment and the experimenter placed near the entrance (south) and the square box placed far into the room (north). The box rested on a 70 cm high table and had individually exchangeable walls (black on one side, white on the other side; 100×100 cm^2; 50 cm high). To polarize the environments, a distinct cue card was placed in each box at a constant location (50 cm high; 25–100 cm wide). The color of the cue card was opposite to that of the box walls. Curtains were not used around the test enclosure to allow the animal a clear view of the light source, a shaded window, and other external cues within each room. A pedestal was placed between the test box and the door of each room, where the rat was rested for 20 min before each trial to establish the spatial reference frame. The rats were also allowed to rest on the pedestal for 5 min between each recording trial. While the rats were resting, the floor of the recording box was washed and each wall was placed along a different side of the box to scramble the odor cues. If a color change was desired, the wall (which was black on one side and white on the other side) was inverted. At the start of the trial, the rat was picked up from the pedestal and, without disorientation, placed into the chamber. Running was maintained by food morsels that were randomly and intermittently scattered on the apparatus floor. The animal was placed into the white box for a 10-min trial,

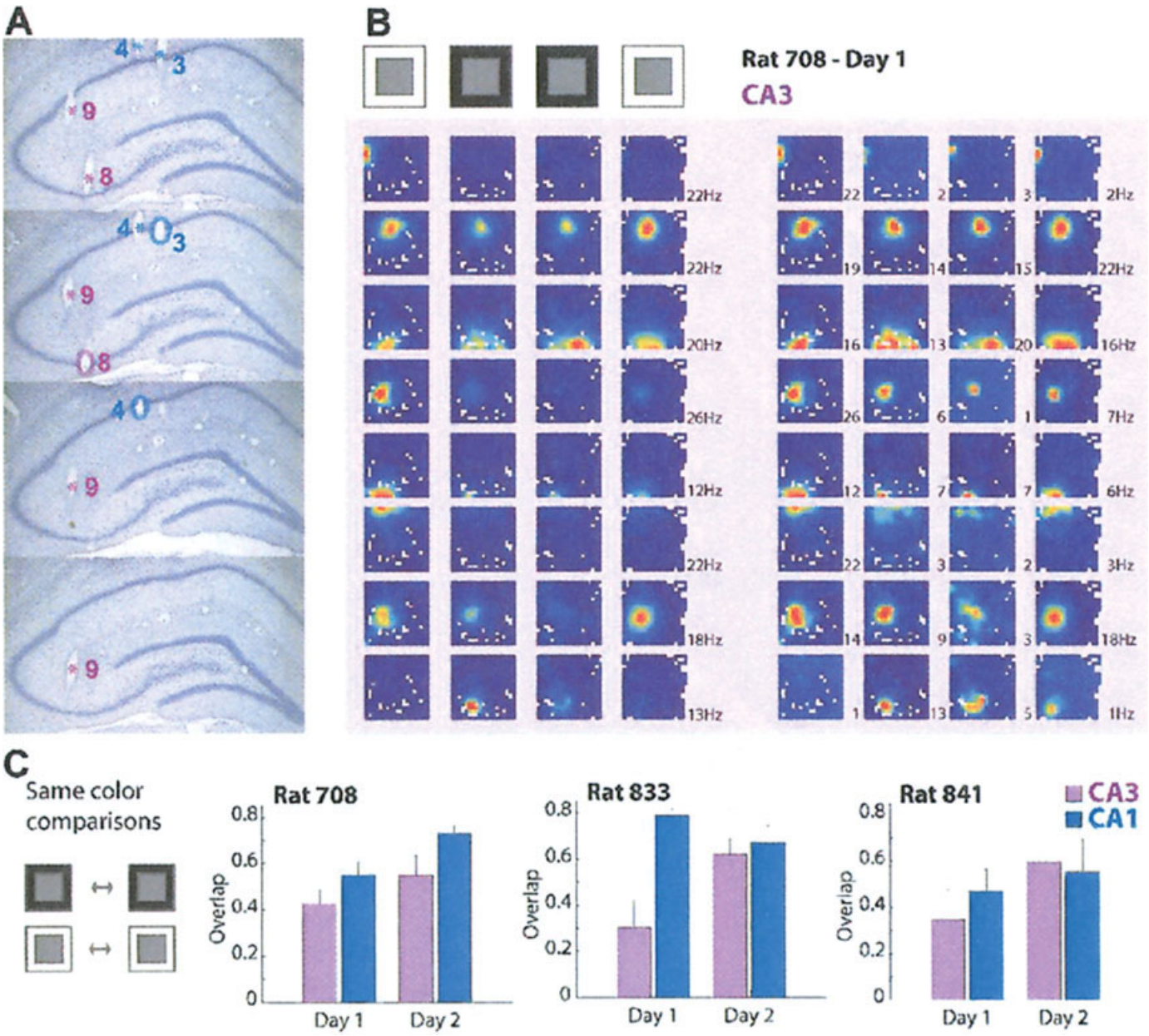

FIGURE 1. Field formation in CA3 ensembles. (A) Recording sites in CA3 and CA1 were identified by following the electrode tracts (*) through serial cresyl violet stained sections. A small angular deviation between the plane of sectioning and the electrode tracts resulted in an apparent downward shift of the tissue damage. The electrode tip (0) is considered to be located in the section before the tissue damage becomes negligible. CA3 tetrodes are shown in purple and CA1 tetrodes are shown in blue. Tetrodes 1–2, 5–7, and 10–14 are located anterior and posterior to the levels that are shown. (B) On the first day of testing in white and black boxes, CA3 cells responded to the novelty of the room, but also changed firing rates in response to box colors. The recording sequence (white–black–black–white, 10 min in each box) is shown on top. Each row represents a cell. All cells with peak rates of >10 Hz are shown (8 of 17). The maps for the four recording sessions are shown twice. On the left, the color scale is the same for all four maps. Red corresponds to maximal firing (as indicated by the number to the right of the four maps). On the right, the four maps are redrawn, but now each map is scaled to its own maximum (as indicated by the number to the right of each map). (C) Comparisons between repeated recordings (10 min each) with the same box color revealed lower overlap scores on day 1 compared with day 2, indicating that the firing rates matured during the first day in the novel room as shown in the example in B. The effect is more pronounced in CA3 than in CA1 (see text for statistics). The corresponding data for animal 939 are shown in Figure 3.

then into the black box for two consecutive 10-min trials, and back into the white box for a final 10-min trial. The cells were thus recorded twice in each condition, using an A–B–B–A design so as to control for recording stability effects as well as possible time-, velocity-, and sampling-dependent shifts in the hippocampal code. Each recording session ended with a 20-min rest period on the pedestal. The training sequence in the white and black boxes was repeated on a second day in all four animals

TABLE 1.

Number of Recorded Cells

	CA1	CA3
Rat 708		
Day 1	23	17
Day 2	21	24
Day 3	29	21
Rat 833		
Day 1	19	10
Day 2	10	11
Rat 841		
Day 1	6	14
Day 2	8	15
Rat 939		
Day 1	17	15
Day 2	27	65
Day 3	30	36
Day 4	33	17
Day 5	38	20
Day 6	22	12
Day 7	20	16
Day 8	15	11
Day 9	29	18
Total		
Day 1	65	56
Day 2	66	115

and on a third day in two animals. The training was continued until day 9 in one animal that initially did not encode the differences between the color configurations. The number of CA3 and CA1 cells recorded during each of the recording days is shown in Table 1.

Data Analysis

Spike sorting

Spike sorting was performed offline using graphical cluster-cutting software. Sleep recordings before and after the behavioral sequence were included in the data file to ensure recording stability and to identify cells that were silent during the behavior. Clustering was performed manually in two-dimensional projections of the multidimensional parameter space (consisting of waveform amplitudes and waveform energies), using autocorrelation and crosscorrelation functions as additional separation tools and separation criteria. Putative excitatory cells were distinguished from putative interneurons by spike width, average rate, and the occasional presence of bursts.

Place fields

Spatial firing rate distributions ("place fields") for each well-isolated neuron were constructed in the standard manner, by summing the total number of spikes that occurred in a given location bin (5×5 cm^2), dividing by the amount of time that the animal spent in that location, and smoothing with a Gaussian centered on each bin. The average rate in each bin x was estimated as

$$\lambda(x) = \sum_{i=1}^{n} g\left(\frac{s_i - x}{h}\right) \Bigg/ \int_0^T g\left(\frac{y(t) - x}{h}\right) dt$$

where g is a smoothing kernel, h is a smoothing factor, n is the number of spikes, s_i the location of the i-th spike, $y(t)$ the location of the rat at time t, and [0 T) the period of the recording. A Gaussian kernel was used for g and $h = 5$ cm. Positions >5 cm away from the tracked path were regarded as unvisited.

Spatial correlation

The spatial similarity of place fields on two trials was estimated for each cell by correlating the firing rates of the cell across all bins of the environment. Sampling errors for cells with low firing rates were minimized by excluding cells with rate vectors (the vector sum of the mean firing in the two trials that were compared) below 0.27 Hz from the calculations. The threshold level was selected after inspecting the data from repeated recordings in identical boxes. High place field correlations are expected for these comparisons, and most correlation values ($>80\%$) below 0.5 were from cells with rate vectors below 0.27. We have previously shown that selecting either a slightly higher threshold (0.50) or a lower threshold (0.10) does not importantly change the results (Leutgeb et al., 2005a).

Rate overlap

Rate remapping between two 10-min recording trials was expressed by calculating an overlap score for each cell. Scores for trial pairs were obtained by dividing the lower average firing rate of the two sessions by the higher average firing rate. The range of possible scores is from 1 (no rate change) to an asymptotic value of 0 (infinite rate change). Cells with low average rates (<0.25 Hz) in both 10-min recordings were excluded from the calculation of the overlap scores. The analysis was performed separately for each day, and also separately for each animal.

Histology

Brains were cut coronally at 30 μm and stained with cresyl violet. Each section was collected for analysis through the relevant part of the hippocampus. All tetrodes of the 14-tetrode hyperdrive bundle were identified and the tip of each electrode was found by comparison with adjacent sections. The recordings from a tetrode were included in the data analysis if its deepest position was in or close to the CA3 or CA1 pyramidal cell layer. The electrodes had not been moved after the recordings.

RESULTS

The Encoding of Novelty

We first determined whether the emergence of new neuronal ensemble patterns in CA3 and CA1 followed different time

TABLE 2.

Overlap Values

	CA1	CA3	CA1 vs CA3
Same box color			
Day 1	0.64 ± 0.03	0.42 ± 0.05	$P < 0.001$
Day 2	0.67 ± 0.03	0.61 ± 0.05	N.S.
Day 1 vs. Day 2	N.S.	$P < 0.01$	
Opposite box color			
Day 1	0.55 ± 0.03	0.35 ± 0.04	$P < 0.001$
Day 2	0.55 ± 0.04	0.38 ± 0.04	$P < 0.001$
Day 1 vs. Day 2	N.S.	N.S.	

courses. When the rats were exposed repeatedly to the same box (i.e., the same color), the distribution of firing rates in CA3 changed more from the first to the second trial on day 1 than from the first to the second trial on day 2 (Fig. 1). Accordingly, the rate overlap between trials on day 1 was smaller than on day 2 in this subfield (Table 2; $t = -2.81$, df = 46, $P < 0.01$), and the overlap scores in CA3 were lower than in CA1 cells on day 1 ($t = 4.45$, df = 65, $P < 0.001$), but were no longer different on day 2 ($t = 0.82$, df = 42, N.S.); on day 2, they corresponded to levels previously reported for CA3 after extended training (Leutgeb et al., 2004). In CA1, there was no difference between the first and the second recording day (Table 2; $t = -0.35$, df = 64, N.S.), which indicates that stable firing rates appeared in CA1 from the beginning. The differential time courses in CA3 and CA1 confirms our previous finding of a slow maturation of the firing rate distribution in CA3 when animals are tested in a new room (Leutgeb et al., 2004). In both the previous and the present studies, the adjustment of the firing rates was observed between recording conditions where the sensory cue configuration remained unchanged, which indicates that the delayed stabilization of the firing rates in the recently activated cell population is related to novelty, but not directly to sensory encoding.

The Encoding of Dissimilarity

The wall color of the recording box was switched from white to black so as to determine whether hippocampal cell populations were able to represent two separate sensory patterns shortly after the change in the cue constellation was seen for the first time. The color reversal gave rise to a strong rate difference in CA3 but not in CA1 (Table 2 and Fig. 2; $t = 4.05$, df = 65, $P < 0.001$). The level of orthogonalization that was reached on day 1 was maintained during recordings on the next day (CA3 vs. CA1; $t = 3.19$, df = 45, $P < 0.01$). Although more pronounced rate changes were detected in CA3 compared with CA1, we observed that the field locations were retained to an equal extent (spatial correlation: 0.51 ± 0.062 in CA3 vs. 0.49 ± 0.042 in CA1 on day 1, $t = 0.43$, df = 66, N.S., and 0.61 ± 0.056 in CA3 vs. 0.60 ± 0.046 in CA1 on day 2, $t = -0.63$, df = 50, N.S.).

Differences in Orthogonalization Between Animals

Different animals exhibited strikingly different levels of orthogonalization. In CA1, the degree of orthogonalization varied between the extremes of either not remapping or completely remapping (animals 833 and 841, respectively, in Fig. 2). Despite the high variability in the degree of remapping between animals, the rate changes were always more pronounced in CA3 than in CA1 (individual mean values ± the standard error: 0.34 ± 0.053, 0.39 ± 0.068, 0.13 ± 0.049, and 0.46 ± 0.077 in CA3 vs. 0.51 ± 0.057, 0.63 ± 0.045, 0.29 ± 0.073, and 0.59 ± 0.035 in CA1, respectively). One animal did initially not show any coding for box color differences in either CA3 or CA1. The failure to initially respond to the color reversal could be due to an attentional deficit (Kentros et al., 2004), although there was a trend toward a rate difference during the initial four recording days in CA3 (Fig. 3A). To test whether continued experience with the two box colors would result in increased encoding of the differences between the black and white box configurations, the recordings were continued for a total of 9 days. A differentiation of the configurations emerged with repeated testing. After the 5th day, the rate differences in CA3 were consistently larger than those in CA1 (all P-values <0.05), while in CA1 they did not encode the difference in box colors during any of the recording days (Fig. 3).

DISCUSSION

In agreement with behavioral data showing a critical role of CA3 for the fast acquisition of new information (Lee and Kesner, 2002, 2004; Nakazawa et al., 2003), we have shown that CA3 cells respond immediately to differences in nonspatial cues, even when these differences occur in a location that is new to the animal. This extends our previous findings of fast orthogonalization in CA3 when the animal is moved between a familiar and a novel room (Leutgeb et al., 2004) and shows that the CA3 ensemble can also immediately encode local differences in the sensory configuration at the new location. The fast encoding of the color reversal suggests that nonspatial information is rapidly associated with the spatial information in the CA3 network as would be expected for an autoassociative circuitry supporting the acquisition of episodic memories.

In contrast to the reliable encoding of input differences by the CA3 network, the encoding of input patterns in CA1 was more variable. In some cases, the differences in cue constellations were apparently not expressed in CA1 even though the place fields were stable during the first minutes of the recording session; in other cases, the responses of the CA1 cells were as distinct as those of the CA3 cells. The absence of remapping in CA1 in some animals is consistent with previous reports of slow orthogonalization of input patterns in CA1. Lever et al. (2002) showed that CA1 cells start responding to local differences only after several days of training. Early during the training, the response to the different sensory input appears to have consisted

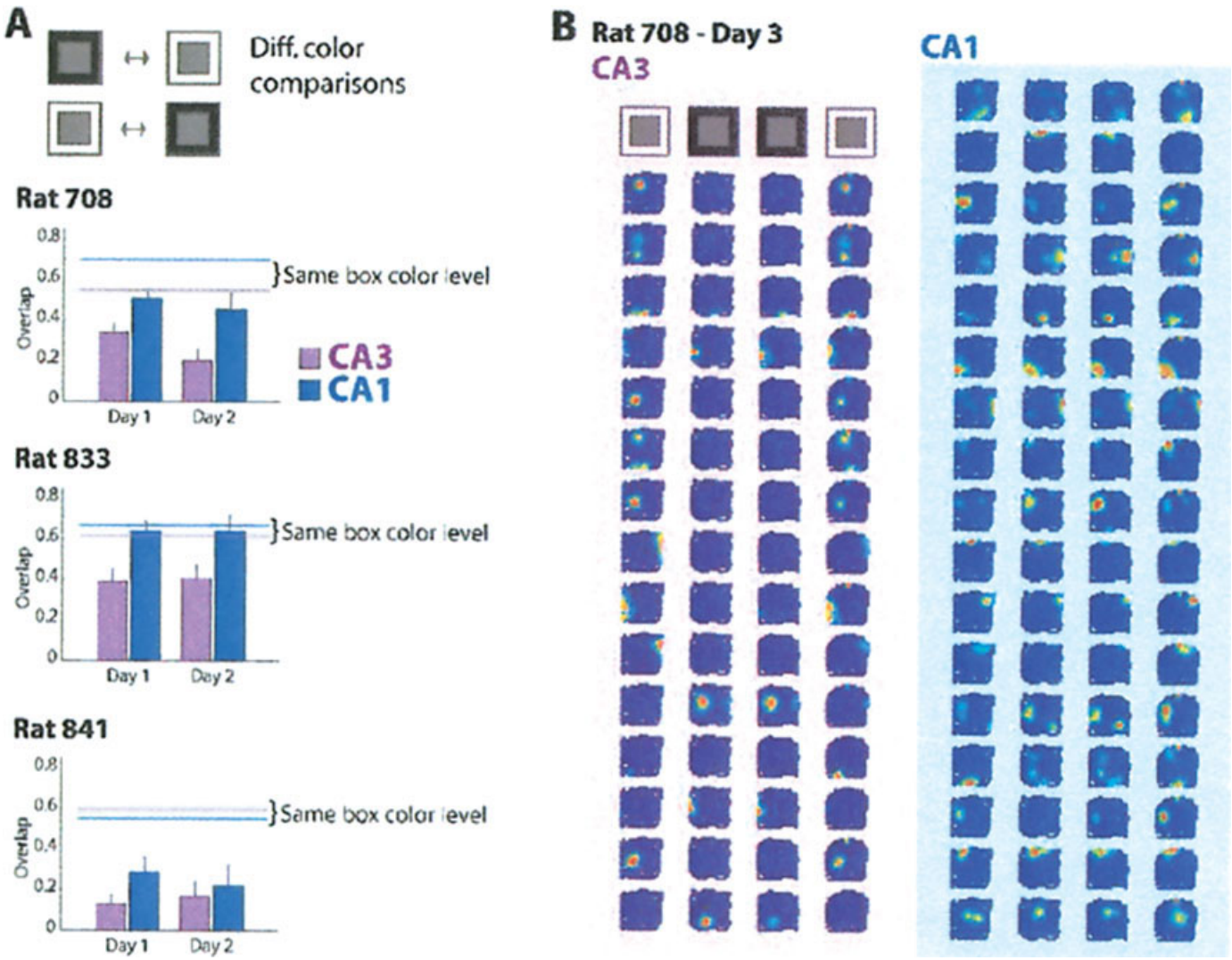

FIGURE 2. Encoding of nonspatial cues at a new location. (A) Differences between box colors were encoded from the beginning, and all animals showed similar levels of orthogonalization on day 2 as on day 1 in both CA3 and CA1. The corresponding data for animal 939, which showed a delayed response, are shown in Figure 3. The same box color levels from day 2 in Figure 1C are redrawn for comparison. (B) The more pronounced response to the color difference in CA3 compared with CA1, which had appeared on day 1 and had been retained on day 2 in animal 708, was also seen on recording day 3. The first and last columns correspond to recordings in white boxes, and the middle two columns correspond to recordings in black boxes. Each row represents a cell, and the scale is the same for the four maps of the cell. Maximal firing is shown as dark gray with a white surround (red in the online figure), and firing close to zero is shown in black (blue in the online figure). Maps are shown for all cells with peak rates > 10 Hz (15 of 21 CA3 cells and 17 of 29 CA1 cells). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

mostly of rate changes within the firing field (Lever et al., 2002; their Fig. 3). At later stages, the ensembles may have remapped globally, or the rate remapping may have become so extreme that the fields were only apparent in one of the two box shapes used for testing. In a similar paradigm, we have recently shown that differences in the shape of an enclosure with flexible walls are encoded exclusively by rate changes, both in CA3 and CA1, with more than 10-fold rate differences in CA3 after several weeks of training (Fig. 4; Leutgeb et al., 2005a). The present data show that rate remapping is not only expressed more strongly in CA3 than in CA1, but that it also is apparent in CA3 right from the beginning.

Rate remapping is often observed in paradigms where proximal cues (either the box color or the box geometry) are changed while testing occurs in the same place (Leutgeb et al., 2005a,b). Using similar paradigms, others have reported more complete remapping in CA1 (Bostock et al., 1991; Kentros et al., 1998; Anderson and Jefferey, 2003; Hayman et al., 2003; Wills et al., 2005). Even though their testing with different cue constellations occurred in the same place, the remapping seems more closely related to the global remapping that we have observed when moving the animal between different box locations (Leutgeb et al., 2005a). It is possible that some (but not all) of these cases reflect an extreme form of rate remapping (see also Fig. 4). In experiments where all cells

in CA3 respond by a change in firing rate only, we sometimes find that some CA1 cells also fire at different locations. A possible explanation for these location shifts is that they correspond to cells with two fields in the enclosure. A substantially decreased firing rate in one field along with an increased firing rate in the other could give rise to an apparent shift in the firing location. Because CA1 cells are more likely to have two fields, it may be more difficult to distinguish rate and global remapping in this subfield. We have frequently observed that rate remapping can suppress the firing to such an extent that the remaining firing fields have peak rates below 1 Hz (Leutgeb et al., 2005a). Cells with fields below this value are sometimes considered to have disappeared (e.g., Anderson and Jeffery, 2003; Hayman et al., 2003).

Although some reports of spatial remapping in CA1 may be reinterpreted as strong rate remapping, such an explanation cannot account for instances when shifts in firing location occur in the majority of simultaneously recorded CA1 cells with spikes in both environments (e.g., Bostock et al., 1991; Kentros et al., 1998; Wills et al., 2005). Under these circumstances, it is more likely that remapping involves the same form of network dynamics as when rats are moved between spatial locations. When global remapping is induced at a constant location, a mismatch between real-world coordinates and those used by the animal could, for example, be instantiated by resetting the animal's path integrator in the medial entorhinal cortex (Hafting et al., 2005). The defining characteristic for global remapping is therefore not necessarily whether it occurs in a single place or in different places, but whether the spatial inputs to hippocampus have changed.

Assuming that global remapping is induced primarily when rats move between different locations (real or perceived) implies that the same cell population should be kept active when the animal remains oriented in the same space. Our observation that most place fields retain their firing location when the animal is tested at a single location suggests that the spatial reference is retained when cells show rate remapping. Can rate remapping therefore only occur in a single location or can it occasionally also occur in two separate locations? One such case has been reported by Hayman et al. (2003). Considerable control of the box walls

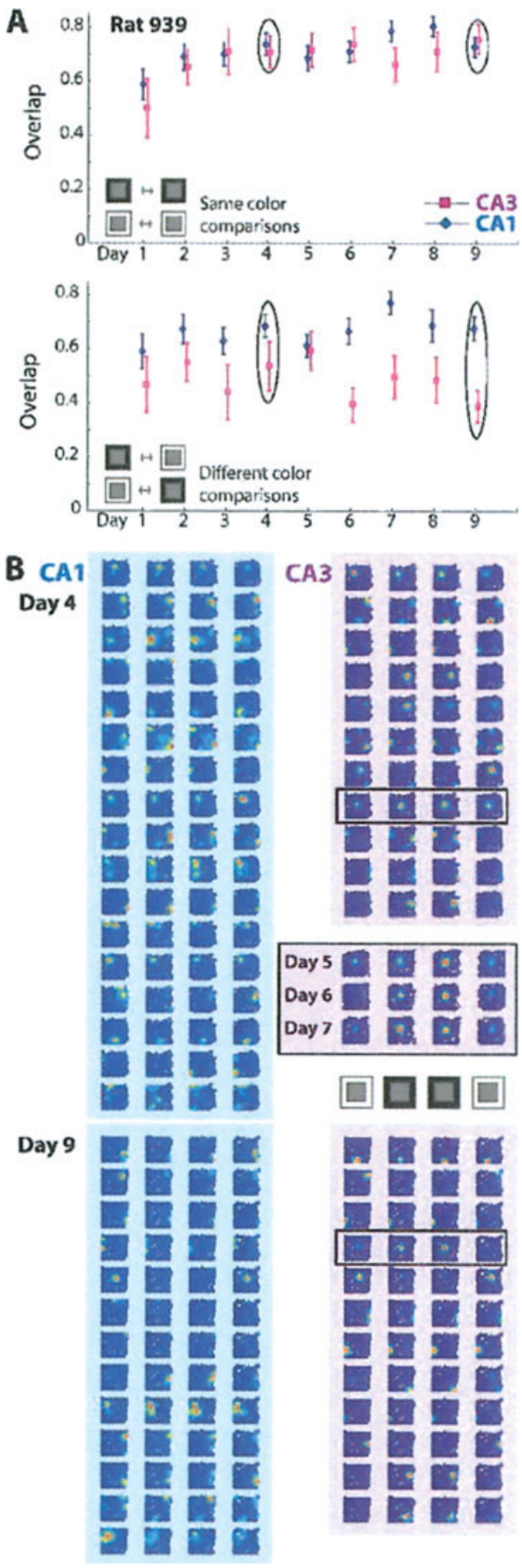

FIGURE 3. CA3 response to nonspatial cues precedes changes in CA1. (A) One of four animals showed only a weak response to the box color reversal during the initial recording days. Continued recordings revealed an increased encoding of the color difference after day 5 in CA3 ensembles, while CA1 cells failed to respond to the box color differences throughout the entire recording sequence. (B) A comparison between encoding the box color differences on day 4 and day 9 illustrates that the rate differences have increased in CA3, but not in CA1. The first and last columns are recordings in white boxes, and the middle columns recordings in black boxes. Each row represents a cell, and the scale is the same for the four maps of the cell. Maximal firing is shown as dark gray with a white surround and firing close to zero is shown in black. One cell (highlighted by black frames) could be identified in recordings on days 4, 5, 6, 7, and 9. Its firing in white boxes decreased between day 5 and 6, which resulted in larger rate differences between the recording conditions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

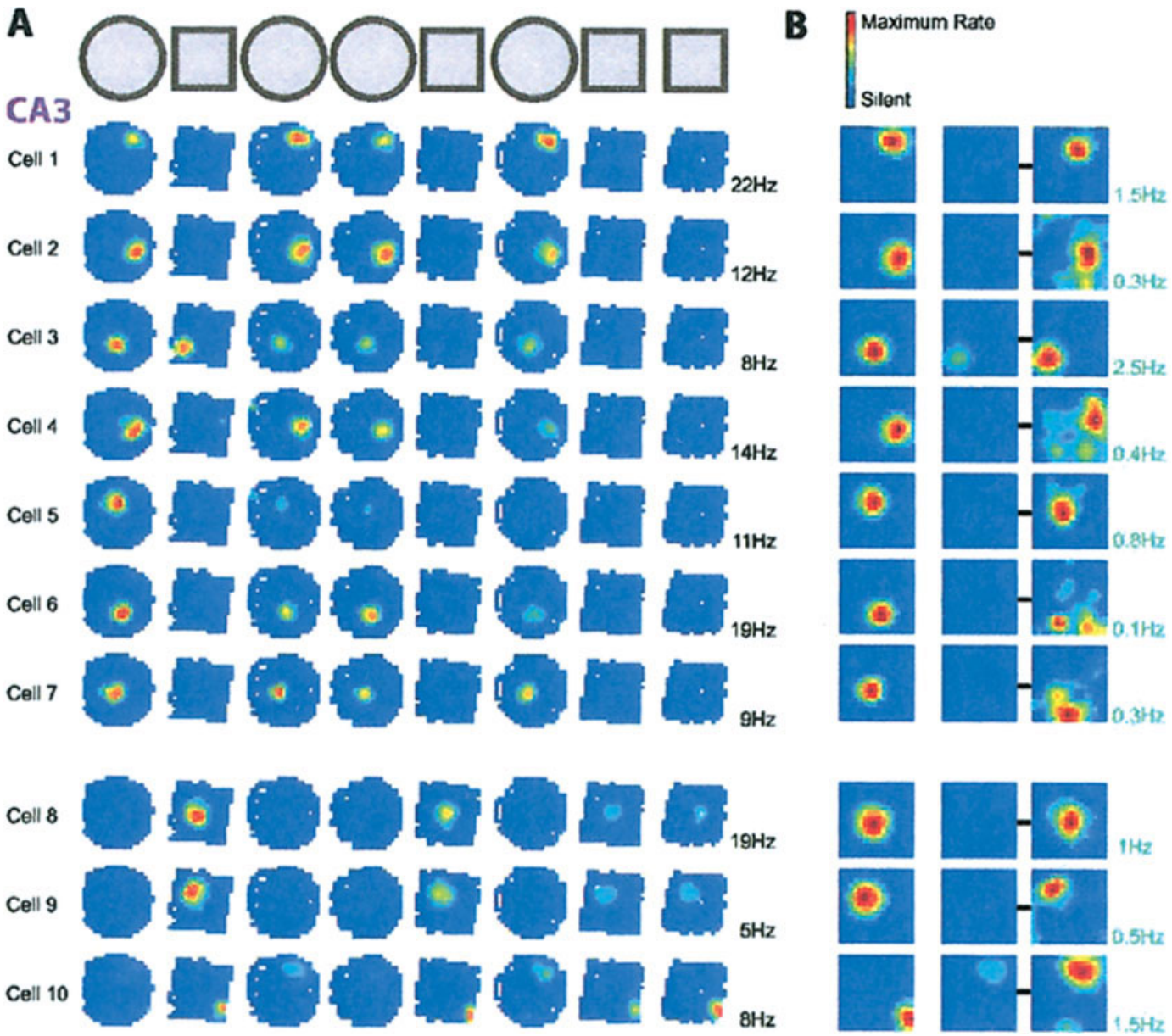

FIGURE 4. Pronounced rate differences without a shift in firing location are observed after 2–3 weeks of training with different box geometries (Leutgeb et al., 2005a). This effect is particularly striking in CA3, where the peak firing rates decreased below 1 Hz in the nonpreferred condition for most cells (median: 0.65 Hz). (A) A random sequence of eight 10-min recordings in four square boxes and four circular boxes was used for training and testing. The rate maps for 10 simultaneously recorded CA3 cells are shown. Each row corresponds to a cell, and each map in the row is scaled to the maximum shown to the right. Cells 1–7 showed a more pronounced firing field in the circle, while cells 8–10 showed a more pronounced field in the square. (B) The rate maps of the four circles and the four squares are averaged and the area that is common to both shapes is cut out. The rate map on the left correspond to the shape where the cell shows its firing preference and the scaling is the same as in (A). The maps in the middle and right columns show the firing in the nonpreferred shape, in the middle at the same scale as for the other maps and on the right scaled to its own maximum. It is apparent that the field location remains unchanged for most cells, even though the firing rate is often reduced by more than an order of magnitude. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

over the firing location of place cells (e.g., O'Keefe and Burgess, 1996; Lever et al., 2002) could have resulted in a realignment of the animal's coordinate system with the box. When resetting of the spatial reference to box coordinates has occurred, rate remapping rather than global remapping might be induced even during recording at different locations. The animal would keep its own coordinates aligned with the box, but the distal cues would be seen in a different way in each place. Rate remapping would now occur as if the animal was in a single location, but now in response to different distal cue configurations (Hayman et al., 2003).

These observations suggest that rate remapping and global remapping reflect different neuronal computations, possibly with

different degrees of hippocampal and parahippocampal contribution. A fast and coherent shift in entorhinal firing fields during global remapping (Fyhn et al., 2005) may provide sufficiently different direct inputs to the hippocampus to activate different cell ensembles with different place fields. The formation of new place fields might in such cases proceed without encoding new information within the hippocampus. In contrast, during conditions when the direct spatial input remains unaltered, further orthogonalization of input patterns may occur downstream of the cortical inputs to hippocampus. In particular in cases when rate remapping is expressed in CA3 but not yet in CA1, it can be assumed that information about stimulus differences is not received via the direct entorhinal inputs to CA1, but rather expressed as a result of intrinsic hippocampal computations. The more rapid expression of rate coding in CA3, as seen in the present study, may therefore be an indication of encoding new information within the hippocampus.

The immediate appearance of a new hippocampal representation ("remapping") in response to changed cues and its persistence during later recording sessions have been considered as one of the benchmarks for a role of hippocampus in memory formation. A fast appearance of stable CA1 fields was also observed here but the majority of the fields remained unresponsive to the change in box color, indicating that the cell population coded for the new location without simultaneously encoding a prominent nonspatial feature (i.e., the box color). Such generalization (i.e., pattern completion) for two related sensory configuration can be seen as appropriate for the retrieval of spatial memories, but not for concurrently encoding nonspatial information. In contrast, CA3 cells responded along both coding dimensions such that they could support the retrieval of spatial locations by using a stable place code and at the same time distinguish between multiple sensory configurations by expressing differences in the rate code (Leutgeb et al., 2005b). By generalizing along one stimulus dimension while encoding the relations between stimuli along a second dimension, the cell population can support the encoding of new, related sensory cues while retaining the information about them occurring at a constant location.

Could the multiplicity in neuronal coding within hippocampal subareas also be important for encoding the "where," "what," and "when" components of episodic memories? An independent representation of the "where" and "what" aspects of episodic memories could be achieved by dedicating the place code to encoding the animal's current location and by distinguishing sensory configurations at each location by rate coding within the place fields. The expression of such rate coding is particularly robust in CA3, where it can result in more than 10-fold differences in peak firing rates within the place field (Leutgeb et al., 2005a,b). However, if differences between sensory configurations are encoded as rate changes within place fields, this may at the same time lessen the accuracy of sequence representations within the theta cycle (O'Keefe and Recce, 1993; Jensen and Lisman, 1996; Skaggs et al., 1996). A substantial reduction in the number of spikes within the place field does not only reduce the peak rate and the field size, but also the number of spikes in each theta cycle. As a consequence, the overlap with spikes from adjacent place fields is reduced, which results in an increased variability in the phase relation between cells that were activated sequentially (Dragoi and Buzsaki, 2006) or, if there is no remaining area of overlap between the fields, in an omission of activated cell pairs. An altered sequence of place cell activation could therefore not only occur when the animal takes a different path in an otherwise unchanged environment, but also when following the same path in a modified environment. A more limited rate variation in CA1 in response to changes in sensory configurations would better preserve temporal sequence information. Differences in computational functions between the two hippocampal subareas (Kesner et al., 2004) could therefore be linked to a trade-off between either fine-tuned representations of sensory patterns or precise representations of sequences by temporal coding. Rate coding in CA3 would allow for refined representations of "what" occurred during an episode while temporal coding in CA1 would more accurately represent "when" it occurred; the "where" aspect is preserved by place coding in both subareas.

The fast encoding of hippocampal-dependent memories in humans and animals requires that some processes take place in the hippocampus that result in an immediate trace of the memory in hippocampus. We found such rapid encoding of information in the hippocampal CA3 network, and also observed that it is not necessarily immediately expressed by activity in CA1. Rate remapping in CA3 has many of the properties that would be expected from a network that supports the fast encoding and storage of memories, and it will be important to find the conditions that result in the successful use of this information. Although recent data are consistent with the proposal that hippocampal rate coding makes an important contribution to encoding in memory tasks (Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Moita et al., 2004; Bower et al., 2005), it remains to be tested more explicitly whether the location-independent coding properties of hippocampal place cells are set aside for this function.

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