

Context-specific acquisition of location discrimination by hippocampal place cells

Robin M. A. Hayman, Subhojit Chakraborty, Michael I. Anderson and Kathryn J. Jeffery

Department of Psychology, University College London, 26 Bedford Way, London WC1H 0AP, UK

Keywords: context, memory, navigation, plasticity, rat

Abstract

The spatially localized firing of rodent hippocampal place cells is strongly determined by the local geometry of the environment. Over time, however, the cells can acquire additional inputs, including inputs from more distal cues. This is manifest as a change in firing pattern ('remapping') when the new inputs are manipulated. Place cells also reorganize their firing in response to non-geometric changes in 'context', such as a change in the colour or odour of the environment. The present study investigated whether the new inputs acquired by place cells in one context were still available to the cells when they expressed their altered firing patterns in a new context. We found that the acquired information did not transfer to the new context, suggesting that the context inputs and the acquired inputs must interact somewhere upstream of the place cells themselves. We present a model of one possible such interaction, and of how such an interaction could be modified by experience in a Hebbian manner, thus explaining the context specificity of the new learning.

Introduction

Pyramidal cells in the rodent hippocampus show spatially localized firing, and have been named 'place cells' (O'Keefe & Dostrovsky, 1971), with the regions of activity called 'place fields'. Following a change to the environment, place cells alter their firing patterns, sometimes dramatically. Such changes have been called 'remapping' (Muller & Kubie, 1987), and indicate that alterations in the environment are reflected by changes in the hippocampal representation. These observations suggest that the cells collectively form a map-like representation of the environment (O'Keefe & Nadel, 1978). Because the hippocampus has long been implicated in spatial learning, the question of whether and how its map becomes modified by experience is of great importance.

Recordings in simplified environments have shown that a strong input to place cells is provided by geometric inputs from the immediate boundaries of the environment (O'Keefe & Burgess, 1996), so that manipulation of these boundaries causes cells to change their firing by shifting their place fields, or changing their shape. This type of remapping (which we have elsewhere called 'geometric remapping'; Anderson *et al.*, 2003) can be contrasted with the type of representational change that occurs when the recording environment is subjected to non-spatial changes, such as changing the odour (Anderson & Jeffery, 2003) or colour (Bostock *et al.*, 1991; Kentros *et al.*, 1998; Anderson & Jeffery, 2003) of the walls. In this kind of remapping, the cells typically respond by switching off their firing in the location of the original field and/or activating a field in a different place. The kinds of changes that cause this type of remapping to occur are many and varied, and similar stimulus changes are often referred to in the behavioural literature as 'contextual'. By contrast with geometric remapping, such contextual remapping causes two different represen-

tations to be instantiated at different times in the same physical and geometric environment. We note here that geometric changes to the environment can sometimes cause place cells to switch their fields on and off (Lever *et al.*, 2002); we have argued elsewhere (Anderson & Jeffery, 2003; Anderson *et al.*, 2003) that this may occur when the geometry of the environment is itself fed back into the hippocampus as a contextual cue.

More recently it has been found that place cells can, with repeated experience, acquire the ability to discriminate two similar recording boxes differing in small details of their geometry (Lever *et al.*, 2002) or location (Jeffery, 2000). As with contextual remapping, this acquired discrimination consists of a switching on/off of place fields, and suggests a reorganization of the inputs to place cells such that place cells develop sensitivity to the stimuli that distinguish the two environments. The present study investigated whether this discriminative ability, acquired in one context, would transfer to an unfamiliar context. Place cells were recorded in alternating trials in two adjacent, identical environments, a procedure that gradually induces remapping of some cells (Skaggs & McNaughton, 1998; Jeffery, 2000). When discrimination between locations was evident as a remapping, the context of the environments was altered by changing the colour of both boxes from black to white, or vice versa to induce a new place cell representation, and alternating trials were then continued. We predicted one of three possible consequences. First, place cells might continue to discriminate locations, suggesting the discrimination is a property of the spatial mapping system as a whole. Second, perhaps only those cells that were active and/or discriminated locations in the familiar context would discriminate in the unfamiliar context, suggesting that discrimination was a function of prior activity/learning in the familiar context. Third, place cells in the new context might fail to discriminate the two locations at all. We found the last of these, leading us to propose a model of context-dependent location discrimination in which the acquired discriminative inputs interact with the context inputs upstream of the place cells.

Correspondence: Dr K.J. Jeffery, as above.
E-mail: k.jeffery@ucl.ac.uk

Received 2 May 2003, revised 17 September 2003, accepted 24 September 2003

Materials and methods

Subjects

Four adult male Lister Hooded rats (395–460 g) were housed individually [11 : 11 light : dark, with 1 hour ($\times 2$) simulated dawn/dusk] on a food-restricted diet (sufficient to maintain 90% of free-feeding weight) with *ad libitum* access to water. Upon arrival at the laboratory, animals were handled individually each day for at least 1 week prior to surgery. All procedures were licensed by the UK Home Office subject to the restrictions and provisions contained in the Animals (Scientific Procedures) Act 1986.

Electrodes and microdrives

Four tetrodes (Recce & O'Keefe, 1989) were each constructed from four interwound 25- μm diameter platinum–iridium wires (California Fine Wire, USA). The tetrodes were held in a microdrive assembly (Axona Ltd, St. Albans, UK) that allowed them to be lowered or raised with one full turn of the screw equal to an increment of 200 μm dorso-ventrally. Just prior to commencement of surgery, three of the tetrodes were cut level with each other; the other was staggered back by approximately 1 mm. This electrode would act as a reference, whilst the other tetrodes recorded hippocampal cell responses.

Surgery

Before the start of the experiment the rats were surgically implanted with moveable microelectrodes in order to record multiple neurons as follows. Anaesthesia was induced with 0.2 mL midazolam and fentanyl/fluanisone (2.7 mL/kg *i.p.*) and was maintained with isoflurane and oxygen (3 L/min). After a surgical level of anaesthesia was achieved, animals were placed in a stereotaxic frame, with lambda and bregma in the horizontal plane. The eyes were covered with Vaseline to prevent corneal damage during surgery and the body was covered with bubble-wrap to maintain body temperature. The rats were monitored throughout the surgery to ensure a satisfactory level of anaesthesia by frequent inspection of reflexes and respiration. The scalp was incised and retracted to expose the skull surface, and seven 1-mm burr holes were drilled through the skull for placement of jewellers' screws to hold the microdrive assembly in place. One screw had a ground wire soldered to it to enable the rat to be electrically grounded. A 2-mm diameter trephine hole was made above the right hippocampus at stereotaxic coordinates 3.9 mm posterior and 2.6 mm lateral to bregma. The dura was then retracted to expose the cortical surface and the electrode wires were introduced to a depth of 1.5 mm from the surface of the dura. A metallic sleeve was pulled down over the remaining exposed wire. Dental acrylic was applied to secure the microdrive assembly in place on the skull. Antibiotic neomycin powder was applied around the edges of the assembly and the animal was given 0.1 mL enrofloxacin (*s.c.*) and 0.1 mL buprenorphine (*i.m.*) postoperatively and placed in a cage to recover. The rat was periodically monitored until it awoke. All animals were given at least 1 week to recover following surgery.

Recording protocol and manipulations

Initially, the floors and walls of the two box environments, North and South, were always the same colour (the 'familiar context': black for three rats and white for one rat). Alternating 4-min trials were run between the two locations, always starting in the North position. A minimum of at least three trials in each location were run each day; usually eight trials in each location were run (a total of 16 trials overall). Between each trial the walls and floor of the environments were interchanged so the rats experienced a unique configuration of local cues (marks on the walls, olfactory cues on the floor, etc.) during

each trial. The purpose of this manipulation was to ensure that the local cues would not be a valid reference for discriminating location. Once remapping between the two locations had occurred, the colour of the walls and floors in both box locations was changed to the other colour (the 'unfamiliar context'). The boxes remained in the same absolute location within the experimental room. Alternating 4-min North/South trials were run, as before, and walls and floors were again interchanged between each trial (Fig. 1).

Single-unit recording

Animals were handled regularly for at least 2 days after the 1-week recovery period prior to commencement of recording. On recording days, the rats were connected to the recording equipment (Axona Ltd) via lightweight wires and a socket that connected to the microdrive plug. The potentials recorded on each of the 16 electrodes were passed through AC-coupled, unity-gain operational amplifiers mounted on the rat's head, and led to multi-channel recording equipment (Axona Ltd), where the signal was amplified and filtered. For unit recording, the signal was amplified 25,000–40,000 times and bandpass filtered (500 Hz – 7 kHz). Each of the four wires of one tetrode was recorded differentially with respect to one of the wires of the other. One of the channels served to record an EEG signal. Prior to the start of recordings, the tetrodes were driven down in steps of 25–200 μm daily until hippocampal 'ripples' could be seen. Ripples reflect the synchronous bursting activity of large numbers of cells and are a reliable indicator of proximity to the pyramidal cell layer. During this period, the rat was kept in an elevated holding area within the experimental room. Then the electrodes were lowered in small 25- μm steps until hippocampal complex spiking cells were identified. Position was monitored via a small LED on the head-stage assembly that was tracked by a video-camera in the ceiling directly above the midpoint of the two box positions. The position of the LED (~ 2 cm above the rat's head,

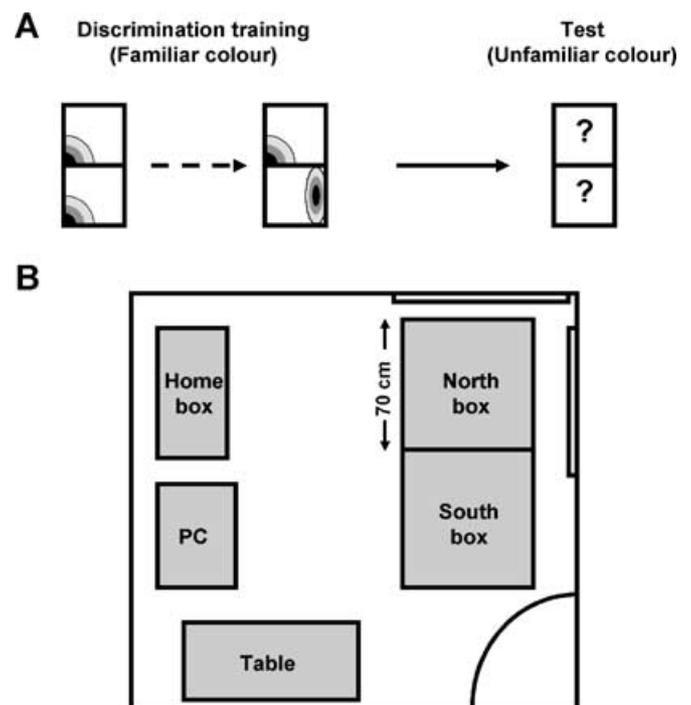


FIG. 1. Experimental room layout and manipulations. During training, trials were run until remapping between North and South boxes occurred in the familiar condition. Test trials were then run in the unfamiliar colour.

directly above the implant) was captured and converted into two camera coordinates. To record neurons, each channel was monitored every 20 μs , and 50 points per channel were sampled whenever the signal on any of the four channels exceeded an empirically pre-determined threshold. Each presumptive spike event was stored on hard disk along with the position of the animal and the time since the start of the recording, and recorded on disk with the unit recordings for later offline analysis. Cells were recorded until no more place cells could be isolated from that electrode location, at which point the microdrive was lowered another 25–50 μm until further cells could be discriminated.

Place field measures

Data analysis was performed offline using cluster-cutting software (Axona Ltd). The path of the rat was smoothed using a boxcar algorithm with a boxcar width of 400 ms. Collected waveforms were distinguished by plotting the peak-to-peak amplitude of one electrode against that of each of the other three on a series of scatterplots. Spikes belonging to a single cell typically appeared as clusters. These clusters were then separated by hand or by an automatic cutting algorithm (based on the manual cut), and these collections of spikes were assigned different cell numbers.

To determine where in the environment the cell's place field was located, the camera viewing area was divided into a 64×64 grid, each point of which was located at the centre of a ~ 2.25 cm square bin. For each bin, the firing rate for a cell was calculated as the number of spikes fired in that bin divided by the amount of time the rat spent there. The firing rate in each bin was then subjected to a smoothing process in which the value in each pixel was replaced with the average of that value plus the surrounding eight pixels. Cells with a peak frequency (taken from the pixel with the highest rate) of less than 1.0 Hz in any trial were excluded from further analysis. Also, it was sometimes necessary to discard the first few trials, as place fields were sometimes initially messy and poorly defined. A poorly defined place field was one with three or more separate peaks or a total number of spikes below 30. A place field was therefore defined as a region of location-specific firing in which the peak rate following smoothing was greater than 1.0 Hz.

Quantifying remapping

We assessed remapping using a correlation procedure as follows. Following a change to the environment (either location or colour), cells were considered to show remapping if the location of the field changed or the cell started or stopped firing (cessation of firing was classified as an averaged firing rate below 1.0 Hz). In terms of the present analysis, a cell that stopped firing upon a change of condition was coded as having remapped and no further numerical analysis was conducted. For each cell with a field in more than one condition, remapping was assessed as follows. A smoothed firing rate map was generated for each condition where the field was present. Each map was then decomposed into a 64×64 -element matrix. Then each pixel in one map was correlated, by a Pearson's correlation, with its equivalent pixel (in terms of its absolute position) in the other map. Pixels that had a zero firing rate in both maps were discarded so that all the common areas where the cell was not active did not artificially inflate the correlations. In some cases, the place fields of a single cell in two conditions were only distinguished by a difference in their respective firing rate (i.e. the cell was firing in the same location in two different conditions). A difference in firing rate was assessed by a one-tailed *t*-test comparing all of the same-condition rates with all of the different-condition rates. A significant difference ($P < 0.05$) was taken to indicate that remapping had occurred.

For a cell that was active over 16 4-min trials (eight alternating North/South trials in one colour and eight in the other colour) in a session, the following correlation coefficients were produced.

Within-condition correlations:

North (colour 1 vs. colour 1) – generating 6 correlations;

South (colour 1 vs. colour 1) – generating 6 correlations;

North (colour 2 vs. colour 2) – generating 6 correlations;

South (colour 2 vs. colour 2) – generating 6 correlations.

Between condition correlations:

North (colour 1 vs. colour 2) – generating 16 correlations;

South (colour 1 vs. colour 2) – generating 16 correlations;

Colour 1 (North vs. South) – generating 16 correlations;

Colour 2 (North vs. South) – generating 16 correlations.

The within-condition correlations for each colour [North (colour 1 vs. colour 1) and South (colour 1 vs. colour 1)] were averaged to produce a single correlation coefficient for each colour, designated within-condition correlation coefficient colour 1 or 2. Typical within-condition correlations for colour were about 0.6.

The between-condition correlations for each colour showed the relationship between maps in the two different locations in one colour (North-black vs. South-black). For a cell that had remapped, the overall between-condition correlations for colour were roughly 0.1 to 0.2. The between-condition correlations for each location showed the relationship between maps in the same absolute location in the experimental room, but under different colour conditions (i.e. North-black vs. North-white).

The correlations were plotted and were sufficiently normally distributed to justify using a parametric test. The within- and between-condition correlations were thus compared with a one-tailed *t*-test. A significant difference would indicate that remapping had occurred.

Histology

At the end of the experiment, each animal was anaesthetised with isoflurane followed by an injection (i.p.) of sodium pentobarbital, then transcardially perfused with saline, followed by a 4% paraformaldehyde solution. The brains were removed and stored in a 4% paraformaldehyde solution for at least 1 week before sectioning began. Brains were sectioned at 40 μm and 50 μm . All sections were stained with a Cresyl violet method to verify electrode placement. Electrodes in all rats were histologically confirmed to have been placed in region CA1 of the hippocampus.

Results

A total of 50 cells from four rats ($n = 13$, $n = 9$, $n = 17$, $n = 11$), matching the acceptance criteria described in the Materials and methods, were recorded across all conditions (see Materials and methods). Of this total, 39 cells were active in the familiar box and 32 were active in the unfamiliar box, with 17 active in both boxes.

We assessed whether a cell fired differently following a change to the recording environment (either the location of the box or the colour of the box, or both) by first looking at the firing rate to see whether the cell switched off ('rate remapping'). If the cell fired in both conditions, we then tested to see whether the firing location had changed ('location remapping'). This was assessed by correlating the first firing rate map with the second (see Materials and methods). A high correlation indicates a highly similar firing location and hence no remapping, while a low correlation indicates a change in the firing location and hence remapping. Two kinds of correlation were made. Within-condition correlations tested how much a place field varied between recording sessions composed of the same stimuli (location and box colour), and served as a measure of the stability of the representation.

Between-condition correlations were made for recording sessions differing in the location of the box, the colour of the box or both, and provided a measure of remapping.

The within-condition correlations for the four different conditions (familiar North, familiar South, unfamiliar North and unfamiliar South) were distributed around a mean of $0.61 (\pm 0.02)$ and did not differ between conditions ($F_{3,116} = 1.90$, NS). These values were therefore grouped together for further comparison using *t*-tests and analysis of variance.

Remapping to colour

As previous studies have also found (Bostock, *et al.*, 1991; Kentros *et al.*, 1998; Jeffery *et al.*, 2003), changing the colour of the recording box from black to white caused a change in the firing patterns of the place cells (remapping), which was quantified using the correlation analysis described in the Materials and methods. Firing rate maps were compared between familiar and unfamiliar boxes in the North and South locations. The mean between-colour correlations were $0.22 (\pm 0.04 \text{ SEM})$ and did not differ for North and South locations (two-tailed $t_{34} = -0.27$, NS). The low coefficient values indicate that the place fields in one colour bore little relation to place fields in the other colour, as was expected, and this remapping was as strong for the North box location as for the South.

Remapping between North and South

Remapping between North and South was quantified using the between-condition correlation for each colour, which reveals the relationship between place fields recorded in the same colour box but in different absolute locations in the experimental room (e.g. black-North vs. black-South). Remapping between North and South was strong in the familiar context, with a mean between-condition correlation coefficient of only $0.23 (\pm 0.05 \text{ SEM})$, which is as low as the correlation between boxes of different colours and indicates substantial remapping. When two or more cells were recorded at the same time, all the cells exhibited the same behaviour: i.e. all remapped or all failed to do so.

Overall, this indicates that the cells were discriminating the two locations on the basis of the distal extramaze cues. Cells either switched on and off (one rat), shifted the locations of their firing fields (two rats) or changed their rate substantially (one rat). This rat-specific behaviour is discussed in greater detail below. We never saw fields stretch in the way that O'Keefe & Burgess (1996) did, which suggests to us that the distal extramaze cues were acting in a different manner from the box walls. This is also discussed below.

Despite showing robust remapping in the familiar box, many cells failed to discriminate these same locations in the unfamiliar colour (Fig. 2). This was borne out by the correlation analysis, which showed a between-condition correlation coefficient of $0.43 (\pm 0.06 \text{ SEM})$. A one-tailed *t*-test confirmed a significant difference between the between-condition correlation coefficients in the two colours ($t_{58} = -2.64$, $P < 0.01$). This indicates that cells in the familiar colour condition had unrelated place fields between the North and South locations (i.e. had remapped and were now discriminating), whereas cells in the unfamiliar colour condition had closely related place fields between the North and South locations. The correlations between the various conditions are shown schematically in Fig. 3.

The between-condition correlation value, while relatively high, was nevertheless significantly different from the within-condition value ($t_{99} = -3.84$, $P < 0.001$), suggesting some degree of remapping. The reason for this result can be explained by the results from the third rat. Here cells remapped extremely quickly in the unfamiliar environment (see below for details).

Animal-specific remapping patterns

A closer examination of the pattern of remapping in individual animals revealed that there were clear differences between animals in the overall behaviour of cells. For two of the animals (rats 1 and 2), when cells remapped location they almost always did so by remapping their fields to novel areas of the environment (Fig. 4A). Of a total of 17 cells recorded from these two animals that remapped location, only one switched off, with the rest shifting their place fields to novel positions. However, a different pattern was observed in another animal whereby

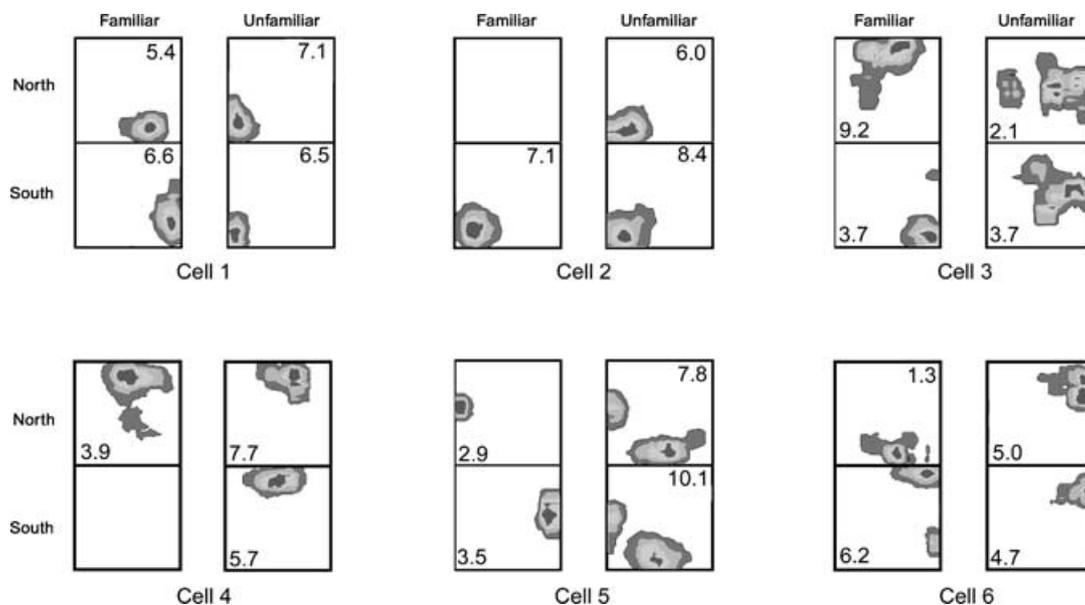


FIG. 2. Place fields from six cells recorded in the North and South box locations, first in one context ('Familiar') and then in another ('Unfamiliar'). Place fields are displayed as contour maps with five levels, each level representing a 20% portion of the peak firing rate for that map. The peak rate (Hz) is shown alongside each place field. Although these cells remapped in the familiar context, either by shifting their fields or by switching off in one of the boxes, they failed to transfer this discrimination to the unfamiliar context.

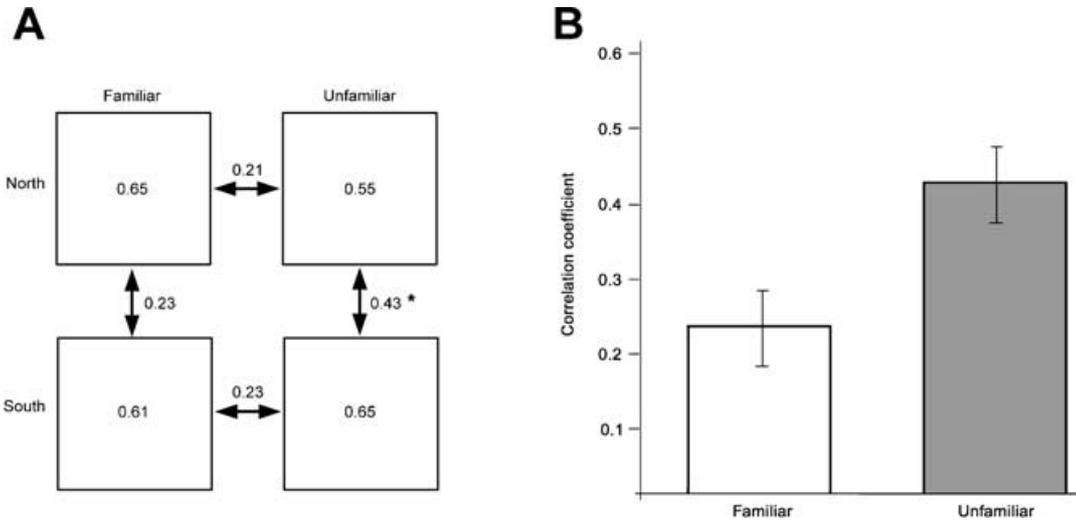


FIG. 3. (A) Schematic diagram showing mean within- and between-condition correlations for place cells recorded in the familiar boxes or unfamiliar boxes in the North and South locations. In the familiar context, the between-condition correlations across location (0.21 and 0.23) were not significantly different from the between-condition correlations for location in the familiar (0.23) and unfamiliar contexts (0.43) reveals a significant difference. Asterisk indicates significance at $P < 0.01$. (B) Mean correlation coefficients (\pm SEM) for location in the familiar and unfamiliar contexts with error bars.

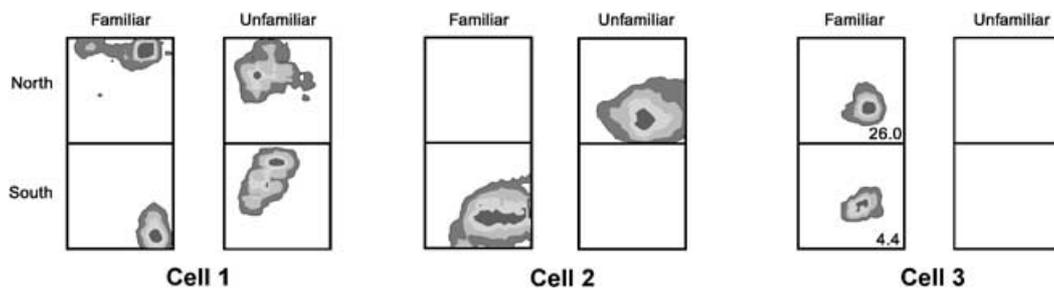


FIG. 4. Animal-specific remapping patterns. Each place field demonstrates behaviour typical for the majority of cells recorded from that animal. Cell 1 remapped location in the familiar context by shifting its field to a new place within the recording box. The fields in the unfamiliar context are highly similar. Cell 2 remapped by switching on/off, both in the familiar and unfamiliar contexts. This cell was particularly interesting because it (unusually) seemed to express the same field in both contexts, but in opposite locations. While this might reflect a new field coincidentally occurring in the same place in the box, it might also reflect a configural 'binding' of the inputs (see text for details, and Fig. 9 for a proposed explanation). Cell 3 remapped location in the familiar context by a change in firing rate (shown in H3 in bottom right-hand corner).

approximately half (9/17) of the recorded cells remapped by either switching on or switching off (Fig. 4B). These differences in individual patterns of remapping were compared using a χ^2 -test. There was a significant difference between rats in the type of remapping seen (either cells switching on/off, shifting location or rate remapping) ($\chi^2 = 53.25$, d.f. = 6, $P < 0.001$).

Whereas the cells recorded from rats 1, 2 and 4 took time to develop a discrimination between locations in the familiar box and rarely, if at all, remapped location in the unfamiliar box, the cells recorded from rat 3 discriminated location rapidly in both environments. As mentioned above, this is the reason for the between-condition correlation value of 0.43 (which lies between the average within-condition value of 0.62, i.e. no remapping, and the 0.23 value for the between-condition correlation in the familiar environment, i.e. successful remapping).

Another pattern of remapping was observed in a further animal (rat 4). Here, instead of remapping fields to novel parts of the environment or becoming active or silent, the cells either increased or decreased their firing rate, whilst their fields remained in the same location with reference to the box (Fig. 4C). The data from one of these cells are shown in Fig. 5, where a cell that was recorded for 2 weeks consistently

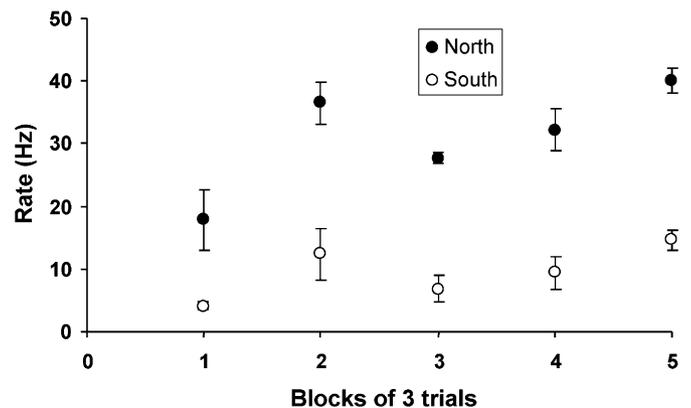


FIG. 5. Data from the rate-remapping cell (cell 3) shown in Fig. 4, illustrating the reliability and stability of the rate differential across multiple trials, spanning several days. Cells like this were only found in one rat, and constituted the most common type observed in this rat.

fired in a higher rate in one location than in the other. Cells like this were only observed in one rat (seven of 11 cells recorded from this rat). Throughout this period, the cell's place field was in an equivalent position in both box locations. In order to quantify the firing rate differences, *t*-tests were conducted on the firing rates of cells that had identical fields in two box locations. Some cells expressed their high rate in the North box and some in the South, ruling out some general arousal or other factor specific to one of the box locations. Thus, this 'rate remapping' seems qualitatively different from the more commonly observed switching on or off of fields.

Because the cells recorded from this animal signified a change in location by increasing or decreasing their firing rate whilst maintaining the same place field, this impacts on the overall between-condition correlation for colour. When the cells recorded from this animal were removed from the overall between-condition correlation for colour, then the values for the familiar and unfamiliar colours became 0.09 and 0.43, respectively. A *t*-test conducted on these revised values revealed an even more significant difference between the between-condition correlation coefficients in the two colours ($t_{47} = -4.410$, $P < 0.001$).

We draw attention to one further observation which, while anecdotal, may shed light on the structure of the contextual signal reaching the place cells. This cell, shown in Fig. 4 (cell 2), was recorded from the rat whose cells quickly learned to discriminate the locations in the unfamiliar context too. This cell expressed a particular field in the South in the familiar context, and the same field in the North in the unfamiliar context. The possible significance of this observation is detailed in the Discussion.

Our results thus show that newly acquired discriminative information about distal cues is expressed by place cells in a context-dependent manner. This indicates that the spatial inputs onto the cells can be modulated independently of each other and that the acquired inputs act at this level, rather than on the place cell itself. In the Discussion, we present a model of how this might occur.

Discussion

This study found that a spatial discrimination acquired by place cells in a box of one colour did not necessarily transfer to a box of a different colour. Initially, rats were exposed to two highly similar environments that differed only in their positions in the experimental room. Following the repeated exposure of the rats to these environments, place cells acquired the ability to remap (change their firing patterns) between the two locations, presumably on the basis of the different configuration of distal cues visible from the two locations. Once remapping was reliably occurring in the familiar boxes, the colour was altered to induce a reorganization of the place representation ('remapping'). As in previous studies, introducing such a colour change resulted in a complete remapping taking place (Quirk *et al.*, 1990; Bostock *et al.*, 1991): active cells switched off or formed novel fields in new locations, or previously silent cells became active. We find here that the previously learned discrimination between locations was not transferred to the new colour. In general, neither cells that had discriminated North from South successfully in the familiar boxes, nor newly active cells were able to discriminate in the unfamiliar boxes. There is thus an interaction between remapping to location and remapping to the colour change.

Below, we propose an explanation of our results. This explanation draws on our previous proposal that non-geometric cues such as colour can modulate the geometric determinants of place fields by interacting with them upstream of the place cells (Jeffery & Anderson, 2003). We henceforth refer to these non-geometric cues as 'context' cues, to reflect the assumption that colour is merely one of a variety of different

non-geometric stimuli that can exert such a modulatory effect (see Anderson *et al.*, 2003 and Anderson & Jeffery, 2003 for a more detailed discussion of this issue). We first review our proposal regarding how place cell activity might be modulated by contextual cues, in order to provide a framework in which to set the present results. We then discuss how place cells may acquire the discriminative inputs that allow them to distinguish the two box locations and, finally, we discuss how these factors interact: in other words, why does this discrimination fail to transfer to a new context?

Contextual modulation of place cell activity

In order to explain how place cells can express different fields in the differently coloured environments, we have previously postulated (Jeffery & Anderson, 2003) an interaction between information supplied by the geometry (the walls) and that provided by the context (in this case the box colour). We have suggested that the inputs that control place cell firing can be differentiated into boundary inputs (following Hartley *et al.*, 2000) and contextual inputs. According to this model (shown here in Fig. 6), the boundary inputs (controlling field location) are driven by the environmental boundaries (the walls of the box in the present experiment), and the context inputs (such as the colour of the box) control which, if any, boundary inputs are expressed by the cells in a particular environment. This hierarchical organization of the inputs, whereby the spatial inputs are modulated by the context inputs, allows the individual fields of a cell to be switched on or off independently of each other. Contextual remapping thus reflects the recruitment of a new set of boundary inputs by new contextual inputs.

Acquisition of location discrimination

In the present experiment, after repeated experience of the North and South box locations, place cells began to discriminate these. The development of such location discrimination usually involved the switching off of a place field in one of the locations, and either development of a new field, or else no field at all, in the other location. There are two possible explanations for this. One is that the new, discriminative stimuli (coming presumably from the 'extramaze' cues outside the box) are inhibitory, and work by switching a field off in one

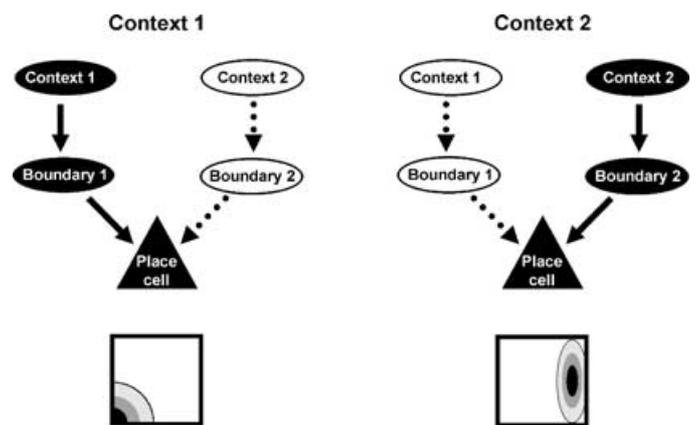


FIG. 6. Possible explanation for why a place cell shifts its field (remaps) in response to a context change (see Jeffery & Anderson, 2003). The cell in this example receives two sets of boundary inputs, one for each field, with each boundary input being controlled by a context input. Active elements (inputs) are shown in black (solid lines), inactive elements in white (dotted lines). (Left) In context 1 (e.g. black box), the boundary input set activated by black drives place cell firing in the South-West corner of the box. (Right) In context 2 (e.g. white box), the other boundary input set is activated and the cell is driven to fire along the East wall.

or other location. The other is that a new excitatory input forms from the distal cues [by a process of synaptic strengthening: long-term potentiation (LTP)], together with a reduction in the strength of the drive from the existing inputs [by a process of synaptic weakening: long-term depression (LTD)] so that the box alone does not provide all the conditions necessary for a field to be expressed. We prefer this explanation as LTP and LTD are well documented in the hippocampus, and the development of inhibitory feedforward connections less so. This process is shown in Fig. 7.

What kind of inputs did the cells receive from the distal inputs? As discussed in the Introduction, manipulation of geometric inputs typically causes stretching or splitting of fields (O'Keefe & Burgess, 1996;

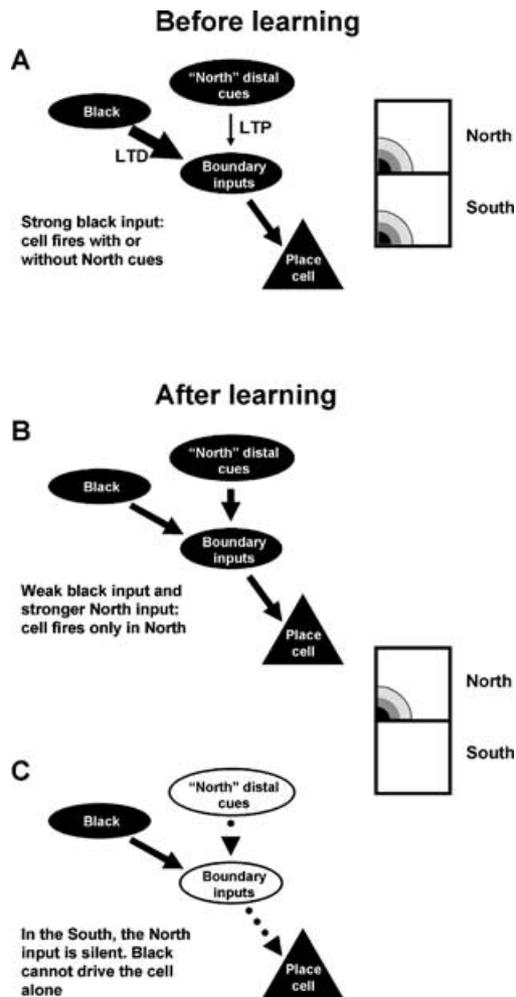


Fig. 7. Hypothesized acquisition of location discrimination, by a cell whose field becomes specific to the North box. Active elements (inputs) are shown in black (solid lines), inactive elements (inputs) in white (dotted lines). Thickness of lines indicates relative strength of inputs. (A) Before learning, the cell initially receives strong inputs from the contextual cues (in this case black), which drive the boundary inputs in the North or the South. Thus, the place field is present in both boxes. With repeated experience of the two boxes, only one of which (the North) activates the distal 'North' inputs, the distal inputs become stronger by a process of Hebbian (coactivity-driven) potentiation (long-term potentiation, LTP), and the existing contextual inputs become weakened by a normalization process (long-term depression, LTD) that keeps the total synaptic drive constant. (B) and (C) After learning, when the synapses have changed their strengths, the cell will now only fire when both the (weakened) contextual inputs and the distal inputs are co-active, in the North (B). In the South (C), the weakened context inputs cannot drive the boundary inputs alone, and the field is absent.

but see Lever *et al.*, 2002 for an exception which we discussed earlier), whereas manipulation of contextual cues causes fields to switch on or off. The discrimination between locations that we saw in the present experiment consisted of a switching on and off of place fields, rather than a deformation or splitting, and we thus believe that the acquired inputs from the distal cues served as additional context cues, rather than additional geometric cues.

Context specificity of location discrimination

Because the discrimination between locations was specific not just to a given place cell but to a given field, as a given cell might discriminate when expressing one of its fields but not the other, it appears that the modulation of this discrimination by context must take place upstream of the point at which the spatial inputs arrive at the cell. In other words, the contextual inputs act by switching on and off a field rather than switching on and off a cell. We propose that the context-specific nature of the new inputs arises because the newly acquired inputs become part of the ensemble of context cues that collectively drive a particular set of spatial inputs onto a place cell. To explain the switching off of the field of a discriminating place cell, it is necessary to postulate a simultaneous weakening of the existing contextual inputs, so that after learning, a place cell now needs both the original cues and the new cues in order to fire. Thus, the acquisition of discriminative ability consists, we believe, of the addition of new cues to the existing set of modulating contextual inputs, together with a normalization process that maintains the level of drive of the contextual inputs more-or-less constant.

Why did a newly acquired discrimination fail to transfer to an unfamiliar context? We propose that discrimination occurs in the familiar environment because weakening of the pre-existing contextual inputs to the place cells means that the correct distal cues also need to be present for a cell to express a given field. We assume this process is activity-dependent, so that only those inputs that were active at a given time will show synaptic strength changes. This proposed activity dependence provides a pointer to why information learned (by synaptic strength changes) in one environment did not transfer to a new environment, which triggers newly active inputs. In the unfamiliar environment, with a new set of never-yet-activated contextual inputs, no such weakening has occurred and the cell can express its field whether the distal stimuli are present or not.

Our model of how new inputs are acquired context-dependently is shown schematically in Fig. 8. Prior to learning, a place cell fires when one of its boundary input sets is driven by its associated context inputs (see Fig. 6). We suggest that the boundary inputs receive, as well as colour modulation, a weak input from the distal cues that becomes stronger over time by a process of Hebbian coactivity and synaptic strengthening (LTP). At the same time, the other inputs become weaker (LTD) so that now the cell will only fire when in the right colour box and the right location to drive the distal cue inputs. Because this learning required coactivity, the connections routed through the other boundary input sets (those activated by different contexts, not yet experienced by the rat) do not change, and so the cell will remain non-discriminating in these contexts.

Figure 9 shows how the model can be applied to explain the various kinds of remapping observed. In all cases, a particular place field becomes expressed when a given boundary input set is activated, and remapping reflects activation of different boundary inputs under different conditions. The most usual pattern (Fig. 9A) occurs when a cell that has learned to discriminate North from South in the familiar context expresses a new field that fails to discriminate in the unfamiliar context. As discussed above, we postulate that this occurs because synaptic rearrangement means that those boundary input sets that were active in the familiar context come to depend on a combination of both

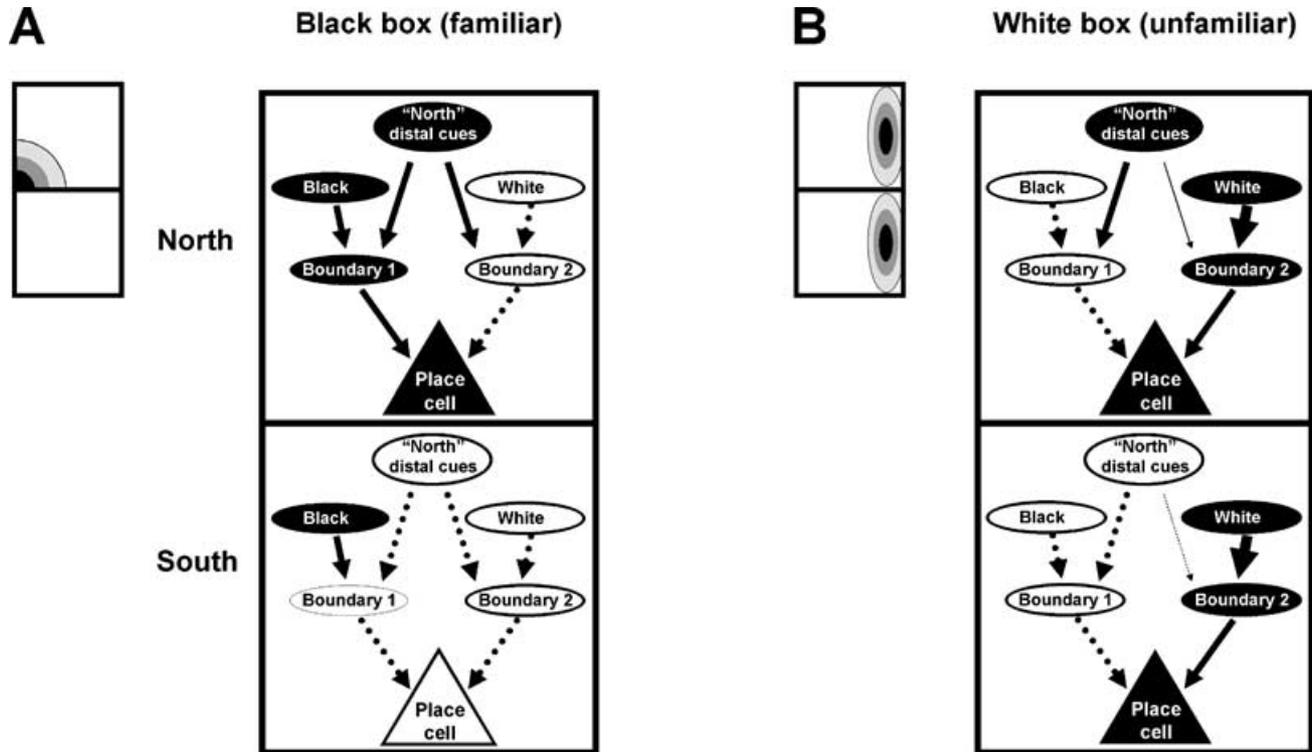


Fig. 8. Hypothesized mechanism for the context-specificity of location discrimination, for a cell that location-discriminates in the familiar context – in this case black – and develops a non-discriminating new field when the context is changed to white. The place fields are shown in the insets. Active elements (inputs) are shown in black (solid lines) and inactive elements (inputs) in white (dotted lines). (A) In the familiar environment, after learning (see Fig. 7), the inputs have altered so that the original contextual inputs are weaker but the inputs from the distal (in this case, North) cues have strengthened. Now, for the place cell to express a particular field (driven by the boundary inputs), both the correct contextual and correct distal cues must be present. Thus, the cell only fires in the North box. (B) When the context is changed, a new set of contextual elements becomes active and these drive a second set of boundary inputs, producing a new place field. Because no activity (i.e. experience)-dependent changes have yet happened to these newly active inputs, the contextual inputs are still strong enough to drive the boundary inputs by themselves, so the cell can express this field in either the North or South locations.

the correct contextual and the correct distal cues. Another pattern, seen more rarely, occurred when a cell expressed a discriminating field in the familiar context, and the same field in non-discriminating form in the unfamiliar context (Fig. 9B). Here, we suppose that the boundary input set for that field receives either weak (familiar) contextual inputs, in which case these must be paired with the distal cues in order to fire, or the as-yet-unweakened (unfamiliar) contextual cues, which can still drive the boundary inputs by themselves.

The third pattern (Fig. 9C) is that of the cell discussed previously in the Results. This cell is interesting because it exhibits a kind of behaviour commonly known as 'biconditional' (O'Reilly & Rudy, 2001), because it requires the pairing of two conditions (in this case, the correct box colour with the correct location) to produce a given response (place field). Biconditional responding is of significance to animal learning theorists because it suggests the formation of some kind of configural representation – a binding of the two conditions prior to the response stage. In the present case, assuming that the place field in the two contexts is generated by a common boundary input set, this biconditional pattern could only occur if the preceding inputs were paired so that black and South become bound as a common input, and similarly with white and North. This observation therefore suggests that the inputs driving the fields are combined into some kind of configural representation upstream of the place cell. However, we only observed this pattern once (albeit in a cell with a distinctive field, and in a pattern repeated over multiple alternating trials), so the observation must remain anecdotal at this stage. Nevertheless, it raises the possibility of a configural context representation occurring upstream of the place cells.

The final pattern modelled in Fig. 9D is that of the rate-remapping cell illustrated in Figs 4 (cell 3) and 5. In this case, it is assumed that the cell has a single set of boundary inputs that receive a strong input from the North cues and a weak input from the South cues.

We note here that the above model differs from prevailing neural network accounts of hippocampal function (e.g. Samsonovich & McNaughton, 1997). Most instantiations of attractor network models posit that the major inputs to a place cell come from within the hippocampal network itself, although the relative influences of extra- vs. intrahippocampal sources of place information on place cell activity are not clear (Tsodyks, 1999). The boundary cells that drive the place-specific firing of cells in the above model are presumed to be cortical in origin, following Hartley *et al.* (2000), although we acknowledge that there are currently not sufficient anatomical data to resolve this issue.

In summary then, we propose an explanation for the context-specificity of location discrimination in which activity-dependent alteration of synaptic strengths occurs in the familiar context. Because these changes occur at a synapse upstream of the place cells, the place cell itself either discriminates or does not, depending on which sets of inputs are being activated.

Plastic changes underlying development of context-specific location discrimination

The process of LTP at hippocampal synapses is largely determined by the activity of *N*-methyl-D-aspartate receptors (NMDARs; Bliss & Collingridge, 1993; Morris *et al.*, 2003). Supporting evidence for the

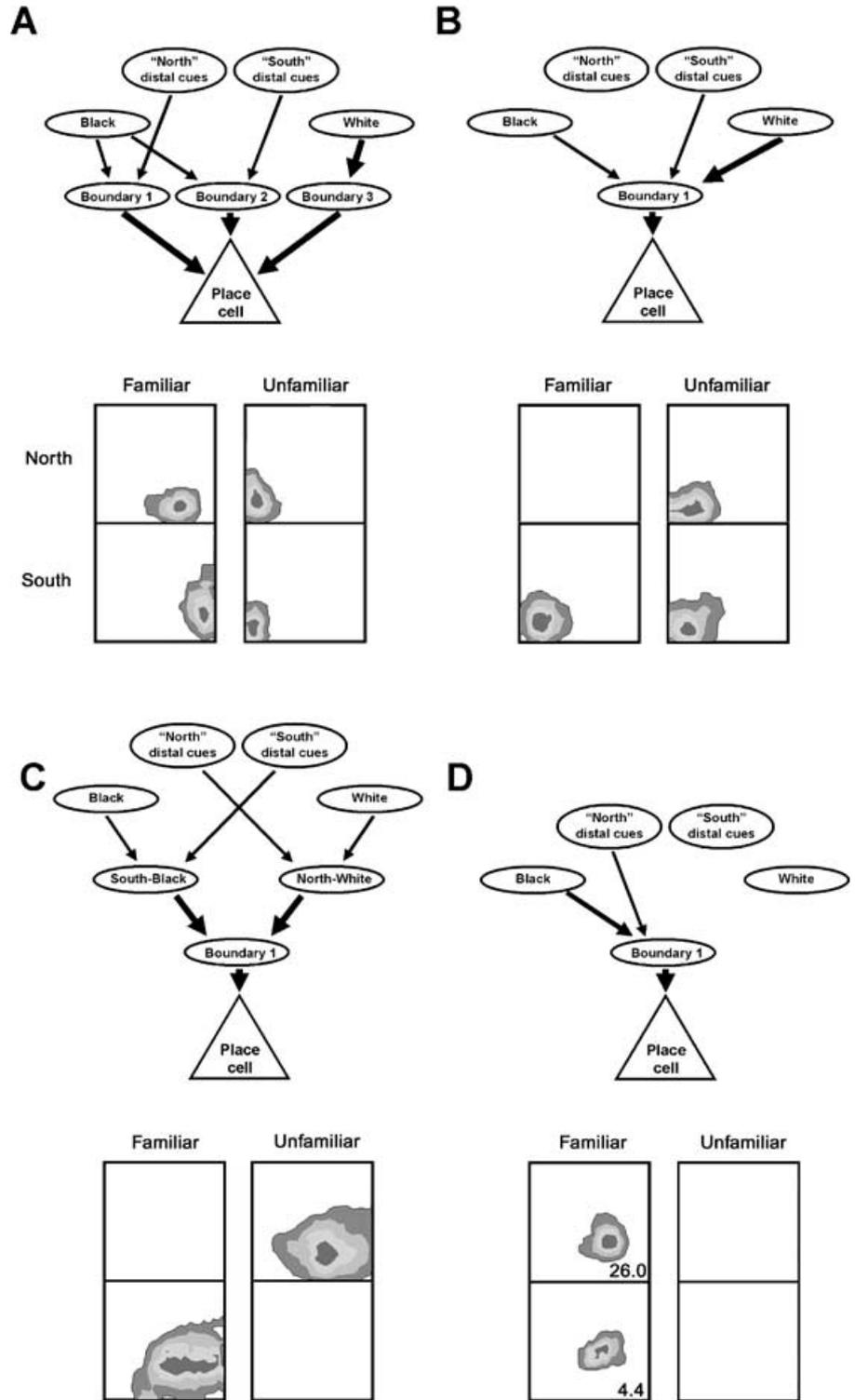


FIG. 9. How the model can explain the varieties of remapping pattern observed. (A) The most usual behaviour, of a cell that discriminated the North box from the South in the familiar context but not the unfamiliar one. It is assumed that the cell possesses three sets of boundary inputs, each of which generates a place field when activated. In the familiar environment, the contextual inputs (black) have become weakened by LTD (see text, and Fig. 8 for explanations). The cell will therefore only express this field when the box is both black and in the North. In the South, the cell expresses its second field, which needs both black and South inputs to be active. In the unfamiliar context, the contextual inputs drive the third set of boundary inputs. Because no rearrangement of input strengths has yet taken place, these inputs can drive the boundary inputs, and hence generate the place field, in either the South or the North box locations. (B) A cell that discriminates North from South in the familiar context but fails to do so with the same field in the unfamiliar context. In this case it is assumed that the same set of boundary inputs generates the place field in both contexts. In the familiar context, the contextual inputs have become weakened so that both the correct context and the correct distal cues are needed. In the unfamiliar context, the same boundary inputs receive a strong drive from the context inputs alone, and thus can drive the place field in either location. (C) Biconditional behaviour of a place cell from a rat whose cells rapidly learned to discriminate the two locations in the unfamiliar context too. The cell expresses only one place field, but this is in the South when in the black context and in the North when in the white context. We assume that this field is controlled by a single set of boundary inputs, and this pattern could be explained if it is assumed that the contextual and distal discriminative inputs have become 'configured' (bound together) so that Black-South and White-North both drive the boundary input, but White-South and Black-North do not. (D) Rate remapping, in which a cell discriminates by expressing the same field but at different strengths. Here, it is assumed that the boundary inputs receive a stronger drive in the North than they do in the South.

above view (that the links between the various inputs to place cells are LTP/LTD modifiable) comes from studies that have selectively blocked the activity of NMDARs in area CA1 (i.e. Kentros *et al.*, 1998). Here, place cells were active upon initial entry to an environment and successfully form place fields, demonstrating that NMDARs were not required for the initial establishment of place fields. Additionally, when exposed to a previously experienced environment, this time under NMDAR blockade, the same two maps were expressed.

However, upon a second exposure to a novel environment (the first exposure occurring during NMDAR blockade), the previously established map was replaced with a new one. We suggest that the initial selection of boundary inputs to place cells is random and that NMDARs are required for the long-term stabilization of these boundary inputs to place cells. Once the map has become stabilized (via NMDAR-dependent LTP), the processes of LTP/LTD allow synaptic strength-scaling to the boundary inputs, as proposed above.

Functional consequences of context-specific plasticity

What is the adaptive significance, if any, of context-specific plasticity by place cells? Several theoretical accounts of hippocampal function have suggested that the hippocampus may act as a context processor (Nadel & Willner, 1980; Rudy & O'Reilly, 2001), forming a conjunctive representation consisting of spatial and non-spatial cues so that an animal has a specific representation of place with which it can associate specific expectations or behaviours. By this view, the hippocampus instantiates a more richly populated representation of the environment than the mere physical layout. Stimuli known to modulate place field expression include not only physical features of the environment but also factors internal to the rat, such as its intentions or expectations (Markus *et al.*, 1995; Wood *et al.*, 2000). If our account of the present findings is correct, the context-specificity of the acquired inputs to the cells allows new cues to be added to one context representation without interfering with the other. In this way, the animal can express different behaviours in the same physical place, depending on what other context cues are present, and thus be better equipped to exploit the changing properties of its environment.

Acknowledgements

We thank R. Bunce, S. Burton and J. Donnett for technical assistance. This work was supported by Wellcome Trust and BBSRC grants to K.J. and a BBSRC studentship to R.H. The authors declare that they have no competing financial interests.

Abbreviations

LTD, long-term depression; LTP, long-term potentiation; NMDAR, *N*-methyl-D-aspartate receptor.

References

- Anderson, M.I., Hayman, R., Chakraborty, S. & Jeffery, K.J. (2003) The representation of spatial context. In Jeffery, K.J. (Ed.), *The Neurobiology of Spatial Behaviour*. Oxford University Press, Oxford.
- Anderson, M.I. & Jeffery, K.J. (2003) Heterosynaptic modulation of place cell firing by changes in context. *J. Neurosci.*, **23**, 8827–8835.
- Bliss, T.V. & Collingridge, G.L. (1993) A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature*, **361**, 31–39.
- Bostock, E., Muller, R.U. & Kubie, J.L. (1991) Experience-dependent modifications of hippocampal place cell firing. *Hippocampus*, **1**, 193–205.
- Hartley, T., Burgess, N., Lever, C., Cacucci, F. & O'Keefe, J. (2000) Modeling place fields in terms of the cortical inputs to the hippocampus. *Hippocampus*, **10**, 369–379.
- Jeffery, K.J. (2000) Plasticity of the hippocampal representation of place. In Holscher, C. (Ed.), *Neuronal Mechanisms of Memory Formation*. Cambridge University Press, Cambridge.
- Jeffery, K.J. & Anderson, M.I. (2003) Dissociation of the geometric and contextual influences on place cells. *Hippocampus*, **13**, 868–872.
- Jeffery, K.J., Gilbert, A., Burton, S. & Strudwick, A. (2003) Preserved performance in a hippocampal-dependent spatial task despite complete place cell remapping. *Hippocampus*, **13**, 133–147.
- Kentros, C., Hargreaves, E., Hawkins, R.D., Kandel, E.R., Shapiro, M. & Muller, R.V. (1998) Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. *Science*, **280**, 2121–2126.
- Lever, C., Wills, T., Cacucci, F., Burgess, N. & O'Keefe, J. (2002) Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature*, **416**, 90–94.
- Markus, E.J., Qin, Y.L., Leonard, B., Skaggs, W.E., McNaughton, B.L. & Barnes, C.A. (1995) Interactions between location and task affect the spatial and directional firing of hippocampal neurons. *J. Neurosci.*, **15**, 7079–7094.
- Morris, R.G., Moser, E.I., Riedel, G., Martin, S.J., Sandin, J., Day, M. & O'Carroll, C. (2003) Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **358**, 773–786.
- Muller, R.U. & Kubie, J.L. (1987) The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J. Neurosci.*, **7**, 1951–1968.
- Nadel, L. & Willner, J. (1980) Context and conditioning. *Physiol. Psychol.*, **8**, 218–228.
- O'Keefe, J. & Burgess, N. (1996) Geometric determinants of the place fields of hippocampal neurons. *Nature*, **381**, 425–428.
- O'Keefe, J. & Dostrovsky, J. (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res.*, **34**, 171–175.
- O'Keefe, J. & Nadel, L. (1978) *The Hippocampus as a Cognitive Map*. Oxford University Press, Oxford.
- O'Reilly, R.C. & Rudy, J.W. (2001) Conjunctive representations in learning and memory: principles of cortical and hippocampal function. *Psychol. Rev.*, **108**, 311–345.
- Quirk, G.J., Muller, R.U. & Kubie, J.L. (1990) The firing of hippocampal place cells in the dark depends on the rat's recent experience. *J. Neurosci.*, **10**, 2008–2017.
- Recce, M.L. & O'Keefe, J. (1989) The tetrode: a new technique for multiunit extra-cellular recording. *Soc. Neurosci. Abstr.*, **15**, 1250.
- Rudy, J.W. & O'Reilly, R.C. (2001) Conjunctive representations, the hippocampus, and contextual fear conditioning. *Cogn. Affect. Behav. Neurosci.*, **1**, 66–82.
- Samsonovich, A. & McNaughton, B.L. (1997) Path integration and cognitive mapping in a continuous attractor neural network model. *J. Neurosci.*, **17**, 5900–5920.
- Skaggs, W.E. & McNaughton, B.L. (1998) Spatial firing properties of hippocampal CA1 populations in an environment containing two visually identical regions. *J. Neurosci.*, **18**, 8455–8466.
- Tsodyks, M. (1999) Attractor neural network models of spatial maps in hippocampus. *Hippocampus*, **9**, 481–489.
- Wood, E.R., Dudchenko, P.A., Robitsek, R.J. & Eichenbaum, H. (2000) Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron*, **27**, 623–633.