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Behavioral Correlates of the Distributed Coding of Spatial Context

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ABSTRACT: Hippocampal place cells respond heterogeneously to elemental changes of a compound spatial context, suggesting that they form a distributed code of context, whereby context information is shared across a population of neurons. The question arises as to what this distributed code might be useful for. The present study explored two possibilities: one, that it allows contexts with common elements to be disambiguated, and the other, that it allows a given context to be associated with more than one outcome. We used two naturalistic measures of context processing in rats, rearing and thigmotaxis (boundary-hugging), to explore how rats responded to contextual novelty and to relate this to the behavior of place cells. In experiment 1, rats showed dishabituation of rearing to a novel reconfiguration of familiar context elements, suggesting that they perceived the reconfiguration as novel, a behavior that parallels that of place cells in a similar situation. In experiment 2, rats were trained in a place preference task on an open-field arena. A change in the arena context triggered renewed thigmotaxis, and yet navigation continued unimpaired, indicating simultaneous representation of both the altered contextual and constant spatial cues. Place cells similarly exhibited a dual population of responses, consistent with the hypothesis that their activity underlies spatial behavior. Together, these experiments suggest that heterogeneous context encoding (or ''partial remapping'') by place cells may function to allow the flexible assignment of associations to contexts, a faculty that could be useful in episodic memory encoding. © **2006 Wiley-Liss, Inc.**

KEY WORDS: hippocampus; place cells; context; episodic memory; behavioral analysis; navigation; remapping; cognitive map

INTRODUCTION

Episodic, or autobiographical, memory is one of the great mysteries of cognition. The ability to recollect events from their own past endows humans with an enormously useful capacity to reflect on experience, learn from it and transmit it, via language, to others of our species. Understanding episodic memory will thus shed light on an important aspect of human experience, as well as opening many therapeutic doors to the treatment of amnesic disorders such as Alzheimer's disease. To this end, neural studies of the analogue of episodic memory that is postulated to exist in other mammals (Morris, 2001) and birds (Clayton and Dickinson, 1998) potentially provide important information regarding the nature of episodic encoding.

All events occur in a place (in fact we even use the term "take place" to describe events), and the place of occurrence seems to be an important part of an episodic memory. For example, returning to a place often brings back a flood of related memories of events that happened there previously, and voluntary episodic recall in humans frequently involves first bringing to mind the location of the episode, and then recalling the sequence of events that occurred there. Thus, it seems that *where* something happened is very much interwoven with *what* happened, and recall involves retrieving both (Tulving, 1983).

It has long been known that the hippocampus has an important role in the subtype of human memory that we now, following Tulving's seminal proposal, call "episodic" (Scoville and Milner, 1957; Burgess et al., 2002). The finding that it also plays a particularly important role in spatial representation (O'Keefe and Nadel, 1978) raises the possibility that the "where" part of an episodic memory is encoded by the spatially specific hippocampal neurons known as place cells. The purpose of the present article is to focus on the functional role of the hippocampal place cells in representing the background against which events occur. How does place cell activity relate to what the animal "knows" about the world, and how might it enhance the efficacy of episodic memory encoding?

The background cues in an animal's environment are often referred to as the "context," and we have previously followed Mizumori et al. in using the term "spatial context" to describe the combination of spatial and contextual cues that make up a given environment (Mizumori et al., 1999; Jeffery et al., 2004). By our view, spatial context has two separable components: geometric (comprising information about the metric features of the environment, such as its shape and orientation) and contextual (nonmetric information such as color and odor). Together, these cues are able to tell the animal both which environment it is in, and where it is within it. Since place cells respond to both metric (for review see Barry et al., 2006) and contextual (Jeffery et al., 2004) information, and hippocampal lesions impair processing of spatial context, a reasonable hypothesis is that place cells are the site of this which/where spatial-contextual "knowledge" that the animal has about the environment. The present study aimed to explore this hypothesis.

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Relating place cell activity to an animal's knowledge (revealed by its behavior) is complicated by the finding that has emerged in recent years that place cells may respond heterogeneously to changes in the animal's environment (Shapiro et al., 1997; Tanila et al., 1997; Skaggs and McNaughton, 1998; Mizumori et al., 1999; Lever et al., 2002), and thus the representation of the environment as a whole seems to be distributed across a population of neurons. This behavior, in which only some cells are sensitive to partial changes in the environment, is called "partial remapping," and it contrasts with the "complete remapping" seen when an animal enters a completely different environment (Muller and Kubie, 1987), when all cells alter their firing patterns together. Partial remapping of place cells is hard to interpret in terms of what the animal "knows." If the environment changes, and only some cells change their behavior, does this mean that the animal is unsure of whether the environment is the same or not?

This is a hard question to answer without having a good way of assessing an animal's knowledge about the world, and the purpose of the present article was to use two naturalistic behavioral measures to try and discover something of what the animals "know" about their environment, and to see whether this correlates with the activity of place cells under the same or similar conditions. The data from the two experiments have led us to propose two hypotheses about why it might be adaptive for a representation of the environment to be distributed across a population of neurons. The first is that partial remapping allows for stimuli to be combined into so-called "configural" representations (Sutherland and Rudy, 1989), and the second is that it allows the animal to simultaneously represent both that the environment is much the same and also, at the same time, that something in it has changed. Both of these, as discussed later, may be useful in creating an index of significant events to facilitate later memory retrieval.

EXPERIMENT 1—CONFIGURAL ENCODING OF CONTEXTS

In psychological terms, a configural representation is formed when stimuli are combined so that together, they have different consequences than when not together. To behaviorally associate different consequences to different combinations of cues, it is necessary for an animal to form unique neural representations from different sets of inputs, even though some of the inputs may be common to more than one set. It has been hypothesized that one role of the hippocampus might be to support such configural learning (Rudy and Sutherland, 1989). While the evidence for this hypothesis in the general domain of all stimuli has been weak (Gallagher and Holland, 1992), it may still be true within the more restricted domain of contextual and spatial stimuli.

Motivated by our observations of partial remapping in place cells to changes in context (Anderson and Jeffery, 2003) in which place cells responded heterogeneously to combinations of color and odor, we have been led to look for parallel behavioral evidence that rats, as a whole, can form configural representations of contextual stimuli. Although such an observation would not prove that heterogeneous (partial) place cell remapping underlies this behavior, it would at least be consistent with it.

One difficulty with testing for configural representation formation in rats is that simultaneous discrimination tasks, which are traditionally used to probe perceptual processes in rodents, may induce the animals to try and apply a featural (i.e., nonconfigural) rule to solve the discrimination, even though the animals themselves may be capable of configural representation. For example, we recently found that when asked to discriminate between squares and rectangles, rats did not spontaneously configure the height with the width of a visual stimulus to extract the aspect ratio, which is the simplest descriptor of "shape" (Minini and Jeffery, 2006). Instead, they based their discrimination on unidimensional features such as height alone or width alone, even though these were less informative, and though it seems likely that rats can perceive shape as a whole. We speculated that discrimination tasks possibly force animals to try to apply featural rules even though they may have the configural representations available, which thus makes these tasks of little use in probing configural cognitive processes.

To circumvent this problem, we therefore took a different approach, which is to use the spontaneous behavior of the animals, instead, as a guide to their perceptual processes. The spontaneous behavior that we chose is rearing up on the hind legs, a behavior that rats exhibit when exposed to a novel context (Lever et al., 2006). Rats initially rear intensively when first placed in a new context (at least if it has walls), habituate as they become familiar with the environment and then dishabituate (begin rearing again) if the context is changed. Habituation and dishabituation of rearing can thus be used as a measure of the processing of context familiarity and novelty, respectively. We used this procedure, as described below, to determine whether rats would treat a new configuration of familiar context elements as a new context. The first experiment aimed to validate the method, by determining whether rats would rear to a novel context if this consisted of change of a single context element in a compound (two-element) context. The second experiment investigated whether they would show novelty-induced rearing if the context change consisted of reconfiguration of familiar context elements, rather than introduction of new ones. Such behavior would imply that rats can indeed form configural context representations, and raise the possibility that heterogeneous context encoding by place cells might be the representational substrate for such configurations.

Materials and Methods

Subjects

The experiments were carried out on 32 male Lister hooded rats (16 in each experiment), which were kept in groups of four in wire cages. The rats were all under 1 yr of age and allowed to free-feed and drink water as they required, except during the trials.

Lighting in the room where the animals were housed was kept at half strength between 7 am and 8 am (simulated

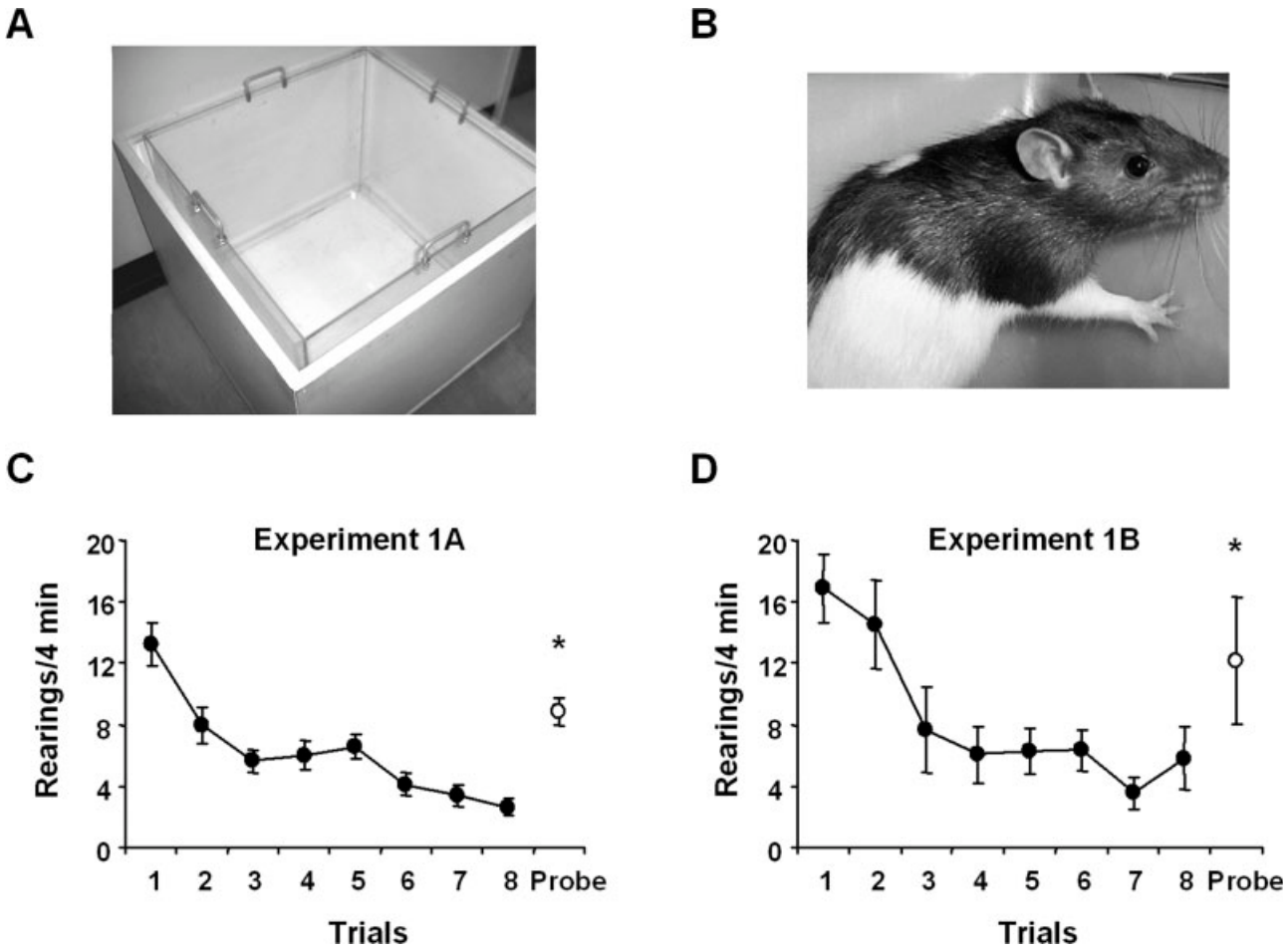

FIGURE 1. (A) The "context box" in its white configuration, showing the Plexiglas insert seated inside painted casing. (B) A rat showing novelty-induced rearing, in this case supported against a wall. (C) and (D) Pattern of rearing habituation (Trials 1–8) and dishabituation (Probe trial) in a 4-minute period after being placed in a context box, for experiment 1A (C) and 1B (D). Note the increase in rearing in the probe trials, induced by the context change. The dishabituation in experiment 1B suggests that the rats were able to form a configural representation of the color and odor of the context box, and thus detect—and respond to—a novel combination of these elements.

dawn), full strength between 8 am and 7 pm (simulated day time), half strength between 7 pm and 8 pm (simulated dusk). They were completely turned off between 8 pm and 7 am (simulated night). All procedures in this study were licensed by the UK Home Office, subject to the restrictions and provisions contained in the Animals (Scientific Procedures) Act of 1986.

Apparatus

The apparatus was the same "context box" as that used in a previously published study of place cells (Anderson and Jeffery, 2003). Briefly, it consisted of two wooden boxes, one painted black and one white (Fig. 1A), into which could be placed one of two Plexiglas inserts of dimensions 60 × 60 cm × 50 cm high. One of the Plexiglas inserts was scented with lemon and one with vanilla. This meant that four compound contexts could be created, black-lemon, black-vanilla, white-lemon, and white-vanilla. At the start of each trial, the selected insert was refreshed with the appropriate scented food flavoring by extracting 1.0 ml of the flavoring from the bottle using a clean syringe, applying this to a paper towel and then wiping the towel over the inner surface of the Plexiglas insert. The odor was reapplied before every trial, and the walls of the box were wiped in a different order each time. The scented insert was then placed inside the corresponding wooden box. The context box was situated in the center of a well-lit laboratory room, the rest of which contained ordinary laboratory furniture: a table and chair, computer, electrophysiology equipment, etc.

Procedure

The procedure for habituation and dishabituation was the same for both experiments. Rearing (Fig. 1B) was scored by two experimenters, who counted the number of times the rat reared in the first 4 min after being placed in the context box, and subsequently averaged their scores. Each rat received a total of nine 4-min exposures to the box, with an interexposure interval of only 1 or 2 min, this being the amount of time it took to prepare the next configuration of the casing and insert. After being placed in the box, the rat was free to do as it chose and was not

given any reinforcement or inducements to explore. The experimenters stood close to the box and tallied rearings on a sheet of paper, and timed the trials using a stopwatch.

Both experiments consisted of eight habituation trials followed by a probe trial. In experiment 1A, two habituation contexts were used, differing only by one of the two elements (color, $n = 8$ or odor, $n = 8$). For reasons not relevant to the current study, eight of the rats were exposed first to four trials of one context and then four of the other, whereas the other eight experienced the two contexts presented alternately. In the probe trial, the previously unchanging element was replaced with a novel one to see if the rats responded to this novelty.

In experiment 1B, the eight habituation trials consisted of four exposures to two nonoverlapping contexts: for example, black-lemon and white-vanilla. The trial types were counterbalanced across subjects and pseudo-randomly presented, with a given stimulus pair occurring no more than twice in succession. After eight habituation trials, the contexts were reconfigured so that they were now formed from a novel recombination of these now-familiar elements. Since there are two possible recombinations for a pair of paired elements, half the rats in a given group received one and half the other. The trials also had the constraint that the probe trial did not result in presentation of one of the elements for the third successive time.

Results

The results for experiment 1A are shown in Figure 1C. The rats showed a marked habituation to the two pre-exposure contexts across the exposure trials, reducing their rearing from a mean of 15.16 to 2.72 rearings in the 4-min trials. The slight peak in the middle of the habituation curve is due to the fact that half the rats had received blocked exposure to the two contexts and half the intermixed exposure. The peak is thus due to a slight novelty-induced resurgence of rearing in the former group when the relevant element was changed. That this was not more pronounced is due, presumably, to the fact that habituation was still relatively undeveloped at this stage.

When the context was changed on the ninth trial by altering one of the elements, there was dishabituation of rearing, which increased again to a mean of 9.28. A single factor repeated-measures analysis of variance (ANOVA) comparing the first, eighth, and probe trials revealed a significant effect of trial [$F(2, 15) = 40.10$, $P < 0.0001$]. Post hoc pairwise comparisons revealed a significant difference between trials 1 and 8 ($P < 0.0001$) and between trials 8 and probe ($P < 0.0001$). There was also a significant difference between trials 1 and probe ($P < 0.005$), showing that rearing, despite having increased significantly, was not as frequent in the probe as it was on the first trial of the series.

In experiment 1B, rats again habituated to the two contexts, which this time differed in both context elements. Over the eight habituation trials, rearing decreased from 16.91 to 5.78 times per 4-min trial. On the ninth probe-trial, the elements were reconfigured so that the rat was exposed to a novel pairing of familiar stimuli. Figure 1D shows that the animals showed significant dishabituation, comparable with experiment 1A, with rearing increasing again to 12.16. ANOVA revealed, as before, a significant effect of trial [$F(2, 15) = 18.10$, $P < 0.0001$]. Pairwise comparisons revealed a significant difference between trials 1 and 8 ($P < 0.0001$) and trials 8 and probe ($P < 0.01$) suggesting that the reconfigured context was perceived as novel. Again, there was also a slight but significant difference between the first and the probe trial ($P < 0.05$), showing that some habituation still persisted, despite the novel configuration of cues.

These experiments show, first, that rearing is a reasonably sensitive measure of context novelty detection in rats, and second, that—using this measure—it seems that rats are able to detect novel reconfigurations of familiar context elements. This finding is consonant with earlier findings that place cells respond individually to single elements within the stimulus compound (Anderson and Jeffery, 2003), and therefore, that the place cells in principle represent the information needed to detect stimulus recombinations. This does not, of course, prove that the activity of the place cells underlies such behavior. The only way to test this hypothesis rigorously is to manipulate the place cells by direct interventions, such as drug infusion, and show that this has effects on the animals' novelty-response behavior. Nevertheless, the above findings lend support to our speculation that one function of heterogeneous context encoding by place cells might be to allow representations of context configurations to be established.

EXPERIMENT 2—DUAL ENCODING OF STABILITY VS. CHANGE

As well as configural encoding, partial contextual remapping by place cells may have an alternative function, which is to allow place cells to simultaneously represent conflicting sets of information about a given place. This hypothesis arose from observations made in the course of a place preference experiment, described below, that had been designed to find out how rats would react to a context change made while they were executing a learned spatial navigation task.

The experiment was motivated by the previously-noticed paradox that though place cells are responsive to both metric and contextual cues, these can sometimes signal different things. Metric cues are those that provide distance and/or directional information: such as environmental boundaries (Barry et al., 2006) and directional landmarks (Goodridge et al., 1998). Contextual cues are those (usually, but not invariably, nonmetric) cues that populate the metric features with information unique to a given environment, such as color and odor (Anderson and Jeffery, 2003), texture, or even the kind of task the animal is performing (Markus et al., 1995). That metric and contextual cues can be dissociated (Jeffery and Anderson, 2003) raises the question of what happens if the cues send out conflicting signals—how do place cells resolve this conflict, and does this correlate with how the animal as a whole resolves it?

The standard view of the relationship between place cell activity and behavior is that of the "cognitive map" theory of

O'Keefe and Nadel (1978), which proposes that the activity of the place cells underlies navigational behavior: implying, in essence, that the collective activity of the place cells constitutes the animal's "knowledge" about where it is. Introducing a conflict in the cues that drive place cells, and which also drive behavior (perhaps via the place cells, but perhaps not) offers the possibility of eliciting dissociations between the neural activity and behavior, and thus the opportunity to falsify the cognitive map theory. In other words, by dissociating environmental cues, it may be possible to disconnect place cell activity from behavior. If this happened, the implication would be that either place cells are not the repository of the animal's spatial "map," or that the animal uses more than just this map to navigate with.

A previous attempt to explore the results of such a conflict found that a change in context, in the face of unchanged spatial cues, caused place cells to alter their firing patterns, apparently completely, and yet the rats continued to navigate reliably to a previously learned goal (Jeffery et al., 2003). This at first glance looks like a falsification of the place-cells = place-knowledge hypothesis—it seems to imply that the rats could not have been using their place cells to perform the navigational task, even though acquisition of the task was shown to be hippocampal dependent. However, one possible explanation for this is that the task had been so over-learned that it was no longer hippocampal dependent at the time of testing. In other words, the rats had learned a habit-based strategy: coming, over time, to use individual cues in the room to disambiguate the four corners of the box. The present experiment was designed to foil this strategy by providing a much more unconstrained environment in which, we hoped, individual cues could not be used to solve the task. Navigating in such an environment would, according to theoretical considerations, be more likely to require the hippocampus, and—if the theory is correct—the place cells.

In the place preference task used here, rats were trained, in a particular context, to visit an unmarked zone located on the surface of a 1 m diameter arena. This task ought to be hippocampal dependent, because its successful execution is completely dependent on processing of the spatial relations among distal environmental cues, and provides few or no opportunities for more cue-based, "taxon" navigation. If the cognitive map hypothesis is correct, then altering contextual cues should therefore, alter both place cell activity (i.e., induce remapping) and disrupt navigation.

Once the rats had been well trained on the place preference task, some of them were implanted for the recording of place cells. The purpose of this was to see how the cells responded to a change in context (i.e., change in the color of the arena from black to white or vice versa), and how this change related to the behavior of the animals. Other rats were implanted with injection cannulae for hippocampal inactivation, with the intention of revealing the hippocampal dependence of the task. Since this procedure proved to be ineffective, and since we lacked the ability at that time to determine whether this was because the task is hippocampal independent or (more likely) because the injections failed to inactivate the hippocampus, only the behavioral data are reported from those animals.

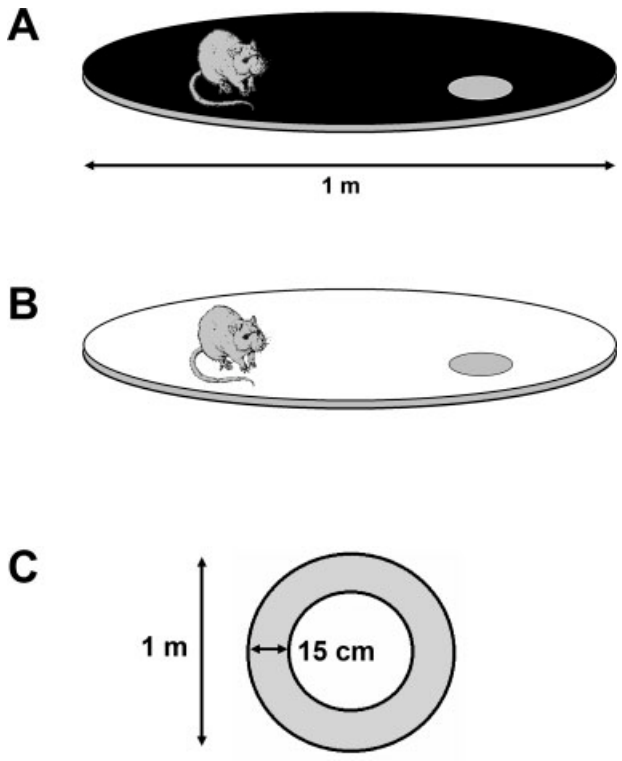

FIGURE 2. Place preference arena. (A) Rats were trained to navigate to a fixed unmarked reward zone (gray circle) in a black or white circular arena 1 m in diameter that was enclosed by a low wall. Entry to the reward zone triggered the delivery of a sucrose pellet to a random location in the arena. (B) Rats trained in the black arena underwent novel arena testing in the white arena, and vice versa. (C) Aerial schematic of the arena, showing the location of the outer and inner annuli used to measure thigmotaxis. Levels of thigmotaxis were quantified by measuring the total occupancy time, for each rat in each trial, in a 15 cm wide imaginary annulus placed at the edge of the arena. The proportion of time spent in this annulus was calculated by dividing the annulus occupancy time by the trial time.

Materials and Methods

Subjects

The subjects were eight male Lister-hooded rats (weighing approximately 250 g on arrival) obtained from the Biological Services Unit at UCL, and housed in same facility as described in experiment 1. They were fed standard rat food to maintain 90% of their free-feeding weight and were allowed unlimited access to water. Initially rats were housed in groups of four in Plexiglas cages; after surgery they were housed in separate cages to ensure their well-being. All procedures in this study were licensed by the UK Home Office, subject to the restrictions and provisions contained in the Animals (Scientific Procedures) Act of 1986.

Experimental apparatus and protocol

The rats were trained in a standard place preference protocol (Fig. 2) in a quiet room containing a rich array of cues. The task required the rats to locate an unmarked zone in a large cir-

cular arena surrounded by extra-arena cues and in which intra-arena cues had been rendered irrelevant for the purposes of navigation. In the present experiment, the rats were trained to navigate reliably in an arena of one color (e.g. black; the 'familiar arena'), then tested on their navigational ability in a differently colored arena (e.g. white; the 'novel arena'). The experiment was counterbalanced so that four rats were trained in the black floored arena (the white arena was therefore the novel context for these rats), and the other rats were trained in the white floored arena (the black arena was the novel context for these rats). Each rat within these groups was trained to approach a different reward zone. Because of time constraints, the two groups of rats were tested at different times by different experimenters. There were slight differences in the procedures: rats in the first group were trained in the familiar context and then tested in the novel context prior to surgery; they were then retrained in the familiar context and retested in the novel context. Rats in the second group were trained in the familiar context, underwent surgery, were then retrained in the familiar context and then tested in the novel context. Since all comparisons between familiar and novel environments were made within a given subject, these slight between-subject differences would not have been pertinent.

The details of the arena are as follows: it was a circular platform 100 cm in diameter (Fig. 2), which was painted black on one side and white on the other, and had a 5 cm wall all the way round on both sides to prevent the food pellets from rolling off but without obstructing the rats' view of the extra-arena cues. The arena was raised 40 cm above the floor to prevent the rats from escaping. A circular 25 cm diameter unmarked zone was allocated to each of the four quadrants of the arena, centered on the mid-point of the radius. For each rat, one of these was defined as the reward zone, one as the clockwise adjacent zone, one as the anticlockwise adjacent zone, and one as the opposite zone.

A monochrome video camera positioned directly above the arena recorded the movement of the rat in the arena by tracking an infrared light strapped to the rat by an elastic harness. The video image was passed to a tracking system (Axona, Herts, UK), which extracted the position of the LED in x–y coordinates and stored the data for later analysis. Path trajectories, the time elapsed since the beginning of the trial, and the number of entries to each zone in the arena were also stored. Entry to the reward zone, as detected by the tracking system, led to the sounding of a 150 μs 750 Hz tone together with the dispensing of a small food pellet to a random location in the arena from a pellet-hopper located in the ceiling above the arena (but with the criterion that 3 s must have elapsed since the last entry). Because of technical problems with the hopper, pellets were sometimes dispensed manually.

All rats underwent 3 days of pretraining prior to place preference training. Each group of rats was placed together in the arena for 15 min on the first day; food pellets scattered all over the floor encouraged the rats to forage. On the next 2 days, rats were introduced individually into the pellet-filled arena for 15 min. No place-preference training was conducted on these days. Beginning on the next day, rats underwent place-preference training in two 15-min trials per day. Each day the rats were brought individually into the experimental room, fitted with the harness bearing the LED, then placed in the center of the arena to begin the first trial. The rats were always placed in the same location in the arena, facing away from their reward zone. At the end of the first trial, the rat was removed and placed in a holding box at the side of the room. The arena was then cleaned, rotated (to prevent the use of olfactory cues as landmarks), and the rat began its second trial. The intertrial interval was $\sim$4 min. Rats were run in a pseudorandom order each day. Training continued until rats were performing consistently. When all rats had developed a clear preference for their designated reward zone, they each underwent two 15-min trials on the other side of the arena (i.e., in the novel color; the "novel arena test day"). Nothing other than the color of the arena differed between familiar and novel context trials.

It was hypothesized that the arena color change would cause place cells to remap, and that any detriment in place preference performance might therefore be attributable to the disruption of the hippocampal cognitive map. No detriment in performance would suggest either (a) that the task was not hippocampal-dependent, (b) that the cognitive map somehow remained intact despite the remapping, or (c) that the rats were able to rapidly relearn the task in the novel arena. To refute the last possibility, on the day after the novel arena test day, rats were tested with two additional 15-min trials in the familiar arena in a novel room with different extra-arena cues (the "novel room test day").

Behavioral analyses

Each rat's performance on the place preference task was scored using the formula

$$(E_r - \text{mean}(E_{cw} + E_{acw} + E_{opp}))/(E_r + \text{mean}(E_{cw} + E_{acw} + E_{opp}))$$

where E_r = number of entries to the reward zone, E_{cw} = number of entries to the clockwise zone (relative to the reward zone), E_{acw} = number of entries to the anticlockwise zone, and E_{opp} = number of entries to the opposite zone. This score ranged between +1 (when the rat only makes entries to the reward zone) and -1 (when the rat never enters the reward zone and makes at least one entry to one of the other zones); a score of zero indicated no preference for the reward zone over the other zones.

The trajectory of the rats in the arena was also examined by measuring the proportion of time rats spent near the edges of the platform (thigmotaxis). An imaginary annulus with external diameter equal to the arena diameter and internal diameter 30 cm less was positioned over the arena and the amount of time rats spent within this 15 cm circular corridor in each trial was calculated (Fig. 2C). The proportion of the trial time spent in this annulus was calculated by dividing the annulus occupancy time by the total trial time to give a score which ranged between 0 (no time spent in the annulus) and +1 (all trial time spent in annulus). This measure also indicated whether or not

the rats responded to the novel stimuli during testing (arena and room).

Surgery

Two rats from each group were unilaterally implanted with tetrodes for the purpose of recording hippocampal place cells; the other two rats from each group were bilaterally implanted with stainless steel cannulae to permit infusion of an inactivating agent into the hippocampus (though, as mentioned above, the infusion data were noncontributory: thus, these rats served as sham controls for the behavioral procedure). One rat did not survive the surgery and therefore data for this rat are included in the first training stage only.

During surgery, rats were anesthetized with isoflurane and oxygen, and given a subcutaneous injection of antibiotic (enrofloxacin). They were mounted in a stereotaxic frame, the scalp was shaved and cleaned, and the skull was exposed by means of a midline incision followed by cleaning. Designated rats were implanted with tetrodes mounted on a microdrive, others with stainless steel cannulae. The tetrodes were implanted in the right hemisphere 3.8 mm posterior to bregma, 2.5 mm lateral to the midline, and 1.5 mm ventral to the brain surface; cannulae were implanted bilaterally at the same coordinates. The injection cannulae extended 1.1 mm below the tip of the implantation cannulae and were aimed at the middle of the hippocampus, between CA1 and CA3. Jewellery screws and dental acrylic were used to securely attach the microdrive or cannulae to the skull. At the end of surgery, rats were given an intramuscular injection of an analgesic (buprenorphine) and returned to their home cages. Rats recovered for at least 5 days before training recommenced.

Place cell recording and analysis

Four of the rats were implanted with tetrodes mounted on a microdrive that allowed the tetrodes to be advanced together through the brain in steps as small as 25 μm. To obtain place cell recordings, each rat was screened daily after recovery from surgery. Full details of the screening and recording procedure have been described previously (Anderson and Jeffery, 2003) and will only be given briefly here. Before the first trial of the day, rats were connected to the recording equipment (Axona, Herts, UK), and activity on the tetrodes was monitored for both complex spike activity and ripples, both reliable indicators of intrahippocampal electrode positioning. If neither sign was evident, the microdrive was advanced by 25–200 μm per day, and the trials were run without place cell data recording. Because of the inherent difficulty in obtaining place cell recordings at the same time as maintaining place preference performance, no strict criteria signaled the end of training and the beginning of testing. Instead rats within each group were trained for the time it took to obtain stable place cells in as many rats as possible. Once place cells were detected, recordings were made in the familiar arena on what became the final day of training, followed on the next day by recording in the novel arena. Cells were not recorded in the novel room trials. For unknown reasons, no place cells at all could be recorded in two of the four rats implanted with tetrodes; once it became clear that no cells would be obtained from these rats, they were tested in the novel arena without further recordings.

Single neuron data were isolated using cluster cutting software (Tint: Axona, Herts, UK). Firing rate maps were then constructed by dividing the arena floor into square pixels of side $\sim$2 cm: the firing rate for a given cell in each pixel was determined by dividing the number of spikes in that pixel by the amount of time the rat spent there. The firing rate maps were smoothed using an algorithm that replaced the value in each pixel with the average of the value in that plus the adjacent eight pixels. Place fields were visualized as contour maps with five levels, each level representing a 20% portion of the peak firing rate for that map. Putative interneurons and complex spiking cells were discriminated on the basis of spike shape, firing rate, and place field size.

Additional analyses were conducted using programs custom-written in Matlab (The MathWorks, Natick, MA). A cell was defined as having a place field if its peak rate after smoothing (taken from the pixel with the highest rate) was $\geq$1 Hz and the number of spikes in its cluster was $\geq$20. Place fields were assessed for remapping or nonremapping using pixel-to-pixel correlations between place cell firing rate maps (for details see Anderson and Jeffery, 2003). Only pixels in which the cell had fired in at least one of the maps entered the correlation, to prevent artificially high correlations from being generated by large numbers of zero-zero correlations. Cells classed as 'remapping cells' had differences between mean same and different condition r values of $\geq$0.4 (see Results); nonremapping cells typically had values close to zero (for rat 2, only those place fields that remained stable in the same-condition trials were included in this analysis).

RESULTS

Eight rats were trained in the place preference task, but the rat that died during surgery only contributed training data. The first group of rats was trained for 42 days and was then tested in the novel arena and, on the following day, in the novel room; this was then followed by surgery and recovery, then a further 11 days of retraining and then retesting in the novel arena. The second group of rats was trained for 33 days prior to surgery. After surgery and recovery, the rats were retrained for 19 days, and then tested in the novel arena and, on the following day, in the novel room.

The novel arena behavioral data for the first group presented here were obtained in the first exposure (i.e., prior to surgery); the place cell recordings were made during the second exposure.

Behavioral Analysis

Figure 3 shows the mean ($\pm$, the standard error of the mean, SEM) for all rats of both the place preference and thigmotaxis

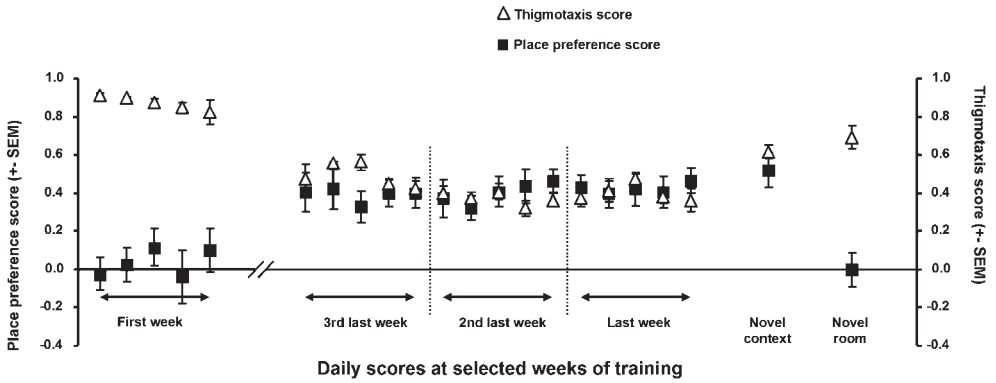

FIGURE 3. Behavioral results of place preference training. Place preference performance (black squares) and amount of thigmotaxis (white triangles) are displayed together. During the early stages of training, rats displayed little preference for their reward zone and showed a high degree of thigmotaxis; as training progressed, rats showed better place preference performance and less thigmotaxis. An interesting dissociation occurred in the novel arena and novel room; in both conditions rats responded to the novelty with increased thigmotaxis and yet only in the novel room did they show chance place preference performance.

measure for the first week of training, the three weeks of training prior to testing, and the testing in the novel arena and then in the novel room. Rats initially, as expected, showed no preference for their reward zones and high levels of thigmotaxis. By the end of training, place preference performance levels rose compared with the first day of training, while levels of thigmotaxis fell. Scores on the first trial for the pertinent training days (first and last) and testing days (novel arena and novel room) are displayed in Figure 4.

Place Preference Analysis

There was a main effect of day (F (1.86, 11.12) = 16.94, $P < 0.001$, Greenhouse-Geisser corrected) on place preference performance. Planned paired t test comparisons revealed a significant difference between first training day and last training day ($P < 0.005$), no difference between the last training day and the novel arena day (ns), and significant differences between last training day and novel room day ($P < 0.001$), and between novel arena day and novel room day ($P < 0.01$). This shows that the rats learned to navigate to the rewarded zone over the course of training, continued to navigate there successfully when the arena was changed in color, and did not transfer this preference to a novel room (thus ruling out rapid relearning as an explanation for the transfer to the novel arena).

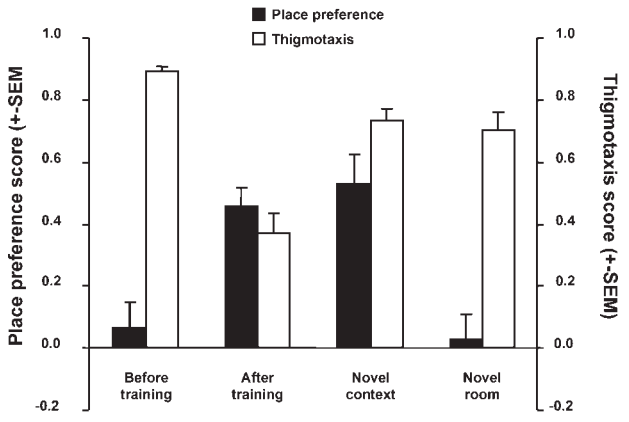

FIGURE 4. Averaged place preference and thigmotaxis scores for pertinent training and testing days. See Results section for details of the statistical analysis. Note the presence of thigmotaxis together with preserved navigation in the novel-context trial, contrasting with continued thigmotaxis but impaired navigation in the novel-room trial.

Thigmotaxis Analysis

There was also a main effect of day (F (3, 3) = 29.65, $P < 0.05$) on the thigmotaxis score. Planned paired t test comparisons revealed significant differences between first training day and last training day ($P < 0.05$) and between last training day and novel arena day ($P < 0.05$) but not between the novel arena day and novel room day. Thus, changing the contextual cues on the arena caused a large increase in thigmotaxis, as much as changing to a novel room altogether, despite the fact that the rats were continuing to navigate successfully in this new context.

In summary, there was an interesting dissociation between place preference performance and thigmotaxis in the novel arena and novel room conditions. In the novel arena, place preference performance was unchanged compared with the final day of training in the familiar arena, and yet thigmotaxis was increased, i.e., this increased thigmotaxis occurred despite the fact that the rats continued to prefer the rewarded zone over the other zones. In the novel room, however, while thigmotaxis was again higher than on the final training day, place preference performance fell to chance levels. The last result rules out the possibility that the rats were able to quickly learn a novel location, supporting the contention that preservation of performance in novel arena in the familiar room was due to preservation of the underlying place representation, on the basis of the unchanged spatial cues. Figure 5 displays representative paths and occupancy rate maps from pertinent phases of the experiment.

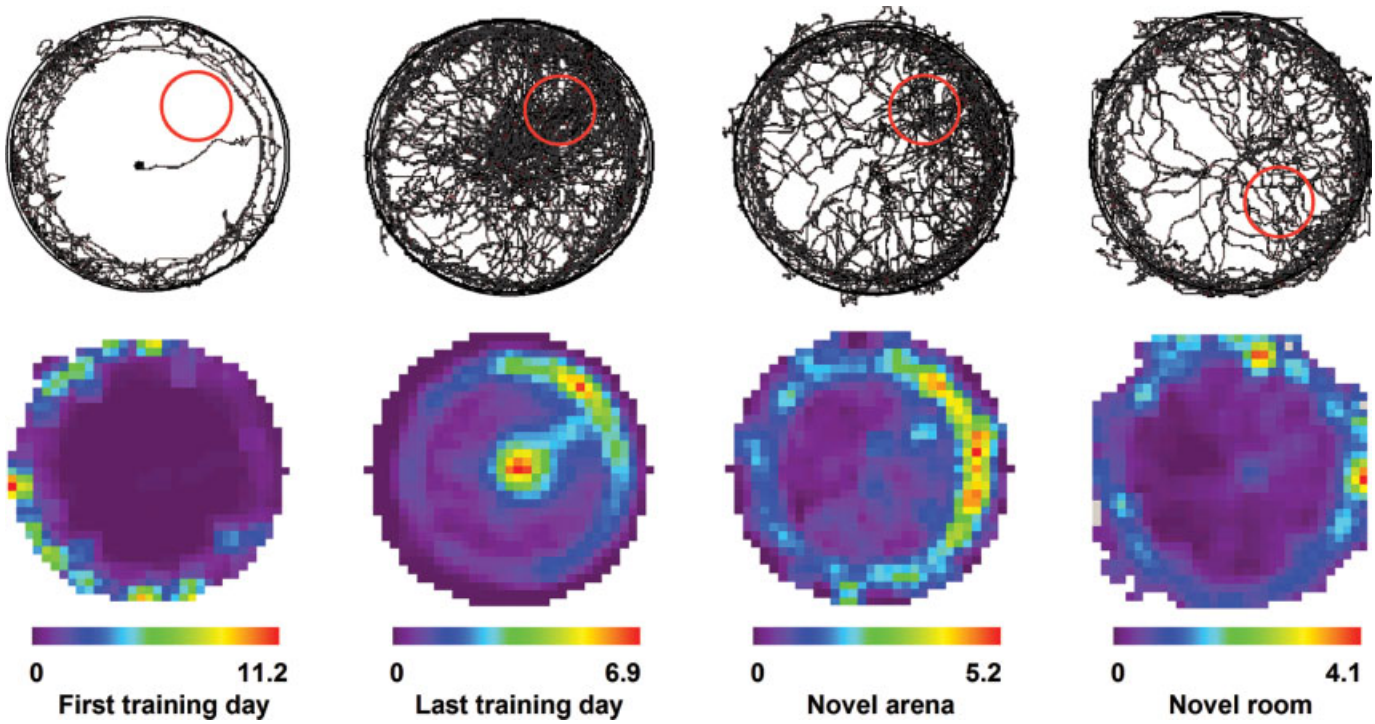

FIGURE 5. Rat trajectories (upper panels) and occupancy rate maps (lower panels) from representative trials on pertinent training and testing days. On the trajectory maps, the large circle indicates the boundary of the platform, the black line shows the path of the rat during the 15 min trial and the red circle indicates the rewarded zone (altered in the new room). Early in training rats displayed high levels of thigmotaxis (boundary-hugging), while by the end of training, rats covered most of the arena floor, spending more time in the reward zone. In the novel arena and novel room trials, thigmotaxic behavior returned markedly. Performance in the novel arena trials was unaffected. It appears that rats were able to leave the platform perimeter at the correct location in order to enter the reward zone. By contrast, place preference performance in the novel room was at chance levels, ruling out rapid relearning as an explanation for preserved performance in the altered context/familiar room.

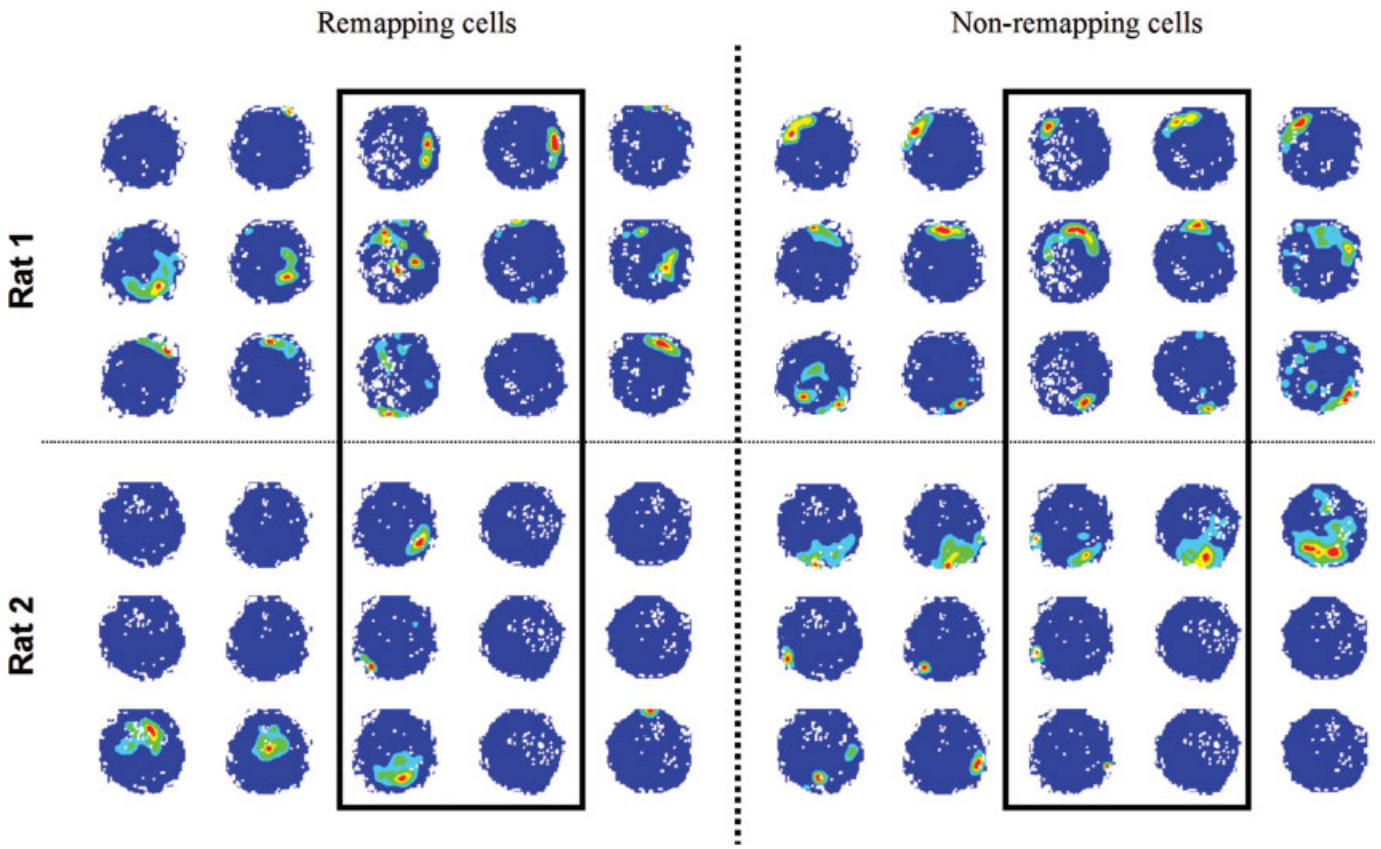

FIGURE 6

Thigmotaxis might be expected to, nevertheless, have some deleterious effects on the navigation accuracy measure. Indeed, correlation of the two scores did reveal a significant negative relationship between place preference and thigmotaxis (-0.67, $P < 0.01$), with the propensity for rats to circle the arena being in inverse proportion to the number of visits to the rewarded zone. That the rats nevertheless continued to spend significantly more time in the rewarded zone lends even stronger support to the notion that the processing of spatial cues in this task remained intact after the context change.

Place Cell Analysis

All recordings were made from electrodes located in the CA1 region. Only cells meeting the criteria for place cells (reliable spatially localized firing with a peak rate $>$ 1 Hz) were considered. Nineteen cells were isolated in total (7 from one rat and 12 from the other), of which 12 (6 from each rat) were place cells. The firing fields from these cells are shown in Figure 6. Both place-cell sets showed stable firing in the two trials before the novel arena trial. In response to the novel arena, a contextual change that would be predicted to induce place cell remapping, both sets of cells showed partial remapping, i.e., some place cells remapped, some did not. In each case, it was a 50-50 split, with 3 cells remapping, and 3 cells not remapping.

Pixel-to-pixel correlations between the firing rate maps in the same condition trials (i.e., familiar–familiar or novel–novel correlations) for all cells showed a mean r value of 0.61 ($\pm$, 0.07 SEM) for rat 1, and 0.42 ($\pm$0.17 SEM) for rat 2; correlations between the firing rate maps in different condition trials (familiar-novel correlations) for nonremapping cells only showed a mean r value of 0.61 ($\pm$0.10 SEM) for rat 1, and 0.39 ($\pm$0.08 SEM) for rat 2 while for remapping cells the mean r values were 0.09 ($\pm$0.04 SEM) for rat 1, -0.06 ($\pm$0.06 SEM) for rat 2. Thus, the differences between the mean same and different condition r values for nonremapping cells were 0.00 for rat 1 and 0.03 for rat 2; differences between mean same- and different-condition r values for remapping cells were 0.52 for rat 1 and 0.45 for rat 2.

This splitting of the place representation, whereby some cells remapped and some did not following a context change, offers itself as a possible substrate for the "splitting" of behavior exhibited by the rats, in which the rats simultaneously registered contextual novelty but persisted in their previously learned spatial behavior. As discussed below, this may be illustrative of an adaptive feature of heterogeneous place cell encoding: namely, that it allows the association of different items of information with different subsets of the place representation.

FIGURE 6. Place fields from cells recorded from two rats on exposure to the novel context. Firing rate maps are shown (contours at 20% steps of the peak firing rate) for two trials in the familiar arena on the day before testing, two trials during testing in the novel arena (outlined) and one final trial on the subsequent return to the familiar arena on the following day. Place cells in the two rats show partial remapping in the novel compared with the familiar arena, with three remapping and three nonremapping cells recorded from each rat. Place cells in rat 2 displayed partial remapping in the first exposure compared with pretesting familiar trials, and were unstable in the second trial in the novel arena (barring cell 5), which may possibly represent ongoing plasticity of the new representation.

DISCUSSION

The present experiments were designed to explore the interaction between contextual and spatial cues, with regard both to how they influence behavior and to how they influence place cell activity. The particular question of interest was: why do place cells show heterogeneous encoding of context—that is, partial remapping—in response to partial changes in contextual cues? What are the functional consequences of partial remapping?

We used two naturalistic measures of context processing in rats: rearing, in a nongoal directed situation, and thigmotaxis, when the animals were trying to navigate to a goal. Using rearing, we found that rats would habituate to repeated presentations of a familiar context and then dishabituate again if the context was changed. We then found that such dishabituation would also occur if the context change consisted of a reconfiguration of familiar context cues. This indicates that the rats were able to form a configural representation of the contextual stimuli, i.e., they "knew" which color and odor had previously occurred together, and thus recognized that the recombination was novel. This observation accords with previous observations of place cells in the same apparatus (Anderson and Jeffery, 2003), in which different place cells were found to respond to different subsets of the context elements, so that population activity was different for the recombined contexts even though the elements themselves were not novel. We suggested that this distributed encoding of context allows for configural context encoding, which could be useful to an animal in, for example, enabling it to disambiguate contexts that have a number of elements in common.

The second experiment in the present study was designed to look at the effect of dissociating contextual and spatial cues to test a prediction of the cognitive map theory. This theory proposes that place cell activity underlies navigation. If so, then altering this activity should alter navigational behavior. Since place cells are known to respond to both spatial and contextual cues, and yet only spatial information is (theoretically speaking) needed for navigation, then using a contextual cue manipulation to alter place cell activity should, if the theory is correct, alter place behavior.

We had hoped to induce complete place cell remapping (alteration of the entire pattern of place cell activity) by manipulating the context of the navigation arena, but this did not occur: about half of the cells were unperturbed by the manipulation. Although this was initially disappointing, in retrospect it seems that this may have been an inevitable outcome if the

place cells do indeed underlie an animal's spatial knowledge. Given that we provided the rat with sufficient spatial cues to continue navigating with, it is possible that under these circumstances, complete remapping is impossible, i.e., the very information that enables the rat to navigate to the same place necessarily also provides the place cells with enough information to retain some of their fields. In fact, one could go further and propose that this spatial information enables continued navigation *by* keeping some of the place fields unchanged. If this is true, then the only way to induce complete remapping in the place cells would have been to alter so much environmental information that the rat could no longer navigate, either. Thus, the present results can be viewed as being consistent with cognitive mapping theory. Our interpretation of the results is that by splitting their representation in the way that they did, the place cells were able to encode different aspects of the same environment, using the same population of neurons. Thus, with a distributed code, it is possible to simultaneously represent, for example, both that some aspects of the environment have changed and that some have remained the same.

A similar proposal was recently advanced by Leutgeb et al. (2005), who observed that local changes to an environment (such as to color, what we have here called "contextual") tended to induce changes only in firing rate, particularly in CA3 neurons, and they proposed that this "rate remapping" could allow the discrimination of different events occurring at a given location. By contrast, global environmental changes (moving the recording apparatus to a different room, a change that we would call "metric") induced changes in field location, perhaps implying recruitment of a new spatial map. We generally do not see rate remapping in response to change of local cues, and did not in this experiment either, but this may be because our recordings are from CA1 neurons. Our interpretation of the rate/location dichotomy is that rate remapping reflects a modulation of drive, or "confidence," of a particular field, whereas location remapping reflects a switch to a different field (via different inputs). We have previously proposed that the function of the context cues is to, as it were, set this switch (Jeffery et al., 2004).

Although our results are consistent with the cognitive map theory, it should be noted that they by no means prove it. It is possible that the rats, after the prolonged training required to reach above-chance performance, had managed to develop a habit-based strategy for locating the goal area, and were no longer using the place cells at all. This is one of the possible explanations for why a previous study of ours found that even complete place cell remapping was associated with only a minor decrement in navigational performance (Jeffery et al., 2003). Although we attempted to thwart this in the present study by using an open-field arena, in which habit-based navigation is much harder to acquire, this possibility could only be completely ruled out by disrupting hippocampal activity after the animals had learned the task, to see whether they were now impaired (if the task was still hippocampal dependent) or if they could still navigate (suggesting use of another system, such as striatum). Such a test was the motivation behind the implantation of injection cannulae in some of the animals, as it happened, the injections, as far as we could tell, were ineffective. We lacked the means to distinguish, however, whether this was because the hippocampus was not successfully inactivated or because it was no longer needed for the task. This issue needs to be explored in future experiments because the interplay between hippocampal and nonhippocampal navigation systems is complex, and without knowing which system the animals are using at any given moment, it is hard to draw conclusions about the concomitant neural activity and how it relates. Until then, the present results must be regarded as merely being "not inconsistent" with cognitive mapping theory. Nevertheless, the observation of a representational split (partial remapping) in the place cells that paralleled the split behavior of the animals is suggestive and deserves further study.

Some Speculations About the Role of the Spatial Context Representation in Episodic Memory

The above experiments show that the place cell representation of spatial context has properties consistent with those of the spatial-contextual behavior of the animals, suggesting that the one may underlie the other. Given that the place cells have these properties, why, then, is the hippocampus so crucially important in human (and probably animal) episodic memory? It is hard to link the activity of place cells, whose firing is predominantly driven by metric and contextual cues and is remarkably stable over long periods of time, to the encoding of episodes, which by their nature involve many different kinds of stimuli and are fleeting, one-off occurrences. Do place cells also have a role in the encoding, storage and/or retrieval of episodic memories?

A number of studies have, indeed, reported place cell activity occurring in association with important events. In an early series of studies, Berger and Thompson showed that hippocampal neurons in rabbits developed conditioned responding to paired presentations of a tone with a corneal airpuff (Berger et al., 1976). Eichenbaum and colleagues have reported that hippocampal neurons fire in response to behavioral events such as cue-sampling and goal approach (Eichenbaum et al., 1987; Wiener et al., 1989; Wood et al., 1999), and a number of studies have found activity of place cells that seems to be related to the goal area in an environment, a place where important events (goal discovery) repeatedly occur (Breese et al., 1989; Wiebe and Staubli, 1999; Hollup et al., 2001). Intriguingly, in-field modulation of place fields by events was reported by Moita et al. (2003), who found an increase in place cell activity evoked by an auditory conditioned stimulus when the animal was in the cell's place field, but not when it was outside it.

The above studies are certainly suggestive of the possibility that place cells encode events. However, it is of potential significance that these studies have all involved events which occur, repeatedly, at the same place in the environment. Thus, it might be possible to make the argument that the events had, by virtue of their spatial constancy and repetition, come to

form part of the descriptor of the place, in other words, part of the context. It is certainly the case that place cells are often *not* active in event-rich situations: for example, even in environments in which important (i.e., behavior-modifying) events are occurring, if these are not occurring in a constant location then place cells rarely show much activity outside the zone of their own firing fields (e.g., Jeffery et al., 2003). Thus, if place cells encode events too, then such activity must be sparse. This may not be unreasonable, however, given the number of events that the hippocampus must—if it encodes events at all—encode over the lifetime of an animal.

The above notwithstanding, an alternative, and perhaps more plausible, possibility is that the role of the hippocampus is not to encode the events themselves, but rather to form a link, or index, between the representation of the place in which the events occurred and the memory traces of these events elsewhere in the brain (presumably neocortex). This would mean that when the animal returned to that place, and reactivated that representation, the memory itself would also be reactivated. Such memory-index theories have been proposed a number of times, though first and most elegantly by Teyler and DiScenna (1986). The role of the hippocampus in their model is to bind together the disparate elements of an experience, which belong with each other by virtue of having occurred at the same time and place. Burgess and co-workers (Burgess, 2002; Burgess et al., 2002) have taken this a step further, and proposed that the hippocampus is also required for the imposition of a viewpoint onto the retrieved memory, so that the event is able to be re-experienced, as it were, from a particular viewpoint.

To conclude, then: studies of place cells in rats suggest a role in the encoding of spatial context, a proposal that is supported by correspondences such as the ones we demonstrated here, between the properties of the place cell representation (partial remapping) and the properties of spatial-contextual behavior. It is suggested that this representation, as well as providing information useful for navigation, also serves as an index of events that occurred there, with the memory traces of the events themselves being stored in neocortex. When the animal returns to a place these memories are thus reactivated. In humans, returning to the place may be a mental rather than physical event; in this case, the hippocampus can be used to impose a viewpoint on the mental image, so as to enable reconstruction of the locations of salient object and people in the memory. To the extent that this is the case, recall of episodic memory is not a veridical replay of the original sensory stream, but is really a reconstruction of the events comprising a sensory experience. The heterogeneous, distributed encoding of context, contributed by the place cells, may allow flexibility in how associations are made between contexts and their associated events.

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