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Local remapping of place cell firing in the Tolman detour task

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Abstract

The existence of place cells, whose discharge is strongly related to a rat's location in its environment, has led to the proposal that they form part of an integrated neural system dedicated to spatial navigation. It has been suggested that this system could represent space as a cognitive map, which is flexibly used by animals to plan new shortcuts or efficient detours. To further understand the relationships between hippocampal place cell firing and cognitive maps, we examined the discharge of place cells as rats were exposed to a Tolman-type detour problem. In specific sessions, a transparent barrier was placed onto the maze so as to block the shortest central path between the two rewarded end locations of a familiar three-way maze. We found that rats rapidly and consistently chose the shortest alternative detour. Furthermore, both CA1 and CA3 place cells that had a field in the vicinity of the barrier displayed local remapping. In contrast, neither CA1 nor CA3 cells that had a field away from the barrier were affected. This finding, at odds with our previous report of altered CA3 discharge for distant fields in a shortcut task, suggests that the availability of a novel path and the blocking of a familiar path are not equivalent and could lead to different responses of the CA3 place cell population. Together, the two studies point to a specific role of CA3 in the representation of spatial connectivity and sequences.

Introduction

Since the discovery by O'Keefe & Dostrovsky (1971) of place cells, whose activity is related to the rat's location in the environment, the hippocampus has been considered to be a key component of the neural system involved in spatial representations of the environment (O'Keefe & Nadel, 1978). Supporting this hypothesis, place cells carry information that is important for spatial navigation (O'Keefe & Speakman, 1987; Lenck-Santini *et al.*, 2001, 2005), and altering their activity greatly alters navigation performance (O'Keefe & Nadel, 1978; Poucet & Benhamou, 1997).

Although the strongest correlate of hippocampal place cells is the animal's current location, a current issue is whether place cell firing also includes more extensive information about the environment or the animal's internal state. In particular, several investigators have proposed schemes in which place cells and the hippocampal machinery provide the animal with the information required to compute optimal paths through the environment. Some models depend on topological relationships whereby the rat gets from its current location to the goal by traversing a series of places along previously experienced routes (e.g. Schmajuk & Thieme, 1992; Blum & Abbott, 1996; Gerstner & Abbott, 1997; review in Trullier *et al.*, 1997). Other models do not rely on previously taken paths, and allow the animal to find optimal paths from any starting point to any goal location in a familiar environment (reviews in Meyer & Filliat, 2003 and Poucet *et al.*, 2004). A common feature of the latter models is their assumption that a major function of the hippocampus is the coding of sequences of events (review in Eichenbaum & Fortin, 2005) or states (e.g. Gaussier *et al.*, 2002), thus allowing prediction of the next state from the current state. In this view, connections between places can be represented by transitions whose metrics are provided by the length of the path connecting them and therefore the time needed for the animal to go from one place to the other. The encoding of such connections has been suggested to occur between pairs of CA3 cells (Muller *et al.*, 1996). In this model, the distance between the firing fields of connected CA3 place cells would be encoded as synaptic resistance, the inverse of synaptic strength. Interestingly, long-term potentiation has recently been shown to be influenced by the relative timing of action potentials from pairs of place cells (i.e. by the distance separating their fields), thus suggesting that synaptic strength could theoretically participate in the encoding of the structure of the environment by place cells (Isaac *et al.*, 2009). Furthermore, modifications of synaptic strength could reflect structural changes in the environment that affect the paths between two locations (Muller *et al.*, 1996).

In earlier work, we explored the effects of altering the spatial structure by removing a barrier in the environment. This manipulation resulted in the establishment of a new connection between previously unconnected regions of space, that is, a shortcut (Alvernhe *et al.*, 2008). Under these circumstances, CA1 and CA3 place cells underwent changes in activity that mainly affected firing

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fields near the removed barrier, a result consistent with other data (Muller & Kubie, 1987; Rivard *et al.*, 2004). Much smaller effects were found for fields away from the barrier, and these were mostly observed for CA3 cells. Noticeably, effects on fields away from the barrier cannot result directly from sensory or motor changes induced by barrier manipulation, and this strongly supports the idea that the hippocampus represents changes in the constraints imposed by the local structure of the environment on the animal's movements (Poucet, 1993; Muller *et al.*, 1996). Finally, these alterations in place cell activity were reflected in immediate changes of path choice behavior, with rats consistently using the shortcut path during barrier removal sessions. Thus, this study provides important clues as to how place cell activity embeds information about both the connectivity of space and locations, and how this information affects rats' shortcut behavior. It also strengthens the idea that hippocampal activity is important for the buildup and use of a spatial cognitive map (Tolman, 1948; O'Keefe & Nadel, 1978). A basic tenet of the concept of a cognitive map is that it should allow for the flexible planning of novel trajectories in space. This can happen either when never experienced but shorter paths are suddenly made available to the animal, as in the study of Alvernhe *et al.* (2008), or when a familiar path is suddenly blocked, requiring the animal to flexibly use another, initially non-preferred, path, as in detour experiments (Tolman, 1948; Poucet *et al.*, 1983).

In the present study, we sought to investigate whether changes in place cell activity and behavior in response to changes in the environmental structure could be extended to a detour situation. We recorded hippocampal place cells while rats were required to choose the most appropriate detour in a highly familiar maze resembling the one used by Tolman & Honzik (1930). A major difference from the shortcut situation of the study of Alvernhe *et al.* (2008) was that using the detour imposed by the addition of a barrier in the maze required the rat to flexibly adapt its choice behavior to shift from a highly preferred path to a non-preferred, but familiar, path. This shift did not require the formation of a new connection between places in the apparatus, as the rats had ample opportunity to explore the non-preferred path during previous exposures to the apparatus. The aim was therefore to analyze the effect of path blocking on both place cell activity and path choice behavior in two detour problems that differed in the number of afforded solutions, so as to examine the effect of task difficulty on place cell activity.

Materials and methods

Subjects

Thirteen naïve Long–Evans black hooded male rats (R. Janvier, St-Berthevin, France) weighing 300–350 g were housed one per cage at 20 ± 2 °C, under natural lighting conditions. They had free access to water, and were food-deprived to 85% of *ad libitum* body weight. All procedures complied with both European and French institutional guidelines.

Apparatus

The apparatus was a modified version of the maze used by Tolman & Honzik (1930). It was composed of three connected alleyways (10 cm in width), made of wood and painted matte black (Fig. 1A). The whole maze was elevated 55 cm above the floor. Each part of the apparatus was bounded by 5-cm raised edges. The center alley (straight path) was rectilinear and 130 cm long. At both extremities (shown as A and B in Fig. 1), the straight path ended with a transverse wall (20 cm in height), behind which a remote-controlled food dispenser was fixed. When activated, the food dispenser delivered a 20-mg food pellet. The two other alleyways were C-shaped, and were connected with the center alleyway on each side. The left alleyway (short detour path) was 100 cm long, and the right alleyway (long detour path) was 250 cm long (Fig. 1). The maze was arranged so that, in order to move back and forth between the two food dispensers, rats had the choice between the three possible routes, that is, the straight path, the short detour path and the long detour path. The straight path could be blocked by adding a transparent Plexiglas barrier (10 cm in width; 30 cm in height) at two different positions (P1 or P2; Fig. 1A). According to the position of the barrier, the rat was left with either one detour path (barrier at position P1) or two detour paths (barrier at position P2) to move from location A to location B. Therefore, the aim of our experiment was to look at the rat's choices when departing from location A (as in Tolman & Honzik's, 1930) while recording the changes in place cell firing field when the topological structure of the maze was changed in these ways. The apparatus was at the center of an evenly lit area surrounded by numerous distal visual cues placed in the room. A video camera and radio tuned to an FM station were fixed to the ceiling above the apparatus. The unit recording system, TV monitor and equipment for controlling the food dispensers were located in an adjacent room.

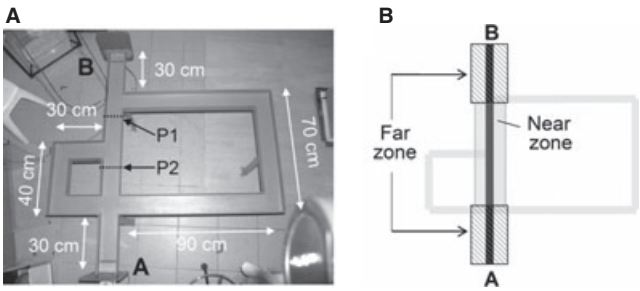

FIG. 1. Apparatus. (A) Photograph of the maze. (B) Schematic representation of the two zones (near and far) used for calculating field similarity scores. The maze was made of two C-shaped alleyways connected to a linear center alleyway (path 1) on each side (path 2 on the left; path 3 on the right). Two food dispensers at the end locations, A and B, of the central alley were remotely controlled to keep the rat reliably running back and forth in the maze.

Behavioral procedures

After 1 week of daily handling and 10 habituation (free exploration) sessions in the apparatus, each of duration 5 min, rats were individually trained to commute back and forth between the two end locations of the maze (A and B), where food dispensers were located. To this end, the rat was introduced into the maze at location A and simply required to move to location B to receive a food reward, whatever the path chosen. To obtain another reward, the animal then had to return to location A, and so forth. Two 20-mg food pellets were delivered each time the rat visited one end location of the runway after it had earned the same reward at the other end location. Each animal was trained in 15-min daily sessions for 5 weeks. Electrodes were implanted when the rat could consistently perform 50 runs between the two end locations of the runway in a 15-min session.

Electrode implantation

After behavioral training, a drivable bundle of four tetrodes was implanted surgically under sterile conditions and general anesthesia

(ketamine/xylazine, 0.88 mL/kg). Each tetrode was composed of four twisted 25-μm nichrome wires. The four tetrodes formed a bundle threaded through a piece of stainless steel tubing (Kubie, 1984). Each wire was attached to a pin on the outside of a rectangular connector. The tubing was attached to the center pin of the connector, and served as the animal ground as well as a guide for microwires. The connector, tubing and wires could be moved down through the hippocampus by turning drive screw assemblies cemented to the skull. Before surgery, the wire tips were gold-plated to reduce their impedance to 200–400 kΩ. The tips of the tetrode bundle were implanted above the dorsal hippocampus (3.8 mm posterior, 3.0 mm lateral and 1.5 mm dorsoventral to dura) (Paxinos & Watson, 2005). As a postoperative treatment, rats received an injection of antibiotic (clamoxil, 0.05 mL) and of analgesic (tolfedine, 0.04 mL).

At the completion of the experiment, animals were killed with a lethal dose of pentobarbital. Just prior to death, positive current (15 μA for 30 s) was passed through one microwire to deposit iron that could be visualized after reaction with potassium ferrocyanide (Prussian blue). Then, rats were perfused intracardially with 0.9% saline followed by 4% formalin. The brains were removed and stored for 1 day in 3% ferrocyanide. Later, coronal sections, 25 μm in thickness, were taken and stained with cresyl violet for verification of electrode placements.

Recording methods

Beginning 1 week after surgery, the activity from each tetrode was screened daily while the rat underwent additional training in the maze. If no waveform of sufficient amplitude was found, the tetrodes were lowered by 25–50 μm. A period of several hours (usually 24 h) was allowed to elapse between successive screening sessions conducted in the same rat, so as to guarantee electrode stability. Recordings were made only if the rat performance was adequate (i.e. at least three runs from A to B per minute). Ideally, recorded cells had fields distributed over different parts of the maze. When a set of units was isolated, it was recorded for three 15-min sessions, according to the testing protocol described below. Screening and recording were performed with a cable attached at one end to a commutator that allowed the rat to move freely. The other end of the cable was connected to the rat headstage, which contained a field effect transistor amplifier for each wire. The signals from each tetrode wire were further amplified 10 000 times, bandpass-filtered between 0.3 and 3 kHz with Neuralynx amplifiers (Neuralynx, Bozeman, MT, USA), digitized (32 kHz), and stored by a DataWave Sciworks acquisition system (DataWave Technologies, Longmont, CO, USA). A light-emitting diode (LED) attached to the headstage assembly, 1 cm above the head and 1 cm behind the headstage, provided the position of the rat's head. The LED was imaged with a CCD camera fixed to the ceiling above the maze, and its position was tracked at 50 Hz with a TV-based digital spot-follower. The LED position was located on a grid of 64 $\times$ 64 square pixels with 23-mm-long sides.

Testing protocol

When a cell, or set of cells, was judged to be suitable for recording, it was recorded for three successive 15-min sessions. As during training, at the beginning of each test session, the rat was placed at location A of the center alleyway. The first session (standard 1) was conducted while the rat performed the task with the apparatus in the standard configuration used during training. At the end of the first session, the rat was placed in a nearby waiting box with water available, while it was still connected to the recording system. During this time, the experimenter performed the manipulations out of the current rat's visual field. A transparent barrier was placed at either position P1 or position P2 on the center runway (Fig. 1A). The barrier position was balanced between rats and between exposures for a given rat. The second (detour) session was then conducted with the rat running the reconfigured maze for 15 min. When placed at position P1, the barrier rendered both the straight path and the short path useless for reaching location B from location A. As a result, the only path leading from location A to location B was the long detour path (condition one-detour). In contrast, when placed at position P2, the barrier blocked only the straight path, and the rat could run between location A and location B using either the short or the long detour paths (condition two-detours). At the end of the detour session, the rat was placed in the waiting box with water available while the experimenter removed the blocking barrier that had been added in session 2. The third (standard 2) session was conducted with the maze in its standard configuration. The purpose of this last standard session was to check that, whatever the changes in cell firing observed during the detour session, we could ensure that the same cells had been recorded during the first two sessions by restoring the initial firing patterns. This protocol was repeated for each rat whenever a new cell or set of cells was isolated. The apparatus was cleaned with water between sessions.

Unit discrimination

Cells selected for analysis had to be well-discriminated complex-spike cells with clear location-specific firing in at least one region of the environment. Moreover, because our purpose was to measure changes in the same cell across different manipulations, cells that were lost before the session series was completed, or whose waveforms changed too much between two sessions, were not used for further analysis. The first step in off-line analysis was to define boundaries for waveform clusters. Candidate waveforms were discriminated on the basis of characteristic features, including maximum and minimum spike voltage, spike amplitude (from peak to trough), time of occurrence of maximum and minimum spike voltages, spike duration, and voltage at several experimenter-defined points of the waveforms. Waveforms were then processed with Plexon Offline Sorter (Plexon, Dallas, TX, USA), which permits additional refinement of cluster boundaries and provides autocorrelation functions. Interspike interval histograms were built for each unit, and the whole unit was removed from analysis if the autocorrelogram revealed the existence of interspike intervals < 2 ms (refractory period), which is inconsistent with good isolation. When necessary, the quality of waveform isolation was further checked to ensure that the observed effects were not caused by poor waveform discrimination. To do this, a waveform similarity score was obtained by calculating the gamma correlation between the mean waveforms (defined as series of 32 points for 1 ms) of a putative single cell recorded across distinct sessions. If the gamma correlation fell below 0.95, the cell was discarded from the analyzed sample (gamma correlations calculated for mean waveform randomly shuffled across cells yield a mean value of 0.75). When single units were well separated, autoscaled color-coded firing rate maps were created to visualize firing rate distributions (Muller *et al.*, 1987). In such maps, pixels in which no spikes occurred during the whole session are displayed as yellow. The highest firing rate is coded as purple, and intermediate rates are shown as orange, red, green and blue pixels, ranging from low to high. A firing field was defined as a set of at least six contiguous pixels with a firing rate above the grand mean rate. To allow comparisons between positional firing rate distributions

across several sessions for a cell, the rate categories used for subsequent sessions were the same as for the first session.

Data presentation and analysis

Our aim was to analyze the responses of individual firing fields to changes in maze structure. As the rats almost always used the straight path and only rarely took the detour paths during standard sessions, we focused our analyses on the representation of the center straight path, although we also looked at individual fields located in the detour paths whenever possible. The straight path was divided into two equally sized zones, each centered on a given region of the maze. The first zone, referred to as the near zone, comprised the two possible barrier positions (P1 and P2) and extended from the intersection closest to location A to the intersection closest to location B (Fig. 1B). The second zone, referred to as the far zone, matched the remaining parts of the straight path and included the choice-points.

To estimate firing field similarity between two successive sessions, we computed two complementary scores. The first score, S, represented the spatial (positional) similarity of the firing fields before and after the addition of the barrier, and is based on the pixel-by-pixel correlation between the positional rate distribution in the field zone for the first session and the superimposed positional rate distribution in the same zone for the second session. Because correlation coefficients are not normally distributed, similarity scores were converted into z-scores with Fisher's z-transformation, and all statistical analyses were performed on the z-scores. Furthermore, because within-session z-scores during the standard session revealed that intrinsic stability was lower in our CA1 sample than in CA3 cells, we further normalized the similarity index by the within-session z-scores. Thus, the similarity score S was calculated from $S = (z_{max} - z_{intra})/(z_{max} - z_{inter})$, where z_{intra} is the within-session z-score for the first (standard) session, z_{inter} is the between-session z-score for the first (standard) and second (detour) sessions, and z_{max} is the greatest similarity score ($z_{max} = 2.65$). Greater values of S indicate greater similarity between the firing rate maps. The second score, R, represented the change in discharge frequency in each zone. Basically, it is a chi-square test calculated as $R = [(a - b)^2/(a + b)] \times [(b - a)/|a - b|]$, where a and b are the firing rates for the first (standard) and the second (detour) sessions, respectively. A negative value of R reflects a decrease in discharge, and a positive value reflects an increase. To measure the change in firing rate at the population level, the absolute value of R was used. Finally, scores of spatial similarity and firing rate change were calculated for identified fields (see above) in the near and far zones separately.

Behavioral performance was measured in two ways. First, we counted the number of rewards earned by the rat at location B (which reflects the number of A–B runs) during all recording sessions, to obtain an overall performance score. Second, during detour sessions, we counted separately the number of complete runs from location A to location B in which the rat selected either the short or the long detour path.

Results

Behavior

Behavioral data were obtained from 13 rats tested in 104 complete sequences of three sessions, standard–detour–standard. Each rat experienced the complete sequence four times with the barrier at position P1 (condition one-detour) during the detour session, and four times with the barrier at position P2 (condition two-detours). At the beginning of each detour session, a well-trained rat would first take the straight path and encounter the barrier. In all instances, the rat was observed to spend a significant amount of time exploring the barrier zone before moving back to the starting location A and making the choice of another path to reach the other maze end location. It was only after a few runs between the two maze end locations that the rat was consistently seen to take one of the two detour paths. The average number of runs from location A to location B decreased from standard sessions to detour sessions (from 25.1 ± 0.4 A–B runs to 7.9 ± 0.7 A–B runs and 13.5 ± 0.9 A–B runs in conditions one-detour and two-detours, respectively). Furthermore, performance improved over successive exposures to the barrier in the two detour conditions (Fig. 2A). This improvement was confirmed by two-way ANOVAs with number of runs as the repeated measure, which revealed a significant effect of exposures in both conditions ($F_{3,36} = 4.35$, $P < 0.02$, and $F_{3,33} = 3.14$, $P < 0.05$). A further analysis confirmed that the number of runs was greater in condition two-detours than in condition one-detour ($F_{1,23} = 7.82$, $P < 0.02$). In contrast, the interaction between condition and performance was not significant, showing equivalent improvement in the two conditions [$F_{3,69} = 0.25$, not significant (NS)].

An interesting aspect of the rats' behavior was the path that was selected during detour sessions. In fact, whereas both the short and long detour paths connected start location A to goal location B when the barrier was set at position P2 (condition two-detours), only the long detour was useful when the barrier was set at position P1 (condition one-detour). Thus, if rats optimized their choices, they should show a preference for the short detour path in condition two-detours, but a preference for the long detour path in condition one-detour, as this was the only path leading to location B. In a first analysis, we compared the frequency with which the two paths were run in each condition. The results revealed a statistically significant preference for the short detour path in condition two-detours ($F_{1,24} = 8.01$, $P < 0.01$), and an even stronger (and expected) preference for the long detour path in condition one-detour ($F_{1,22} = 179.3$, $P << 0.001$). No significant variations across successive detour sessions was observed in either condition ($F_{3,36} = 1.61$, NS, and $F_{3,33} = 0.26$, NS, respectively). Therefore, whereas rats optimized their path choices when there was only one useful path (Fig. 2B), they did so to a much lesser extent when they had the choice between two possible detour paths (Fig. 2C). We then investigated which path the rats would take on their very first exposure to the barrier in each condition. We found that, after facing the barrier and returning to start location A in condition one-detour, most rats used the long detour path to reach goal location B on the very first run (12/13 rats, 92%, $P < 0.002$, binomial test). In contrast, only half of the rats in condition two-detours used the short detour path (6/13, 46.2% of rats), the remaining rats choosing the long detour path. On the second run from location A to location B in this condition, however, a majority of the rats (10/13 rats, 76.9%, $P < 0.05$, binomial test) chose the short detour.

Together, these results suggest that rats were efficient in adapting path choice to the new topological configuration. The changes in behavior occurred very quickly, either immediately or during the very first minutes of exploration of the modified maze.

Finally, we looked at path preference during the last session of each daily sequence, that is, during the standard session that followed the detour session. Although a clear preference for the straight path was restored during this session (15.3 ± 0.3 runs per session on average, i.e. 85%), the trend was less pronounced than during the standard session that preceded the detour session (23.6 ± 0.2 runs per session, i.e. 94%; $F_{1,103} = 17.4$, $P < 0.001$). Further analyses revealed a persisting choice of the long detour path in condition one-detour (long

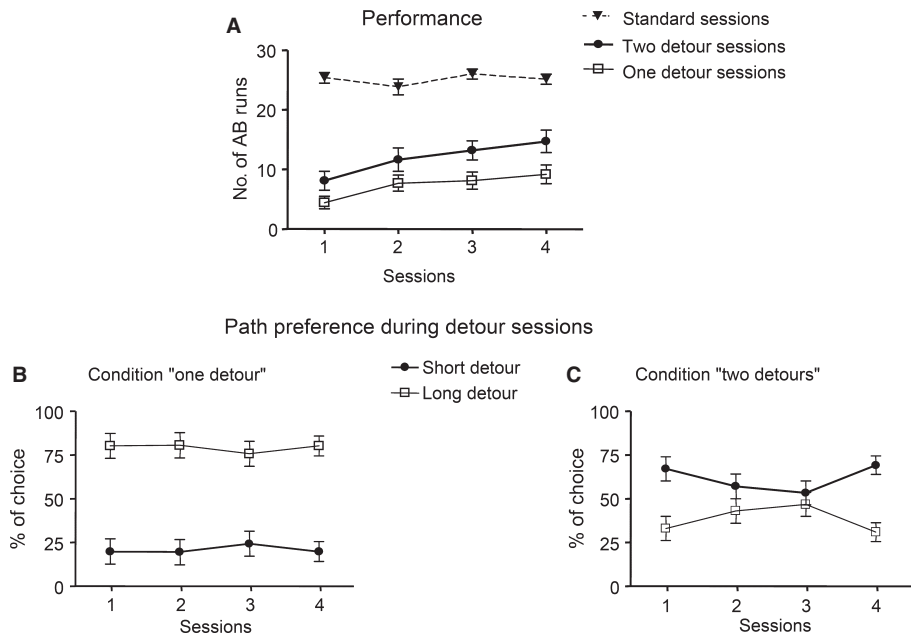

FIG. 2. Behavioral measures. (A) Performance during standard and detour sessions. Performance measured by the number of runs from location A to location B during a session improved with repeated exposure of rats to the detour. (B and C) Path preference. Path preference did not vary very much across successive exposures to the two detour situations. In condition one-detour (barrier at position P1), rats used the long detour path almost exclusively. In contrast, in condition two-detours, they preferred the short detour path in about two-thirds of the trials.

detour, 2.12 ± 0.13 runs per session; short detour, 0.63 ± 0.04; $F_{1,31} = 18.6$, $P < 0.001$) and of both detour paths in condition two-detours, with no clear preference ($F_{1,26} = 1.4$, NS).

Electrophysiological data

General characteristics of cell samples

Putative locations of recorded units were reconstructed on the basis of the final electrode placement as seen from visual inspection of brain slices under the microscope, and the experimenter's daily record of electrode number and depth. From an initial pool of 320 cells recorded from seven of the 13 rats, 214 cells [CA1, $n = 90$; CA3, $n = 87$; CA2, $n = 15$; dentate gyrus (DG), $n = 22$] were selected for further detailed analyses. The analyzed cells had to be complex-spike pyramidal cells or granule cells with waveforms > 100 μV in amplitude (baseline noise ~ 30 μV) that were repeatedly recorded across all three sessions of the recording sequence. Furthermore, they had to have a clear spatial firing pattern during the first standard session, which, to some extent, was restored during the last standard session. The above criteria excluded putative interneurons, silent or noisy pyramidal and granule cells, and cells whose across-session or intra-session firing was unreliable to the extent that no significant conclusions could be drawn from their changes in activity. Overall, 79 hippocampal cells (36 from CA1, 28 from CA3, six from CA2, and nine from the DG) had a firing field close to the barrier in the near zone (near fields); 135 other cells (54 from CA1, 59 from CA3, nine from CA2, and 13 from the DG) had a field in the far zone, away from the barrier (far fields; see Fig. 1B for definition of near and far zones).

Field changes during the detour session – effect of field location relative to the barrier

The addition of the barrier during the detour session was associated with noticeable changes in place cell activity in the near zone (close to the barrier) and with weaker changes in the far zone (away from the barrier). Figure 3 shows representative examples of field changes following addition of the barrier. Although a complete remapping was not observed in any instance, selective changes were found in most cases. Figure 4A shows mean spatial similarity (S) and mean change in firing rate (R) between sessions 1 (standard) and 2 (detour), for near and far fields. Place cell activity during the detour session was much more affected in the near zone than in the far zone, as shown by significant differences for both S ($t_{213} = -3.98$, $P < 0.0001$) and R ($t_{213} = 3.93$, $P < 0.0001$). Firing rate changes in the near zone were more consistently associated with a decrease in discharge (63% of the cells) than with an increase (37% of the cells, $\chi^2 = 5.4$, $P < 0.02$). As the sign of the changes in firing rate in the near zone was cell-dependent, there was no correlation between the rate change of individual cells and the decrease in locomotion speed induced by barrier addition ($r = 0.182$, d.f. = 78, $P > 0.10$).

Finally, no gross difference in remapping was observed between the two detour conditions (Fig. 4B), as shown by a two-way ANOVA, which failed to reveal any effect of barrier position for either near or far fields (near fields, S, $F_{1,77} = 0.34$, NS; near fields, R, $F_{1,77} = 0.01$, NS; far fields, S, $F_{1,133} = 0.66$, NS; far fields, R, $F_{1,133} = 0.15$, NS).

Field changes during detour sessions – CA1 vs. CA3

Because only CA1 and CA3 provided enough cells for more specific analyses, CA2 and the DG were not used for further comparisons between hippocampal regions. The effects seen at the level of the whole population were also observed for CA1 and CA3 cells. Thus, near fields in both CA1 and CA3 were more strongly affected during the detour session than far fields (Fig. 5A). This observation was supported by a two-way ANOVA for similarity scores pooled across the two detour conditions, which revealed a significant effect of field location (far vs. near – $F_{1,173} = 9.43$, $P < 0.01$), but no effect of hippocampal region (CA1 vs. CA3 –

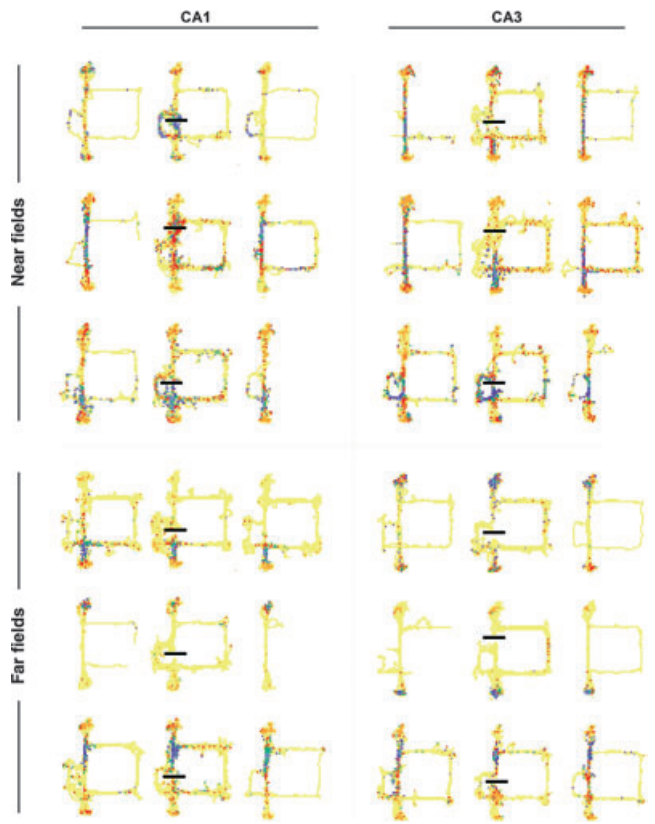

FIG. 3. Firing rate maps for place cells across the three sessions of a recording sequence. In all maps, yellow indicates no firing, and purple indicates maximum firing (orange, red, green and blue indicate intermediate firing rates from low to high). The same color code was used for all three sessions (standard–detour–standard) of a recording sequence. The black continuous line in each map indicates the location (position P1 or position P2) of the barrier during the detour session. Near fields were more strongly affected than far fields for CA1 and CA3 cells.

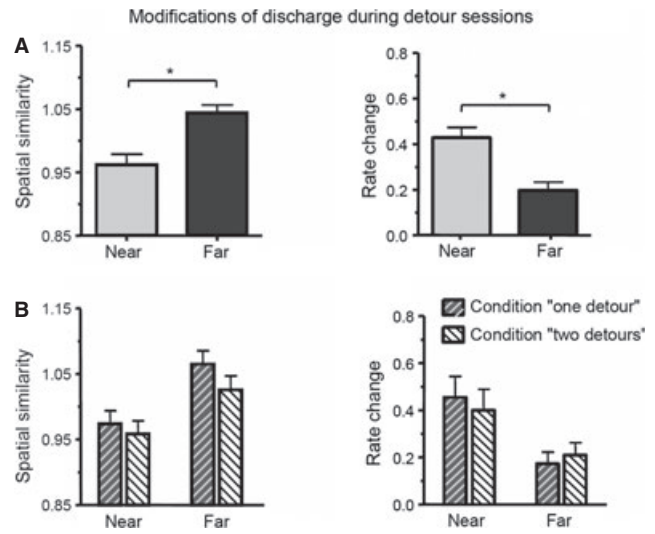

FIG. 4. Firing modifications following barrier addition. (A) Mean spatial similarity and firing rate change for near and far fields (± standard error of the mean). Both scores compare the spatial firing patterns between the initial standard session and the detour session. Near fields were more affected than far fields. *$P < 0.001$. (B) Mean spatial similarity and firing rate change scores in conditions one-detour (barrier at position P1) and two-detours (barrier at position P2). There was no effect of barrier position.

$F_{1,173} = 2.44$, $P > 0.05$), and no interaction between field location and hippocampal region ($F_{1,173} = 0.26$, NS). The same conclusion was reached when rate changes were analyzed (Fig. 5B), with a significant effect of field location (far vs. near – $F_{1,173} = 13.66$, $P < 0.001$), but no effect of hippocampal region (CA1 vs. CA3 – $F_{1,173} = 0.56$, NS), and no interaction between field location and hippocampal region ($F_{1,173} = 0.08$, NS). Finally, the lack of barrier position effect observed at the whole population level in the two detour conditions was confirmed when CA1 cells (near fields, *S*, $F_{1,34} = 0.26$, NS; near fields, *R*, $F_{1,34} = 0.94$, NS; far fields, *S*, $F_{1,52} = 0.24$, NS; far fields, *R*, $F_{1,52} = 3.14$, NS) and CA3 cells (near fields, *S*, $F_{1,26} = 0.48$, NS; near fields, *R*, $F_{1,26} = 0.93$, NS; far fields, *S*, $F_{1,57} = 0.02$, NS; far fields, *R*, $F_{1,57} = 0.56$, NS) were considered separately.

Analysis of changes in cell discharge in relation to path choice behavior

Most of the field modifications seen during detour sessions can be captured by simply analyzing the changes in discharge frequency for cells that had a field near the barrier. For this reason, we further examined the temporal time-course of near field activity both across and within detour sessions. First, the firing changes seen for near fields during detour sessions were constant across successive exposures (Table 1), much like the changes in path preference (Fig. 2B and C), but in contrast to the improvement seen in performance (Fig. 2A).

Second, much as behavior changed quickly during detour sessions, the data suggest that firing modifications also occurred rapidly. To estimate the speed of these changes, we computed a score of within-session discharge modification by dividing each session into two periods of equal duration (Fig. 6A), and found that the scores for detour sessions and for standard sessions were not different (CA1, $F_{1.35} = 0.33$, NS; CA3, $F_{1.27} = 0.06$, NS). Thus, the changes observed in cell discharge during detour sessions were established in the first half of the sessions.

Finally, some signs of hysteresis were found for CA1 but not for CA3 cells during the final standard sessions that followed detour sessions (Fig. 6B). This phenomenon must be considered in relation to the observation that use of the straight path was not perfectly restored during the final standard session, with rats maintaining, to some extent, the path preferences established during detour sessions. To measure hysteresis, we compared the changes in firing rate between the two standard sessions ($R_{1–3}$ for sessions 1 and 3) and between the detour session and the final standard session ($R_{2–3}$ for sessions 2 and 3). For CA1 cells, we found that $R_{1–3}$ was greater (0.54 ± 0.09) than $R_{2–3}$ (0.30 ± 0.10, $F_{1.35} = 4.34$, $P < 0.05$), indicating a greater difference in discharge between the two standard sessions than between the detour and final standard sessions. In contrast, the opposite pattern was observed for CA3 cells, with $R_{1–3}$ (0.18 ± 0.10) being weaker than $R_{2–3}$ (0.50 ± 0.11, $F_{1.27} = 4.35$, $P < 0.05$), indicating greater similarity between the two standard sessions than between the detour and final standard sessions. As the rat was not disconnected between sessions, electrode drift was unlikely to explain these effects. Furthermore, waveform similarity between sessions was very high (> 0.95; see Materials and methods).

Discussion

We recorded hippocampal place cells while rats traversed a familiar three-way maze for food located at the two end locations of the maze.

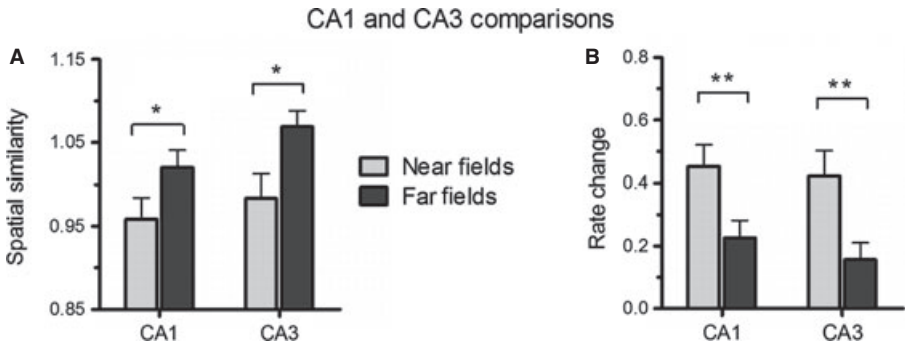

FIG. 5. Comparison between CA1 and CA3 place cells for spatial similarity (A) and firing rate change score (B) after barrier addition. In both CA1 and CA3 cells, near fields were significantly more altered than far fields (*$P < 0.01$; **$P < 0.001$), but no difference was found between the two hippocampal subregions.

TABLE 1. Place field modifications across the four detour sessions (1–4)

	Session						
	1	2	3	4	*n*	*F*	*P*
CA1							
Near	0.65 ± 0.20	0.26 ± 0.19	0.62 ± 0.23	0.62 ± 0.28	29	3.29	NS
Far	0.17 ± 0.14	0.34 ± 0.13	0.21 ± 0.16	0.18 ± 0.20	47	0.70	NS
CA3							
Near	0.59 ± 0.70	0.82 ± 0.29	0.34 ± 0.26	0.15 ± 0.29	20	0.59	NS
Far	0.25 ± 0.18	0.14 ± 0.07	0.11 ± 0.07	0.12 ± 0.07	34	0.10	NS

Firing rate changes were calculated between the initial standard session and the detour session for each successive exposure to the detour situation. There was no effect of repeated exposures on firing rate change scores for near and far fields, or for CA1 and CA3 cells.

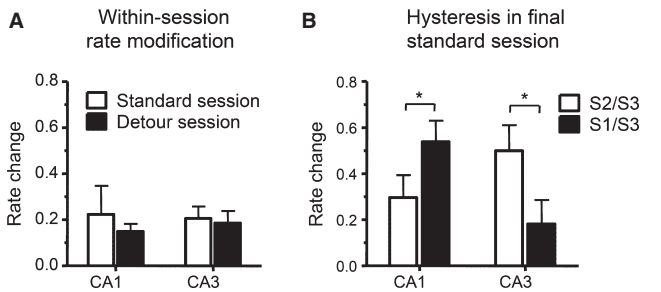

FIG. 6. Dynamics of discharge modifications. (A) Comparison of rate change within standard and detour sessions. Each session was divided into two periods of equal duration, and the rate change score reflects the change between the first half and the second half of the session. No difference was found between the within-session scores for the standard and detour sessions, suggesting that firing modifications occurred rapidly, that is, were established during the first half of detour sessions. (B) Hysteresis during the final standard session (session 3) was measured by comparing firing rate changes (R) between the two standard sessions (sessions 1 and 3) or between the detour and final standard session (sessions 2 and 3). For CA1 cells, we found that $R_{1–3}$ was $> R_{2–3}$, thus indicating hysteresis. In contrast, no hysteresis was found for CA3 cells, as $R_{1–3}$ was weaker than $R_{2–3}$. *$P < 0.05$.

In specific sessions, a transparent barrier was placed onto the maze so as to block the shortest central path between the two goal locations. Depending on where the barrier was placed, the most appropriate choice for the rat (based on topological constraints and distances) was to take either a short or a long detour path. In these sessions, rats consistently used the most optimal detour path, wherever the barrier was placed, and this preference was established very rapidly, if not immediately. This finding confirms that rats can flexibly and rapidly adapt to changes in spatial connectivity. Likewise, the firing activity of CA1 and CA3 hippocampal place cells was immediately and strongly affected in the vicinity of the barrier, but was much less affected at locations away from it. The changes seen in both CA1 and CA3 fields are best described as strong increases or decreases in firing discharge in the barrier zone. Thus, the addition of a barrier that blocked a familiar route was reflected mainly by local remapping (Rivard *et al.*, 2004). Finally, signs of hysteresis were found only for CA1 cells, in which firing was not perfectly restored during the last recording session, when the barrier was removed. Interestingly, this effect on place cells was paralleled by a similar change in behavior in the last session, during which, to some extent, the route preferences established during the preceding detour session were seen to persist.

The most remarkable findings in the present study were that rats flexibly and rapidly shifted to the appropriate route in detour sessions, thus demonstrating the existence of a spatial representation of the maze structure, and that the concomitant major change in neuronal activity accompanying this behavioral change was a local remapping in the vicinity of the barrier. Although we did not directly assess the contribution of the sensory and motor alterations induced by the barrier (for example, by including a control condition in which the barrier would still allow the rat to reach the goal), several independent lines of evidence suggest that the local changes in place cell firing can hardly be explained by simple barrier-induced sensory and motor alterations. First, insertion of a transparent barrier (similar to the one used here) in place of an opaque barrier was not seen to elicit activity changes in a previous study (Alvernhe *et al.*, 2008). Second, the change in discharge could be either an increase or a decrease in firing frequency, making it difficult to reconcile with an explanation in terms of across-cell general sensitivity to purely sensory or purely motor alterations. Third, lasting effects of the barrier were seen even when it was removed in the final recording session. Such hysteresis effects make it unlikely that firing changes can be exclusively attributed to sensory or motor effects. It is, however, possible that the transparent barrier locally affected cell firing through a more abstract representation of the physical boundaries of the apparatus. In this view, location-specific discharge results from putative cortical inputs tuned to environmental boundaries that are a certain distance and direction from the rat (Gothard *et al.*, 1996b; O'Keefe & Burgess, 1996; Hartley *et al.*, 2000; Barry & Burgess, 2007). Much as place cell firing is more affected by manipulation of local sensory landmarks than by

manipulations of distant cues (e.g. Gothard *et al.*, 1996a; Hetherington & Shapiro, 1997; Rivard *et al.*, 2004; Lenck-Santini *et al.*, 2005), boundary-tuned cells might also be sensitive to the distance to boundaries. Therefore, place cells with fields near the barrier would be more affected than those with distant fields, by virtue of being influenced by the modified input from their associated boundary-tuned cells. Although this view emphasizes that coding is based on the sensory aspect of boundaries, it is conceptually compatible with the idea that the changes in cell activity reflect the changes in spatial structure, as such boundaries necessarily constrain the animal's movements in space.

To understand better the significance of the present findings, it is necessary to discuss them in the light of our previous study, in which, rather than imposing a detour by adding a barrier in the maze run by the rat, we instead allowed the rat to take a shortcut by removing an existing barrier (Alvernhe *et al.*, 2008). Like the current study, the study of Alvernhe *et al.* showed that both CA1 and CA3 fields were strongly altered in the zone of the barrier that was manipulated, an effect that was expected on the basis of previous results (Muller & Kubie, 1987; Rivard *et al.*, 2004). In contrast to the present findings, however, the study of Alvernhe *et al.* (2008) revealed that CA3 fields were also strongly affected at locations far away from the removed barrier, that is, where neither sensorial nor trajectory changes happened. Another important difference between the two studies is that, whereas hysteresis was found to occur in the same proportions for both CA1 and CA3 cells in the shortcut study of Alvernhe *et al.* (2008), the present study revealed hysteresis in CA1 but not in CA3 cells. The fact that hysteresis can happen only for CA1 cells (and behavior) is in line with the slower time-course of adaptation of place cells in CA1 than in CA3 (Lee *et al.*, 2004b; Leutgeb *et al.*, 2006; Miyashita *et al.*, 2009), which itself suggests involvement of CA3 in the rapid encoding of new information (Lee & Kesner, 2002; Nakazawa *et al.*, 2003; Daumas *et al.*, 2005; Rolls & Kesner, 2006), and involvement of CA1 when memories have to be retained over time intervals (Lee & Kesner, 2002, 2003; Kesner *et al.*, 2005; Farovik *et al.*, 2010).

How can these two major across-study differences be explained? Because many aspects of the specific procedures were the same (e.g. apparatus size, behavioral training and performance level), we can see only two explanations. The first concerns the fundamental difference between shortcut and detour situations, as only the first leads to the availability of a brand new path. Briefly, it is possible that experiencing a new path in an otherwise familiar environment (as in Alvernhe *et al.*, 2008) induces more extended and durable modifications of the hippocampal spatial representation than updating existing paths within the explored space (as in the present study). It has been proposed that the network of CA3 neurons is able to flexibly store a large number of spatial representations influenced by the rat's experience with the varying structure of the maze (Jensen & Lisman, 1996; Muller *et al.*, 1996; Touretzky & Redish, 1996; Trullier & Meyer, 2000). According to the cognitive graph model of Muller *et al.* (1996), the CA3 place cell network would be shaped via synaptic strength changes depending on the time required by the animal to link different places. Thus, place cells representing neighbor locations would have their synaptic weight strengthened because of the short time lag required to move between them. In contrast, cells representing locations far from each other would undergo the reverse effect; that is, their synaptic weights would be weakened. The model therefore assumes that the CA3 network contains enough information to find optimal paths in open space and to compute detours and shortcuts. When new paths become available [the shortcut study of Alvernhe *et al.* (2008)], synaptic strengthening will occur between new pairs of place cells (representing graph nodes). Conversely, when new obstacles arise (present detour study), the cognitive graph will be updated by the removal (or recoding) of nodes at obstacle locations by synaptic weakening (Muller *et al.*, 1991, 1996). With regard to these putative synaptic changes, however, it is important to note that, whereas synaptic potentiation has indeed been reported between co-firing CA3/CA1 place cells (Isaac *et al.*, 2009), synaptic depotentiation has not yet been demonstrated. It is therefore not known whether the dynamics of synaptic potentiation and putative synaptic depotentiation are similar. Thus, if we assume that synaptic weakening relies on a more gradual process (e.g. passive fading) than synaptic strengthening, its propagation with the network could be more time-consuming. In other words, network synaptic weight rearrangements could follow different dynamics according both to the type of change in the environment and to the structure of the CA3 connections between place cells representing nearby or distant locations. In this hypothesis, it would therefore take more time to remove existing nodes (i.e. to weaken synaptic weights) than to add new nodes (i.e. to strengthen synaptic weights). As a result, the synaptic weight changes caused by a detour would require more time, especially for cells representing locations away from the barrier, than those caused by a shortcut, and the modifications in place cell activity following barrier manipulations would reflect this difference.

The second plausible, although less attractive, explanation of why CA3 place cells were less affected in the present detour experiment than in our shortcut experiment (Alvernhe *et al.*, 2008) is the incidence of external visual cues. Indeed, whereas the shortcut study was performed in an enclosed apparatus with 30-cm-high opaque walls, the present study relied on the use of an elevated maze, thus allowing greater perception of room distal cues. There is strong evidence that distal cues can compete with proximal intra-apparatus cues (or even dominate them) for the control of place cell activity, both in CA1 and in CA3 (O'Keefe & Speakman, 1987; Cressant *et al.*, 1997, 1999; Lee *et al.*, 2004b; Renaudineau *et al.*, 2007; Siegel *et al.*, 2008). It is thus possible that the wealth of constant distal cues may override the changes produced by alterations to the maze topology and mask their effects. Note, however, that the barrier itself, in spite of being visible at a distance in the present study, did not appear to influence very strongly the firing of place cells with remote fields.

Whatever the reason for the discrepancy between the the shortcut study of Alvernhe *et al.* (2008) and the present detour experiment, it is interesting to note that, from a purely computational point of view, local remapping is the best way to remove (and replace) a node from the putative cognitive graph described above (Muller *et al.*, 1991, 1996). The fact that remapping was of the same magnitude in both detour conditions, that is, whether one route or two routes out of the three possible routes were blocked, supports the strictly local nature of the modifications affecting place cells. The fact that CA3 and CA1 cells with fields away from the barrier were equally affected, in spite of reportedly greater internal consistency in CA3 than in CA1 (Nakazawa *et al.*, 2002; Lee *et al.*, 2004b; Vazdarjanova & Guzowski, 2004), suggests that such consistency is not a hallmark of the CA3 population. These cells can undergo both partial remapping (Markus *et al.*, 1995; Shapiro *et al.*, 1997; Lee *et al.*, 2004b; Renaudineau *et al.*, 2007; Siegel *et al.*, 2008) and more global remapping, according to the circumstances (Lee *et al.*, 2004a; Vazdarjanova & Guzowski, 2004).

Finally, the present results confirm that rats can choose optimal paths when necessary, in agreement with the cognitive map theory (Tolman, 1948; O'Keefe & Nadel, 1978). In addition, they show that removing and adding a obstacle, thus opening a new route (the shortcut study of Alvernhe *et al.*) or closing an existing route (this

detour study), are not equivalent for the place cell system, and especially for the CA3 network. We suggest that the local remapping seen in both CA1 and CA3 cells reflects updating of the local structure of the maze. More extended coding of the connections within the maze could rely on the properties of instantaneous firing during sequential replay (e.g. Gupta *et al.*, 2010), which unfortunately were beyond the scope of the present study. Further experiments should be conducted to examine sequential replay during maze alterations, to determine whether changes in possible routes may be more reflected in instantaneous firing than in overall firing.

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Abbreviations

DG, dentate gyrus; LED, light-emitting diode; NS, not significant.

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