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Instability in the Place Field Location of Hippocampal Place Cells after Lesions Centered on the Perirhinal Cortex

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The perirhinal cortex appears to play a key role in memory, and the neighboring hippocampus is critically involved in spatial processing. The possibility exists, therefore, that perirhinal–hippocampal interactions are important for spatial memory processes. The purpose of the present study was to investigate the contribution of the perirhinal cortex to the location-specific firing ("place field") of hippocampal complex-spike ("place") cells. The firing characteristics of dorsal CA1 place cells were examined in rats with bilateral ibotenic acid lesions centered on the perirhinal cortex ($n = 4$) or control surgeries ($n = 5$) as they foraged in a rectangular environment. The activity of individual place cells was also monitored after a delay period of either 2 min, or 1 or 24 hr, during which time the animal was removed from the environment.

Although the perirhinal cortex lesion did not affect the place field size or place cell firing characteristics during a recording session, it was determined that the location of the place field shifted position across the delay period in 36% (10 of 28) of the cells recorded from lesioned animals. In contrast, none of the place cells (0 of 29) recorded from control animals were unstable by this measure.

These data indicate that although the initial formation of place fields in the hippocampus is not dependent on perirhinal cortex, the maintenance of this stability over time is disrupted by perirhinal lesions. This instability may represent an erroneous "re-mapping" of the environment and suggests a role for the perirhinal cortex in spatial memory processing.

Key words: rhinal cortex; spatial memory; parahippocampal; cognitive map; Alzheimer's disease; aging; navigation; dorsal hippocampus; rat; single unit recording

The hippocampus is an important component of the medial temporal lobe memory system (Zola-Morgan et al., 1994; Buffalo et al., 1998). Damage to the hippocampus appears to produce some degree of amnesia (Rempel-Clower et al., 1996), and the integrity of the hippocampus has been shown to be important for the performance of spatial memory tasks (Jarrard, 1995). It has been suggested that this latter function is dependent on the fact that hippocampal pyramidal neurons (place cells) appear to encode the location of an organism in the environment, because these cells increase their firing rate when an animal is in a particular position (place field), independent of other behaviors (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978).

The location of the place field of an individual place cell is normally stable over several days of recording in an unchanged, familiar environment (Muller et al., 1987; Thompson and Best, 1990), although the animal may be removed from that environment for extended periods. This feature of place cell activity may determine whether an animal perceives an environment as familiar or not, and because recognition of an environmental context may be an important hippocampal function, it is of primary interest to determine what factors and brain structures contribute to place cell stability.

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Although a number of previous studies have investigated the environmental and developmental factors that affect the stability of the hippocampal place cell signal (Knierim et al., 1995; McHugh et al., 1996; Rotenberg et al., 1996; Stackman and Taube, 1996; Barnes et al., 1997; Kentros et al., 1998; Shapiro and Eichenbaum, 1999), few studies have examined what brain regions support this characteristic. It has been determined, however, that place cells show significantly decreased stability after major damage to the dentate granule layer (McNaughton et al., 1989), lesions of the septal area (Leutgeb and Mizumori, 1999), or lateral dorsal thalamus (Mizumori et al., 1994). Other lesion studies have, however, shown no effect of damage to afferent structures (Mizumori et al., 1989; Shapiro et al., 1989) or have not specifically described the locational stability of the place fields in an unchanged, familiar environment (Miller and Best, 1980).

The aim of the present experiment was to examine the contribution of the perirhinal cortex to the locational stability of dorsal CA1 hippocampal place cells in a familiar environment. The perirhinal cortex is connected to the hippocampus both directly and via the entorhinal cortex (Deacon et al., 1983; Burwell et al., 1995; Liu and Bilkey, 1996a, 1997; Burwell and Amaral, 1998a; Naber et al., 1999; Shi and Cassell, 1999), and it appears to be critically involved in object recognition memory (Meunier et al., 1993; Murray, 1996; Buckley et al., 1997). It is possible, therefore, that functional interactions between these regions are crucial for mnemonic processes that rely on the integration of spatial and object information. The perirhinal contribution to this process may involve maintaining a representation of some aspect of the environment, for example, cue position, such that this information can be used by the hippocampus at a later time.

MATERIALS AND METHODS

Surgical procedures. Nine male Sprague Dawley rats weighing between 300 and 400 gm were anesthetized with sodium pentobarbitol (60 mg/kg, i.p.) and placed in a Kopf stereotaxic apparatus such that bregma and lambda were in the same horizontal plane. Body temperature was maintained at 37°C, and a midline incision was made to expose the skull.

Rats were divided into three groups and received either bilateral ibotenic acid (IBO) lesions of the perirhinal cortex (lesion; $n = 4$), no lesions ($n = 3$), or sham lesions ($n = 2$). In the treatment and sham animals, holes were drilled in the skull at 4.5, 5.5, and 6.5 mm posterior to bregma and 5.5 mm lateral to the midline. A guide tube (23 gauge needle) containing an obturator (30 gauge needle with sealed end) that extended (1.1 mm beyond the end of the guide tube, was then angled 10° laterally and located in the perirhinal cortex at a depth of ≈4.5–5 mm from the dural surface. In the case of the treatment animals, the obturator was withdrawn from the guide tube, the microinfusion cannula was inserted, and 0.3 μl of IBO (dissolved in a PBS, pH 7.4, at a concentration of 10 μg/μl) infused into each site over 4–5 min using a 5 μl syringe (5BR-5-RA8, SGE) connected to an automatic syringe pump (Bee Syringe Pump, MF-9090, BAS). The microinfusion cannula consisted of a 30 gauge dental needle (containing enough IBO for the whole surgery) that extended ≈1 mm beyond the end of the guide tube, attached to a length of plastic tubing filled with distilled water, and separated from the IBO by a 0.3 μl air bubble. The microinfusion cannula was ≈0.1 mm shorter than the obturator to ensure that it did not become blocked by tissue situated at the end of the guide tube. The cannula was left in the brain for 5 min after each infusion to allow for diffusion of the drug and then withdrawn from the guide tube and wiped down with a cotton swab. In the case of the sham lesions, the guide tube containing the obturator was inserted at each infusion site without any infusions being made.

A unit recording electrode consisting of a bundle of 6–7 (25 μm) formvar-coated nichrome wires mounted in a moveable "Scribe" microdrive (Bilkey and Muir, 1999) was then unilaterally ($n = 7$) or bilaterally ($n = 2$) implanted in the hippocampus at coordinates based on Paxinos and Watson (1998) (3.8 mm posterior to bregma, 2.5 mm lateral, ≈1.8 mm ventral). In unilateral surgeries, the implanted hemisphere was counterbalanced across animals. A stainless steel screw attached to the skull functioned as the ground. The area between the microdrive and the skull was sealed with Vaseline, and the microdrive was cemented in place with dental acrylic. A protective plastic ring was then cemented in place around the base of the microdrive. Stitches were placed anterior and posterior to the assembly, and penicillin was injected into the surrounding tissue. The rat was then placed in a heated recovery box and left to awaken from the anesthetic.

Apparatus and behavioral procedures. The experimental chamber consisted of a black rectangular chamber (120 × 60 × 60 cm) with a metal floor and an open top, within which the rat was allowed to move freely. Surrounding the chamber was a sheet of black polythene that loosely followed the lines of the chamber walls almost to the ceiling. Two back-lit cues were positioned in clearly visible locations on the inner walls of the chamber; a large crescent shape was positioned approximately one-quarter of the way along the long wall at a height of 35 cm, and a smaller star shape was positioned centrally on the end wall nearest the crescent at a height of 45 cm. After at least 10 d recovery after surgery, rats were habituated to the experimental chamber for 30 min/d and put on a schedule of food deprivation until they reached ~85% of their free-feeding weight (which was then maintained for the duration of the experiment). During the period of habituation, animals learned to forage throughout the chamber to recover chocolate-flavored pellets placed randomly on the floor of the apparatus.

Animals were carried directly to the experimental room in an open top box. The room light was extinguished immediately before placing the animal in the chamber (always from the same location in the room, facing the star cue). When at least one unit with a satisfactory signal-to-noise ratio was isolated, a baseline recording session was begun. Each recording session lasted until 10–30 min of data had been recorded, during which time chocolate-flavored pellets were distributed throughout the experimental chamber to keep the rat moving. The unit was then recorded again after 2 min, 1 hr, and 24 hr delays with the order of these delays counterbalanced for different units. A unit recorded over all delays, therefore, was recorded over a 2 d period. The animal was returned to its home cage during the delay period for all delay durations, and the box was wiped clean. Only units that demonstrated (1) a low (<4 Hz) mean firing rate (FR) (averaged over all sessions), (2) a maximum firing rate (averaged over all sessions) of <30 Hz, and (3) a clear place field (PF) based on observation of the unit firing and location and behavior of the animal during a session, were categorized as place cells. In addition, almost all of these cells exhibited a peak-to-peak spike width of >400 μsec (Fox and Ranck, 1981). Furthermore, because it was important to ensure as much as possible that the same unit was being recorded in repeated sessions, only units that exhibited stable spike amplitudes and consistent waveforms within and between sessions were included in the present analysis. In most instances, the waveform characteristics of a given unit were consistent enough within and between sessions that the same cluster boundaries could be used in Datawave Discovery to uniquely identify the unit across all sessions. On some rare occasions in which the identity of the unit was not in question, some small adjustments were made to the cluster box of a unit to maintain accurate isolation. At the end of this procedure, or if no unit was present, the electrode was lowered ≈20–40 μm, and the animal was returned to its home cage until the next day. Once the electrode had been lowered and a "new" unit isolated, any similarities in waveform characteristics or place field properties between the new unit and an immediately preceding unit would result in the unit not being considered new and the electrode being lowered again.

After presentation of all the delay sessions, some units were recorded during additional cue rotation sessions. These rotation sessions were normally conducted on the day after the last delay session, although sometimes this involved two additional days of recording. For these sessions, animals were treated as for the delay sessions except that they were usually disoriented before entry to the recording chamber by covering and slowly rotating the transport box for 1 min as the experimenter randomly traversed the laboratory. Cues were manipulated by 180° rotations of (1) the visual cues only, (2) the recording chamber only (i.e., visual cues in the normal location relative to the rat's entry point), or (3) both the recording chamber and visual cues.

Electrophysiological procedures. All signals were amplified and filtered (300 Hz-3 kHz) by preamplifiers (Grass P511K) after being impedance-matched through a field effect transistor headstage. During unit recording, a separate channel of the unit electrode with minimal activity was used as the recording indifferent. An overhead video camera monitored the animal's movement by tracking the position of two different-colored LEDs mounted ~7 cm apart on the headstage. This allowed the simultaneous acquisition of both the location of the animal and its head direction via a computer and custom tracking software (D. Bilkey) that generated DC outputs representing the x and y coordinates of the animal's position. All data were then digitized and recorded to tape for subsequent off-line analysis.

Histological procedures. At the conclusion of the experiment, the final electrode locations were marked by electrolytic lesions. Animals were then perfused with an infusion of saline (0.9%), followed by a 10% formalin solution. The brain was removed and placed in a 10% formalin solution for at least 1 d before being transferred to a 10% formalin, 30% sucrose solution for at least 5 d. Each brain was frozen and sliced (on a cryostat) into 60 μm coronal sections, mounted on slides, and stained with thionin. Subsequent examination of these sections was used to histologically verify the location of the electrode and location and extent of the IBO lesions.

Data analysis. All data were acquired with Datawave Discovery software (sampling rate for units, 22 kHz), and units were isolated using the Datawave Common Processing data analysis package. Position and head direction were sampled from the tracker at 6.25 Hz with linear interpolation being used to more accurately determine animal position for spike firing times occurring between any two of these samples. All data recorded while the tracker had mistracked (i.e., one or both LEDs ceased to be visible to the video camera) was disregarded. FR maps were constructed by dividing the floor of the chamber into a 40 × 20 grid in which each square (pixel) corresponded to 3 cm^2. For each pixel, the number of spikes occurring within it was divided by the amount of time spent in the same pixel (dwell time) to provide a firing rate. Unit data from a pixel where the animal spent <1 sec were considered undersampled and removed, leaving a firing rate map (Fig. 1*A*) that was used for the calculation of: (1) the "mean FR", the average firing rate of the unit, (2) the "mean in-field FR", the mean firing rate inside the place field, (3) the "max in-field FR", the maximum firing rate inside the place field, (4) the "mean out-field FR", the mean firing rate outside the place field, and (5) "spatial discriminability", the mean firing rate inside the place field divided by the mean firing rate outside the place field. To determine the half-amplitude PF size, the location of the peak of the place field and the number of fields, the data received minor

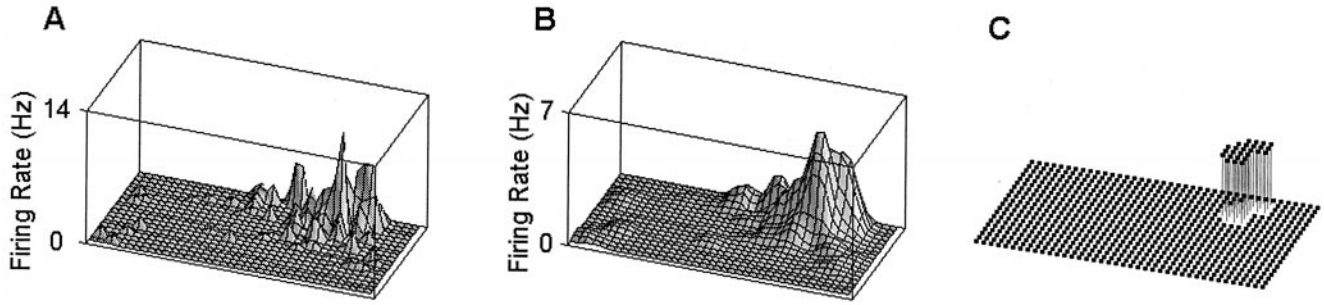

Figure 1. Comparison of firing rate maps. *A,* Raw firing rate map (with undersampled pixels removed). *B,* Smoothed firing rate map. Note that the location of the place field of the unit in the smoothed map is unchanged from its location in the raw firing rate map above. *C,* Place field area (elevated region). Pixels in which the firing rate of the unit was equal to or exceeded half of the maximum firing rate of the unit and that were adjacent to at least two other area pixels were considered part of the place field area for that unit.

smoothing (Fig. 1*B*). This involved filling undersampled pixels in the firing rate maps with the average value of their neighboring pixels and then smoothing using a 3×3 normalized, equally weighted matrix. Place field pixels that were not adjacent to at least two other place field pixels were removed (Fig. 1*C*).

The stability of place field location was measured in three different ways: (1) Pearson's product-moment correlations (spatial correlation) calculated between each smoothed firing rate map were generated for each unit (both between and within sessions). (2) The shift in the location of the place field peak (peak shift) both between and within sessions was used as a second measure of stability and was determined by calculating the distance (in pixels) between the location of maximal firing in each smoothed place field map. The mean and SD of the distribution for units recorded from control animals were then calculated, and units (either from lesion animals or controls) that showed a peak shift of >2.33 SDs from this mean (i.e., $p < 0.01$, one-tailed) were considered to exhibit significant instability in their place field locations. (3) The centroid (the average location of pixels in the field weighted by firing rate) (Fenton et al., 2000) and the subsequent centroid shift between and within sessions was calculated from the raw firing rate maps (with undersampling removed).

For within-session comparisons of peak shift, centroid shift, and spatial correlation, the firing rate map from the first half of the recording session was compared against that of the second half. Note that the peak shift, centroid shift, and spatial correlation were usually based on the average of six values for between-session data (i.e., every possible pairwise comparison of firing rate maps), and the average of four values for within session data (i.e., all sessions: baseline and three delays). All other measures were averaged over all sessions for that unit.

For statistical analyses, the type of *t* test used for pairwise comparisons was determined by a homogeneity of variance test. All *t* tests were two-tailed.

RESULTS

Histology

Examination of the electrode tracks and electrolytic lesions marking the locations of the hippocampal recording electrodes revealed that, in all animals, recording electrodes had passed through dorsal CA1 (Fig. 2). It was also determined that all four animals with IBO lesions displayed bilateral damage to most of the perirhinal cortex (Fig. 2). In all cases, the lesions of perirhinal cortex also encompassed some part of the border region of neighboring temporal cortex. Two animals showed evidence of additional damage (one unilateral, one bilateral) to adjacent ventral CA1 at posterior levels (note that the unit recording electrode was located in the hemisphere contralateral to the hippocampal damage in the animal with unilateral ventral CA1 damage). Some minimal damage to the border region of adjacent lateral entorhinal cortex (two unilateral, one bilateral) at posterior levels in three animals, and damage extending some 600 μm into postrhinal cortex (Burwell et al., 1995; two unilateral, two bilateral) in all animals, was also observed. No lesioned rats displayed any evidence of cell loss in the dentate gyrus or dorsal CA1.

Units recorded

A total of 78 units with a peak-to-peak spike width of >400 μsec were recorded from CA1 in three control ($n = 26$), two sham ($n = 11$), and four lesion ($n = 41$) animals. Of these units, 62 (79%) were determined to be place cells (control, $n = 23$; sham, $n = 8$; lesion, $n = 31$) by the criteria defined earlier.

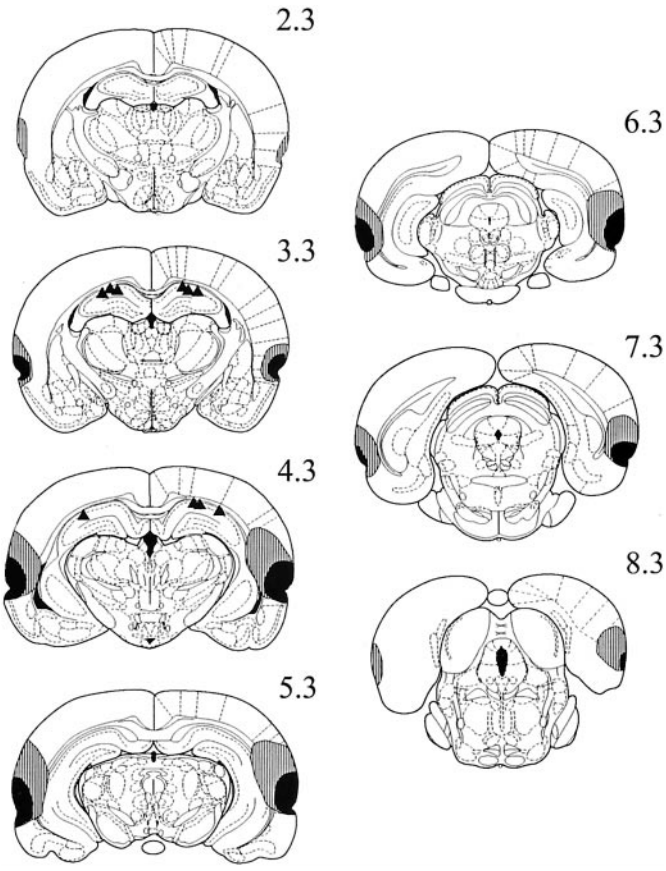

Figure 2. Diagram illustrating the location and extent of the smallest (*black*) and largest (*shaded*) bilateral ibotenic acid lesions of PRC and histologically verified point at which unit recording electrodes passed through region CA1 of the dorsal hippocampus (▲; see *3.3* and *4.3*) in all animals. *Numbers* represent the distance (in millimeters) posterior to bregma (Paxinos and Watson, 1998).

Table 1. Comparison of hippocampal place cell firing properties in control and perirhinal lesion animals

	Control place cells—all ($n = 31$)[a]	Lesion place cells—all ($n = 31$)[a]	Lesion place cells—stable ($n = 21$)[a]	Lesion place cells—unstable ($n = 10$)[a]
Mean FR (Hz)	0.98 ± 0.15	0.92 ± 0.15	1.05 ± 0.18	0.64 ± 0.25
Mean in-field FR (Hz)	4.62 ± 0.56	3.93 ± 0.48	4.67 ± 0.56	2.37 ± 0.70*,***
Max in-field FR (Hz)	10.55 ± 1.11	9.39 ± 1.07	10.96 ± 1.29	6.10 ± 1.51*,***
Mean out-field FR (Hz)	0.76 ± 0.12	0.69 ± 0.12	0.80 ± 0.15	0.44 ± 0.18
Spatial discriminability	8.64 ± 1.02	13.53 ± 3.01	9.45 ± 1.32	22.11 ± 8.59
PF area (pixels)	47.76 ± 4.72	39.64 ± 4.33	37.14 ± 3.13	44.88 ± 11.99
Number of fields per unit	2.03 ± 0.14	2.09 ± 0.19	1.91 ± 0.22	2.48 ± 0.35
Peak shift within sessions (pixels)	6.57 ± 0.64	8.74 ± 1.09	7.97 ± 1.32	10.37 ± 1.95
Peak shift between sessions (pixels)	4.43 ± 0.42	9.24 ± 1.52**	4.11 ± 0.68	18.48 ± 1.74**,****
Centroid shift within sessions (pixels)	5.80 ± 0.48	6.04 ± 0.56	5.42 ± 0.69	7.35 ± 0.85
Centroid shift between sessions (pixels)	4.54 ± 0.46	7.78 ± 1.10*	5.04 ± 0.87	12.71 ± 1.84**,****
Spatial correlation within sessions (r)	0.45 ± 0.03	0.41 ± 0.04	0.47 ± 0.04	0.28 ± 0.05**,***
Spatial correlation between sessions (r)	0.55 ± 0.03	0.42 ± 0.05*	0.57 ± 0.05	0.15 ± 0.04**,****

Values are means ± SE. Comparisons based on two-tailed Student's t tests.

[a]Between session data was acquired from $n = 29$ units from control animals and $n = 28$ ($n = 18$ stable; $n = 10$ unstable) units from lesion animals.

*$p < 0.05$; **$p < 0.01$, compared to units in control animals.

***$p < 0.05$; ****$p < 0.01$, compared to stable units in lesion animals.

Data from all remaining units were discarded because these cells did not possess clearly discernible place fields or failed to meet the criteria in some other way. Recordings of 57 place cells were made over at least one delay (control, $n = 23$; sham, $n = 6$; lesion, $n = 28$), and 40 were recorded at all delays (control, $n = 18$; sham, $n = 4$; lesion, $n = 18$). The proportion of place cells recorded at all delays was the same for all groups ($\chi^2 = 3.198$; NS). On some occasions more than one place cell was recorded at a time. The proportion of place cells over which this occurred was similar across the three groups (control, 33.33%; sham, 33.33%; lesion, 36.36%).

Group structure

Place cells from the sham lesion group exhibited significantly higher firing rates than those from the no-lesion group on all firing rate measures (mean FR, mean in-field FR, max in-field FR, mean out-field FR, spatial discriminability; $p < 0.05$, t tests), possibly attributable in part to the lower number (and hence, higher variability) of place cells recorded from sham lesion ($n = 8$) versus no-lesion ($n = 23$) animals. There was, however, no significant difference in any measures of place field stability or size (PF area, number of fields per unit, peak shift between and within sessions, centroid shift between and within sessions, spatial correlation between and within sessions, NS, t tests) when units from the no-lesion and sham lesion groups were compared. Units from the no-lesion and sham groups were, therefore, treated as a single group (control, $n = 5$ animals) for the purposes of the present study.

Place cell instability after perirhinal cortex lesions

The summary of place cell firing properties for units from control and lesion animals is presented in Table 1. These data show that the basic firing characteristics of all place cells from control animals and all place cells from lesion animals were similar on most measures (leftmost columns). There was, however, a significant difference in the three measures of place field stability after a delay (peak shift between sessions, centroid shift between sessions and spatial correlation between sessions). All of these measures indicated that the place field location was significantly more unstable between sessions in units from lesion animals as compared with controls. For example, the peak of the place fields shifted by approximately twice as much in units from lesion animals as compared with controls.

The mean and SD of the distribution of peak shifts for units recorded from control animals were then calculated, and units (either from lesion animals or controls) that showed a peak shift

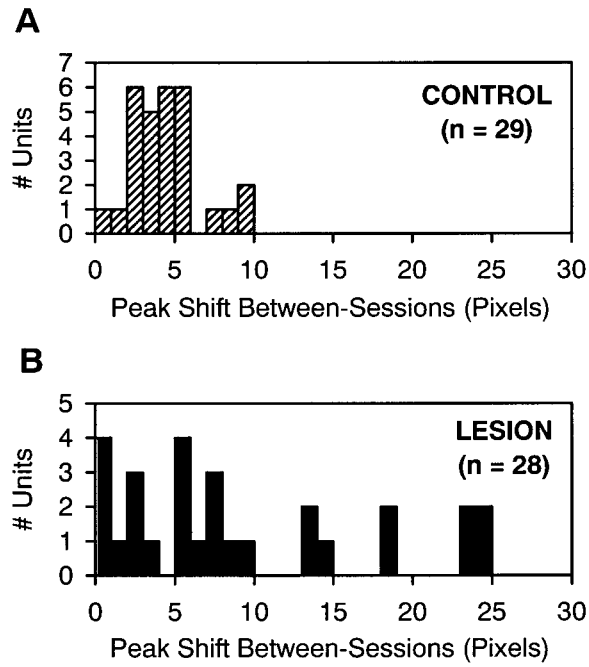

Figure 3. Distribution of the peak shift between sessions for units (place cells) recorded from control (*A*) and perirhinal-lesioned (*B*) animals. Of units recorded from lesion animals, 36% (10 of 28) demonstrated a peak shift between sessions that was significantly greater than those observed in the controls ($p < 0.01$; one-tailed).

Table 2. Number of stable and unstable hippocampal place cells recorded in control and perirhinal lesion animals

	Stable place cells recorded	Unstable place cells recorded	Total
Control animals			
C2	1	0	1
C4	18	0	18
C5	4	0	4
S2	6	0	6
S3	2	0	2
Total	31	0	31
Lesion animals			
B4	2	2	4
B5	8	5	13
B6	8	3	11
B7	3	0	3
Total	21	10	31

of >2.33 SDs from this mean (i.e., $p < 0.01$, one-tailed) were considered to exhibit significant instability in their place field locations. Overall, 36% (10 of 28) of units recorded from lesion animals demonstrated a peak shift between sessions that was significantly greater than those observed in the controls. In contrast, no place cells recorded from control animals (0 of 29) exhibited any such between-session place field instability (Fig. 3). The distribution of these stable and unstable units across animals can be seen in Table 2, and examples of stable units from control animals and unstable place fields in units recorded from lesion animals are illustrated in Figures 4 and 5, respectively.

There did not appear to be a systematic pattern in the way that place fields shifted location between sessions in these ten unstable units. For example, one unit began with a stable field in one corner of the box that abruptly changed to another corner after a 24 hr delay, whereas others had fields that began in the center and moved to be against a wall or vice versa (Fig. 5). Furthermore, shifts did not appear to be simple rotations of the original location of the field. The location shift in these units was also not stable, in that, after a large location shift, units would often shift again in subsequent recording sessions. These repeated shifts sometimes represented a return to the original location of the place field, although such shifts were uncommon. On occasions when simultaneous recordings of multiple units were made, it appeared that this instability could occur as either an all-or-none or a partial phenomenon. That is, all simultaneously recorded units could respond similarly (all stable, 3 of 8; all unstable, 1 of 8) or in a mixed manner (both stable and unstable, 4 of 8) in a given session.

To determine whether this between-session instability was delay-dependent, the peak shift between sessions was compared across the various delays. The analysis examined whether the slope of the line fitted by linear regression to the log of the delay durations in minutes versus peak shift between sessions (i.e., the amount of peak shift associated with increasing delay durations) was significantly different from zero for units from lesion and control animals (Fig. 6*A*). The results showed that units from neither lesion ($t_{26} = 1.622$; NS) nor control ($t_{22} = 0.246$; NS) animals had slopes that were significantly different from zero or slopes significantly different from each other ($t_{37.09} = 0.601$; NS). Similar regression analyses showed that the slopes of the regression lines for centroid shift between sessions (Fig. 6*B*) and spatial correlation between sessions (Fig. 6*C*) were also not significantly different from zero in units recorded from either control (centroid, $t_{26} = 0.758$, NS; *r*, $t_{26} = -0.295$, NS), or lesion animals (centroid, $t_{22} = 0.131$, NS; *r*, $t_{22} = 0.081$, NS) and that the slopes of these lines did not differ between groups (centroid, $t_{48} = 0.384$, NS; *r*, $t_{48} = 0.262$, NS).

An analysis of within-sessions measures of place field stability demonstrated that there were no significant differences between the place cells recorded in lesion and control animals. There was, however, usually less stability within sessions than between sessions for both groups. It should be noted, however, that within-sessions and between-sessions measures of place field location stability cannot be directly compared because (1) the within-sessions firing rate maps were calculated using sessions that were half the duration of those used for between-session firing rate maps, and (2) within-session place field stability measures for each unit were based on the average of a maximum of four comparisons, not six as was the case for between-sessions place field stability measures.

Firing properties of unstable place cells

To examine the firing properties of the units showing significant peak shifts between sessions they were treated as a separate group and compared with the remaining (stable) units from lesion and control animals (Table 1, rightmost columns). The results of these comparisons showed that the units with unstable place fields, in addition to being significantly less stable on all measures of between-session place field stability, possessed mean in-field FR, max in-field FR, and spatial correlation within-sessions measures that were significantly lower than those of the remaining (stable) lesion or control units ($p < 0.05$; *t* tests). These unstable units did not, however, differ from the stable units in measures of mean FR, PF area, or spatial discriminability (NS; *t* tests). Furthermore, a subset of units were selected from the control group beginning with the unit exhibiting the lowest max in-field FR and then adding units with increasing firing rates until the group exhibited approximately the same mean max in-field FR as that of the group of unstable units. When these control units ($n = 18$), were compared with the unstable units, there were no significant differences (NS; *t* tests) between the groups on any measures other than those describing place field location stability between sessions ($p < 0.05$; *t* tests). When lesion cells with unstable place fields were removed from the lesion group, all differences between the remaining lesion units and control units became nonsignificant (NS; *t* tests), with the exception of session duration ($t_{12.54} = 2.196$; $p < 0.05$).

Session duration

On further examination of the data, it was evident that the average session duration (after removal of data during mistracks) was significantly shorter for units from the lesion animals ($\bar{x} = 21.86$ min) than controls ($\bar{x} = 24.01$ min; $t_{51} = 2.171$; $p < 0.05$). This was attributed to the fact that five units were initially recorded using a shorter session duration, which was subsequently increased to allow for better sampling of less visited areas of the environment and to increase the sampling accuracy of the within-session measures. Of the units recorded for shorter durations, four were from lesion animals and one was from a control. If these five units were excluded from the analysis, the difference in average session duration between groups became nonsignificant ($t_{43.63} = 2.032$; NS). Most importantly, however, the differences in peak shift between sessions ($t_{26} = -2.594$; $p < 0.05$) and centroid

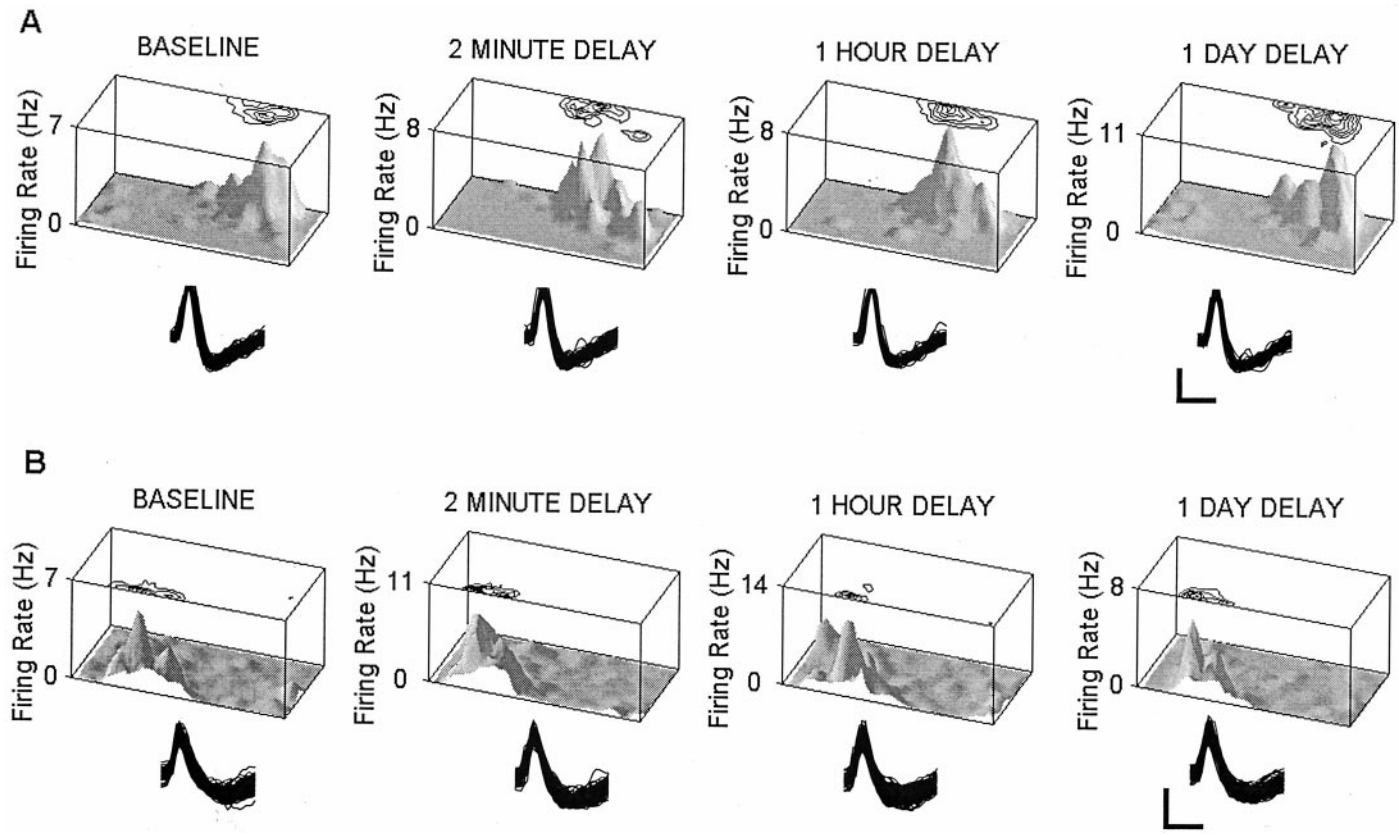

Figure 4. *A*, *B*, Examples of firing rate maps (plotted across the rectangular recording environment) and spike waveforms of two units (place cells) recorded from CA1 of the hippocampus in control animals. All place cells recorded from control animals exhibited a high degree of stability in the location of their place fields over a delay period. The maps for each unit are shown in the order (from left to right) that the delay sessions were recorded. Calibrations: 100 μV, 500 μsec, negativity up.

shift between sessions ($t_{29} = -2.400$; $p < 0.05$) remained significant, indicating that the difference in session duration did not contribute to the instability effect. Furthermore, the units recorded from lesion animals for shorter duration sessions, although significantly less stable in their spatial correlation within sessions ($t_8 = -2.460$; $p < 0.05$) because of reduced sampling time, were no more likely to show instability in their peak shift within sessions or place field locations between sessions (measured by peak shift or spatial correlation) than those units from lesion animals recorded at longer durations (NS; *t* tests).

Distribution of place fields in the environment

The distribution of the location of place fields throughout the environment was compared between units from the control and lesion animals by dividing the box into a 4×4 grid and calculating the percentage of fields, averaged over all sessions, that fell into each bin. There was no clear difference between the groups, with fields from both groups tending to cluster more in the corners (control: mean, 38.06%; lesion: mean, 41.23%) and along the walls (including corners) (control: mean, 82.49%; lesion: mean, 81.77%) of the box and less in the center (control: mean, 17.51%; lesion: mean, 18.23%) than expected by chance (corners, 25%; walls, 75%; center, 25%). This is in accordance with data from normal animals in previous studies (Hetherington and Shapiro, 1997).

Cue control of place fields

Observation of the place fields from sessions involving cue manipulations with animal disorientation showed that place cells in both control and lesion animals were controlled by environmental cues. In 26 cue rotation sessions conducted with 21 units in control animals, the place fields always rotated with rotation of the visual cues and recording chamber together (12 of 12 sessions), but never rotated with the visual cues only (0 of 8 sessions). In sessions in which the chamber but not visual cues was rotated, place fields rotated in three of six sessions.

In lesion animals, 27 cue rotation sessions were conducted with 14 units. As with controls, place fields always rotated when the visual cues and recording chamber were rotated together (11 of 11 sessions) and never with the visual cues only (0 of 7 sessions). Fields rotated when the chamber but not the visual cues was rotated in eight of nine sessions. This latter effect was not, however, significantly different from that observed in control animals (three of six sessions; Fisher's exact test, NS). Note that none of the units recorded from lesion animals during the cue rotation sessions had exhibited unstable place fields in the earlier delay sessions.

Place field instability and extraperirhinal damage

Some animals in the present experiment exhibited some additional damage to adjacent ventral CA1 at posterior levels. This damage cannot, however, account for the instability in the between-session location of place fields because unstable units were also found in animals exhibiting no hippocampal damage. All animals that had unstable place fields also had a small amount of either unilateral ($n = 2$) or bilateral ($n = 2$) damage to

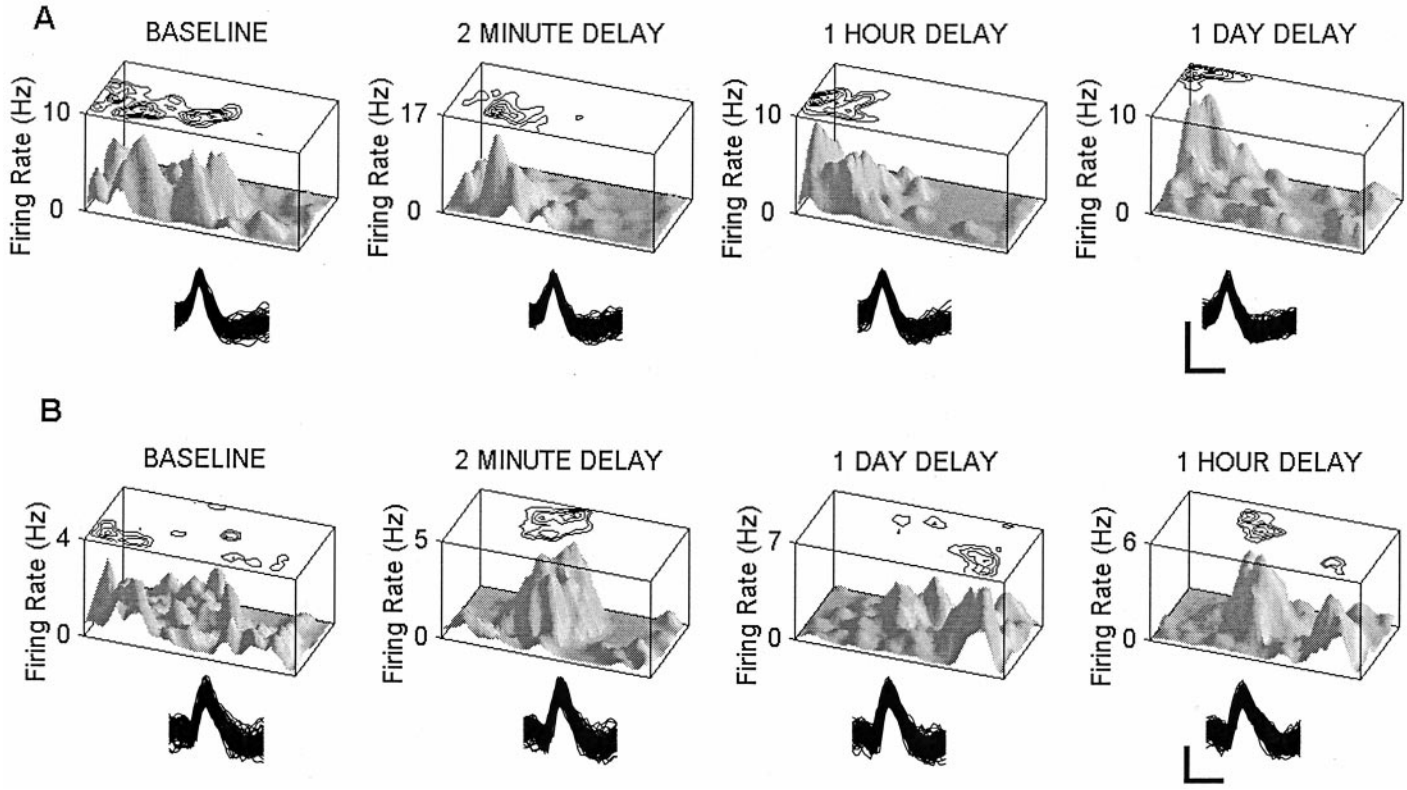

Figure 5. *A*, *B,* Examples of firing rate maps (plotted across the rectangular recording environment) and spike waveforms of two units (place cells) recorded from CA1 of the hippocampus in perirhinal-lesioned animals. An instability in the location of place fields after a delay period was observed in a number of place cells recorded from perirhinal-lesioned animals. The maps for each unit are shown in the order (from left to right) that the delay sessions were recorded. Calibrations: 100 μV, 500 μsec, negativity up.

postrhinal cortex. We cannot, therefore, rule out the possibility that this postrhinal damage was a factor in our observations.

DISCUSSION

The stability of place cells recorded from region CA1 of the hippocampus was compared in control animals and animals with bilateral lesions centered on perirhinal cortex. It was determined that ~36% of units recorded from animals with lesions of the perirhinal cortex had place fields that shifted location across a delay period. In contrast, no control place cells were unstable by this measure. Place cells in the two groups of animals did not, however, differ significantly on measures of within-session stability.

The most parsimonious explanation of this finding is that it is a direct result of the loss of input from the perirhinal cortex to the hippocampus. That is, although the perirhinal cortex is not necessary for the formation of the place field firing of hippocampal place cells, it contributes information necessary to the maintenance of their location specificity across a delay interval. Alternative accounts, for example, that it is a result of the small between-group difference in average session duration can be discarded on the basis of comparisons of short and long recording sessions described in the previous section. Furthermore, the possibility that the instability effects were an artifact of a reduction inspatial discriminability (lower in-field firing rates) in unstable units can also be ruled out because there were no significant differences on any measures (except those describing between-session stability) when these unstable units were compared with a

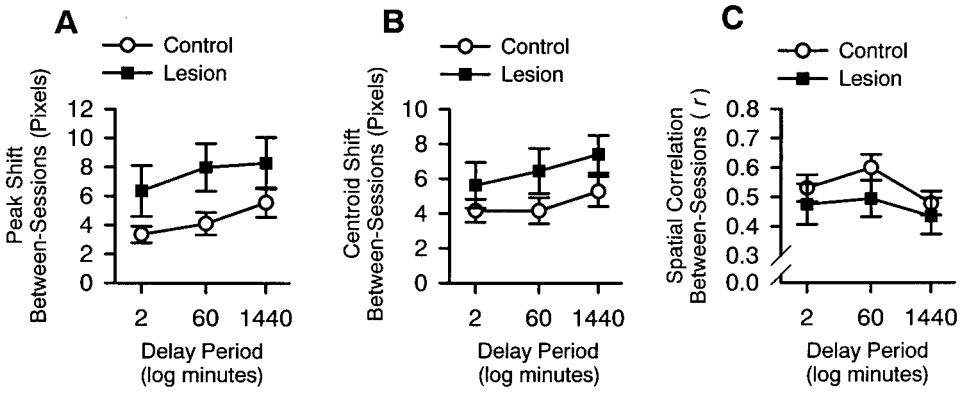

Figure 6. *A*, Peak shift between sessions; *B,* centroid shift between sessions; and *C,* spatial correlation between sessions over 2 min, 1 hr, or 24 hr delay periods for units from control and perirhinal-lesioned animals. The between-session instability observed in units from lesion animals was not delay-dependent on any measure. Error bars indicate SEM.

group of control units with similarly low firing rates. Although we cannot completely rule out the possibility that the instability resulted from a movement of the electrode in lesioned (but somehow, not control) animals, we believe that this is unlikely as waveform amplitudes and waveshapes were highly stable across recording sessions.

Previous studies have shown that under normal conditions place fields can be stable for very long periods when an animal is repeatedly exposed to a familiar environment (Thompson and Best, 1990). In a novel environment, however, the location of the field can be completely unrelated to that in the familiar environment (Muller and Kubie, 1987). This change appears to result from the creation of a new representation of the novel environment (a "remapping"), which, once formed, is stable without affecting the integrity of existing maps (Bostock et al., 1991). The unstable units in the present study may, therefore, represent a remapping of the environment. It would be difficult to determine whether this is a "partial" (Knierim and McNaughton, 2001) or a "full" remapping without recording from a large number of place cells simultaneously. On the basis of the few cases in which several neurons were recorded at the same time in the present study, however, it is possible that both partial and full remapping may occur.

Remapping could result from a lesion-induced loss of mnemonic information regarding the animal's previous exposure to the recording chamber. In this situation, an animal might experience the chamber as a novel environment on each experimental session. The proposal that hippocampal place cell instability is a result of a loss of mnemonic information required to reconstruct a spatial representation is consistent with the results of previous behavioral studies in which it has been shown that the perirhinal cortex has an involvement in both spatial (Wiig and Bilkey, 1994a,b; Nagahara et al., 1995; Otto et al., 1997; Liu and Bilkey, 1998a,b,c; Murray et al., 1998; Wiig and Burwell, 1998; but see Glenn and Mumby, 1998; Aggleton and Brown, 1999) and object (Meunier et al., 1993; Mumby and Pinel, 1994; Wiig and Bilkey, 1995; Ennaceur et al., 1996: Murray, 1996; Buckley et al., 1997; Brown and Xiang, 1998) memory. This proposal is also consistent with a recent finding that cells in the perirhinal cortex exhibit place-specific responses (Burwell et al., 1998) that are modified by changes in the sensory environment. Furthermore, the perirhinal cortex has been shown to be involved in processing information related to the recognition of stimuli in multiple modalities (Otto and Eichenbaum, 1992; Suzuki et al., 1993; Young et al., 1997; Brown and Xiang, 1998) and the associations between stimuli (Bunsey and Eichenbaum, 1993; Higuchi and Miyashita, 1996; Buckley and Gaffan, 1998; Erickson and Desimone, 1999; Murray et al., 2000), suggesting that this region may have an important role in integrating object and spatial information (Murray et al., 1998) during memory processing.

Barnes et al. (1997) reported that aged rats displayed a similar instability in place field location in ~30% of recording sessions conducted in a familiar environment but separated by a delay period of up to 1 hr. In contrast, young animals almost always showed stable place fields. It was suggested by these researchers that the instability of the place fields reflects the fact that the aged rats sometimes retrieve the incorrect cognitive map after a delay period because of an inability to recognize the environment as being familiar (Redish et al., 1998). Because perirhinal cortex is one of the earliest regions affected by neurofibrillary tangles in Alzheimer's disease and normal aging in humans (Arriagada et al., 1992; Price and Morris, 1999), it is of interest to speculate that this region is also damaged in aged rats. In this model, therefore, the deficits observed in the Barnes et al. (1997) study may be causally related to those observed in the present experiment.

Barnes et al. (1997) also suggested that place field instability may be because of the disruption of long-term potentiation (LTP) mechanisms in aged animals. This idea is consistent with findings that NMDA-dependent processes are important for maintaining the stability of place fields (Hargreaves et al., 1997; Kentros et al., 1998; for review, see Shapiro and Eichenbaum, 1999). Future studies could explore this possibility using interventions that selectively block LTP (Bilkey, 1996; Liu and Bilkey, 1996a,b; Cousens and Otto, 1998; Ziakopoulos et al., 1999) in the perirhinal cortex (PRC)-CA1 and/or PRC-entorhinal (Deacon et al., 1983; Burwell et al., 1995; Liu and Bilkey, 1996a, 1997; Burwell and Amaral, 1998a,b; Naber et al., 1999; Shi and Cassell, 1999) pathway. This could involve the intracerebral infusion of NMDA antagonists into these regions while simultaneously monitoring hippocampal place cell activity.

In previous behavioral studies it has been shown that animals with damage to perirhinal cortex have intact memory over periods of ~0–60 sec but exhibit memory deficits for intervals of ~2 min or longer (Liu and Bilkey, 1998a,c). Although we did not observe a delay-dependent instability effect in the present study, this may be attributable to the fact that we could not test animals with a delay shorter than 2 min. This limit resulted from the time required to disconnect the animal from the recording apparatus, wipe down the chamber, return the animal to its home cage for a moment, and then replace the animal in the apparatus. It is possible, therefore, that if a shorter delay had been used in the present study (e.g., removal for 30 sec), a delay-dependent effect may have been observed.

The lack of a delay-dependent effect raises the possibility that the observed instability of place field locations is not memory-related, but is a consequence of the removal of some sensory input to the hippocampus. A number of previous studies have, however, determined that minimal deficits in visual (Mumby and Pinel, 1994; Buffalo et al., 2000) or spatial discrimination (Liu and Bilkey, 1998a,b,c; Wiig and Burwell, 1998) occur at short delays after lesions of the perirhinal cortex, arguing against a perceptual deficit in these cases. In addition, visual input, which normally exerts strong control over place field locations, is not necessary for stable place field firing (Muller and Kubie, 1987; Quirk et al., 1990; Save et al., 1998, 2000).

An alternative non-mnemonic explanation is based on the finding that the repeated disorientation of animals before entry to an unchanged, familiar environment can result in a between-session instability in place field locations (Knierim et al., 1995; but see Dudchenko et al., 1997). Because disorientation was also used in the current study during the few cue rotation sessions, it is possible that this interacted with the perirhinal cortex damage to produce the present effect. This is, however, unlikely, because the disorientation procedure used by Knierim et al. (1995) was much more intensive (e.g., disorientation on every trial, disorientation both on the journey from the home cage and on the return, and placement into the cylindrical recording apparatus from a random location). Furthermore, in the present study, an unstable place field occurred in a lesion animal that had not experienced any previous disorientation episodes.

In summary, lesions of the perirhinal cortex may disrupt an animal's ability to reliably make use of cues from multiple modalities or to use the associations between these cues, for the purposes of recognizing the environment as a whole. The animal

may, therefore, sometimes fail to correctly identify the environment as familiar after a delay, a process that may correlate with the hippocampus retrieving an incorrect spatial representation or inappropriately generating a new map for the familiar environment (remapping). This effect may explain recent findings that indicate that under some circumstances the perirhinal cortex contributes to spatial memory processes (Liu and Bilkey, 1998a,b,c; Murray et al., 1998; Sacchetti et al., 1999; Mumby and Glenn, 2000).

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