Behavioral/Systems/Cognitive

Local Sensory Cues and Place Cell Directionality: Additional Evidence of Prospective Coding in the Hippocampus

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In tasks involving goal-directed, stereotyped trajectories on uniform tracks, the spatially selective activity of hippocampal principal cells depends on the animal's direction of motion. Principal cell ensemble activity while the rat moves in opposite directions through a given location is typically uncorrelated. It is shown here, with data from three experiments, that multimodal, local sensory cues can change the directional properties of CA1 pyramidal cells, inducing bidirectionality in a significant proportion of place cells. For a majority of these bidirectional place cells, place field centers in the two directions of motion were displaced relative to one another, as would be the case if the cells were representing a position in space ~5–10 cm ahead of the rat or if place cells were subject to strong accommodation or inhibition in the latter half of their input fields. However, place field density was not affected by the presence of local cues, but in the experimental condition with the most salient sensory cues, the CA1 population vectors in the "cue-rich" condition were sparser and changed more quickly in space than in the "cue-poor" condition. These results suggest that "view-invariant" object representations are projected to the hippocampus from lower cortical areas and can have the effect of increasing the correlation of the hippocampal input vectors in the two directions, hence decreasing the orthogonality of hippocampal output.

Key words: **neural ensembles; CA1; *in vivo* unit recording; behavior; hippocampus; spatial; population coding; multiple single-unit recording; cognitive map**

Introduction

The dynamics of hippocampal principal cells and the factors (internal and external) that determine their activity have been the subject of an extensive body of literature (for review, see McNaughton et al., 1996; Redish, 1999; Best et al., 2001). Under some circumstances, principal cell (i.e., pyramidal cells in CA1–CA3; granule cells in dentate gyrus) activity is highly correlated with the animal's location, leading to the notion that these cells participate in the generation of a "cognitive map." In many other cases, however, place cell activity can be better described as tied to nonspatial factors (Young et al., 1994; Wood et al., 1999), or at least not organized according to simple two-dimensional metrics (three-dimensional if the animal explores a nonflat environment). Place fields can be altered by manipulating sensory cues. The manipulation may maintain the internal geometric coherence of the place fields (Muller and Kubie, 1987) or may cause a distortion of the cognitive map by changing the size and shape of the place field (O'Keefe and Burgess, 1996), rearranging the distances between place fields (Gothard et al., 1996b), or overrepresenting regions in space proximal to some salient cue (Hetherington and Shapiro, 1997).

Head direction or direction of locomotion is another important correlate of spatially selective firing. Whether or not this is a main determinant of place field activity seems to depend on the characteristics of the environment and of the task: directional place fields seem to be prevalent when the animal is constrained to relatively stereotyped trajectories, either by running on one-dimensional tracks (McNaughton et al., 1983a) or by task requirements (Markus et al., 1995). In these cases, the hippocampal representations of the two journeys are typically uncorrelated (Gothard et al., 1996b). When trajectories through a given location are not constrained to a particular path or by a particular set of origins and destinations, however, place cells do not show directionality (Muller et al., 1987). The factors that determine the directional properties (or lack thereof) of place fields are currently poorly understood, although several theoretical proposals have been made (Sharp et al., 1996; Brunel and Trullier, 1998).

The present study is based on the hypothesis that local cues may contribute to disambiguating adjacent locations, increasing the information content of the hippocampal representation. However, if the sensory cues can be represented in a direction-invariant manner, they may provide a link between the representations of the same location regardless of the direction of motion, thus attenuating the directional characteristics of place cells. If this were the case, a larger number of cells should present "bidirectional" place fields in environments that are rich in local sensory cues, compared with locally homogeneous environments. Evidence for such an effect was sought from hippocampal ensem-

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ble activity in three different environments. Some of these results have been published previously in abstract form (Battaglia et al., 2002; Sutherland et al., 2002).

Materials and Methods

Animal subjects, surgery, electrode assembly, and recording technology

Eight adult male Fisher 344 or Brown Norway/Fisher 344 hybrid rats were used for these experiments. They were housed individually and maintained on a 12 hr light/dark cycle. Recordings took place during the dark phase of the cycle. Surgery was conducted according to National Institutes of Health guidelines for rodents and approved Institutional Animal Care and Use Committee protocols. Before surgery, the rats were administered bicillin (30,000 U, i.m., in each hindlimb). The rats were implanted, under pentobarbital or isofluorane anesthesia, with a circular array of 14 separately moveable microdrives ("HyperDrive"). This device and the parallel recording technique have been described in detail previously (Wilson and McNaughton, 1993; Gothard et al., 1996a). Briefly, each microdrive consisted of a drive screw coupled by a nut to a guide cannula. Twelve guide cannulas contained tetrodes (McNaughton et al., 1983b; Recce and O'Keefe, 1989), four-channel electrodes constructed by twisting together four strands of insulated 13 μm nichrome wire (H. P. Reid, Neptune, NJ). A full turn of the screw advanced the tetrode 318 μm. During surgery, a 3-mm-diameter circular craniotomy was performed over the right dorsal hippocampus at stereotaxic coordinates 2.0 mm lateral to midline and 3.8 mm posterior to bregma, and seven to eight anchor screws were attached on the skull, one being used as the ground for recording. The dura was removed from the craniotomy area, the recording device was implanted with the cannulas flush to brain surface, and the craniotomy was sealed with silicon rubber (World Precision Instruments, Sarasota, FL) before the implant was cemented in place with dental acrylic. After surgery, rats were administered 26 mg of acetaminophen (children's Tylenol; McNeil, Fort Washington, PA). They also received 2.7 mg/ml acetaminophen in the drinking water for 1–2 d after surgery and oral ampicillin on a 10 d on/10 d off regimen for the duration of the experiment. The tetrodes were lowered gradually after surgery into the hippocampus and allowed to stabilize above the CA1 hippocampal subregion. Two of the tetrodes served as reference electrodes. The four channels of each tetrode were attached to a 50-channel unity-gain headstage (Neuralynx, Tucson, AZ). A multiwire cable connected the headstage to digitally programmable amplifiers (Neuralynx). The signals were amplified by a factor of 1000–5000, bandpass-filtered between 600 Hz and 6 kHz, and transmitted to the Cheetah Data Acquisition system (Neuralynx). Signals were digitized at 32 kHz, and events that reached a predetermined threshold were recorded for a duration of 1 msec.

Spikes were sorted off-line on the basis of the amplitude and principal components from the four-tetrode channels by means of a semiautomatic clustering algorithm (BBClust; P. Lipa, University of Arizona, Tucson, AZ). The resulting classification was corrected and refined manually with custom-written software (MClust; A. D. Redish, University of Minnesota, Minneapolis, MN), resulting in a spike train time series for each of the well isolated cells. No attempt was made to match cells from one daily session to the next. Therefore, the numbers of recorded cells reported does not take into account possible recordings from the same cells on consecutive days; however, because the electrode positions were frequently adjusted from one day to the next, recordings from the same cell over days were probably relatively infrequent. Putative pyramidal neurons and interneurons were identified by means of standard parameters (firing rate, burstiness, spike waveform shape). Several diodes were mounted on the headstage to allow position tracking. The position of the diode array was detected by a TV camera placed directly above the experimental apparatus and recorded with a sampling frequency of 60 Hz. The sampling resolution was such that a pixel was approximately equivalent to 0.3 cm.

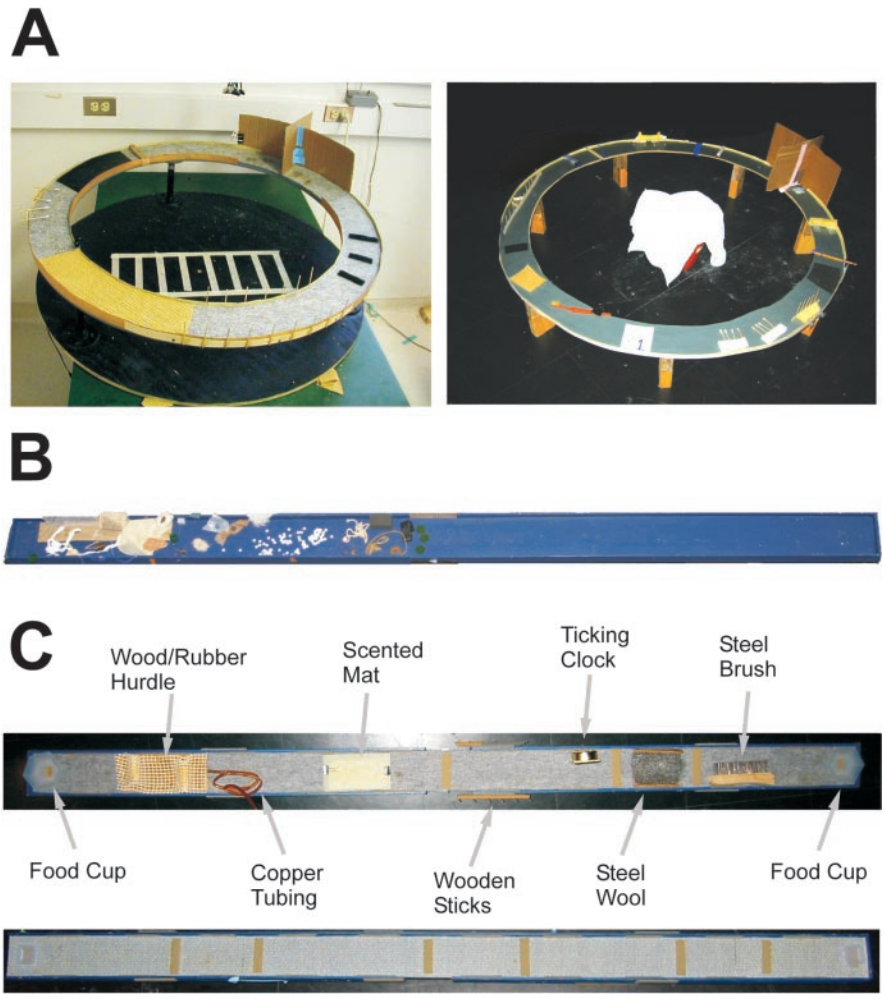

Figure 1. Photographs of the tracks used in experiments A–C. *A*, The 91 cm circular track (left) and the 130 cm circular track (right) used for experiment A (cue-rich circular tracks). *B*, The cue-rich– cue-poor combined linear track used for experiment B (combined cue-rich– cue-poor linear track). *C*, The cue-rich (top) and the cue-poor (bottom) tracks used for experiment C (independent cue-rich– cue-poor tracks).

Behavioral training and experimental protocols

The experiments described below are all variants of the shuttling task, in which the rats ran back and forth on a track and received food reward at the ends.

Experiment A (cue-rich circular tracks). Before surgery, two rats were handled until comfortable with human contact, food-deprived to 80–85% of *ad libitum* weight, and trained to shuttle back and forth on one of two circular tracks, one with a diameter of 91 cm (rats 1 and 2) and one with a diameter of 130 cm (rat 2). Different portions of the track floor were covered with materials of different textures (carpeting, rubber net mat, Velcro loops) and were enriched with local cues that activated different sensory modalities, such as vertically oriented wooden sticks placed at regular intervals on the track sides, in such a way as to stimulate whiskers as the animals passed, cotton swabs pregnated with odorants (a cleaning agent derived from orange peel), hurdles that the rat had to step

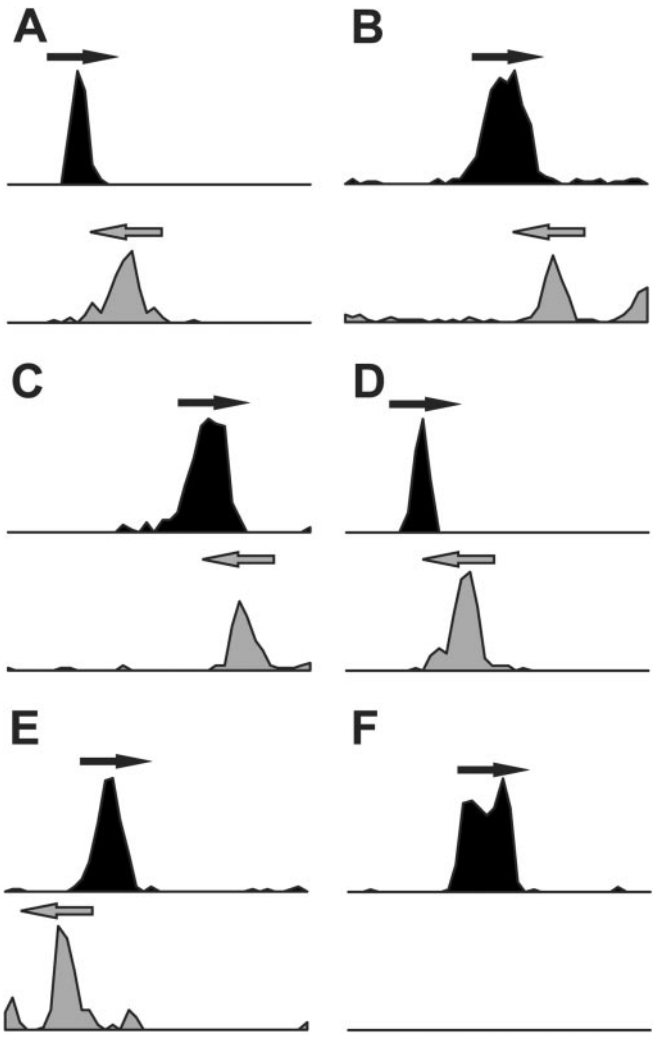

Figure 2. Examples of bidirectional place fields and prospective shift. Six place field profiles from cells recorded in experiments B (combined cue-rich–cue-poor linear track) and C (independent cue-rich–cue-poor linear tracks) are shown. The firing rate profiles recorded during the leftbound journey (gray) and during the rightbound journey (black) are shown separately. The place fields in *A–E* are bidirectional (i.e., the profiles in the two directions show elevated activity in the same region of the track). *A–D*, Place fields showing examples of the prospective backward misalignment, a pattern observed in the majority of bidirectional place fields (supplemental Table 2, available at www.jneurosci.org) (Fig. 5). The place fields in the two directions were not perfectly aligned; rather, they were displaced backward with respect to the rat's direction. *E*, A bidirectional place field showing the opposite (retrospective) misalignment. *F*, An example of unidirectional place field. Y scale, arbitrary units.

over (Fig. 1*A*), a stream of air delivered via a rubber tube, gauze impregnated with grape scent, etc. The rats shuttled between two adjacent locations on the track that were separated by a cardboard barrier used to prevent the animals from going directly from one reward location to the other. Training continued until the rats ran at least 50 laps in a 15 min session. Food deprivation was suspended during the few days immediately preceding surgery and resumed after the animals recovered from surgery, while the rats were rehabituated to the track and the task. Recording sessions started when the rats ran steadily again during the training sessions, and after the tetrodes were gradually lowered to CA1.

In a recording session, the rats were allowed to rest in a towel-lined flower pot placed next to the track for 20–25 min (rest 1 epoch). Afterward, they performed the shuttling task on the track for 15 min (track epoch), and then rested again in the flower pot for another 20–25 min (rest 2 epoch). The recordings during the two rest epochs were used to assess cell stability.

Experiment B (combined cue-rich–cue-poor linear track). Before surgery, four rats were pretrained to shuttle back and forth in an enclosed alley for food reward. Before participating in the present study, the rats underwent training and single-unit recording in one or more additional environments that were substantially different from the apparatus used here and were placed in different rooms.

For the recordings, a blue-painted wooden linear track (180 × 8 cm) was used. One-half of the track was covered with materials with different textures (gravel, rubber, plastic, fabric, etc.) and had a number of small objects (tea bags, rubber bands, screws, paper clips, tacks, shoe strings, coins, cotton balls, etc.) glued onto it, creating a "cue-rich" environment (Fig. 1*B*). The other half was left unadorned ("cue-poor" half). Only one recording session was performed for each rat, representing the animal's first exposure to the track and the recording room.

Experiment C (independent cue-rich–cue-poor tracks). Before surgery, two rats were food-deprived and trained to shuttle back and forth, on alternating days, on a circular track and a linear track (formed by the two opposing arms of an eight-arm maze) placed in different rooms. Neither these tracks nor the rooms were used during the subsequent recording sessions. The training was designed to familiarize the animals with the task without tying it to a particular experimental setup. When the animals were performing the task reliably, they underwent surgery. After recovery, they were trained again in the environments described above until they ran reliably again.

For the recording sessions, two structurally identical wooden tracks (180 × 8 cm) were used. The two tracks were covered with different materials (one with carpeting, the other with rubber, under-carpet webbing) and placed in two adjacent recording rooms, each equipped with a recording setup. One track (cue-rich track) was enriched with local cues including steel wool, cotton, odors (vanilla essence), and various kinds of hurdles over which the rats were required to climb, or the accessible width of the track was limited (Fig. 1*C*). The cues used for experiment C were more salient than the cues used in experiment B; in experiment B, the cues were mostly small objects, not very tall compared with the rats' height, and they could easily be stepped over. No local cues were placed on the other track (cue-poor track).

The first recording session represented the rats' first exposure to the experimental apparatus. The recording rooms were surrounded by a black curtain, and they contained many distal landmarks, all visible to the rat while on the track. The sets of distal landmarks were distinct and, in principle, allowed differentiation between the two rooms. The rats were carried from the colony to the recording rooms in a transporting dish, with free visibility. No attempt was made to disorient the animals at any point in the experimental protocol.

During each recording session, the rats began in one of the two rooms (a different one on alternating days). They rested in a towel-lined flower pot for 20 min (rest 1 phase), shuttled on the track for 15 min (track 1 phase), and then rested in the flower pot (rest 2 phase). At the end of rest 2, the rats were quickly disconnected from the recording apparatus, moved to the other room, connected to the recording apparatus there, allowed to shuttle on the second track for 15 min (track 2 phase), and then rested in a flower pot in the second room for 20 min (rest 3 phase).

Data analysis

Position data. From the two-dimensional position data, a one-dimensional coordinate φ was extracted. For the linear tracks, this represented the rat's linear distance from one end of the track, with 0 corresponding to one reward location and 1 corresponding to the other reward location, and for the circular tracks φ was a normalized angular coordinate, also varying between 0 and 1. The animal's instantaneous speed was calculated from the two-dimensional x–y trajectory and smoothed by convolution with a Hamming window that was 0.3 sec long. In addition, a threshold criterion was applied to exclude from the analysis those times when the rats were not moving. The position coordinate φ was segmented into bins corresponding to 4.5 cm on the tracks (40 bins for the linear tracks, 64 bins for the 91-cm-diameter circular track, 90 bins for the 130-cm-diameter circular track).

Spatial selectivity determination, information measures. To determine which putative pyramidal cells were spatially selective, instantaneous fir-

ing rates were computed over 100 msec intervals. Activities occurring during the journeys in the direction of increasing φ ("rightbound" journeys) and in the direction of decreasing φ ("leftbound" journeys) were considered separately. Mutual information was computed between the binned spike trains and the position φ and corrected for finite sampling size (Skaggs et al., 1992; Panzeri and Treves, 1996). A cell was considered to be spatially selective (i.e., to have at least one place field on the track) in a certain journey type (leftbound vs rightbound) if its average firing rate during the run periods was at least 0.3 Hz and if it carried at least 0.25 bits/spike of spatial information. The total information, combining location and direction of motion, was also computed for the cells firing at least 0.3 Hz during the runs.

Directional characteristics of place cells. To assess the directionality characteristics of the spatially selective cells, place field profiles $P(\varphi)$ were obtained by computing the average firing rate at each of the N_{bins} space bins. For cells that were spatially selective in both directions, the overlap r between the profile for the rightbound journeys and version of the profile for the leftbound journeys shifted by s was computed by means of the following formula:

$$r(s) = \frac{2\sum_{\varphi} \min(\tilde{P}_{\text{right}}(\varphi + s), \tilde{P}_{\text{left}}(\varphi))}{\sum_{\varphi} (\tilde{P}_{\text{right}}(\varphi) + \tilde{P}_{\text{left}}(\varphi))},$$

where

$$\tilde{P}_{\text{right,left}}(\varphi) = \frac{N_{\text{bins}} P_{\text{right,left}}(\varphi)}{\sum_{\varphi} P_{\text{right,left}}(\varphi)}.$$

This overlap measure is invariant for rescaling of the place field profiles, and it assumes the limit values of 0 for nonoverlapping place field profiles and of 1 for profiles that are identical except for a global rescaling of the activities. The overlap was computed for values of the alignment parameter s varying from −10 bins to +10 bins. The maximum value of $r(s)$, R, and the s value for which it occurred, S, were computed.

A cell was classified as a bidirectional place cell if it was spatially selective in both directions and had a maximum overlap R of at least 0.35. In this way, a place cell was only considered bidirectional if the place fields in each direction covered overlapping or adjacent portions of the track. A spatially selective cell was otherwise classified as a unidirectional place cell. In general, the centers of the place fields in the two directions were not aligned at the same place. The value of the misalignment S gave an indication of the relative position of the two fields. A positive value for S indicated that the place field profiles in the two directions were shifted in a direction opposite to the rats' motion ("prospective" misalignment) (Fig. 2), whereas a negative misalignment denoted a place field profile that was shifted in the direction of the rats' motion ("retrospective" misalignment) (Fig. 2). Place fields that "wrap around" the reward sites can be considered to span a single, continuous portion of the rat's trajectory with uninterrupted cell firing. To avoid considering these place fields together with place fields with two disconnected directional components, activity occurring when the rats were within four space bins, or 18 cm, from the reward location was excluded from the analysis.

Comparison of cell activity on the two tracks in experiment C. In experiment C, recordings were performed on both the cue-rich and the cue-poor track during a single session. Although the recordings were performed on different setups, for at least some cells it was possible to match the recordings based on waveform parameters. For this cell population, the response characteristics on the two tracks were compared, in particular to assess whether there was a tendency of some cells to be spatially selective, or bidirectional, on both tracks. In the case of statistical independence between the spatial selectivity properties of the cells on the cue-rich and cue-poor tracks, if F_{rich} and F_{poor} were the probability that a cell was selective or bidirectional on the rich or poor tracks, respectively, the observation of the selectivity or bidirectionality of a cell on both tracks is a binomially distributed variable with expected frequency $F_{\text{both}} = (F_{\text{rich}})(F_{\text{poor}})$. The SEM across cells of this observation is $F_{\text{both}}(1 - F_{\text{both}})/\sqrt{(N_{\text{cells}})}$. These values are taken as the mean and variance of the chance distribution.

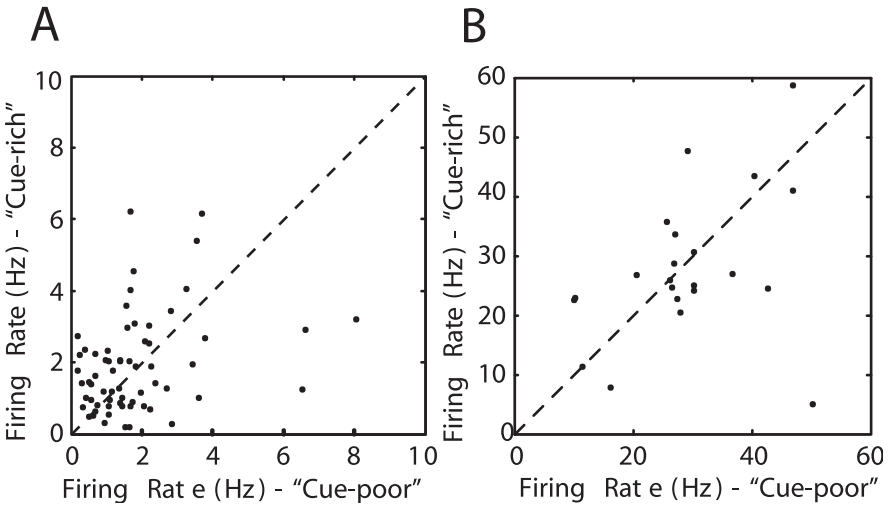

Figure 3. Comparison of average firing rates on the two tracks of experiment C. *A*, Average firing rates for 64 putative pyramidal cells that exhibited place fields on both the cue-poor (*x*-axis) and the cue-rich (*y*-axis) tracks in experiment C (independent cue-rich– cue-poor tracks). There was no systematic difference in firing rate between the two environments (repeated-measures *t* test; not significant) and only a small correlation ($r = 0.318$; $p < 0.05$). *B*, Same comparison for 22 putative interneurons recorded on both tracks, showing no difference in the average firing rate between the environments (repeated-measures *t* test; not significant). The correlation coefficient between interneuronal firing on the cue-rich and the cue-poor track was $r = 0.389$. Note the difference in scales on the two graphs. Dashed lines, 45°.

Population vector analysis. Population vectors provide a representation of how the cell population as a whole encodes each location. These vectors were computed by taking the place field profiles $P(\varphi)$ for the spatially selective cells, normalizing them so that the profile peak value was 1, and then compiling a list of the normalized firing rates for each space bin for all cells. The population vector correlation matrix provides a measure of how quickly the spatial firing patterns change with distance (i.e., how quickly the vectors decorrelate) and also of how similar the representations of a given location are in the two directions of travel.

From the population vectors for all of the locations, the population vector sparseness was computed according to the following formula:

$$a(\varphi) = \frac{1}{N_{\text{cells}}} \frac{\left[\sum_{i=1}^{N_{\text{cells}}} P_i(\varphi)\right]^2}{\sum_{i=1}^{N_{\text{cells}}} P_i^2(\varphi)},$$

where φ is the location on the track and $P_i(\varphi)$ is the place field profile for the ith cell. In the limit of binary firing rates, sparseness reduces to a measure of the fraction of active cells in the sampled population. A lower sparseness value indicates that a smaller proportion of cells is highly active at a certain location, as would be the case if the place fields spanned a smaller portion of the environment.

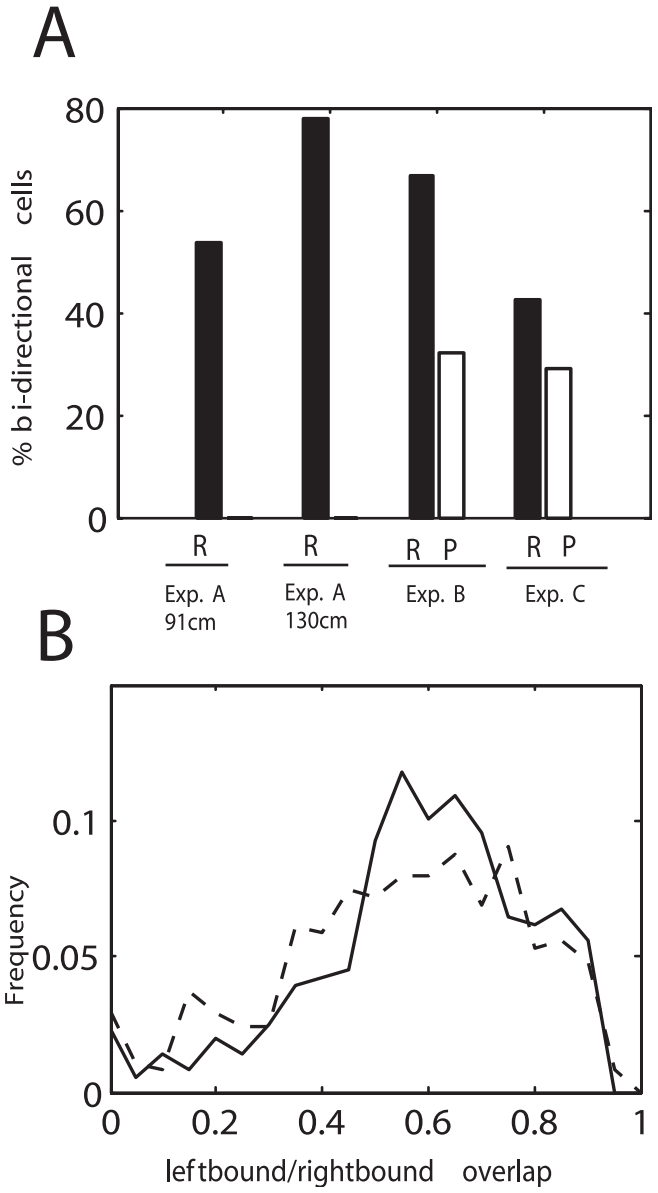

Figure 4. Proportion of bidirectional place cells over the total spatially selective cells. *A*, The fraction of spatially selective cells that were bidirectional is shown for experiments A (two tracks), B, and C, for the cue-rich (R) and cue-poor (P) environments. Experiment A only had a cue-rich condition, and experiments B and C allow the direct comparison of the cue-rich and cue-poor conditions. *B*, Histogram of the overlap values for the cells recorded in the cue-rich (solid line) and cue-poor (dashed line) environments in experiments B and C.

A related, but distinct quantity is the place field profile sparseness given by the following formula:

$$s_i = \frac{1}{N_{\text{bins}}} \frac{\left[\sum_{\varphi} P_i(\varphi)\right]^2}{\sum_{\varphi} P_i^2(\varphi)},$$

which gives a measure of the amount of track surface covered by the place field profile; a place field profile sparseness of 1 is obtained for a place field that covers uniformly the entire track, and the minimum possible value of $1/N_{\text{bins}}$ indicates that the activity is confined to only one spatial bin.

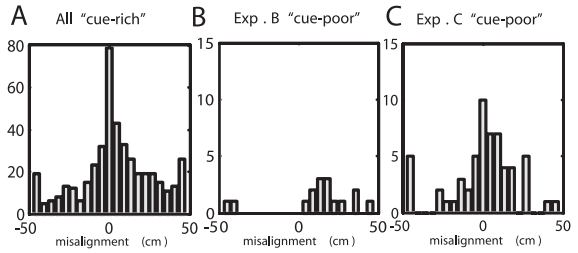

Figure 5. Place field prospective misalignment. *A*, Histograms of the misalignment values between the rightbound and leftbound journey firing profiles for bidirectional place cells recorded from all cue-rich environments, yielding the largest overlap between the two profiles for all of the experiments combined. *B*, Histogram of the misalignment values for the bidirectional place cells recorded in the cue-poor half of experiment B. There was a preponderance of cells with positive misalignment. Note, however, that 6 of the 14 bidirectional cells in experiment B had place fields centered near the middle of the track, starting well into the cue-rich area. These place fields may be an effect of the sensory cues in the cue-rich area and of the border between the cue-rich and cue-poor areas, also a salient landmark. *C*, Histogram of the misalignment values for the cue-poor track in experiment C. The average misalignment was slightly negative and nonsignificantly different from zero. The slight majority of cells with a positive misalignment did not reach significance either (supplemental Table 2, available at www.jneurosci.org).

Results

Recording yields, behavioral measures

In experiment A (cue-rich circular tracks), the rats were run only in a local sensory cue-enriched condition, whereas experiments B (combined cue-rich–cue-poor linear track) and C (independent cue-rich–cue-poor tracks) allowed comparison between the cue-rich and cue-poor conditions. The main behavioral parameters, the recording yields, and the basic physiological measures from the recorded cells are summarized in supplemental Table 1 (available online at www.neurosci.org).

The rats ran 4–93 laps (average, 30.8 ± 17.8 SD) in each session (or subsession for experiment C). Rats ran faster in the cue-poor environments than in the cue-rich environments in both experiments B and C (supplemental Table 1, available at www.neurosci.org), even after the times when they completely stopped were excluded from the analysis. Overall speed was lower in experiment B, probably because of the fact that each rat only performed one session, representing its first exposure to the track, and engaged in considerable exploratory behavior. In experiment C, the difference in speed between the cue-rich and cue-poor track was also present in the sessions after the first one.

Cell activity statistics, spatial selectivity, place field directionality

The average population firing rates for all of the experiments are shown in supplemental Table 1 (available at www.neurosci.org). Based on the values of the waveform parameters on the four tetrode channels, approximately one-half of the recorded cells were confidently matched in the data from the two different tracks in experiment C. Not all of the recordings could be matched, probably because of small discrepancies in the electronics used in the two setups, even with the same nominal parameters, and perhaps because of some electrode displacements that may have occurred as the rats were disconnected from one apparatus and reconnected to the other.

There was no difference in average population firing rates recorded in the cue-rich and cue-poor environments, despite the higher running speed recorded in the cue-poor environments. Figure 3*A* shows a comparison of firing rates on the cue-rich and the cue-poor track for cells that could be identified on both tracks

of experiment C. This was also true for a group of 22 interneurons for which recordings on the two tracks of experiment C could be matched. Firing rates for these cells on the two tracks were not significantly different (repeated-measures *t* test; not significant) (Fig. 3*B*).

The proportion of spatially selective cells was not different between the cue-rich and cue-poor environments. The main factor differentiating the cell activity in the cue-rich and cue-poor environments was place cell directionality; significantly more cells exhibited bidirectional place fields in the cue-rich environments than in the cue-poor environments. The fraction of cells with bidirectional place fields was similar in all of the cue-rich environments (supplemental Table 1, available at www.jneurosci.org) (Fig. 4*A*). The effect was significant both when the fraction of bidirectional cells over the number of spatially selective cells and when the fraction of bidirectional cells over the total number of recorded cells were taken into consideration. A significant difference was present even when taking into consideration simply the number of cells with place fields in both the rightbound and the leftbound journeys (i.e., regardless of the overlap measure) (supplemental Table 1, available at www.jneurosci.org). Indeed, almost all of the cells showing spatial selectivity on both journeys fulfilled the overlap condition, showing that whenever a cell had place fields on both journeys, they tended to occur in the same region of the track.

The average overlap between place fields in the leftbound and rightbound journeys was larger in the cue-rich (0.583 ± 0.011) than in the cue-poor environment (0.545 ± 0.012; $p < 0.02$; two-tailed *t* test) when all of the cells with a firing rate on the track of at least 0.3 Hz were taken into consideration (Fig. 4*B*).

Bidirectional place cells showed larger average firing rates, as expected, because they fire during both the rightbound and leftbound journeys. Bidirectional cells also showed larger peak firing rates in their spatial firing rate profiles than unidirectional cells. Both effects reached statistical significance in all of the experiments (worst case; $p < 0.001$) (supplemental Table 1, available at www.jneurosci.org), except for the peak firing rate in experiment B (combined cue-rich–cue-poor linear track).

An estimate of the number of bidirectional place cells that would be expected from chance because of fortuitously overlapping place fields was computed from the probability for a given cell to have a place field in the rightbound journey and

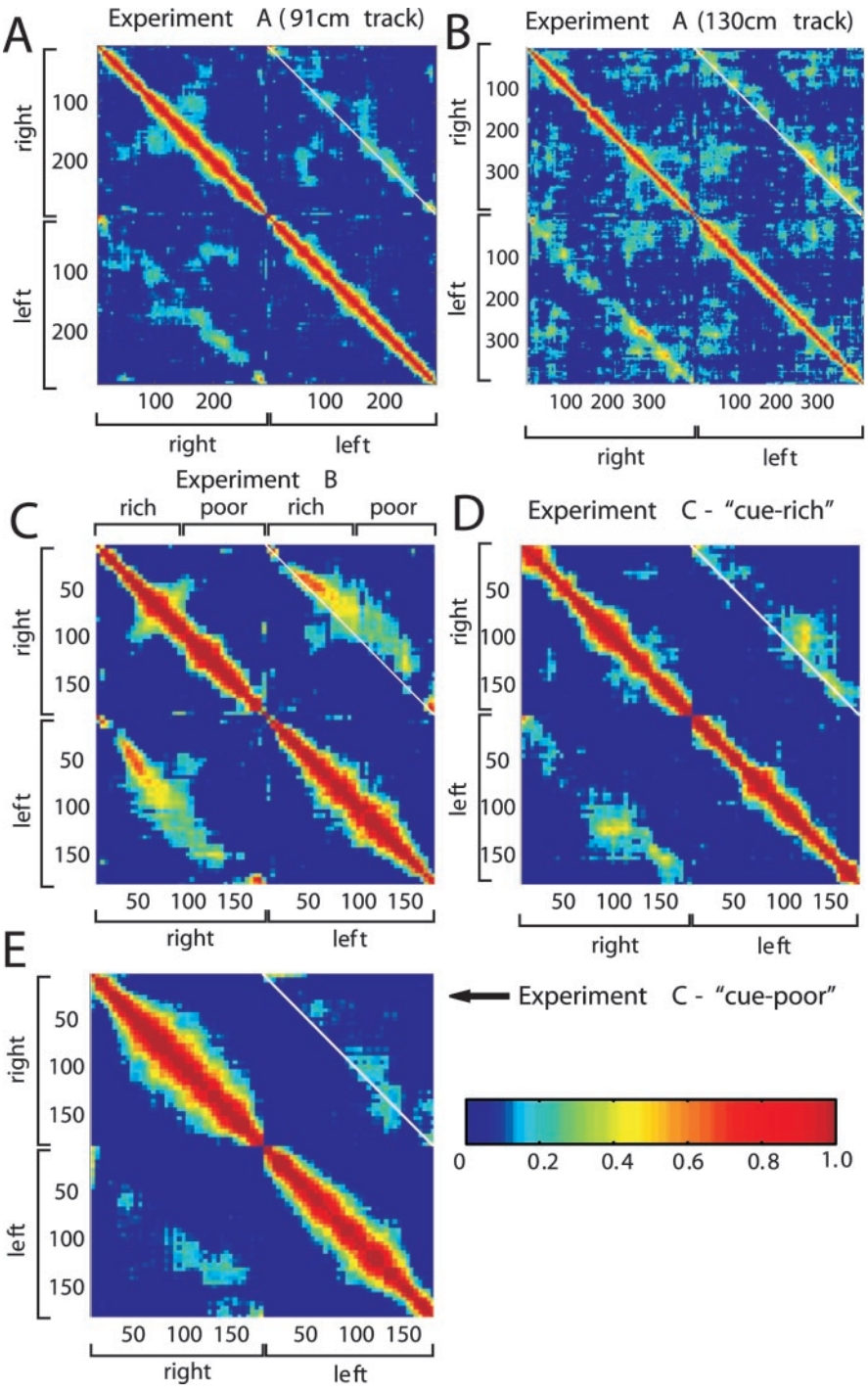

Figure 6. Population vector correlation. In each matrix, the element r_{ij} represents the Pearson correlation between the population vectors computed at location *i* and location *j* on the tracks in experiments A (cue-rich circular tracks), B (combined cue-rich–cue-poor linear track), and C (independent cue-rich–cue-poor tracks). Each matrix is divided in four quadrants. The top left quadrants represent the correlations between population vectors in the rightbound journey, and the bottom right quadrants represent the correlations between population vectors in the leftbound journey. The other two quadrants (one the transpose of the other because of matrix symmetry) represent the correlations between one population vector from the rightbound journey and one population vector from the leftbound journey. The stripe of relatively high correlation on the diagonal, highlighted by the white lines, denotes the similarity between the representations of space in the two directions, induced by the bidirectional place cells. The peaks of the correlation were not exactly on the quadrant diagonal; rather, they were shifted to one side, consistently with the backward shift of most place fields. *A*, *B*, Population vector correlation matrix for the 91 and 130 cm tracks, respectively, of experiment A. For both tracks, a high correlation stripe is evident along the diagonal of the top right–bottom left quadrants. *C*, Population vector correlation for experiment B. The high correlation stripe in the top right quadrant was more evident in the part of the matrix corresponding to the rich half of the track, which is consistent with the greater proportion of bidirectional place cells on that region. *D*, *E*, The population vector correlation matrices for the cue-rich (*D*) and the cue-poor (*E*) track of experiment C (independent cue-rich–cue-poor linear tracks). The stripe of elevated correlation on the leftbound versus rightbound quadrants was more marked for the cue-rich track, indicating a greater similarity between the ensemble representation of the leftbound and

the probability for a field in the leftbound journey. The product of these two probabilities gives the chance probability that a cell has a place field during both journeys. The chance probability that the place fields in the two directions actually overlap enough to be considered to be a bidirectional place field (according to the current criterion) was computed by taking all of the pairs of place fields recorded from all cells and computing the frequency by which their overlap reached the criterion. The overall chance probability of having a bidirectional field is the product of these two factors. In experiment B, in the cue-rich region, there were 37 (23%) bidirectional place fields versus a chance level of 8.49 ± 2.84 (5%). In the cue-poor region, there were 16 (10%) bidirectional place fields versus a chance level of 4.49 ± 2.09 (3%). In experiment C, the number of bidirectional place fields was larger than chance both on the cue-rich track, 91 (23%) versus an expected number of 36.2 ± 5.7 (9%) and on the cue-poor track, 58 (14%) versus an expected number of 23.7 ± 4.7 (6%).

For 204 putative pyramidal cells from experiment C, the recordings on both tracks were matched, allowing the comparison of cell responses between rich and poor tracks. Although the spatial representations of the two tracks were largely uncorrelated (data not shown), the spatial properties of this subset of cells in the two environments were not completely independent; a total of 64 cells (31%) were spatially selective on both tracks, versus a chance level of 48.8 ± 6.1 (24%; $p < 0.02$). Of these, 10 cells were bidirectional on both tracks, versus a chance level of 3.1 ± 1.75 ($p < 0.001$). To test whether these cells were spatially selective in both environments because of a greater general excitability, the firing rates during the rest 1 period were computed for all of the matched cells. The cells that were bidirectional had a mean firing rate of 1.49 ± 0.33 Hz; the overall mean rate for cells that were spatially selective in both environments (i.e., both unidirectional and bidirectional fields) was 0.98 ± 0.14 Hz. Neither group was statistically different from the cells that were not selective on either track (rest 1 firing rate, 1.39 ± 0.25).

Misalignment of the two directional components of bidirectional place fields

Bidirectional place fields showed a consistent pattern across the three experimental situations described here. In the majority of cases, the track regions where a place cell fired in the two directions of motion were not exactly coincident but were shifted backward with respect to the rats' motion (Figs. 2, 5).

The comparisons between the numbers of backward misaligned and forward misaligned bidirectional place cells and the average misalignment are shown in supplemental Table 2 (available at www.jneurosci.org). In all cases, there was a larger number of backward-shifted cells, and except for the cue-poor track in experiment C, the average misalignment was positive (i.e., backward with respect to the direction of travel). With a few exceptions, both effects were statistically significant on all of the environments. In total, of the 428 bidirectional place fields recorded on cue-rich environments, 218 were backward-misaligned and 128 were forward-misaligned (binomial sign test; $p < 10^{-5}$), and the average misalignment was 4.73 ± 1.04 cm (two-tailed t test; $p < 10^{-5}$). In the cue-poor environments, there was still a majority of backward-misaligned place fields, 43 (58%) versus 21 (28%; $p < 0.05$), but the average shift was nonsignificant (3.22 ± 2.49 cm). There was a difference between the effects observed in the two cue-poor environments used. On the cue-poor half of the track in experiment B (combined cue-rich–cue-poor linear track), there was still a significant majority of backward-misaligned cells (14 vs 2, over a total of 16 bidirectional place cells recorded) and a significant average backward shift 12.37 ± 6.04 cm; however, 6 of the 16 bidirectional cells had a place field very close to the middle of the track, which was the boundary between the cue-rich and cue-poor zones, and were assigned to the cue-poor half because the place field center fell in that half. It is possible that those cells were still affected by the cues on the cue-rich half. On the cue-poor track of experiment C (independent cue-rich–cue-poor linear tracks), there was no significant majority of backward misaligned cells, and the average shift was nonsignificant. The effect was also evident at the population vector level (Fig. 6) (see below).

Population vector correlation analysis and effects of local cues on the sparseness of place representation

Bidirectional place cells increase the similarity between the representations of the track in the leftbound and rightbound journeys; this similarity can be visualized by population vector analysis (Gothard et al., 1996b, 2001). In Figure 6, the correlation matrices for the average population vector measures at all points on the three tracks and in the two journey types are shown. The on-diagonal quadrants (i.e., the top left and bottom right ones) of each matrix represent the correlation between the representations of track points on the same journey type. The off-diagonal quadrants (top right and bottom left) show the similarity between the place representations in the two journey types. Figure 6*A* shows the population vector correlation matrix for experiment B (combined cue-rich–cue-poor track). The brighter stripe in the off-diagonal quadrant shows how the bidirectional cell activity increases the similarity between the representations of the same location in the two journeys. The effect is stronger on the cue-rich half of the track, which is consistent with the larger number of bidirectional place fields on that side. The band of increased similarity was not exactly centered on the quadrant diagonal, as would be the case if the place fields in the two journeys were exactly aligned. Consistent with the misalignment described above, the high-similarity band is shifted to one side of the diagonal (Fig. 6, white line). Figure 6, *B* and *C*, represent the population vector correlation matrices for the cue-rich and the cue-poor tracks used in experiment C (independent cue-rich–cue-poor tracks). The high-similarity band is more pronounced for the cue-rich track (Fig. 6*B*) as expected from the larger number of bidirectional fields.

The on-diagonal quadrants of the correlation matrices present a much more evident band of high correlation values around their diagonal. The width of that band represents the distance at which the population vectors representing two locations become uncorrelated. In experiment C (independent cue-rich–cue-poor tracks), this correlation distance is significantly smaller on the cue-rich track (Fig. 7*C*, black lines, plotted with 95% confidence intervals) than on the cue-poor track (gray traces). This is partly a consequence of the sparser population vectors on the cue-rich track than on the cue-poor track (Fig. 7*D*). Such a pattern was not clearly observed in experiment B, where the decorrelation distance on the cue-rich part of the track was only marginally smaller than its counterpart on the

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rightbound journeys. For both tracks, the elevated correlation stripe was shifted to one side of the diagonal, as an effect of the prevalent backward misalignments of bidirectional place fields. The correlation between same-direction representations of nearby locations (top left and bottom right quadrants on each matrix) tended to decay more slowly on the cue-poor track than on the rich track (Fig. 7). The *x*- and *y*-axes are measured in centimeters.

cue-poor side (Fig. 7*A*) and there was no difference in population vector sparseness between the cue-rich and cue-rich track halves. The same pattern is also visible in the place field profile sparseness, which provides a more direct quantification of the spatial span of a place field. In experiment C, place fields were on average significantly sparser (i.e., they had a lower value of the sparseness) on the cue-rich track than on the cue-poor track ($p < 10^{-5}$) (supplemental Table 1, available at www.jneurosci.org). No significant difference was observed for experiment B.

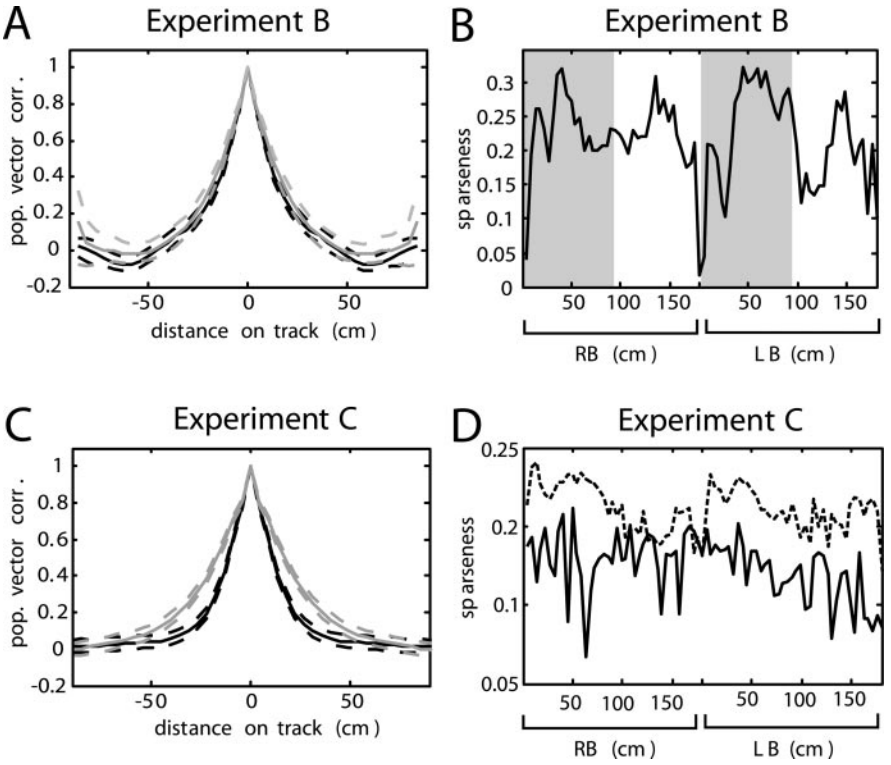

Figure 7. Population vector correlation (pop. vector corr.) decay and population sparseness. *A, C*, The mean population vector correlation as a function of the distance between the locations from which the two population vectors were recorded for experiments B (combined cue-rich– cue-poor linear track; *A*) and C (independent cue-rich– cue-poor tracks; *C*). *A*, The correlation decay for the cue-rich half of the maze (black) and for the cue-poor half (gray) in experiment B are displayed. The dashed line denotes the 95% bootstrap confidence interval. Population vector correlation tended to decay more slowly with distance on the cue-poor track, but the effect did not reach significance. *C*, The population vector correlation decay on the cue-rich track (black) and on the cue-poor track (gray) in experiment C are displayed. The correlation on the cue-poor track decayed significantly more slowly than on the rich track, showing that on the latter track the hippocampus was somewhat more capable of orthogonalizing the representation of nearby locations. *B, D*, The average population sparseness at each location for experiments B and C, respectively. *B*, There was no detectable difference in sparseness between the cue-rich (shaded) and the cue-poor halves of the track of experiment B. *D*, The solid line depicts the population vector sparseness for the cue-rich track. The dashed line shows the sparseness on the cue-poor track. Coding was sparser (i.e., the sparseness value was lower) on the cue-rich track. RB, Rightbound journey; LB, leftbound journey.

Discussion

When rats make repeated forward and return journeys along the same route in the absence of distinct local cues, hippocampal ensemble activity is uncorrelated in the two directions of travel (McNaughton et al., 1983a; Muller et al., 1994; Markus et al., 1995). In contrast, during unstructured foraging in two dimensions, hippocampal spatial selectivity is nondirectional (Muller et al., 1987, 1994). The source of these differences remains a matter of conjecture (Sharp et al., 1996; Brunel and Trullier, 1998), but numerous examples occur in the literature of "remapping" or "orthogonalization" of hippocampal activity when variables other than simply spatial location change (Quirk et al., 1990, 1992; Bostock et al., 1991; Barnes et al., 1997; Shapiro et al., 1997; Kentros et al., 1998; Knierim et al., 1998; Lever et al., 2002; Bower, 2003). These observations support a nonlinear relationship between the overlap of hippocampal input patterns and the overlap of the corresponding output patterns (Marr, 1971; McNaughton, 1989; Treves and Rolls, 1992; O'Reilly and McClelland, 1994). This nonlinear behavior may both maximize storage capacity (Marr, 1971) and facilitate the formation of unique hippocampal patterns suitable as index elements of specific experiences distributed among neocortical sites (McNaughton et al., 2002). Thus, directional selectivity on linear tracks and the lack of directionality during random foraging can potentially be the result of an increased differentiation of hippocampal input in the former case attributable to, for example, consistent inputs to the hippocampus about the origin and/or destination of the current journey (Bower, 2003).

The main finding reported here is that on cue-rich tracks, many place cells are bidirectional, and the overlap between the hippocampal representations of the two journeys is substantially greater than chance and greater than on cue-poor tracks. Although differences in the animal's initial behavior might account for the increased bidirectionality on cue-rich tracks, this seems unlikely, because bidirectionality does not appear in rats during their first exposure to linear tracks in general (our unpublished observations), during which extensive exploratory activity occurs. A better assessment of this issue would require further study with a different protocol. The most parsimonious explanation is that rats can generate, in lower cortical areas, view-invariant representations of proximal cues, which increase the similarity of the hippocampal input patterns in the two directions. Although multiple, centrally placed landmarks do not affect place fields during random foraging in a two-dimensional space (Cressant et al., 1997), this observation is not inconsistent with the current results and interpretation, because most fields are already omnidirectional in such situations.

It is important to distinguish between the concept of explicit object representation and the reduced orthogonality of hippocampal ensemble patterns that may result from view-invariant object representations at the input. Hippocampal neurons appear not to have context-invariant responses to specific objects. For example, cells that fire near a discrete landmark and with fields that realign with the landmark when its location shifts within one environment have firing that is completely unrelated to the same object in a different environment (Gothard et al., 1996a). Also, hippocampal ensemble patterns can change completely within the same environment when either behavioral context (Markus et al., 1995) or the orientation of the landmarks relative to the internal head-direction representation (Knierim et al., 1998) change. Thus, a priori decoding of neural activity to infer the presence of specific objects at the input, which might be possible at lower levels of the visual system, would not be possible in the hippocampus.

In experiment C, the trend for more cells than expected by chance to exhibit both spatial selectivity and bidirectionality on both tracks, a trend that cannot be explained by greater excitability, may hint at the effect of having identical track geometry and task in both cases.

Even in the case of random allocation of place fields, a cell may exhibit bidirectional spatial firing simply because it happens by chance to have overlapping place fields in each direction. In the present data, the number of bidirectional place cells in the cue-poor environments in the present study was higher than expected by chance, possibly because of uncontrolled local cues on the track (olfactory, etc.) or perhaps as an effect of previous experience. For example, in experiment C, the slight excess of bidirectional cells on the cue-poor track and the slight overabundance of cells with fields on both tracks might reflect a weak pattern completion effect on the cue-poor track resulting from the experience on the cue-rich track. In experiment B, however, bidirectional fields in the cue-poor region were clustered near the transition to the cue-rich region, suggesting that they were actually influenced by cues within the cue-rich section.

Local cues also increase the spatial information useful to disambiguate nearby locations, and the intrinsic spatial scale of the hippocampal ensemble activity pattern might change accordingly. Indeed, the density of place fields was found by Hetherington and Shapiro (1997) to be higher in regions of a cue-rich environment, leading them to conclude that place fields "preferentially encode regions of relatively high spatial information." Other studies have reported a preponderance of place fields near edges, walls, or corners (O'Keefe and Conway, 1978; Muller and Kubie, 1987; Wiener et al., 1989; Hetherington and Shapiro, 1997) or near sites of reinforcement or escape (Eichenbaum et al., 1987; Breese et al., 1989; Kobayashi et al., 1997; Hollup et al., 2001). In the present data, however, there was no effect of local cues on the density of place fields, but the sparser population code and the faster decline in the population vector correlation on the cue-rich track in experiment C suggest an orthogonalizing effect of the local cues on the representations of nearby locations. The population vector decorrelation rate is in fact a measure of the intrinsic spatial scale in the hippocampal representation. However, the same effect was not evident in experiment B, possibly because of lower statistical power. Also, the cues in experiment B were relatively small compared with those in experiment C and did not require large changes in locomotor pattern.

Most bidirectional place field centers were displaced backward with respect to the rat's direction of motion, as if the activity best represented a position a few centimeters (or perhaps a few moments in time) ahead of the rat. It is important here to discriminate between bidirectional place fields attributable to chance allocation of fields in the two directions of travel and bidirectionality that results from reduced orthogonality of the hippocampal ensemble pattern in the two directions. If the ensemble code is prospective, the latter fields would exhibit a net positive misalignment, whereas the former would not. On the cue-poor track of experiment C, bidirectional fields did not exhibit an alignment bias, and this was the only environment not showing a significant average misalignment. Conversely, in the cue-poor region in experiment B, the few bidirectional fields observed did display a net positive misalignment; however, as mentioned previously, approximately one-half of these were clustered near the poor–rich transition. Thus, overall, the present data are consistent with the presence of prospective coding, in which the peak firing in a place field anticipates the arrival of the animal at a particular point in space. Evidence of a different nature for prospective coding has been obtained in some experiments in which animals foraged in two dimensions (Muller and Kubie, 1989; Skaggs et al., 1996), and prospective coding is implicit in some models (Jensen and Lisman, 1996; Skaggs et al., 1996; Tsodyks et al., 1996) for the origin of the θ phase precession phenomenon discovered by O'Keefe and Recce (1993) and with models and findings about the effects of experience-related plasticity on place cell activity (Mehta et al., 1997, 2000; Ekstrom et al., 2001). The positive misalignment effect would be compatible with other interpretations as well. Rats direct their gaze ahead of themselves as they locomote, and thus, rodent hippocampal activity might be influenced by gaze location, as observed in primates (Rolls, 1999). Another hypothesis is that the input to a hippocampal cell is best correlated with the rat's current position on the track, but that the cell adapts (Harris et al., 2002) as the animal traverses the place field, so that the terminal portion of the place field is cut off. For bidirectional fields, the peaks in the two directions would appear misaligned. Contrary to expectation based on the accommodation model however, place field size is relatively unaffected by the substantial changes in firing rate associated with different running speeds (Ekstrom et al., 2001).

Overall, the results suggest that rodents may encode proximate objects in a view-invariant manner, that this encoding results in increased correlation of inputs to the hippocampus in two directions of travel (with a consequent increase in the correlation of the hippocampal output), and that, regardless of mechanism, the peak firing of a CA1 pyramidal cell does anticipate the arrival of the animal at a point in space ahead of it, as first suggested by Muller and Kubie (1987).

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