

Preserved Performance in a Hippocampal-Dependent Spatial Task Despite Complete Place Cell Remapping

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ABSTRACT: The spatially localized firing of hippocampal place cells is thought to underlie the navigational function of the hippocampus. Performance on a spatial task learned using a particular place cell map should therefore deteriorate if the map is disrupted. To test this prediction, we trained rats on a hippocampal-dependent spatial task in a black box and tested them in a white box. Although the change from black to white induced remapping of most place cells, navigational performance remained essentially intact. Furthermore, place cell activity was also unrelated to specific aspects of the task such as tone onset, response, or goal location. Together, these results imply that the spatial information needed to solve this navigation task is represented outside the hippocampus and suggest that the place cells encode some other aspect, such as the spatial context. *Hippocampus* 2003;13:133–147. © 2003 Wiley-Liss, Inc.

KEY WORDS: hippocampus; cognitive map; place cells; remapping; spatial learning; navigation

INTRODUCTION

Many lesion, single-unit, and functional imaging studies have shown collectively that the mammalian hippocampus is of critical importance in navigation. Complex-spiking cells in the rodent hippocampus display location-specific activity (“place fields”), leading to the hypothesis (O’Keefe and Nadel, 1978) that these “place cells” together form a cognitive map used in the computation of a goal trajectory. The architecture of this map is of interest for the insights it can offer into how neurons can collectively form cognitive representations to drive adaptive behaviors such as navigation.

The present study addressed a paradox that has gone relatively unnoticed in the place cell literature, which is this: most hippocampal dependent spatial tasks, such as the Morris watermaze task or the Olton radial maze task, require that the rat use extramaze cues for orientation, since the apparatus itself is usually symmetrical and rotated between trials. In contrast, environ-

mental manipulations show that place cells can respond predominantly to intramaze cues, such as the walls of the apparatus (O’Keefe and Burgess, 1996); context cues, such as the “color” or odor of the box (Bostock et al., 1991; Anderson and Jeffery, 2001); or the expectations or intentions of the rat (Markus et al., 1995; Wood et al., 2000; Frank et al., 2000). The role of the extramaze cues in driving place cells may lie more in setting the directional orientation of the map as a whole (O’Keefe and Speakman, 1987; Knierim et al., 1995). If place cell firing can be controlled predominantly by intramaze cues, and yet behavior can be controlled predominantly by extramaze cues, it follows that the place cell map may not be tightly coupled to behavior, since it should, in theory, be possible to disconnect the two phenomena by manipulating the two sets of cues independently.

The present study set out to do just this. Rats were trained in a tone-cued spatial navigation task that could not be solved by the use of intramaze cues alone, due to the symmetry of the apparatus. Hippocampal lesions made in some of the rats before training prevented the learning of the task, confirming its dependence on an intact hippocampus. The remaining rats were implanted with electrodes to record place cell activity. The intramaze cues were then altered to induce place cell remapping and the rats were tested to see whether they could still navigate accurately. According to the cognitive map hypothesis, performance of a spatial task learned with a particular place cell map should be disrupted if the map is altered, since the goal location should have been associated with the original map and not the novel one. Alternatively, according to the account of navigation described above, change of the intramaze cues should not affect performance, since the rats should be using other sources of information, such as the extramaze cues, to solve the task. The design of the task, in which place cells were recorded while the rat was in the region of the goal but not actually navigating there, also allowed us to assess whether place cells represent the goal differently from

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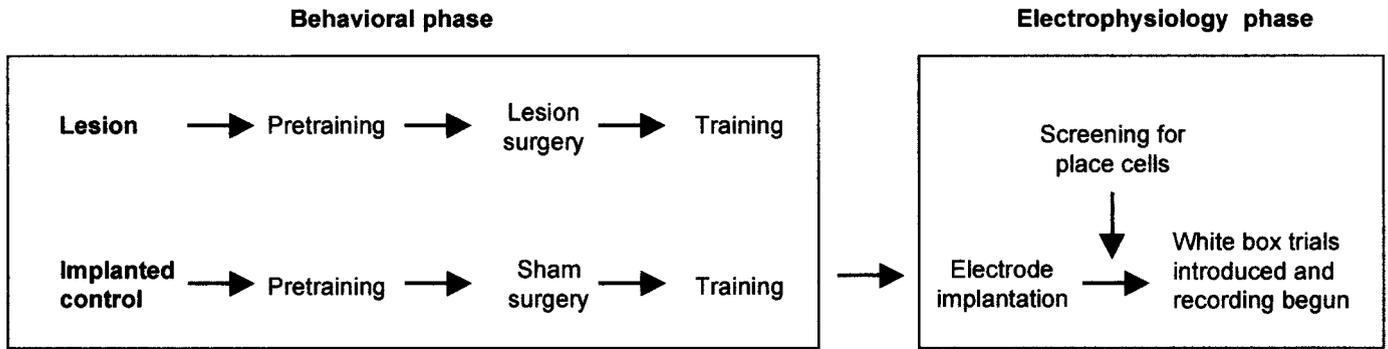


FIGURE 1. Schematic showing the sequence of events over the course of the experiment.

other places and whether they behave differently during navigation from during foraging.

MATERIALS AND METHODS

Subjects

Male Lister hooded rats (250–350 g) were housed singly in Perspex cages and were maintained on a 11:11 h light/dark schedule with lights half on from 7 PM to 8 PM (simulated dusk) and 7 AM to 8 AM (simulated dawn). Each rat was given sufficient food to maintain 90% of its free-feeding weight and allowed unlimited access to water.

Eight rats were pretrained; they then underwent either sham (scalp incision alone) or lesion surgery. It was intended to lesion four animals, but two died as a result of the lesions so two more naïve rats were recruited to replace them. One of these was assigned to the lesion group and one to the control group, for a final total of eight rats, four lesioned animals and four controls. The sequence of events in the experiment is shown in Figure 1.

Apparatus

The experiment took place in a room of dimensions 2.57 m long, 2.38 m wide, and 2.30 m high, which had cream-colored walls. Two posters were placed high on the north wall to act as additional directional cues. All training and place cell recording took place in a 72 × 72-cm-square wooden box with sides 50 cm high, situated approximately in the center of the room. The interchangeable walls of the box were painted black on one side and white on the other, so that some or all of the box could be changed from black to white, while keeping other aspects of the environment the same. The floor of the box was covered in black or white foamboard, which was not replaced (although it was rotated) throughout the experiment, to keep the olfactory context constant. Between trials, the box was either rotated or the walls shuffled, to prevent specific odor cues from being used as landmarks to solve the task, or from gaining control of place fields (Save et al., 2000).

In each corner of the box was a small food hopper covered by a flap that could be locked or released via a solenoid. The cue for

food availability was a 3-s long, 2-kHz tone generated by the computer, after the foraging period had finished. At the end of the tone, the solenoids released the food flaps and locked them again after the rat had made its choice by lifting one of the flaps. For the first half of training, all the hoppers were baited but food was only accessible in the goal (being wedged under wire mesh in the non-goal corners and outside the mesh in the goal). The rats learned slowly, and it was thought this might be because of the confusing effect of food being present in all four corners (albeit inaccessible in three of them). Training was therefore suspended for 3 weeks, and the box was modified so that food could be delivered into the goal hopper by the experimenter (via a tube leading into the hopper) only after the rat had made its choice.

Behavioral Training

Rats were pretrained before surgery by being placed in the box and allowed to retrieve food from the food wells by lifting the food flaps, which were lowered progressively over several days. Once they were comfortable with lifting the flaps from the completely closed position, the rats received their lesions or sham incisions and then training proper began.

During the training phase of the experiment, when rats were brought into the experimental room, they were always set down in the same place, lifted out from the carrying box in the same way, and placed in the same part of the test box facing the same direction. This was done to enable the rats to maintain a sense of direction, thus helping them disambiguate the walls of the symmetrical box. After placing the rat in the box, the experimenter scattered grains of honeyed rice around the floor (~1 grain per 10 s) to encourage the rat to forage over the entire floor of the box. When the 2-min period ended, the rat continued foraging until it entered a predetermined and pseudo-randomly varying start square (1/9th of the box area—not one containing a food hopper), at which time the experimenter activated the 3-s, 2-kHz tone, which signaled imminent food availability. At the end of this time, the computer released the solenoids and unlocked the flaps. When the rat lifted one of the flaps, signaling a choice, the flaps were locked again, preventing further attempts to choose. For any given rat, food was only available in one of the corners (varied among animals but constant across days). Before modification of the box, the reward consisted of half a candy-coated chocolate (“Smartie”).

Afterward, the reward was replaced by 45-mg fruit-punch flavored Noyes sucrose pellets. The computer stored the time of the tone and the rat's choice, as well as which choice it made and whether this was correct.

At the end of each trial, the rat was placed back into the carrying box and taken back to its home cage. The intertrial interval in this phase of the experiment therefore ranged from 30 min to several hours. The trials were separated in time and space so that the rats could not use path integration to return to the goal corner; they were also discouraged from inappropriately trying to use a win-shift strategy in locating the goal. The rats were run in a pseudo-randomly varying order, so as to block the use of olfactory guidance cues. After each trial, the box was rotated and/or the walls shuffled, to further discourage the use of olfaction and to force the rats to learn a spatial strategy for locating the food. Approximately eight trials per day were run during this phase. Rats were scored by their latency to make a choice and on whether the choice was correct or incorrect.

For the first ~120 trials of training, until the pause for modification of the apparatus, the experiment was run blind with the experimenter unaware of which animals were lesioned and which were controls. The experimenters were unblinded at the end of this time, to determine whether the slow learning was contributed to by a lesion effect. This proved to be the case, with a significant difference between the groups already apparent, and training continued unblinded from that point on.

The procedure for running trials was changed slightly for the four rats that continued into the electrophysiology phase of the experiment. After electrode implantation (see below), when they were being screened for place cells, the rats would sit on a holding platform (a cage bottom on a pedestal) between trials. From here, the rats could see the whole room, which gave them an additional opportunity for directional orientation. After each trial was run, the rat was removed from the box and placed back on the holding platform, where it remained until the next trial. The intertrial interval in this phase was therefore sometimes as short as a few minutes.

When training was completed at the end of the behavioral phase, the four lesioned rats were removed from the experiment and sacrificed for histological examination. The control rats continued into the electrophysiology phase of the experiment (Fig. 1) and were implanted with electrodes for single-unit recording. After they had reached a criterion of eight consecutive correct choices, the rats began to receive blocks of four probe trials in which the box was now in its white configuration. This was accomplished by replacing the black foamboard floor with the white one, and by turning the walls around so that the white face of each wall now faced inward. The box as a whole was also rotated to remove any influence of odors associated with a particular food hopper. The wall shuffling and rotation were repeated after each trial. Trials were run and scored in the same way as in the black box condition. Each block of four white box trials was separated from the next by at least one block of black box trials. At around this time, place cells began to be isolated and so their activity was recorded alongside the behavior of the rat.

At the end of the experiment, the box was moved into another room, and the implanted rats were given a new goal corner to learn. The layout of this room and the location of the new goal were chosen so as to minimize any possibility of generalization between the two rooms (e.g., the computer, the carrying box, the holding platform, the experimenter, and the door were all in different relative locations, and the goal was chosen to resemble the previous goal as little as possible with respect to these landmarks). The rats were given 16 trials on this new problem, to determine whether they could rapidly relearn a new goal.

Lesions

Ibotenate hippocampal lesions were made at the end of pretraining (Fig. 1), before training proper commenced. The two rats that died as a result of the lesioning procedure were replaced with naive animals, one of which was assigned to the lesion group and the other to the control group, to make four rats in each group. For lesioning, subjects were anesthetized with a mixture of isoflurane, N₂O, and O₂, given a 0.1-ml intramuscular (i.m.) injection of buprenorphine (0.3 mg/ml) for analgesia, and a 0.1-ml subcutaneous (s.c.) injection of enrofloxacin (25 mg/ml) as a prophylactic antibiotic. The rats were mounted in a Baltimore stereotactic frame, the scalp was shaved and surgically cleaned, and a midline incision was made to expose the skull. The skull overlying the target area was removed with a trephine drill. For the lesioned rats, bilateral injections of ibotenic acid (10 µg/µl, pH 7.4; Sigma, Poole, UK) were made by pressure injection of 40-µl quantities, using the coordinates given by Jarrard (Jarrard, 1989; Burton et al., 2000). These animals also received a 3–10-ml intraperitoneal (i.p.) injection of physiological saline to replace fluid lost during the operation. The four control rats received a midline scalp incision followed by suturing. Behavioral training resumed 2 weeks after surgery.

Electrode Implantation

Implantation of electrodes for place cell recording took place in the controls toward the end of black box training (Fig. 1) and proceeded as follows. The rats were anesthetized with isoflurane and O₂ and were given a s.c. injection of enrofloxacin (2.5 mg) as a prophylactic antibiotic. A 2-mm-diameter hole was drilled in the skull overlying the right dorsal hippocampus with a trephine bit, and four 4-wire electrodes (tetrodes) were implanted into the overlying neocortex (bregma –3.8 mm AP, 2.2 mm ML, the deepest tetrode positioned 1.5 mm below brain surface). The tetrodes were slightly staggered (by ≤500 µm), so that while one tetrode was in a cell layer recording hippocampal cells, another was in a cell-free zone acting as a reference. Each tetrode was made from four twisted strands of 25-µm diameter HM-L-coated platinum-iridium wire (California Fine Wire), and the four tetrodes were held by a cannula attached to a microdrive, allowing the electrodes to be advanced through the brain in small steps. The assembly was attached to the skull by means of jeweler's screws and was cemented in place with dental acrylic. A wire attached to one of the skull screws was soldered to a flexible wire in the microdrive to enable the rat to be

grounded. After surgery, the rats were given an i.m. injection of buprenorphine (45 μ g) for postoperative analgesia.

Recording Protocol

Screening for cells began at least 1 week after implantation surgery. Each rat was placed in a shallow holding box (a cage bottom) sitting on a pedestal and located \sim 1 m from the experimental box. The rat was connected to the recording equipment via lightweight hearing-aid wires and a socket that fitted onto the microdrive plug. The potentials recorded on each of the 16 electrodes were passed through RC-coupled, unity gain operational amplifiers mounted on the rat's head, and led to an 8-channel recording system (Axona Ltd, Herts, UK) where the signal was amplified (20 000–40 000 times) and bandpass filtered (500 Hz to 9 kHz). Each of the four wires of one tetrode was recorded differentially with respect to one of the wires of the other. Two of the four tetrodes could be recorded at any one time, with the appropriate tetrodes (those detecting cells) being switched in by a breakout box located on the preamplifier. The tetrodes were advanced by \leq 200 μ m daily in 50–100- μ m steps, until hippocampal ripples and sharp waves appeared. Advancement then proceeded in 25- μ m steps until complex spikes appeared.

When place cells had been isolated, their activity was recorded while the rats performed the task described above. Unit activity was captured by monitoring each channel at 48 kHz and storing 50 points per channel whenever the signal from any of the four electrodes exceeded a given threshold (a presumptive spike). Each spike event was stamped with the time since the start of the recording and the location of the animal.

During the unit recording, the position of the rat was monitored by a monochrome video camera mounted directly above the apparatus. The location of the rat in the camera viewing area was converted into x,y coordinates by a TV tracking system (Axona Ltd) that detected a small DC infrared light mounted on the recording cable near the rat's head. Every 20 ms, the position of the rat was stored along with the unit data, so that the whereabouts of the rat during activity of a given cell could subsequently be determined.

The computer also logged the time of the tone and the time of the rat's choice to enable analysis of possible event-related activity. The unit, position, and event data were stored on a hard disk and analyzed off-line. If place cells were identified during a recording session, the rats received blocks of white box trials interleaved with the ordinary blocks of black box trials.

Analysis of Place Cell Activity

This was performed offline using a cluster-cutting program (Tint, Axona Ltd.). The collected waveforms were displayed as clusters by plotting each spike's peak-to-peak amplitude on one electrode against that on each of the other three (see Fig. 6). The clusters were then separated by hand or by an automatic clustering algorithm using parameters derived from a manual cut. The parameters were the centroid of the cluster in multidimensional space, and a cluster boundary formed by an ellipse whose long axis passed through the origin and whose length and width were three standard deviations from the centroid (e.g., Fig. 6).

To determine the place correlates of a cell's activity, the camera viewing area was divided by a 64×64 grid, with each point located at the center of a 2.25-cm-square bin. The firing rate in each bin was determined by a smoothing process in which overlapping squares of size 20×20 cm were centered on each grid point. For each bin (centered on a grid point), the firing rate for a given cell was determined by dividing the number of spikes it fired in that region by the amount of time the rat had spent there. A place field was defined as a region of reproducible (see below) location-specific firing in which the peak rate after smoothing was >1.0 Hz. Only cells with clearly isolated clusters (see Fig. 6 for examples) were analyzed, and these only if firing was stable across several trials in the same condition.

Tests for Goal-Related Activity

To test for goal-related activity, a rate map was generated from a representative trial for each place field, as follows. After the smoothing described above, the firing rate in each pixel was plotted and the pixels corresponding to the area within the box rotated en bloc so that the goal corners for the four rats were aligned. Firing rates were determined for each quadrant and for the 1/16th of the box enclosing each corner. The values for the goal and non-goal corners were then compared using analysis of variance.

Tests for Task-Related Activity

To test for task-related activity, two types of analysis were performed. First, segments of the path of the rat between the tone onset and the lifting of the food flap were plotted for each trial, with the spikes fired by each cell superimposed on the path. Each of these paths was visually inspected to look for evidence of cell activity related either to the tone onset or the food flap opening. Second, peri-event time histograms (PETHs) were generated for the time surrounding either the tone or the flap opening. Bin size was either 10 ms or 100 ms, to allow for possible detection of either fast (millisecond range) or slow (second range) changes in neural activity in response to the events. Firing rates were averaged for the 0.3 s before and after the event or for the 3.0 s before and after the event, and compared using a two-tailed paired *t*-test.

Tests for Remapping

To enter the remapping analysis, a cell had to meet the criteria for a stable place cell: namely, a well-isolated cluster in which firing was restricted to one or more localized regions of the environment, and in which the pattern of activity was reproducible from one trial to the next of the same condition. For most cells, recordings were alternated in four-trial blocks between the black box and white box twice, to confirm the remapping and check that apparent remapping was not due to movement of the electrodes between one block and the next.

The stability of a cell's activity was assessed by a within-condition correlation procedure as follows. A smoothed firing rate map (\sim 27 pixels square) was generated for each trial and then the map from each trial correlated with each of the others on a pixel-by-pixel basis. Pixels in which the rate was zero in both maps were

discarded, to avoid generating spurious estimates of stability based on high correlation values resulting from many zero-zero pixel correlations. This procedure typically yielded within-cell between-trial correlations of ~ 0.60 and between-cell correlations close to zero. Firing rate maps in which these within-condition correlations failed to exceed 0.35 in either the black box or the white box were discarded as being too unstable. (Figure 8A presents an example of this analysis, applied to four trials.)

Remapping of place fields was assessed using four trials from the white box condition and four trials from the black (usually two from either side of the white box block), for each place cell. Remapping of place fields when the box was changed from black to white took the form of either a rate change (starting or stopping firing) or a location change. The location change was considered to be subordinate to the rate change, since cessation of firing obviously precludes any analysis of location. Therefore, cells were examined for remapping by rate first, and then if they failed to meet the criterion for remapping by rate they underwent analysis for remapping by location.

Rate remapping usually consisted of the cell's complete cessation of firing, as evident from situations in which a cluster was well isolated and did not overlap with other clusters. On occasion, such complete cessation was harder to determine because the parameters that defined a cluster in one box condition sometimes, when applied to the recordings from the other condition, recruited a small number of spikes. Inspection of these usually showed that these were strays from different clusters. Therefore, if there were fewer than 20 of these "strays," these spikes were discarded and the cell's rate assumed to be zero. If such a cut recruited more than 20 spikes, these were treated as continued firing of the cell in both locations, and this cell passed into the analysis for location-specific remapping.

Cells that had a stable place field in at one box condition and either had a place field or reliably fired more than 20 spikes in the other were examined for location remapping as follows. A smoothed firing rate map was generated for each cell in each trial, and this map was compared pixel by pixel (as described earlier) with the other three maps of the same condition, or with the four maps of the other condition, producing 12 same-condition and 16 same different-condition comparisons overall. (An example of this procedure applied to the results from a single cell is presented in Figure 8.)

These same-condition and different-condition correlations were then compared using a one-tailed *t*-test. If the correlations did not differ significantly, the cell was considered not to have remapped. If the correlations were significantly greater for the same-condition comparisons than between conditions then the cell was considered to have remapped. This procedure generated results that agreed almost perfectly with the experimenters' visual assessment of whether remapping had occurred.

Histology

After completing the experiment, each rat was deeply anesthetized and perfused transcardially with saline followed by paraformaldehyde. The brains were removed and stored in paraformaldehyde

and were later sliced on a freezing microtome into 40- μm -thick sections. The sections were mounted and stained with cresyl violet, and every 4th section was examined under a microscope for evidence of cell loss in the hippocampus and surrounding regions. The amount of hippocampal damage in each examined section was established by drawing the area of the lesion onto a line drawing of the corresponding area from Paxinos and Watson (1997). The drawing was overlaid with a grid whose squares corresponded to $200 \times 200 \mu\text{m}$, and the number of squares of the lesioned area was counted and compared with the number of squares of the hippocampal region as a whole.

RESULTS

Histology

For the lesioned rats, histology showed that on average, the hippocampus sustained damage to 76%, 57%, 72%, and 34%, respectively, of its extent. There was considerable unilateral sparing in the latter rat (Fig. 2A) and no discernable extrahippocampal damage in any of them. Thus, the lesions were modest, as intended, and did not appear to involve any other structures.

Acquisition of the task

All the rats quickly learned the procedural aspects of the task (to forage over the whole environment until the tone sounded and then to run to a corner and lift the food flap). The learning of the goal for the control rats versus rats with hippocampal lesions is shown in Figure 2B. Successful learning of the task required an intact hippocampus, since rats with ibotenate hippocampal lesions did not improve their performance above chance over the eight 32-trial blocks, whereas the control rats steadily improved and were reliably choosing the goal corner by the end of the training phase of the experiment. This was confirmed by repeated-measures analysis of variance across the eight 32-trial blocks which showed a significant effect of group (lesion vs control: $F_{(1,6)} = 13.29$; $P < 0.02$), a significant effect of block ($F_{(7,42)} = 4.72$; $P < 0.001$) and a significant interaction ($F_{(7,42)} = 3.75$; $P < 0.01$). Thus, it appears that this task resembles other spatial tasks in being highly sensitive to hippocampal damage.

Place Cell Recording

Forty-six well-isolated cells were recorded from four rats as they performed the spatial task. Since some of these contributed more than one field to the results (due to remapping), and not all cells were assessed for remapping, the numbers in the analyses below do not always equal 46. The cells were all complex-spiking cells, as determined by their relatively low rates, broad waveforms, complex spike bursts and (usually) location-specific activity.

Event-Related Activity Analysis

To test for nonspatial activity related to the behavioral task, event-related analyses were carried out on all 46 cells recorded over

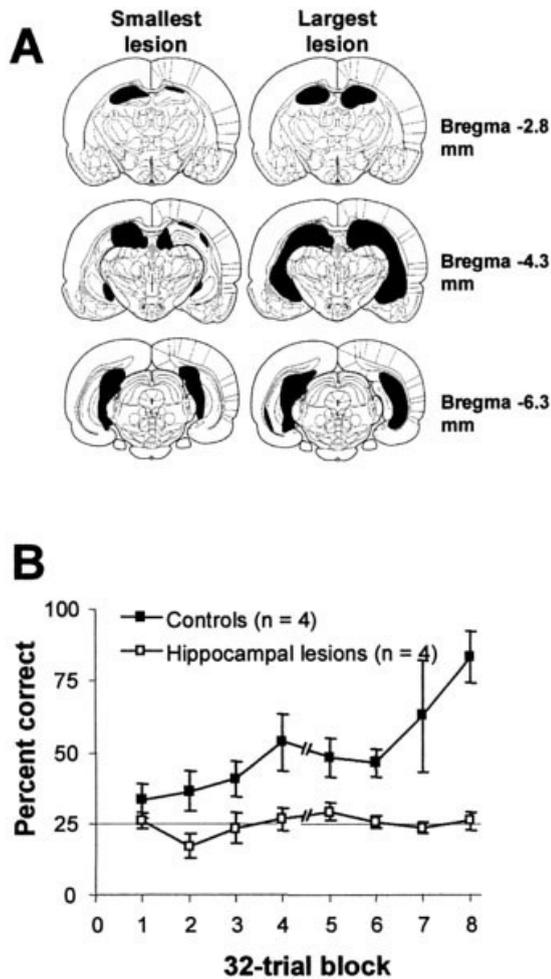


FIGURE 2. (A) Schematic illustration of the smallest and largest lesions from illustrative sections from the anterior, middle and posterior regions of the hippocampus. The lesions were restricted, with considerable unilateral sparing in one animal, and no discernable extra-hippocampal damage. (B) Acquisition curves (means \pm SEM) for the lesioned rats (open squares) vs. the controls (filled squares) in the spatial task. The training was interrupted for 3 weeks between blocks 4 and 5 to allow the food hoppers to be modified. Control rats learned the task whereas the lesioned rats did not improve above chance over the training period.

431 trials. The peri-event time histograms (PETHs) are shown in Figure 3. Comparison of the 0.3 s before and after the tone (Fig. 3A) showed no change in firing rate (mean = 1.96 spikes per bin before the tone and 1.8 spikes per bin after; $t = 0.42$, NS). Similarly, comparison over a longer time scale of the 3.0 s before and after the tone showed no change in firing rate (mean = 16.1 spikes per bin before the tone and 15.9 spikes per bin after; $t = 0.17$, NS). Comparison of the 0.3 s before and after the rats opened the flap (Fig. 3B) showed no change in firing rate (mean = 0.66 spikes per bin before the flap opening and 0.53 spikes per bin after; $t = 1.76$, NS). Over the longer ± 3.0 -s time scale, there was a significant decrease in firing rate related to the opening of the food flap (mean = 13.32 spikes per bin beforehand and 7.58 spikes per bin afterward; $t = 3.69$, $P < 0.05$). This preceded the actual flap opening by ~ 0.6 s. Such a decrease is in the opposite direction to

that which might be predicted on the basis of previous reports of an increase in place cells firing at the goal, and may be due to the slowing down of the rat as it approached and stopped at the goal,

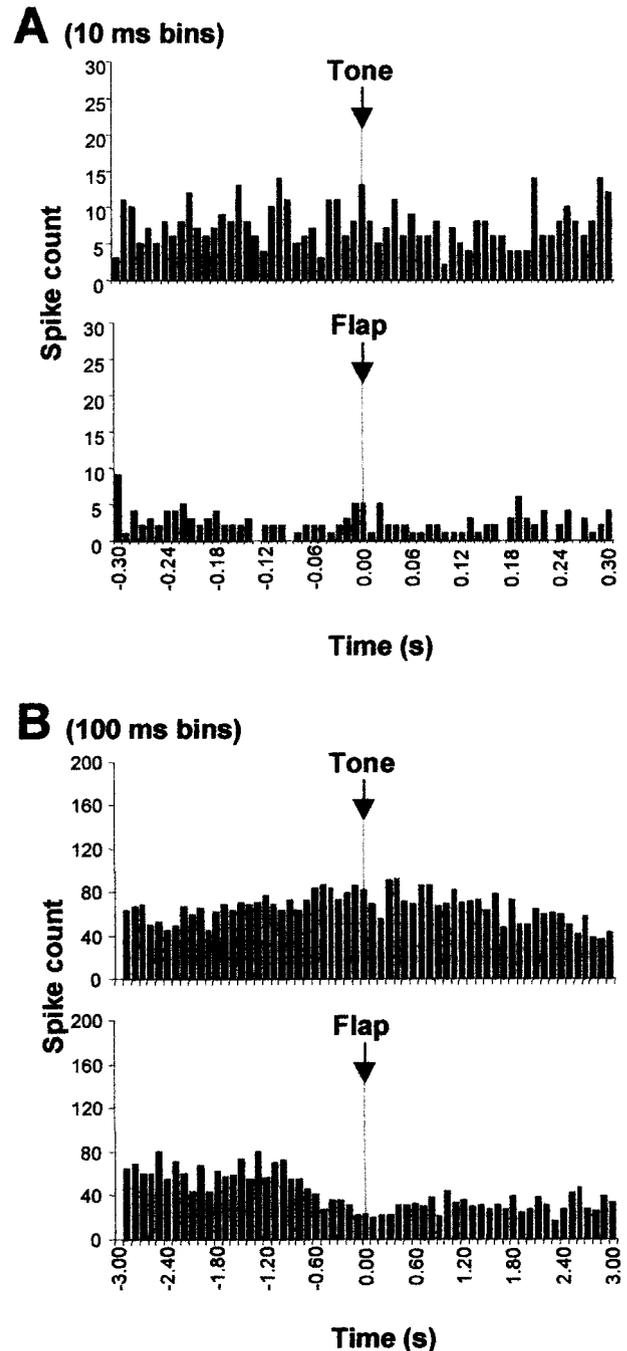


FIGURE 3. Peri-event time histograms showing the activity of the 46 place cells before and after the tone sounded or the rat lifted the food flap. (A) Comparison of the 300 ms before and 300 ms after the events, with the data grouped in 10 ms bins. (B) Comparison of the 3 s before and 3 s after the events, with the data grouped in 100 ms bins. There is no peak of activity associated with either kind of event at either the long or short timescales. At the long timescale, a decrease in activity associated with the flap lifting is evident. This precedes the actual event and may be related to the slowing velocity of the rats as they approached the food well.

since place cells have been shown to have robust velocity correlates (McNaughton et al., 1983; Hirase et al., 1999).

Although the population of cells as a whole did not show any increase in firing activity related to the tone or the goal, it may be that such events are encoded by an ensemble of cells, some of which increase and some of which decrease their firing. To look for such activity, the trajectory of the rat between the tone onset and arrival at the goal was plotted for each trial, along with the spikes of the cells superimposed (e.g., as in Fig. 9). Visual inspection of the occurrence of spikes on the goal trajectories did not reveal any activity related to these events. An attempt was made to quantify this impression by taking a subset of cells and calculating the firing rate before and after the tone onset or the flap opening for 10-ms, 30-ms, 300-ms, and 3-s intervals. The firing rates were so low, however (because of the characteristic absence of firing outside the place fields) that statistical analysis was not feasible in the small number of trials available. Nevertheless, the absence of any appearance of spikes on the trajectory at the critical time periods, combined with the absence of the kinds of population increase previously reported, suggested that in this task, place cells did not encode either the tone or the goal in any robust way.

Goal-Related Activity Analysis

To test for goal-related activity, a representative trial was chosen for each field, and a firing rate map was generated depicting the smoothed and averaged firing rate in each pixel of a 40×40 array covering the area of the box. Some cells contributed two maps, one for each condition, making 54 maps in total. The maps were rotated so that the goal corners were superimposed and were then averaged. The composite firing rate map generated by this superimposition is presented in Figure 4A, which shows that there was no peak of activity near the goal corner (in fact, the peak actually lay in the opposite corner). The firing rates for the 400 pixels in each quadrant were then averaged to produce an overall quadrant rate for each cell, and this rate was compared between the goal and the other three non-goal quadrants, using a one-way analysis of variance (ANOVA). There was no difference in the mean firing rates in the four quadrants, being 0.75 Hz in the goal quadrant and (moving clockwise) 0.80, 0.80, and 0.71 Hz in the remaining three ($F_{(3,53)} = 0.11$, NS). Similarly, for the $1/16^{\text{th}}$ areas surrounding the corners, the rate at the goal was 0.46 Hz; in the other three corners, it was (moving clockwise) 0.39, 0.39, and 0.66 Hz ($F_{(3,53)} = 1.48$, NS). There was thus no evidence for clustering of fields near the goal in this task.

Changing the Box to White

Performance on the behavioral task was compared between the blocks of four white box trials and the four flanking black box trials (2 on either side), making 16 of each trial type. The results are shown in Figure 5. It can be seen that while the change from black to white caused a mild disruption to the rats, performance remained well above chance, with a mean (\pm SEM) of 90.63% ($\pm 1.80\%$) correct in the black box and 69.79% ($\pm 7.86\%$) correct in the white box. A one-tailed paired t -test showed these values to be significantly different from each other ($t(3) = 8.16$, $P < 0.01$),

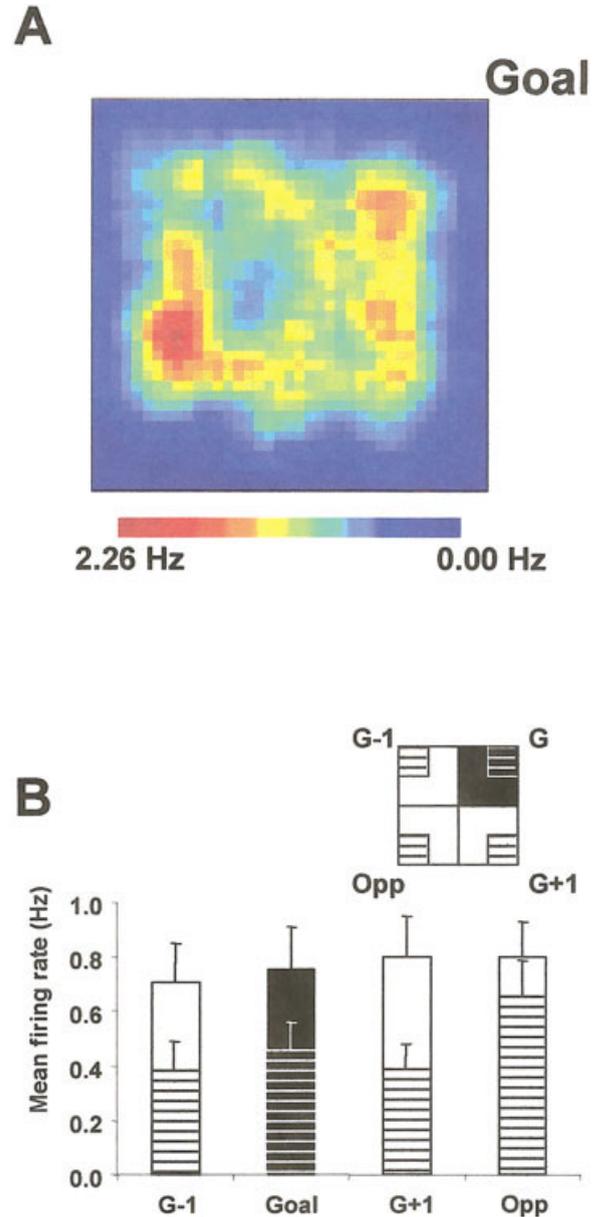


FIGURE 4. (A) Surface plot showing firing rates in the region enclosed by the box, for 54 fields selected from 46 cells. The plot was obtained by generating a pixelated firing rate map for each place field, rotating if necessary so that the goal corner lay to the top right of the plot, and then averaging across all 46 cells. It can be seen that there is no tendency for fields to cluster near the goal corner: in fact, the corner opposite the goal showed the highest rate of firing. (B) Comparison, for the 54 place fields, between the average firing rate in the goal corner vs. that in the three non-goal corners. The plain bars show the rates (mean \pm SEM) for the entire quadrant and the hatched bars show the corresponding rates for the $1/16^{\text{th}}$ of the box enclosing each corner (as shown by the hatched areas in the inset).

but both were also significantly different from chance, i.e., $t(3) = 36.37$, $P < 0.001$ for black, and $t(3) = 43.0$, $P < 0.001$ for white.

Changing the box to white produced a marked change in the activity of the place cell ensemble. Figure 6 shows the cluster data from one rat during a 2-min black box trial and a 2-min white box

trial. There was a substantial shift of the clusters between the two conditions, as shown by the fact that the cluster boundaries of one condition do not overlap with the clusters in the other condition. Further trials switching back and forth between black and white boxes confirmed that this change was not due to electrode instability.

The change in clusters was accompanied by a corresponding change in the location-specific activity of the cells. The locational firing of the cells whose clusters are shown in Figure 6, along with the concomitant behavior of the rat, is shown in Figure 7. Note that the substantial change that occurred when the box was changed could be reversed, confirming that this was not an artifact of instability of the preparation. Despite the remapping of its place cells, the rat continued to make accurate runs to the goal corner with only the occasional mistake.

Such remapping was quantified by the correlational procedure described in the Methods. An example of this procedure applied to the location-remapping cell of Figures 6 and 7 is shown in Figure 8. The same-condition correlation coefficients for this cell in the black box were all >0.5 , confirming its stability across trials. Cells were included in the remapping analysis if their same-condition correlation over four trials in the white box, or the black box was >0.35 . Thirty-four cells met this stability criterion. Of these, 29 cells remapped when the box was changed to white and only five did not (Table 1). Four of the five nonremapping cells were recorded from one rat on 2 consecutive days early in white box training. The remaining cell, from a different rat, was recorded alongside seven other cells that did remap; it may reflect "remapping" to the same place. Of the remapping cells, 14 stopped firing in one of the two boxes and 14 shifted their fields. One cell stopped firing in the first block of white trials but developed a different field in the second block. Remapping was therefore widespread, and seemed to reflect a global change in the place cell representation of the box.

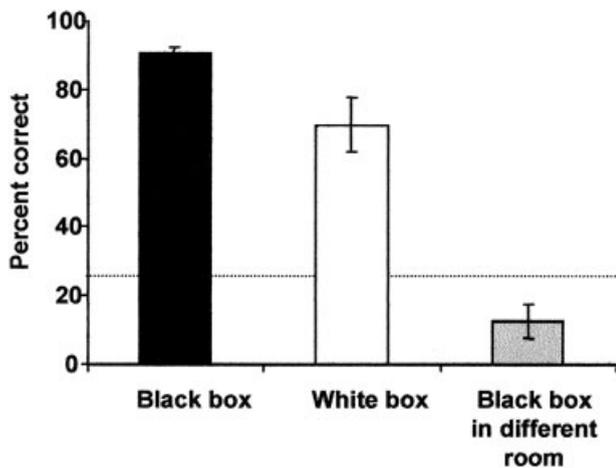


FIGURE 5. Comparison of mean (\pm SEM) performance in 16 white box trials (white bar) against performance in the flanking black box trials (black bar) shows that although performance did decrease slightly in the white box, it remained considerably greater than chance. The gray bar shows performance for 16 trials in the black box in a different room, which remained below chance (due to position habits), thus ruling out fast re-learning as an explanation for the intact white-box performance.

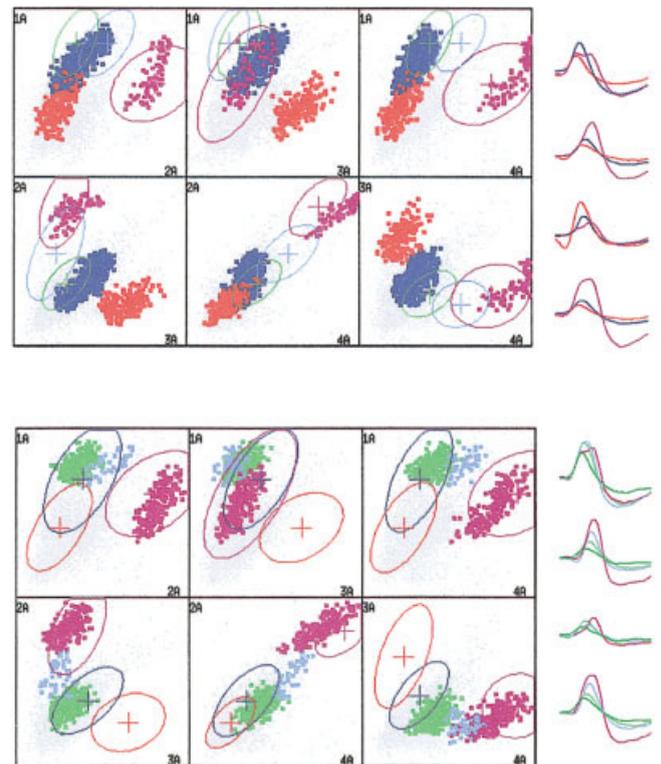


FIGURE 6. An example of the raw unit data from two single two-minute trials, one in the black box (upper panels) and one in the white box (lower panels). Each of the 6 panels is a scatter-plot depicting the amplitude of each spike on one of the four electrodes in a tetrode plotted against the amplitude on another. The colored squares represent magnified points showing the spikes that were allocated to a given cluster, and the corresponding waveforms are shown on the right. When a cluster had been cut, its centroid was determined, and the three-standard-deviation boundary delineated by ellipses whose long axis passed through the origin. The upper panels show the clusters that were isolated from the recording made in the black box, superimposed on which are the cluster boundaries for the cells isolated in the white box. Similarly, the lower panel shows the clusters isolated in the white box, with the black-box cluster boundaries superimposed. Note how the cluster boundaries from one box do not generally overlap the clusters active in the other box, showing how the clusters re-organized (i.e. remapped) when the box was changed. An exception is the pink cell, which was active in both environments. The corresponding place fields of these cells are shown in the next figure.

Because remapping was assessed during the foraging period, but behavior was assessed after the tone sounded, it could be argued that the tone signaled different task parameters and perhaps triggered remapping of the place cells (Markus et al., 1995) to a common, navigation-related representation. The goal trajectories were examined to see whether there was any evidence that such remapping may have occurred. Figure 9 presents some examples in which the rat ran through the location of a cell's field (assessed during foraging) on its way to the goal. The presence of spikes in the usual location of the field suggests that the fields during goal-seeking were unchanged and that no remapping had occurred.

Could relearning of the goal have taken place while remapping was being established? Only two of the four rats had recordable place cells on the day they reached the behavioral criterion for

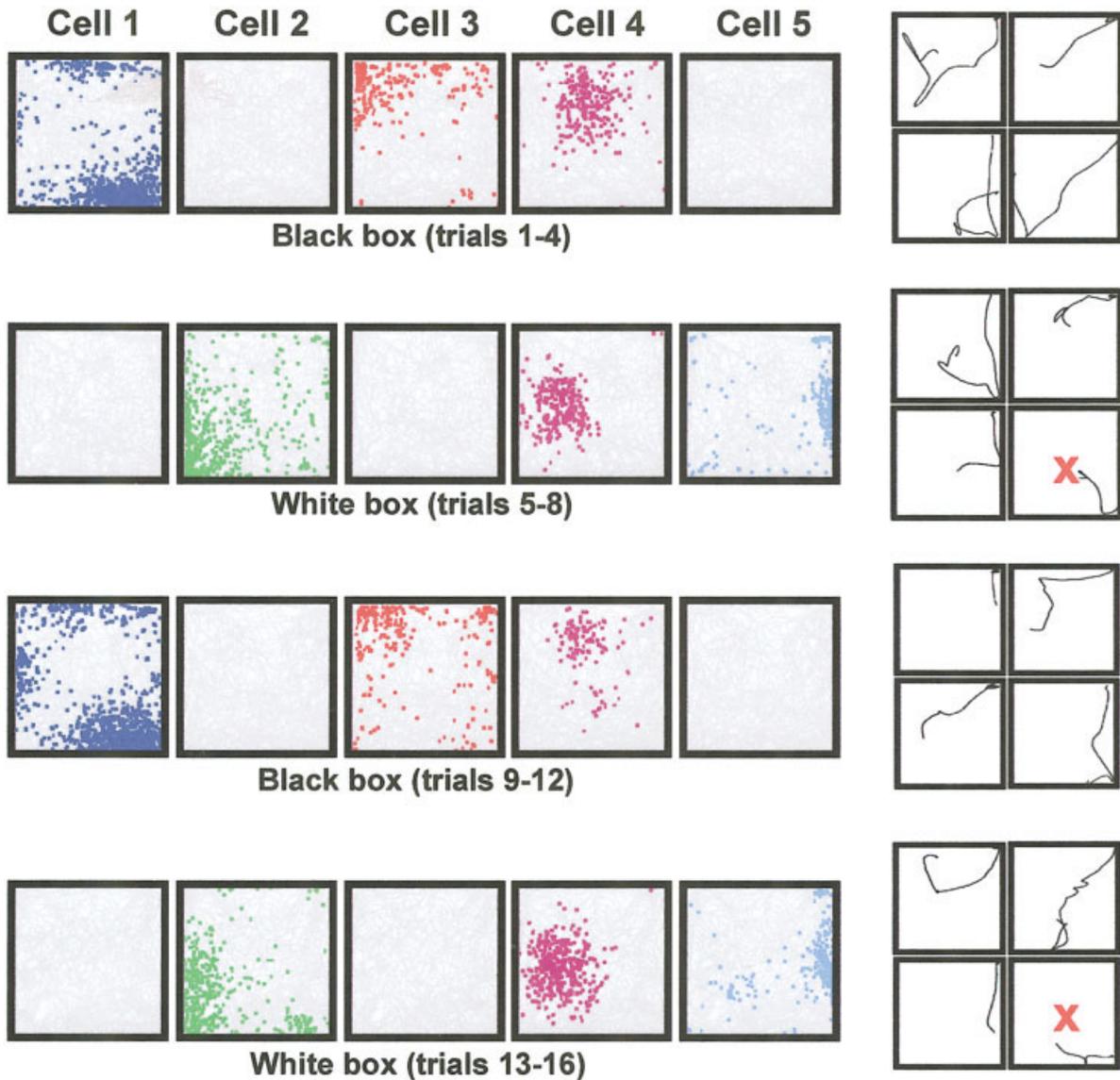


FIGURE 7. Raw data from two blocks of black trials and two interposed blocks of white trials, showing the performance of 5 simultaneously recorded place cells (the cells whose clusters and waveforms are shown in Figure 6). Each box illustrates 8 minutes of recording, this being the composite of four 2-minute trials. The spikes (colored squares) are superimposed on the path of the rat (shown in gray). Cells 1 and 3 fired only in the black box, cells 2 and 5 fired only in the white box while cell 4 shifted its field between the black and white

boxes (see Figure 8 for analysis of this). The individual paths of the rat between the sounding of the tone and the lifting of the food flap are shown in blocks of 4 trials in the traces on the right. The goal corner was in the top right of each box (corresponding to the Southwest of the room). The rat performed all the black-box trials correctly but made one mistake (red cross) in each of the blocks of white-box trials. However the remaining 3 trials of each white-box block were executed correctly, despite the remapping of the rat’s place cells.

commencement of the white box trials, and one of these was the rat in which remapping took time to develop. Remapping on the first trial was, however, observed for the other rat, and in other experiments (data not shown) we have generally observed remapping immediately on exposure to the new environment. To be sure, however, we tested to see whether rats were in fact capable of rapid one-trial (or few-trials) learning of this task. The box was moved to another room and the rats retrained over 16 trials with this new goal. They failed to relearn the goal in this time, performing no differently from chance over the 16 trials ($t = -2.5, P = 0.09$; Fig. 5), confirming that the task was not one that could be acquired

rapidly. Thus, even in cases in which remapping took several trials to develop, it seems unlikely that a “new” goal was being learned during this transition.

DISCUSSION

The present study found that rats continued to perform well on a hippocampal-dependent spatial task despite a contextual change

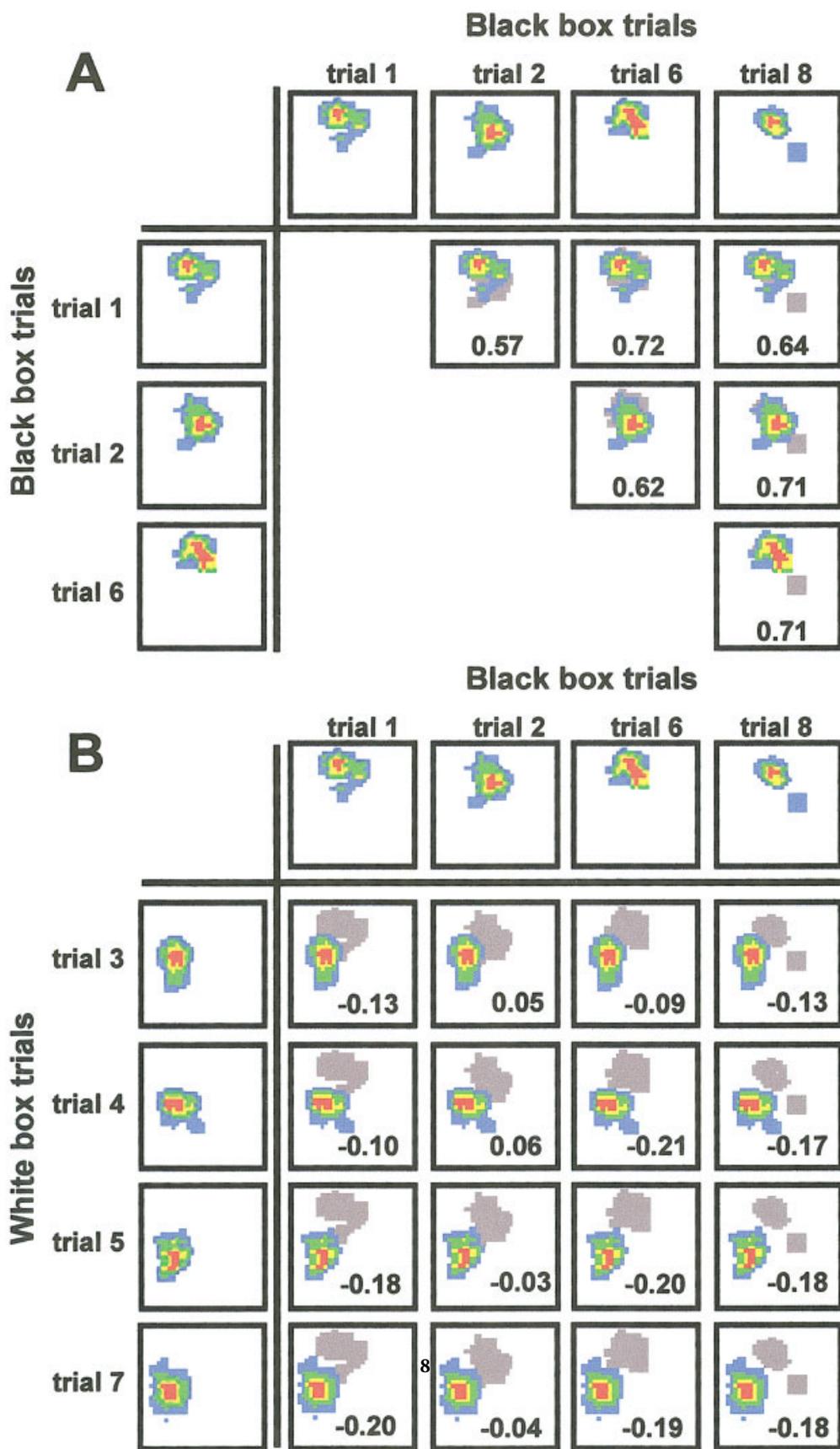


FIGURE 8.

to the environment that induced remapping of most place fields. The behavioral environment was rich in extramaze cues and, since the box was symmetrical and rotated from trial to trial, the rats must have used these cues to solve the task. Nevertheless, changing the intramaze cues alone was enough to cause complete remapping of the place fields. This indicates a decoupling between place cell activity and navigational performance, which is puzzling in view of the widely accepted notion that the place cell map drives performance in navigation tasks (O'Keefe and Nadel, 1978; Morris et al., 1982; O'Keefe and Speakman, 1987). We also investigated whether place cells signal task-relevant information such as the location of the goal, or the occurrence of important events, such as the tone or the lifting of the food flap. We saw no evidence of such activity, suggesting again that the activity of the place cells can be dissociated from the behavior of the rat, even in a spatial task whose acquisition depends on the integrity of the hippocampus. The ramifications of our findings are discussed in relation to current models of hippocampal function. For simplicity, the term "color" is used in the following discussion, to refer to the change of the box from black to white.

The change of the box from black to white did, in fact, cause a small decrement in the rats' performance, from 90% to 70% correct. This disruption in response to a context change was noted previously (Penick and Solomon, 1991) and was found, in that study, to be abolished by hippocampal lesions. Thus, it is possible that the remapping of the place cells might have accounted for the small decrease in performance. More puzzling, though, is why navigation in these rats remained so good in a task that is clearly hippocampal dependent, given that the place cell map reorganized almost completely after the context change.

FIGURE 8. An example of the within-condition (A) and between-condition (B) correlation analyses, applied to trials from cell 4 in the previous figure. Each small box shows the smoothed rate map generated from each 2 min trial, with the values binned into 4 gradations of 20% maximum rate, for illustrative purposes (red = 80-100%, yellow = 60-80%, green = 40-60%, blue = 20-40%). Each map was then compared, pixel by pixel, with each of the other maps in turn. The top row and left-hand column of each grid represent the original trials, and the remaining boxes in the body of the grid show each row trial (colored field) superimposed on the column trial with which it was being correlated (gray field). The resulting correlation coefficient is shown in each box. The fields were the most spatially coherent (for clarity) selected from a session of 18 altogether, and are labeled in the order in which they occurred, to show that the fields were reproducible even when black and white box trials were interspersed. (A) Within-condition comparisons. These are shown for the black box trials only, but another corresponding set from the white box would yield the total of 12 within-trial correlations used in statistical analysis. Note that the overlying (colored) fields overlap the underlying (gray) fields almost completely, showing that the fields were stable across trials. The within-trial correlation coefficients are correspondingly high. (B) Between-condition comparisons. Each of the four trials in the white box was correlated with each of the four trials in the black box. Note that the overlying fields have very little overlap with the underlying fields, and the correlation coefficients are correspondingly low. Thus, this cell had a stable place field that showed a reliable location remapping.

One possibility is that the place cell maps in the two conditions contained a hidden invariance that allowed the rat to transfer performance from one situation to another. According to this view, the structures downstream of the hippocampus can discover this invariance in the output of the hippocampus and use this information to reconstruct a stable representation of the goal. In support of this explanation, Sharp and colleagues found that place fields in the subiculum, the main projection target of CA1 place cells, remained unchanged after manipulations that caused the hippocampal fields to remap (Sharp, 1997). Such invariance might be contained in the small population of hippocampal cells that does not remap.

While a subpopulation of color-invariant cells might explain how the outputs of the hippocampus (both the subicular map and the rat's behavior) could remain unchanged, this explanation does raise the question (1) of how the subiculum "knows" which cells carry the invariant information, and (2) what the function of the remapping cells is, and how their outputs are expressed. An alternative possibility is that there is some transformation that converts the previous place cell map into the new one, and that the subiculum can reverse this transformation in order to extract the spatial information from the altered map. This explanation seems somewhat unlikely, since many previous studies have found no obvious relationship between old and new maps (Kubie and Ranck, 1983; Muller and Kubie, 1987; Bostock et al., 1991; Kentros et al., 1998).

Sharp (1997) suggested that rather than extract an invariance from the CA1 output, the subiculum actually depends on its direct entorhinal input for place information. In support of this explanation, interruption of the trisynaptic circuit at the level of the dentate gyrus (McNaughton et al., 1989) or CA3 (Brun et al., 2002) does not abolish the place-specific firing of cells downstream, suggesting that the direct entorhinal-subicular connections may indeed be the critical components of the circuit underlying both subicular place fields and navigation.

A puzzle arising from the present results is that although this navigation task apparently could be solved without the use of a particular place cell map, an intact hippocampus appeared to be needed, since the lesioned rats were severely impaired in learning the task. One possible explanation is that the hippocampus is needed not for a specific place cell map, but because it somehow supports (perhaps in a noncomputational way) the structure where the computation is taking place. One candidate structure is the nearby head direction system, which is known to use distal cues to set up its representation, and which does not function normally in rats with hippocampal lesions (Golob and Taube, 1999). It may be that normal rats can navigate to the correct box corner using only head direction information, while lesioned rats, having neither a map nor a stable compass, would be impaired. Although the task could, in theory, be solved with the use of the head direction system alone, recent evidence indicates that "remapping" (i.e., redirection) of the head direction system also fails to impair behavior, in a task very similar to the present one (Golob et al., 2001). This question could be resolved by repeating the present experiment in a task like the watermaze, where the directional system alone could not provide enough information to disambiguate locations.

TABLE 1.

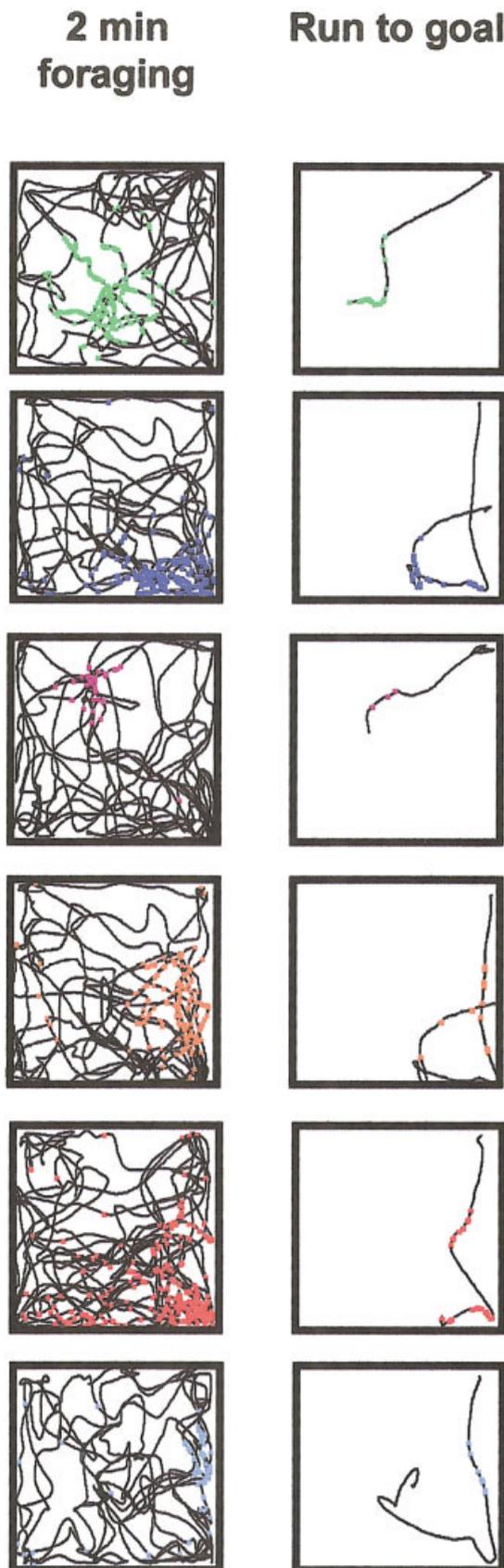
Cell Data

Cell	Peak rate (black)	Peak rate (white)	Correlation (same condition)	Correlation (diff. condition)	Remapping type
A0112(1)1	7.0 (0.6)	0.0			Rate
A0412(1)1	6.7 (0.8)	5.5 (1.6)	0.44 (0.06)	-0.11 (0.02)	Location
A0412(1)2	0.0	17.6 (3.5)			Rate
A0412(2)1	0.0	3.4 (0.4)			Rate
A0412(2)2	6.0 (1.0)	0.0			Rate
B2111(1)1	34.1 (2.9)	16.0 (1.6)	0.8 (0.03)	0.77 (0.02)	None
B2111(1)2	8.8 (3.8)	17.3 (4.7)	0.49 (0.07)	0.54 (0.06)	None
B2111(1)4	4.3 (1.5)	9.5 (2.0)	0.72 (0.05)	0.56 (0.04)	Location
B2111(1)5	3.7 (0.9)	8.4 (2.4)	0.41 (0.05)	0.44 (0.04)	None
B2711(1)1	1.4 (0.4)	2.2 (0.5)	0.64 (0.05)	0.62 (0.05)	None
B2711(1)2	19.7 (2.3)	17.3 (1.4)	0.66 (0.03)	0.51 (0.03)	Location
B0512(1)3	8.2 (0.5)	0.0			Rate
B0512(1)4	0.0	5.4 (0.3)			Rate
B2012(1)1	25.1 (1.2)	0.0			Rate
B2012(1)2	0.0	16.6 (1.6)			Rate
B2012(1)3	0.0	14.5 (1.1)			Rate
B2012(1)4	0.0	12.4 (0.9)			Rate
D0712(1)1	9.1 (0.6)	11.2 (1.9)	0.52 (0.06)	0.31 (0.05)	Location
D0712(1)2	19.4 (1.9)	9.4 (1.2)	0.57 (0.07)	0.3 (0.02)	Location
D0712(1)3	8.1 (1.5)	3.1 (0.6)	0.46 (0.08)	0.18 (0.08)	Location
D1112(1)1	13.0 (3.0)	4.3 (0.5)	0.64 (0.05)	-0.08 (0.02)	Location
D2112(1)1	18.7 (1.9)	10.6 (2.8)	0.64 (0.04)	0.31 (0.04)	Location
D2112(1)2	15.1 (1.9)	0.0			Rate
H0512(1)1	14.5 (2.8)	6.1 (0.5)	0.84 (0.01)	0.76 (0.01)	Location
H0512(1)2	15.0 (1.8)	6.1 (1.6)	0.39 (0.04)	-0.02 (0.02)	Location
H0512(1)3	8.8 (1.3)	5.1 (0.9)	0.51 (0.07)	0.28 (0.06)	Location
H1012(1)2	0.0	12.9 (1.1)			Rate
H1012(1)3	6.6 (1.2)	0.0			Rate
	7.6 (1.3)	8.8 (0.9)	0.47 (0.04)	0.009 (0.04)	Location
H1012(1)4	8.1 (1.4)	12.8 (2.0)	0.52 (0.04)	0.02 (0.04)	Location
H1012(1)5	0.0	8.7 (0.8)			Rate
H1012(1)6	0.0	11.3 (1.2)			Rate
H1012(2)1	16.9 (3.2)	12.1 (1.8)	0.69 (0.03)	0.66 (0.03)	None
H1012(2)2	11.1 (1.4)	16.9 (2.4)	0.63 (0.05)	-0.13 (0.02)	Location
H1012(2)3	9.9 (1.2)	7.0 (2.0)	0.53 (0.06)	0.18 (0.05)	Location

Table showing the remapping characteristics of 34 place cells recorded in both the black and the white boxes. The cells are labeled by rat (A, B, D and H), date of recording (day, month), tetrode number (in brackets) and cluster number. The mean (\pm s.e.) peak rate of the cells (after smoothing) is shown in Hz. Where the cell fired on average fewer than 20 spikes falling within 2 s.d. of the cluster centroid in one of the conditions only, the rate is entered as zero, and the cell labeled as a rate-remapping cell. For cells with firing that exceeded this threshold criterion in both conditions, the correlation coefficients (mean \pm s.e.) are shown in the next two columns. Correlations within a condition (e.g., among all the black-box trials, or among all the white-box trials) are shown in the fourth column, and those between conditions (e.g., all the black-box trials compared with all the white-box trials) are shown in the fifth column. Where these means were significantly different, the cell was labeled as a location-remapping cell. One cell (H1012(1)3) showed a rate-remapping pattern in the first 8 trials and a location-remapping pattern in the second 8 trials.

A further possibility is that neither the head direction cells nor the place cells are needed for the final execution of a well-learned navigation task, but one or both are needed for its acquisition. This could be tested by making lesions to the place and head direction

systems after training to see whether performance is still impaired or now remains intact. If intact, this would imply that the nature of the task changed once it became well-learned, so that it now no longer depended on the hippocampus. Because it is assumed that



the architecture of the hippocampus supports a specific set of computations, such a finding would imply that the navigation in a well-learned task is a fundamentally different process from that operating during acquisition.

The finding in this study of an apparent dissociation between the place cell map and navigation performance stands in contrast to evidence from other studies that remapping in place cells tends to be associated with reduced navigational performance (Barnes et al., 1997; Tanila et al., 1997; Oler and Markus, 2000). While many manipulations that degrade or remap place fields may also diminish performance, such a correlation does not necessarily prove that the place fields supported the performance it may equally well be that the manipulation affected some other factor necessary both for coherent establishment of place fields and for navigation. For example, manipulations that caused the rat to become directionally disoriented could affect both place fields and navigation, even if these things were themselves causally independent. In contrast, the demonstration of a dissociation between place fields and navigation, as in the present case, represents a falsification of the cognitive mapping hypothesis, suggesting perhaps that navigation is a more heterogeneous faculty than is often supposed and that some kinds may be place-cell independent.

Could the rats have used path integration to solve the navigation task? It is very unlikely that they could have done so. In most path integration tasks, rats shuttle back and forth between a start location and a goal, and are thus able to maintain a working memory representation of the homing direction and distance that depends on movement-related (“idiothetic”) cues alone. However, in the present experiment, rats were removed from the apparatus at the end of each trial, placed in a carrying box, and carried back to the home cage, where they remained for minutes or hours. Since path integration is effective over short distances and times only, it is highly doubtful such a process could have supported performance.

In the present experiment, we also looked for and failed to find evidence of either task-related or goal-related activity of place cells. Such activity would have been predicted by the results of other studies using both spatial tasks (Breese et al., 1989; Kobayashi et al., 1997; Hollup et al., 2001) and nonspatial tasks (Wood et al., 1999; Hampson et al., 1999). These studies have found an increase of place cell activity in regions of the environment containing goals.

However, place cells in the present task did not fire more in the goal corner of the box than in other corners, nor did they fire in response to the navigational signal (the tone), or during goal location. In fact, on the contrary we saw a decrease of activity related to the reaching of the reward (which may be due to the slowing velocity of the rat as it stopped at the goal). Our findings are more consistent with those of O’Keefe and Speakman

FIGURE 9. Trials from 6 cells in which the rat ran through the location of the cell’s field on its way to the goal. Left-hand boxes show the two minute foraging period, and right-hand boxes show the run to the goal after the tone sounded. The positioning of the spikes on the path of the rat shows the same fields appear to be present during the run to the goal as during the foraging period. Thus, the tone does not appear to have triggered remapping.

(1997), in which place cell activity was found to be unrelated to goal location. In both O'Keefe and Speakman's study and ours, place cell activity in the region of the goal was able to be assessed while the rat was not actually navigating there at the time, thus removing possible behavioral effects generated by the rats' altered activity at the goal. Possibly, the altered behavior of rats at the goal may produce activity in complex-spiking cells (as arises during immobility-induced LIA EEG activity) that, because it only occurs in that one region, produces an apparent place field. However, some studies have looked for and failed to find such artifactual correlations (e.g., Hollup et al., 2001). An alternative possibility is that goal-related activity only occurs during active navigation, or during certain kinds of navigation but not others. Nevertheless, together with the remapping results, the absence of goal-related activity seen in the present study calls into question the role of the place cells in the performance of navigation tasks like this, and suggest that the spatial information critical for its successful execution may be represented outside the hippocampus proper.

How can these results be reconciled with current models of hippocampal function? The cognitive map theory of the hippocampus is being elaborated in two main ways to account for data that do not fit easily with the original formulation. First, it seems apparent that spatial representation takes place not solely in the hippocampus, but rather is distributed across a network of structures, each (presumably) contributing a different function to navigation. It may be that animals can still navigate when one of these structures is disabled as long as the other structures remain intact. This may explain why place cell remapping does not abolish navigation, whereas a destructive manipulation such as lesioning, which affects many structures in the network, does. The second emerging finding is that the hippocampus clearly plays a role in more functions than just spatial representation and navigation. A growing body of evidence implicates it in the storage and consolidation of episodic memories (at least in humans) (O'Keefe and Nadel, 1978; Squire and Zola-Morgan, 1991; McClelland et al., 1995; Vargha-Khadem et al., 1997; Aggleton and Brown, 1999), and another separate but related body of evidence implicates it in the representation and learning of context (Nadel and Willner, 1980; Penick and Solomon, 1991; Myers and Gluck, 1994). It may be that the dissociation seen in the present experiment between place cell activity and navigational behavior reflects the fact that the place cells do not code place per se, but rather a more elaborate conjunction of cues (both spatial and nonspatial). Such conjunctive coding, which has been proposed many times previously (O'Keefe and Nadel, 1978; Rudy and Sutherland, 1989; Wiener, 1996; O'Reilly and Rudy, 2001), would allow the storage of the spatiotemporal context of events and may form the substrate for episodic memory. This leaves the question of whether there is a region of the brain which truly houses a "cognitive map" in the O'Keefe and Nadel sense of the word, or whether the spatial representation is distributed across so many structures that it cannot really be called a "map" at all.

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REFERENCES

- Aggleton JP, Brown MW. 1999. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci* 22:425–444.
- Anderson MI, Jeffery KJ. 2001. Interaction of sensory cues in the control of place cell remapping. *Soc Neurosci Abs.*, Vol. 27, Program No. 744. 5, 2001
- Barnes CA, Suster MS, Shen J, McNaughton BL. 1997. Multistability of cognitive maps in the hippocampus of old rats. *Nature* 388:272–275.
- Bostock E, Muller RU, Kubie JL. 1991. Experience-dependent modifications of hippocampal place cell firing. *Hippocampus* 1:193–205.
- Breese CR, Hampson RE, Deadwyler SA. 1989. Hippocampal place cells: stereotypy and plasticity. *J Neurosci* 9:1097–1111.
- Brun VH, Otnass MK, Molden S, Steffenach HA, Witter MP, Moser MB, Moser EI. 2002. Place cells and place recognition maintained by direct entorhinal-hippocampal circuitry. *Science* 296:2243–2246.
- Burton S, Murphy D, Qureshi U, Sutton P, O'Keefe J. 2000. Combined lesions of hippocampus and subiculum do not produce deficits in a nonspatial social olfactory memory task. *J Neurosci* 20:5468–5475.
- Frank LM, Brown EN, Wilson M. 2000. Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* 27:169–178.
- Golob EJ, Taube JS. 1999. Head direction cells in rats with hippocampal or overlying neocortical lesions: evidence for impaired angular path integration. *J Neurosci* 19:7198–7211.
- Golob EJ, Stackman RW, Wong AC, Taube JS. 2001. On the behavioral significance of head direction cells: neural and behavioral dynamics during spatial memory tasks. *Behav Neurosci* 115:285–304.
- Hampson RE, Simeral JD, Deadwyler SA. 1999. Distribution of spatial and non-spatial information in dorsal hippocampus. *Nature* 402:610–614.
- Hirase H, Czurko HH, Csicsvari J, Buzsaki G. 1999. Firing rate and theta-phase coding by hippocampal pyramidal neurons during "space clamping." *Eur J Neurosci* 11:4373–4380.
- Hollup SA, Molden S, Donnett JG, Moser MB, Moser EI. 2001. Accumulation of hippocampal place fields at the goal location in an annular watermaze task. *J Neurosci* 21:1635–1644.
- Jarrard LE. 1989. On the use of ibotenic acid to lesion selectively different components of the hippocampal formation. *J Neurosci Methods* 29: 251–259.
- Kentros C, Hargreaves E, Hawkins RD, Kandel ER, Shapiro M, Muller RV. 1998. Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. *Science* 280:2121–2126.
- Knierim JJ, Kudrimoti HS, McNaughton BL. 1995. Place cells, head direction cells, and the learning of landmark stability. *J Neurosci* 15: 1648–1659.
- Kobayashi T, Nishijo H, Fukuda M, Bures J, Ono T. 1997. Task-dependent representations in rat hippocampal place neurons. *J Neurophysiol* 78:597–613.
- Kubie JL, Ranck JB Jr. 1983. Sensory-behavioral correlates in individual hippocampal neurons in three situations: space and context. In: Seifert W, editor. *Neurobiology of the hippocampus*. San Diego, CA: Academic Press. p 433–447.
- Markus EJ, Qin YL, Leonard B, Skaggs WE, McNaughton BL, Barnes CA. 1995. Interactions between location and task affect the spatial and directional firing of hippocampal neurons. *J Neurosci* 15:7079–7094.

- McClelland JL, McNaughton BL, O'Reilly RC. 1995. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol Rev* 102:419–457.
- McNaughton BL, Barnes CA, O'Keefe J. 1983. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp Brain Res* 52:41–49.
- McNaughton BL, Barnes CA, Meltzer J, Sutherland RJ. 1989. Hippocampal granule cells are necessary for normal spatial learning but not for spatially-selective pyramidal cell discharge. *Exp Brain Res* 76:485–496.
- Morris RG, Garrud P, Rawlins JN, O'Keefe J. 1982. Place navigation impaired in rats with hippocampal lesions. *Nature* 297:681–683.
- Muller RU, Kubie JL. 1987. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J Neurosci* 7:1951–1968.
- Myers CE, Gluck MA. 1994. Context, conditioning, and hippocampal representation in animal learning. *Behav Neurosci* 108:835–847.
- Nadel L, Willner J. 1980. Context and conditioning: a place for space. *Physiol Psychol* 8:218–228.
- O'Keefe J, Burgess N. 1996. Geometric determinants of the place fields of hippocampal neurons. *Nature* 381:425–428.
- O'Keefe J, Nadel L. 1978. *The hippocampus as a cognitive map*. Oxford: Clarendon Press.
- O'Keefe J, Speakman A. 1987. Single unit activity in the rat hippocampus during a spatial memory task. *Exp Brain Res* 68:1–27.
- Oler JA, Markus EJ. 2000. Age-related deficits in the ability to encode contextual change: a place cell analysis. *Hippocampus* 10:338–350.
- O'Reilly RC, Rudy JW. 2001. Conjunctive representations in learning and memory: principles of cortical and hippocampal function. *Psychol Rev* 108:311–345.
- Paxinos G, Watson C. 1997. *The rat brain in stereotaxic coordinates*. London: Academic Press.
- Penick S, Solomon PR. 1991. Hippocampus, context, and conditioning. *Behav Neurosci* 105:611–617.
- Rudy JW, Sutherland RJ. 1989. The hippocampal formation is necessary for rats to learn and remember configural discriminations. *Behav Brain Res* 34:97–109.
- Save E, Nerad L, Poucet B. 2000. Contribution of multiple sensory information to place field stability in hippocampal place cells. *Hippocampus* 10:64–76.
- Sharp PE. 1997. Subicular cells generate similar spatial firing patterns in two geometrically and visually distinctive environments: comparison with hippocampal place cells. *Behav Brain Res* 85:71–92.
- Squire LR, Zola-Morgan S. 1991. The medial temporal lobe memory system. *Science* 253:1380–1386.
- Tanila H, Shapiro M, Gallagher M, Eichenbaum H. 1997. Brain aging: changes in the nature of information coding by the hippocampus. *J Neurosci* 17:5155–5166.
- Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. 1997. Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 277:376–380.
- Wiener SI. 1996. Spatial, behavioral and sensory correlates of hippocampal CA1 complex spike cell activity: implications for information processing functions. *Prog Neurobiol* 49:335–361.
- Wood ER, Dudchenko PA, Eichenbaum H. 1999. The global record of memory in hippocampal neuronal activity. *Nature* 397:613–616.
- Wood ER, Dudchenko PA, Robitsek RJ, Eichenbaum H. 2000. Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* 27:623–633.