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Plasticity of the Hippocampal Place Cell Representation

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SYNOPSIS

The role of the hippocampus in the representation of 'place' has been attributed to the place cells, whose spatially localised firing suggests their participation in forming a cognitive map of the environment. That this map is necessary for spatial memory formation is indicated by the propensity of almost all navigational tasks to be disrupted by hippocampal damage. The hippocampus has also long been implicated in the formation of episodic memories, and the unusually plastic nature of hippocampal synapses testifies to its probable mnemonic role. Arguably, the place cell representation should, if it is to support spatial learning, be modifiable according to known principles of synaptic reorganization. The present article reviews evidence that the place cell representation is indeed plastic, and that its plasticity depends on the same neurobiological mechanisms known to underlie experimentally induced synaptic plasticity. Inferences are drawn regarding the architecture of the spatial representation and the principles by which it is modified. Spatial learning is promising to be the first kind of memory which is completely understood at all levels, from molecular through circuitry to behaviour and beyond.

KEY WORDS

hippocampus, place cells, synaptic plasticity, spatial learning, LTP, NMDA receptors

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INTRODUCTION

Evidence from neuropsychology, pharmacology, molecular genetics and electrophysiology has long implicated the hippocampus as having a pivotal role in memory and learning. Lesions of this structure in humans impair the ability to learn new facts and remember life events (episodic memory) while sparing other memory systems (such as procedural and working memory) /24,80/. Animal studies have likewise revealed that lesions or pharmacological and molecular genetic interventions aimed at the hippocampus impair the ability to form new memories, particularly memory for spatial relationships or, at a more superordinate level, spatial context /67,71/. Animal studies have also revealed that the hippocampus prominently expresses a type of synaptic plasticity thought to underlie learning and memory, adding weight to the notion that the hippocampus can act as a mnemonic device of some kind.

Further insight into the contribution made by the hippocampus to spatial and mnemonic processing has come from examining the activity of single cells in this structure. When rodents freely explore an environment, hippocampal cells fire in a restricted portion of the environment, with different cells active in different places, and the population thus representing the whole environment. The discovery of these 'place cells' /70/ was very exciting and prompted the proposal that these cells constituted the basic elements of a map-like representation of a rat's location in its environment /71/. The so-called 'cognitive map' theory has long provided an important theoretical framework for understanding the role of the hippocampus in representing places and, along with places, the events that happen in those places.

The signal carried by place cells provides a unique window into the mechanisms that the hippocampus may employ in laying down new memories. A cognitive representation of 'place'

would not be very useful if it were unable to alter its properties so as to represent new environments, or familiar environments that change, and so it is plausible that the place cell representation would be plastic. If so, then study of the properties and mechanisms of such plasticity would provide our first clear understanding of how complex memories are laid down in the brain. With this in mind, the present article explores what has been discovered to date about how place cells modify their representation with experience. Two guiding principles underlie the analyses to follow. First, manipulations that are known to interfere with plastic processes in neurons should, when applied to the place cells, impair the acquisition and/or expression of new spatial memories; and second, we should see plastic changes in place cell activity as a result of spatial learning. We review experiments in both these domains, and use these data to draw inferences about both the architecture of the spatial representation and the processes by which it is modified.

ASSOCIATIVE MECHANISMS UNDERLYING LEARNING

Before exploring place cell plasticity, it is pertinent briefly to discuss general mechanisms that have been proposed to underlie information storage in the brain, from both a theoretical and a neurobiological perspective. The most intensely investigated hypothesis in the neurobiology of information storage comes from the work of Hebb /32/, who proposed that co-activity of two connected neurons should result in a strengthening of the connection between them. This highly influential proposition lends itself to the idea that such a process could form the basis of associating neural representations of events that, in the experience of the animal, belong together. Crucially, the 'Hebb rule' also implies that neurons whose activity is not synchronous should fail to connect, or, as Stent argued subsequently /84/, actually disconnect. As we shall see, the principles of connection of synchronously active neurons, together with disconnection of asynchronously active neurons, can explain many of the properties of place cell plasticity.

Considerable neurobiological support for Hebb's proposition was found with the discovery in the 1970s, by Bliss and colleagues, of the phenomenon of long-term potentiation (LTP), which is an experimentally induced form of synaptic plasticity in which forced co-activity of neurons leads to an increase in the strength of their connecting synapse(s). Such synaptic plasticity was first elicited in hippocampal pathways /14,15/ and occurs most prominently there, though it is has since also been observed in many other brain regions (see /52/ for review). LTP is a long-lasting activity-dependent enhancement of synaptic strength based on patterns of past activity, and for many reasons, the plastic changes induced through LTP protocols are thought to be the same (or nearly so) as those that underlie learning and memory (see /52,54/ for reviews). The molecular cascades leading from initial co-activation to a change in synaptic strength have been worked out in considerable detail (see /43/ for review). The process is initialised through the binding of glutamate to a particular kind of postsynaptic receptor, the *N*-methyl-D-aspartate receptor (NMDAR). The NMDAR essentially functions as a coincidence detector: opening of its ion channel requires simultaneous postsynaptic depolarisation and binding of glutamate released from the presynaptic neuron. This coincidence requirement has obvious parallels with the type of mechanism proposed by Hebb, discussed earlier. Following NMDAR activation, intracellular calcium levels become elevated which results in the activation of different kinases, such as protein kinase A (PKA) and calcium and calmodulin kinase II (CAMKII). These kinases are able to enter the nucleus and bind to transcription factors such as cAMP response element binding protein (CREB). Activated transcription factors can then recruit the transcriptional apparatus; indeed, high levels of immediate early gene (IEG) activity are seen within minutes of stimulation both *in vitro* and *in vivo*. Activation of IEGs (such as c-*jun* and c-*fos*) can in turn activate late effector genes that encode proteins responsible for structural changes at the synapse.

Each of the elements of the molecular cascade described above has been targeted in various studies that examine the effect of perturbing these

mechanisms on the activity of hippocampal place cells. The insight gained from such studies has been valuable and has contributed to our knowledge of the mechanisms linking learning and memory to hippocampal neurobiology. Before discussing these studies, we briefly review the characteristics of place cells, to provide a background for studies exploring how these characteristics change as a result of experience.

PLACE CELLS

Place cells are complex spiking cells found mainly in areas CA3 and CA1 in the hippocampus, and to a lesser extent in regions afferent to and efferent from it (including entorhinal cortex /76/ and subiculum /8/). Cells with place-related activity have also been found in other areas, such as parasubiculum /87/ and postrhinal cortex /19/ but these have been less well characterised. Place cells have been mainly studied in rats and, more recently, mice, but it is thought that many if not all vertebrates (including monkeys /51/ and humans /25/) probably have cells at least somewhat analogous to these.

The defining feature of place cells in rodents is that they become intensely active when the animal is in a restricted portion of an environment, regardless of which way the animal is facing; this area of activity is referred to as the cell's 'place field'. As the animal's head moves away from the field centre the firing rate of the cell decreases sharply and is usually almost zero outside the place field. An example of the activity of a place cell recorded from CA1 is given in Figure 1. Usually many of these cells are simultaneously recorded; each cell has a unique, cell-specific field that forms within minutes of the animal being introduced to an environment and, if the environment is kept stable and unchanging, appears to be active in the same location of the environment across days, weeks and months /88/. A question that arises from this is: What causes place cells to fire where they do? And, in the context of the present discussion, what - if anything - causes them to alter their firing following experience? Do place cells 'learn' where their fields should be, or is field location hard-wired by pre-existing connectivity? Are learned goal locations privileged in their place cell representations? If the animal experiences an event in an environment, does the representation of that environment change?

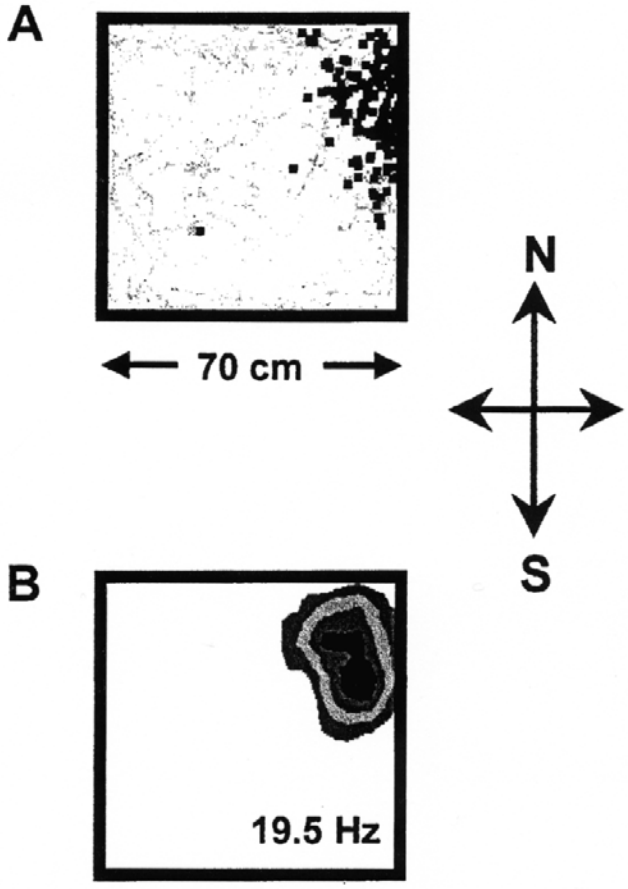

Fig. 1: **A.** Recording of a typical place cell, made as a rat foraged for rice grains in a box 70 cm square with walls 50 cm high. The grey stipples show the path of the rat as it walked around the box. Each small black square represents an action potential fired by the cell when the rat was at that place. It can be seen that this particular cell fires almost exclusively when the rat is in the North-East corner of the box. **B.** Same data as in A but smoothed and averaged, to produce a contour plot of the place field, showing the progressive decline of the field intensity with distance from its centre. Each gradation of the contour plot represents a step of 20% of the peak firing rate (peak rate shown in Hz in the bottom right of the diagram).

Much is now known about what kinds of environmental cues drive place cells under normal circumstances. A given place cell does not fire in response to any single particular sensory stimulus, because place cells will still fire in the same location upon the removal of any salient cues from an environment /72/ provided sufficient cues remain to collectively provide localising information. However, although the activity of cells is reasonably robust in the face of small environmental changes, there comes a point at which the firing patterns of cells *will* change. Thus, cells recorded in two different environments usually have unrelated place fields: that is, the firing pattern recorded in one environment cannot be predicted from that in a dissimilar one (see Fig. 2). The firing patterns in both environments are stable and appear not to interfere with one another /65,66/. When such a reorganization of the hippocampal map occurs in response to an experimental manipulation, the cells are said to have 'remapped' /66/, a term that reflects the original assumption of researchers that the cells are recruiting a new and non-overlapping representation of place. Remapping reflects a change in the activity patterns across the cell population, and as such, can tell us a great deal about the processes underlying the formation of the place representation.

Given that the hippocampus is critical for spatial memory formation, and that its synapses are highly plastic, an important question concerns how the activity of place cells and the prominent plasticity seen in the hippocampus relate to one another. There have been two broad approaches to this question. The first approach, an interventional one, is to examine place cell responses when processes important for synaptic plasticity are manipulated and compromised. The other is to take a more naturalistic stance and systematically manipulate the environmental experience an animal is exposed to in an attempt to induce the place cells to 'learn'. Below, we review the data yielded by these two complementary approaches, and then use these data to draw some inferences about how the place cell representation is organised and modified.

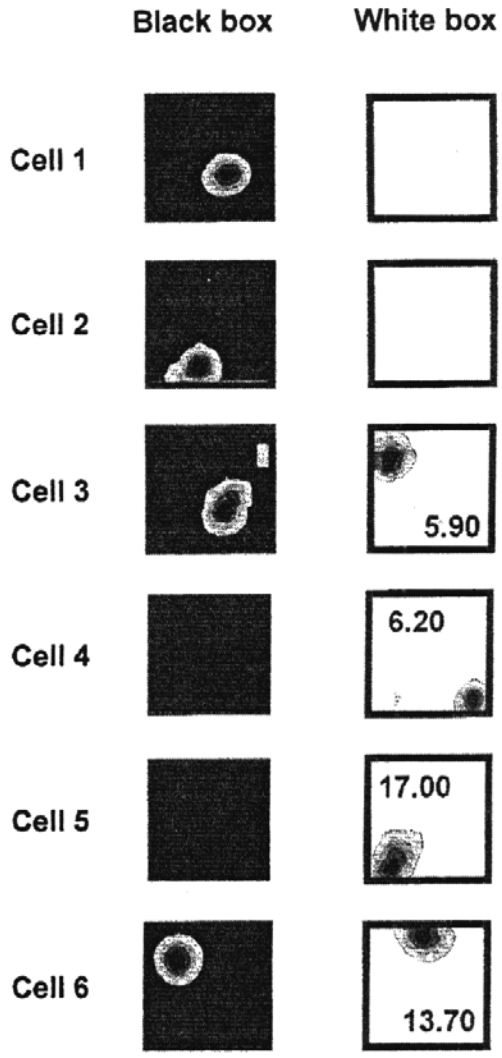

Fig. 2: The response of six place cells to changes in the environment. The rat foraged in a box that was either black or white. The cells fired differently in the two boxes: cells 1, 2, 4 and 5 had place fields in only one of the boxes, whereas cells 3 and 6 had different fields in the two boxes.

INTERVENTIONAL STUDIES OF PLACE FIELD PLASTICITY

If the pattern of place fields in a given environment arises as a result of experience-induced synaptic plasticity, then disruptions of synaptic plasticity should produce effects on the place cell

encoding of that environment. A number of studies point towards the possibility that synaptic plasticity is needed not so much for place field generation *per se*, but in order to consolidate the fields so that on future excursions of the animal into that environment, the same pattern of place fields will be activated. By and large, the kinds of interventions that have been undertaken so far fall broadly into three groups: pharmacological, electrophysiological and molecular genetic. For convenience we also include a fourth group, namely, studies of ageing which - though ageing is not strictly an experimental intervention - involves disruption of plastic processes that produce effects on place cell processing resembling, in many respects, those of more direct interventions.

Pharmacological interventions

A number of studies have investigated the effect of pharmacological interventions on place fields (e.g., /17,55,85,92,49,50/), but such effects as have been seen do not in themselves imply an effect on plasticity, since it may be sensory inputs onto the cells, or properties of hippocampal network processing, that are affected instead. Additionally, drugs have sometimes been employed to block neural activity altogether and thus create a reversible inactivation of a brain area; however, such studies are conceptually more like lesion studies and have not so far really addressed the issue of plasticity *per se*. More recently, experiments have been conducted using drugs known to interfere with LTP, in the expectation that these would affect characteristics of place fields that require synaptic plasticity.

An important contribution along these lines was the finding by Kentros *et al.* that the formation of stable place fields in a new environment requires NMDARs /44/. Acute blockade of NMDARs with the systemically injected competitive antagonist CPP ((±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid) reversibly blocked primed-burst potentiation (which is also dependent on NMDAR activation) in the freely behaving rat. The same dose and method of delivery did not, interestingly, disrupt place fields *per se*, since place cells recorded in the same environment before, and 1 hour after, CPP injections displayed the same fields. Remapping was similarly not affected by NMDAR blockade; distinct maps were seen, as usual, in the two distinct environments, and this new pattern could be recalled when the rats were reintroduced to the novel environment 1.5 hours later. However, the drug did interfere with the stability of the newly formed place fields over at least 16-24 hours. That is, the pattern of place cell activity seen in the novel environment on the first day of recording was replaced with a different map on the second day of recording in the novel environment. Therefore it appears that NMDAR-dependent synaptic plasticity is necessary for the formation of stable, long-term place representations.

Recently these findings have been extended by examining the role that protein synthesis plays in the stability of place fields /3/. LTP is known to have two distinct stages that differ in their reliance upon protein synthesis. The early phase (E-LTP) does not require protein synthesis whereas the late phase (L-LTP) does /63/. Similar to Kentros *et al.*, Agnihotri *et al.* reported that the recall of previously established fields in a familiar environment was not affected by protein synthesis inhibition with anisomycin /3/. However, blocking protein synthesis did affect the long-term stability of place fields: as with the study by Kentros *et al.*, different maps were expressed on two days in the novel environment. This finding accords with the notion that long-term stability of place fields may require long-term (i.e., protein synthesis-dependent) LTP.

NMDARs have also been implicated in short-term experience-dependent plasticity of place fields, in the phenomenon known as 'asymmetric expansion'. This phenomenon is discussed in greater detail in the next section, but in brief, when rats repeatedly run in the same direction across a place field, the field expands slightly towards the direction from which the rat came. The effect is transient and implies some kind of short-term plasticity, perhaps to enable sequence learning /1/. Ekstrom *et al.* found that asymmetric expansion was blocked by CPP /26/, again supporting an LTP-like process underlying the phenomenon.

In summary, then, pharmacological intervention targeted at LTP processes seems to affect long-term stability of place fields but not their existence *per*

se. The latter fact in itself is interesting, because it suggests that a given place field may be to some extent hard-wired, with plasticity determining *which* fields are expressed in a given environment. We return to this point later.

Electrophysiological interventions in the hippocampus

Another way of altering hippocampal synapses is by electrically stimulating them, so as to alter synaptic strength and thus produce changes in the connectivity and/or plasticity of the system. Following synchronous stimulation of many hippocampal afferents, such as via electrodes in the perforant path input from the entorhinal cortex to the dentate gyrus, it is possible to induce hippocampal LTP to an asymptote such that further potentiation is no longer possible /64/. In theory, such synaptic saturation should impair further plasticity and hence learning. Studies of spatial learning following LTP saturation have produced mixed results, with some studies finding an impairment in spatial learning /20,64/ and others failing to see such impairments (see /13/ for review). In the latter cases, it is possible that only a subset of synapses was being saturated /7/, thus leaving enough of the hippocampal network unaffected so as to support learning.

Despite the difficulties of affecting spatial learning using tetanization to asymptote, a similar manipulation has been shown to affect place fields, in an intriguing study by Dragoi *et al.* /23/. Place fields were recorded in animals trained to run clockwise and/or counter-clockwise around a rectangular track. Under normal conditions, some place cells display a directional dependence on such an apparatus, with a given cell sometimes producing a particular field when the rat runs one way around the track but not the other. During the rest periods following exposure to the task, LTP was induced in CA3 and CA1 synapses by stimulating the ventral hippocampal commissure. Subsequent recording sessions revealed that a remapping had taken place, insofar as some cells showed loss of existing place fields and/or development of new ones. Thus, alteration of the strength of hippocampal synapses was able to induce a new pattern of place field activity.

This finding is curious since the random nature of tetanic stimulation would not *a priori* be expected to recruit the exact combination of spatial inputs required to generate a well-formed, elliptical field. As with the drug studies discussed above, the implication is that place cells already have pre-existing fields associated with them, and that manipulations of synaptic plasticity can affect which fields are recruited, and for how long, rather than affecting the morphology of the field itself. Another interesting finding from this study /23/ was that sometimes a given cell remapped a field in only one direction of track-running and not the other. Thus, the tetanization did not affect the whole place cell, only one of its fields. This specificity of action implies some kind of interaction between the pre-existing fields and the new inputs that were recruited by the tetanization. In other words, it seems that the inputs potentiated by the tetanization selectively turned fields on and off, in a switch-like manner. As with the CPP study discussed above, this points to the likelihood that plasticity interventions affect which fields are active in a given situation, rather than the fields themselves.

Molecular genetic interventions

An important advance in the molecular dissection of place cell plasticity and stability has come with the development of genetic engineering technologies that allow the insertion or deletion of genes. In particular, the development of 'knock-out' mice lacking one or more of the genes implicated in synaptic plasticity, together with improved *in vivo* recording technologies, have led to important insights into the contribution of synaptic plasticity processes in the place cell representation /82/. As with pharmacological studies, these techniques are not without interpretational problems. For example, genetic manipulations may not always be localised solely to the structure of interest. Changes in genes sometimes cause compensatory changes that are not always well understood, and may interact in an unpredictable way with genes specific to a particular strain of animal (the 'background'). Furthermore, an animal that is born with a defective gene may be developmentally abnormal, making it hard to

separate effects on adult functioning from effects on development. The latter problem is sometimes overcome by 'inducible knockout' techniques in which a gene is engineered to have a chemical susceptibility, so that administration of the relevant chemical knocks it out in adulthood /74/.

Despite the above difficulties, gene studies have been invaluable in advancing our knowledge of how synaptic mechanisms mediate learning and memory. Knocking out the NMDAR1 subunit of the NMDAR in the CA1 region has been found to produce little effect on many of the basic electrophysiological characteristics of both pyramidal cells and inhibitory interneurons /56/. Although the knockout animals showed no NMDA-dependent plasticity and poor spatial learning /90/, comparable numbers of cells with place-related firing were seen in controls and experimental animals. Additionally, both groups of animals had place cells that were directionally selective on the linear track (see below). However, the place fields of experimental animals were larger, more likely to have multiple peaks, and had more diffuse firing patterns than controls. Cells with overlapping fields, whose firing is usually correlated over short timescales, displayed uncorrelated firing in the mutant animals. The inference drawn from this is that downstream brain areas in these animals could not use correlations, if they normally do so, to learn about place. Furthermore, if the position of the animal was reconstructed based on the firing of place cells, it was found that as the number of cells included in the ensemble increased, the reconstruction error also increased. This indicates a loss of coherence in the ensemble spatial representation, arguably reflected in the poor spatial learning of the animals.

Spatially restricted genetic alterations have also been targeted at NMDARs in cells located in the CA3 region of the hippocampus /68,69/. The CA3 region is of particular interest due to its specialised anatomical connectivity; it receives input from three main sources: mossy fibre input from the dentate gyrus, perforant path input from the entorhinal cortex and, most numerously, from the recurrent collaterals of CA3 itself /4/. The recurrent connectivity of CA3 has led researchers to suggest that this region could be used for the construction of an auto-associative memory /53,57,89/. These models emphasize that Hebbian learning mechanisms occurring in the recurrent connections allow the full retrieval of a representation based on only a partial, fragmented input. This property, known as 'pattern completion', in principle allows a memory to be retrieved in full when the animal is presented with only some reminders of it. Disruption of pattern completion should result in performance decrement in tasks that require use of an impoverished set of spatial reference cues, as the full representation should not be retrievable from the degraded input.

In support of this, Nakazawa *et al.* /68/ tested mice with a deletion of CA3 NMDARs under a variety of conditions. The CA3 knockouts displayed normal acquisition and retrieval of spatial reference memory in the Morris water maze under conditions in which a full cue set was present. Under such conditions there was no significant difference between normal and mutant place fields in terms of place field size or infield firing rate. However when the environment surrounding the animal was degraded (by removing all but one of the salient polarising cues), not only was retrieval of the spatial memory impaired in the mutant mice, but impairment was also seen in the activity of their CA1 place cells (i.e., in cells downstream from the affected cells). In partial cue conditions, cells in the mutant animals showed significant reductions in burst spike frequency, place field size and integrated firing rate as compared to full cue conditions. In contrast to the CA1 NMDAR1 knockouts discussed above, there was no difference in the coordinated firing of pairs of cells with overlapping place fields.

Genetic perturbations affecting intracellular targets of NMDAR activation also disrupt normal place cell activity. Mice expressing altered Ca^{2+}-calmodulin-dependent kinase II (CaMKII) displayed reduced LTP in CA1, severely impaired spatial learning and degraded place cell activity /22/. These deficits were also seen in mice deficient for the α and Δ isoforms of adenosine-3′,5′-monophosphate responsive binding proteins ($CREB^{\alpha\Delta-}$), albeit to a lesser extent. Place cells were recorded from all animals as they explored a four-arm radial maze across three sessions: in a standard position, one rotated through 90 degrees, and a final session identical to the first. In the first session the basic

features of place cell firing were present; there were no differences between either of the mutants and wild-type controls in terms of mean firing rate, the number of fields per cell and place field size. There was an increase in the infield firing rate of the α-CaMKII mutants, however, and there were significant differences in the spatial selectivity of cells in both mutant groups compared to controls (reflected by scattered firing patterns). In the rotated session, roughly two-thirds of the control place fields maintained the same representation as in the first session or rotated concomitantly with the local or distal cues. Only a minority of mutant cells did the same, however; most remapped. In the final session, roughly half of the control and $CREB^{\alpha\Delta-}$ cells showed the same representation as in the first session, whereas only a few of the α-CaMKII mutants cells' representations were consistent with the first pattern of activity.

Place cells have also been recorded in a strain of genetically altered mice that have reduced forebrain protein kinase A (PKA) levels. PKA and other kinases phosphorylate specific proteins (such as receptors and membrane channels), thus altering functional properties such as membrane channels activation kinetics and the duration of a cell's action potential. Behaviourally, these mice showed near normal context conditioning behaviour at short time scales (1 hour) but attenuated freezing behaviour at longer intervals between shock and test (24 hours) /2/. Electrophysiologically, there was near normal early LTP but impaired late LTP. As with acute pharmacological blockade of NMDARs /44/, the place fields in the PKA mutants were stable and comparable to controls over short time periods (~1-2 hours) but lacked stability over 24 hours.

The above studies all examined the effects of interfering with Hebbian NMDAR-dependent processes and their downstream targets. To date, only one molecular genetic study has been conducted on the contribution of non-Hebbian processes to place field formation/stability /95/. These animals lacked the gene for the GluR2 subunit of the AMPA receptor and displayed enhanced non-Hebbian LTP in CA1 neurons /42/. Place cell activity was impaired in these mice; like the CaMKII mutants discussed above, the GluR2 mice had significantly fewer cells that showed location-related firing (~23%) compared to controls (~44%). Additionally, using a coherence measure, the boundaries of the place fields were less well defined in GluR2 compared to wild-type fields. The place fields of the GluR2 mutants were also not as tightly controlled by rotations of a cue card, as were those of the controls. Interestingly, unlike animals with a CA1-specific NMDAR1 mutation, the GluR2 mutants showed no significant difference in the size of their place fields compared to controls.

It thus appears that the mechanisms underlying long-term plasticity are not required for the basic short-term characteristics of place cell firing. Interventions aimed at NMDARs (in CA1 and CA3), GluRs, CamKII, CREB and PKA appear not to affect the basic location-related activity of hippocampal pyramidal cells, though spatial specificity is sometimes reduced. What *does* appear to be affected is the long-term stability of the representations that are created. It is also possible that these plastic processes are also responsible for the increasing refinement in quality of the representation over time /94/.

Ageing and hippocampal processing

Another group of animals in which hippocampal processing is altered are those in late adulthood. Ageing impacts particularly on hippocampus-dependent abilities, such as memory for novel spatial information, and it is accompanied by altered neuronal morphology and physiology (for review see Rosenzweig and Barnes /79/). Most importantly in the present context, ageing has been associated with changes in hippocampal synaptic plasticity, particularly with respect to the duration of LTP. Thus, it might be expected that old animals would also show differences in their place fields.

Despite deficits in spatial learning, changes in hippocampal physiology and a reduced capacity for LTP, aged rats have relatively preserved place cells and place fields /10,27,60/, although there is evidence of reduced spatial specificity /9,96/. Two somewhat contradictory findings have emerged so far from ageing studies. The first is that the place cells in aged rats have a tendency to spontaneously remap in a familiar environment /10/, a phenomenon termed 'multistability'. In the first demon-

stration of this effect, place cells from young adult rats were shown to be stable from one session to the next on an elevated figure-of-8 track, whereas for aged rats the firing patterns were consistent on 70% of trials but completely remapped for the remainder. The bimodality of correspondence between place cell activations was reflected in an analysis of behavioural performance of a separate group of animals all trained on the water maze task. Although place cells were not recorded in the latter group, the implication is that old rats tend to either undergo spontaneous remappings or not, and if so, they have difficulty with the spatial task, whereas if not, they perform normally. The phenomenon of multistability implies a deficiency in the ability of the cells to anchor themselves to features in the outside world, either due to a decrease in the quality of sensory information reaching the hippocampus, or a failure of the hippocampal network to store, synaptically, the relations between place fields and cues in the outside world.

The other observation, which at first glance seems contradictory, is that place cells often *fail* to remap in the face of salient environmental /86,93/ or task /75/ change, where normal rats do. Tanila *et al.* recorded place cells in young and old rats running on a four-arm maze possessing a number of distinctive cues, both on the arms and in the surrounding room. Oler and Markus /75/ found that place cells in old rats were less likely to differentiate between two similar tasks (an 8-arm maze or a plus-maze formed by removing the arcs connecting the ends of the arms).

Rapp /77/ and Redish *et al.* /78/ reconciled these two apparently contradictory findings (remapping in stable environments versus failing to remap in novel ones) by suggesting that in both cases, what is happening is that old rats are failing to represent the contextual aspects of the situation: namely, that the cells do not accurately encode either the stability of the constant environment *or* the novelty of the changed one. Thus, there seems to be a failure of the cells to be accurately controlled by contextual cues. However, as Mizumori and Leutgeb pointed out in the same discussion /61/, a distinction must be drawn in these studies between a failure of appropriate plasticity (linking of contextual cues to the place representation) versus a simple sensory deficit in the old animals.

Aged rats also display a loss of that form of experience-dependent plasticity manifested as place field expansion and backward shift in place fields, (see above), seen in young rats running repeatedly around a track /81/. Initially the place fields of both young and old rats were no different, yet after several laps of a linear track the young animals' place fields had both enlarged and shifted backwards relative to the trial start. The old rats failed to exhibit such plasticity. The mechanisms by which experience-dependent expansion of place fields occurs are not yet fully understood. However, if the theoretical predictions are correct, then it would seem that the place field deficiencies seen here may reflect a failure of an asymmetric LTP-like process in aged rats.

Interventional studies: Conclusion

The most surprising finding to emerge from studies in which synaptic plasticity has been impaired is the degree to which place fields look relatively normal. Admittedly, some manipulations result in coarsening of fields or reduction in their spatial specificity, but by and large, the fields themselves are still well localised and clearly are availed of *some* spatial information. From this we can tentatively conclude, therefore, that the generation of a field *per se* does not require synaptic plasticity, suggesting that the cells are hard-wired (or 'preconfigured' /58/)with the propensity to form place fields even in a novel environment. Such a preconfiguration would be adaptive because it means that when an animal enters new territory it can at least scramble together a quick map of *some* kind, even though it does not yet know about the relevant landmarks.

What *is* clear from the synaptic plasticity studies is that the persistence of the fields over a period of time greater than a few minutes or hours seems to depend on a process very like LTP in its dependence on NMDA receptors and protein synthesis. This suggests that when an animal learns about a new environment, it quickly recruits place fields (a non-NMDA-dependent process) and then associates them, via an NMDAR-dependent process, with the spatial cues so that upon re-entry, the same map can

be recalled. In the next section, we review some of the evidence that the association of cues with fields may be a learned phenomenon.

NATURALISTIC STUDIES OF PLACE FIELD PLASTICITY

Although the interventional studies described above have yielded provocative evidence of a role for synaptic plasticity in place field organisation, a concern arises that the disruptive nature of the interventions possibly drives the place cell system into a pathological state, in which the observed phenomena are merely oddities and do not provide insights into normal processes. A complementary approach, then, is to look at the system in a relatively undisturbed state (biologically speaking) in which cells are availed of their full complement of molecular machinery. In studies of this kind, rats are given the opportunity to learn naturally about the environment they are in, and their place cells are observed to see whether their behaviour changes in a way that might reflect (and indeed, underlie) this learning. It should be noted here that just because an animal has received no biological interventions, this does not mean that the system cannot nevertheless be driven into a pathological state by strange environmental manipulations that would not normally occur in the natural world. Nevertheless, naturalistic studies have many insights to offer in the study of how the place representation is modified by experience.

Naturalistic studies of place cell representational plasticity fall broadly into three classes: studies of goal-directed learning, studies of how experience affects an existing representation, and discrimination studies in which place cells 'learn' to distinguish between two different, albeit closely similar, environments. These are detailed below.

Goal-directed learning

A number of studies have explored whether the place cell representation changes in response to explicit spatial training, as might be expected if a function of the spatial representation is to encode places of special interest to the animal. Such studies are sometimes hard to interpret because spatial training necessarily induces non-homogeneous coverage of the environment by the animals, and under these conditions it can be very difficult to map out place fields reliably. This difficulty is compounded by the fact that when animals stop actively traversing the environment, as they do near a goal, the hippocampus enters the EEG state known as LIA (large amplitude irregular activity) which is associated with the synchronous firing of many cells /71/, which thus appear to have place fields near the goal (by virtue of the fact that they fire only in its vicinity). A third problem is that goal locations often have sensory characteristics that could serve to function as ordinary spatial cues. Despite these difficulties, a number of investigators have attempted to control for these confounds and determine whether goals are over-represented in the environment, and whether the representation changes with training.

In an early investigation of goal-directed behaviour, O'Keefe and Speakman recorded place cells as rats performed a goal location task on a four-arm maze /72,83/, and found that the cells did not appear to represent the goal arm differently from the non-goal arms, and nor did they change their activity when the goal was moved to another arm. A number of subsequent studies, however, reported differences in place fields near goal locations. Breese *et al.* recorded place cells as rats ran to five rewarded locations, one in each corner and one in the centre of a square platform /18/. When the reward contingency was switched from all five cups to just one of them, place cells altered their firing (remapped), sometimes producing a field in the rewarded location. When the reward location was changed, fields sometimes followed the rewarded location, raising the possibility that the goal in this apparatus was selectively represented. In this experiment, the environment was sparse in directional cues with only a cue card to polarise the environment, and it cannot be ruled out that the reward location, when reduced to a single corner, functioned as a more salient directional indicator to the place system and thus caused place fields to rotate as the reward location rotated. In other experiments, however, this explanation would not suffice. For example, Kobayashi *et al.* recorded place cells as rats ran between two rewarded

locations on an open field, and found that fields seemed to be preferentially located near the rewarded zones /46/; and Hollup *et al.* recorded place cells as rats swam to a goal platform in an annular water maze, and saw increased activity of place cells near the platform location /33/. Similarly, Holscher *et al.* saw increased activity of place cells in the rewarded versus non-rewarded arms on a radial maze /34/.

While these studies are in agreement that there is often increased activity of place cells near a goal, they do not allow a determination of whether this is due to the 'goal-ness' of the goal, or to the fact that the rat behaves differently there (for example, stopping to receive reward) or even just to the fact that the goal is a salient spatial location in an environment that is otherwise sparse in spatial cues. To circumvent this problem, Jeffery *et al.* /40/ recorded place cells as rats interspersed periods of foraging with tone-cued runs to the goal corner of a square box. In this paradigm, place cells could be recorded in the goal location when the rat was not actually navigating there (during the foraging periods) and therefore not producing a possibly confounding behaviour. This protocol also allowed determination of whether cellular activity was triggered by the tone signalling availability of reward at the goal. In fact, no difference was found in the representation near the goal, nor was any activity seen that might be related to the auditory signal that triggered navigation to the goal. Similarly, Zinyuk *et al.* did not report goal-related firing of place cells in a place preference task in which rats interspersed runs to an unmarked goal location with foraging /97/. It thus seems that under ordinary foraging conditions, place cells do not represent unmarked goal locations differently from other places, and there is thus little evidence for a learned component to the fields in these conditions.

A number of studies have looked at changes in place cell activity in response to classical conditioning. Many of these studies did not concern themselves with place-related activity and so will not be considered further here. However, Moita *et al.* recorded in an auditory fear conditioning task, in which a series of auditory pips signalled a foot-shock /62/, and found that place cells developed responses to the auditory stimulus when the rat was in the cell's place field but not when it was outside it. Thus, the place-responsiveness of the cells was enhanced by the learned fear-inducing stimulus. Whether this indicates a specific place- or event-learning process, or simply reflects emotional enhancement of a place response (due, for example, to increased arousal) remains to be determined.

Latent learning in a single environment

Leaving goal-directed learning aside for the moment, it is interesting to explore whether place fields show evidence of plastic changes when rats are in the process of familiarising themselves with an environment, and thus presumably consolidating their spatial representation. A number of studies have looked at how place cells react when recorded in a given environment over a period of time.

Normally, if the environment is stable then the place cell representation is also believed to be stable, and indeed some place cells have been observed to show unchanged fields over many days and weeks /88/. This accords with the traditional view of these cells as instantiating the animal's knowledge about a place: if the place does not change, then neither should its neural representation. However, it is a common experience among place cell researchers that sometimes, for no apparent reason, place cells remap spontaneously even when the environment is stable. This phenomenon is rarely acknowledged and is traditionally attributed to the problem, inherent in long-term studies, of possible instability in the recording preparation due to electrode shift, etc. Arguing against this interpretation, a recent report by Kentros *et al.* /45/ suggests that the instability that is particularly pervasive in place cell recordings from mice may in fact be a function, not of methodological artefacts, but of the low attention paid by the animals to the spatial context. As such, it may reflect a real instability in the system. Whether or not such instability serves an adaptive function in mice and rats remains to be seen, but the influence of attention could offer insight into the lack of place cell stability seen in aged rats, as discussed earlier, i.e., perhaps senescent animals are less able to pay attention to and process contextual information, resulting in representational instability (see below).

As well as spontaneous remapping, a number of studies have observed systematic alterations in place fields in response to experiences that the animal has in an environment. The simplest kind of experience is repeated entry into the same environment, and indeed small but pronounced short-lasting changes in place fields have been observed when rats run repeatedly in the same direction along a linear track /59/. In this situation, place fields were found to expand asymmetrically such that cells recorded over multiple laps around the same track displayed place fields that shifted backwards and increased both their firing rate and firing field size (Fig. 3). Because LTP of hippocampal synapses is asymmetric, occurring only if the postsynaptic neuron is depolarised very shortly after the depolarisation of the presynaptic neuron /11/, this result was taken as indirect evidence that asymmetric Hebbian strengthening of the connections between cells was occurring. Because the cells with place fields were always activated in the same temporal order in this task (because of the unidirectionality of the rats' trajectories), it was postulated that the synapses from early firing cells to later firing cells become selectively potentiated, thus causing a given cell to be driven to firing threshold progressively earlier with each lap around the track, with the result that fields tend to shift backwards along the track and increase their field size. As discussed in the previous section, the expansion and backwards shift seen in place fields here appears to be dependent on NMDAR activation, since blocking NMDAR activity with CPP prevents these two processes /26/. It should be noted, however, that these two processes are relatively short-lived; the shifts in place field size and location seen on one day are not seen on the following day. Therefore this process may reflect a short-term form of plasticity in the behaving animal.

Studies of longer-term plasticity have begun to explore how place cells can permanently acquire new information about the environment, in a way that reflects useful knowledge that the system has acquired about the world. An example of this approach comes from a series of studies in which place cells were observed to acquire new information about which cues in the environment could serve as valid directional indicators. Under normal circumstances, place cells use a stable, salient visual cue as a directional reference in preference to the rat's internal direction sense /39/, since the latter is prone to drifting over time if not corrected /29/. However, if the visual cue is experienced as unstable, then the cells cease orienting with respect to the cue and orient with respect to the internal direction sense of the animal instead /35,41/. Thus, it seems that when directional sources of information are placed in repeated conflict, the system 'trusts' the internal cues, derived from vestibular, proprioceptive and motor efferent commands, more than it trusts the visual cue. This kind of learning by the place system is probably adaptive since, in the real world, sudden large discrepancies between a landmark and the animal's internal sense of direction are more likely to be due to movement of the landmark than sudden large errors in the internal direction sense. Also adaptive is the fact that such learning appears to be context-independent, inasmuch as directional cue learning that took place when one place cell map was active persisted when contextual cues were changed to activate a different map /31/ (Fig. 4). Again, this property is useful to the animal since directional cues are typically distant /98/ and stable, whereas local contexts may change. The place system is thus capable of acquiring relatively long-lasting information that is pertinent to the environment the rat experienced.

Latent learning of discriminative responses to two environments

As well as altering their responses to a single environment with repeated exposure, place cells have the capacity to develop differential representations of two closely similar environments, a process conceptually (and perhaps mechanistically) related to perceptual learning. The first demonstration of such a discrimination was provided by Bostock *et al.* /16/. Animals were trained to forage for rice in a standard cylindrical grey environment with a white cue card attached to the wall. Once a place cell was recorded in the presence of the white cue card the colour of the card was changed to black. Initially the place fields rotated in response to this manipulation, but over subsequent exposures the

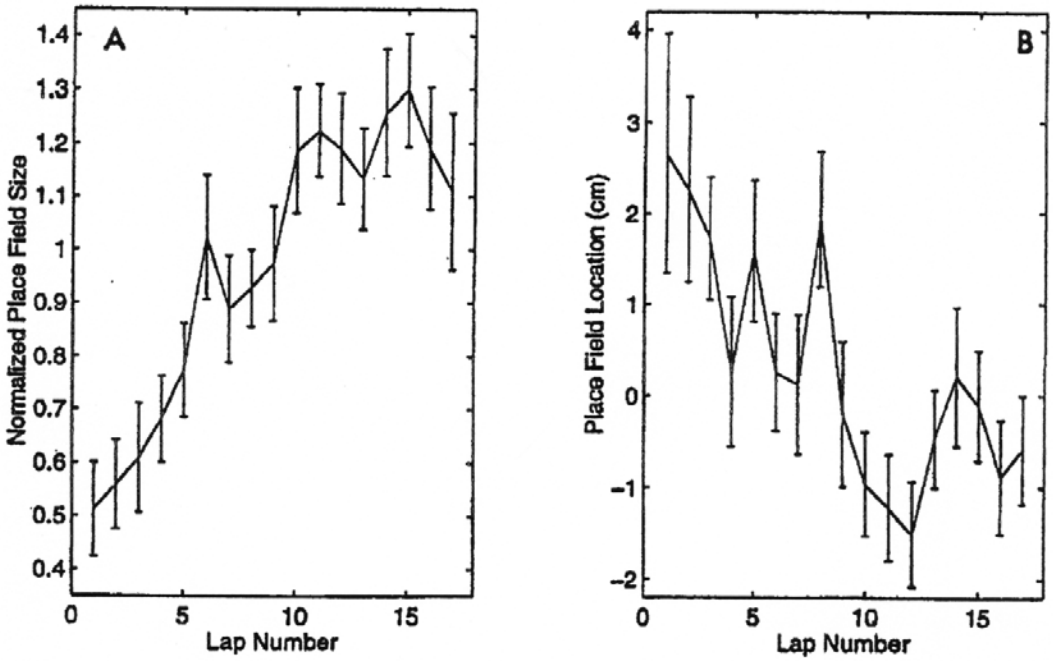

Fig. 3: Asymmetric expansion of place fields as a rat ran repeated laps around a rectangular track. **A.** The size of the place fields gradually increased with increasing number of laps. **B.** The location of the fields gradually shifted backwards, towards the direction the rat was coming from, as the number of laps increased. From Mehta *et al.*, 1997 /59/. © National Academy of Sciences USA.

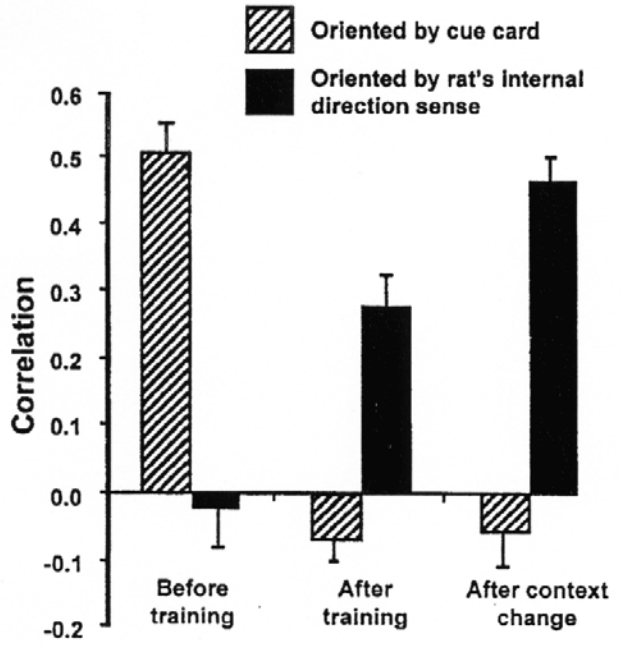

Fig. 4: Histogram showing how, when control of the directional orientation of place fields changed with experience, this transfer of control persisted when the context was changed, even though the place cells had remapped. The y-axis is a correlation measure that reflects how closely the observed control matched the expected: a high correlation indicates control by the relevant factor, and a low correlation reflects loss of control. Initially, the cells were oriented by the cue card (leftmost bar). After experience (middle bar), during which the rat observed that the cue card was mobile, and hence an unreliable landmark, the cells switched the preferred orientation stimulus to the rat's internal direction sense (ascertained by slowly rotating the rat and showing that the place fields aligned themselves according to the rat's rotation and not the cue card). After a context change (rightmost bar), the cells still oriented themselves according to the internal direction sense, showing that the learning acquired in the first context transferred to the new one. Adapted from Chakraborty *et al.*, 2004 /21/. © Elsevier.

representations diverged until distinct place cell activations were occurring in the two environments. This 'complete remapping' was observed in one rat to occur rapidly, within a time frame of 2.5-3 minutes. The time course of this experience-dependent remapping varied between animals; however, once this divergence was seen in one cell all subsequently recorded cells from that animal expressed divergent fields.

The sequential occurrence first of rotational and then of complete remapping is interesting, and suggests two consecutive processes at work. The simplest explanation for the rotational remapping is that when the cue card was changed in colour, the directional system treated the changed card as a new one with an arbitrary angular location, and rotated its orientation (and thus the place fields) accordingly. The subsequent development of complete remapping is harder to explain. It suggests that over time, the place system came to treat the two situations as different, perhaps because the two cards never appeared simultaneously, and thus a new representation formed.

A divergence of firing patterns in two different but highly similar environments has since been reported in three subsequent studies. In the first of these, place cells were recorded as rats foraged for rice in identical boxes in either of two adjacent locations. Initially, place fields in the two locations were highly similar, with the majority of cells showing no remapping. As recording continued, however, an incremental divergence was seen such that a greater proportion of cells began to discriminate the two locations, evidenced as increasing numbers of cells remapping (Fig. 5). Through various probe manipulations it was inferred that the

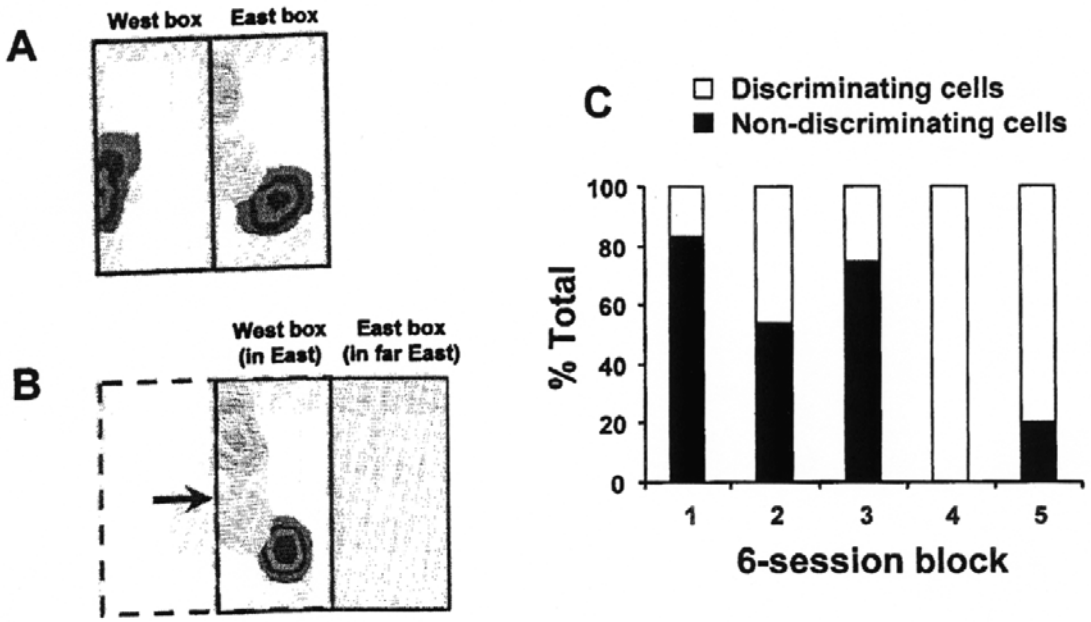

Fig. 5: Learned discrimination of identical environments by place cells. The two rectangular recording boxes were located in adjacent positions within the laboratory, so that the rat could see outside the boxes, and the rat moved from one box to another by walking through a transiently provided gap in the partition wall. Cells initially had identical fields in the two boxes, but over time, an increasing proportion of them began to 'remap' (**A**), firing differently in the two boxes. **B.** A probe test, in which the boxes were moved eastwards, to test whether the discriminative stimulus was a path integration signal from locomotion, or from distal cues in the room. The cells in the West box (now located in the East box's former position) fired in the formerly East box pattern, demonstrating that it was absolute location in the room and not relative location that determined which pattern the cells adopted. **C.** Population data from the rat whose cells are illustrated in A and B, showing gradually increasing development of discrimination over the course of many days of recording. Adapted from Jeffery /36/. © Cambridge University Press.

primary source of discriminative information that allowed the cells to differentiate the two locations was provided by distal, extra-maze, cues.

The second study reporting a gradual divergence of initially similar place cell representations came from an experiment by Lever *et al.*, who recorded place cells in square or circular boxes over a period of many days /47/. The place fields in the circular and square boxes were initially similar but gradually diverged (Fig. 6A). As in the study by Bostock *et al.*, the time it took for this divergence to occur varied depending on the individual animal. The pattern of remapping seen in this experiment was partial, as opposed to the complete remapping seen in the study of Bostock *et al.* The patterns of activation also showed generalization across boxes of the same shape but made of different material, confirming that shape was the relevant discriminand. Additionally, the change in place field activity was persistent, lasting at least a month, and it was experience dependent (i.e., time alone did not account for the shape-specific firing patterns). The authors proposed that the long-term, experience dependent divergence of place cell representations seen in this experiment is commensurate with a system that underlies long-term incidental environmental learning.

The third study was a replication of the first, in which cells learned to distinguish two locations of a recording box, but with an added manipulation /31/. Animals were repeatedly exposed to two identical neighbouring square boxes. As with the studies above, cells active in the two boxes initially displayed highly similar firing fields, but over time the patterns in the two boxes diverged. Interestingly, unlike the studies above, but like that of Bostock *et al.*, when discrimination occurred (usually after about 2 weeks or so) it tended to be complete, affecting all observed cells. Also of interest, different rats showed different patterns of

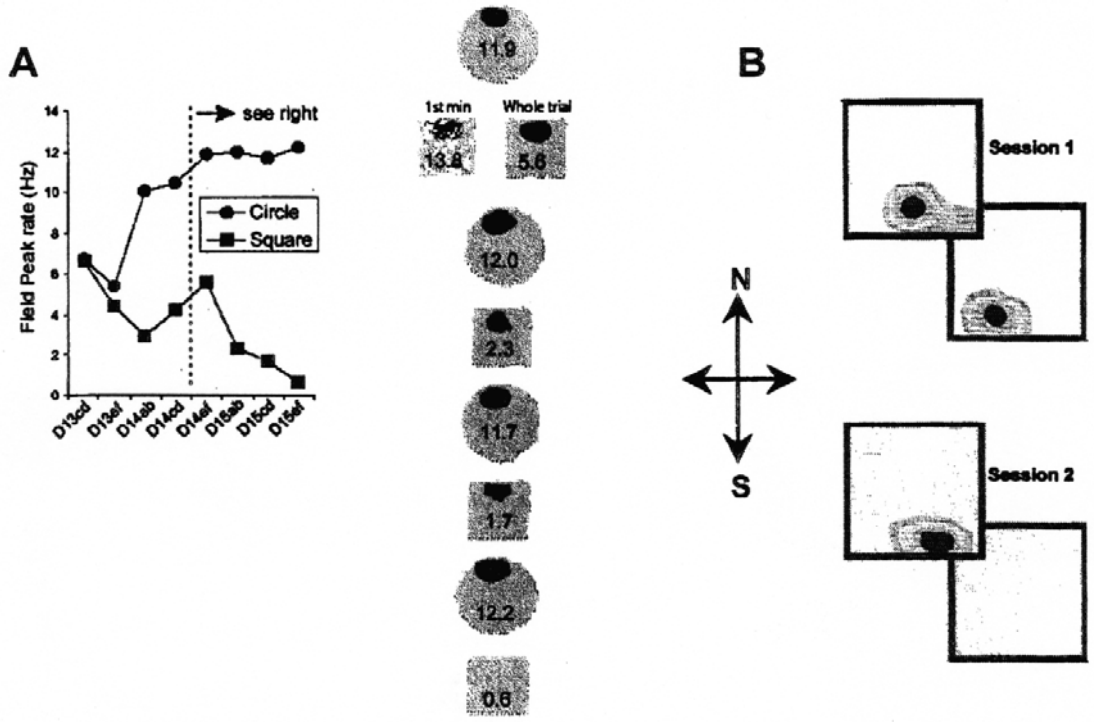

Fig. 6: Observations of the development of discrimination by individual place cells. **A.** Data adapted from Lever (personal communication), showing how a single place cell developed the ability to distinguish a square from a circular recording environment over the course of several sessions across several sessions of recording. **B.** Development of remapping by a single place cell that learned over the course of one session to distinguish two locations of a recording box (unpublished data from Jeffery, 2001 /36/). These observations show that individual cells can acquire the ability to discriminate environments.

remapping, with cells in one rat tending to switch fields on and off, cells in another rat tending to shift them, and cells in the third rat showing a change in rate. The new manipulation was that following acquisition of the discrimination, the two-box procedure was repeated, but now the boxes were of a different colour, a procedure that tends to induce complete remapping (e.g./37,40,6/). The aim was to see (a) whether discriminating cells carried their discrimination into the new context, and (b) whether newly active cells would be discriminating right from the beginning. Somewhat surprisingly, it was found that the discrimination evident in the first context was not displayed in the second, either by those cells that had discriminated the original environments that also had (remapped) fields in the new context, or by newly active cells (Fig. 7). Thus, the same place cell appeared to be able to distinguish North from South in one context but not the other. This surprising finding places some constraints on the kinds of mechanism that could explain the discrimination, which are discussed below.

POSSIBLE MECHANISM FOR ACQUISITION OF DISCRIMINATIVE PLACE CELL RESPONDING

The four experiments discussed above show that place cells can gradually acquire diverging responses to two sets of similar but non-identical stimuli, a type of discriminative responding that is commonly known as 'pattern separation'. Such experience-dependent change in responsiveness to environmental stimuli strongly implies some kind of plasticity in the inputs to place cells, though not necessarily localised within the hippocampus itself. In the simplest explanation of discrimination, one can postulate a Hebbian process that causes a change in the discriminative inputs as a result of co-activity, with postsynaptic drive coming from the pre-existing, common inputs, and presynaptic activation supplied by the initially weak discriminative inputs. The proposal that discriminative inputs become strengthened in a Hebbian manner by co-activity is straightforward, and is supported by evidence that LTP is prominently found in inputs to CA1, as elsewhere in the hippocampal circuitry.

Less straightforward is the weakening of common inputs that must occur in parallel. Recall that what is observed in discrimination experiments is that discrimination involves the *loss* of a field in one or other environment /36,47/. Although in most cases this is merely inferred, in a few cases individual cells have been tracked long enough for the loss of a field to be directly observed (see Fig. 6). Thus, LTP of the discriminative inputs is not enough to explain the development of discrimination by a cell, because the cell was already active in both environments: strengthening of a

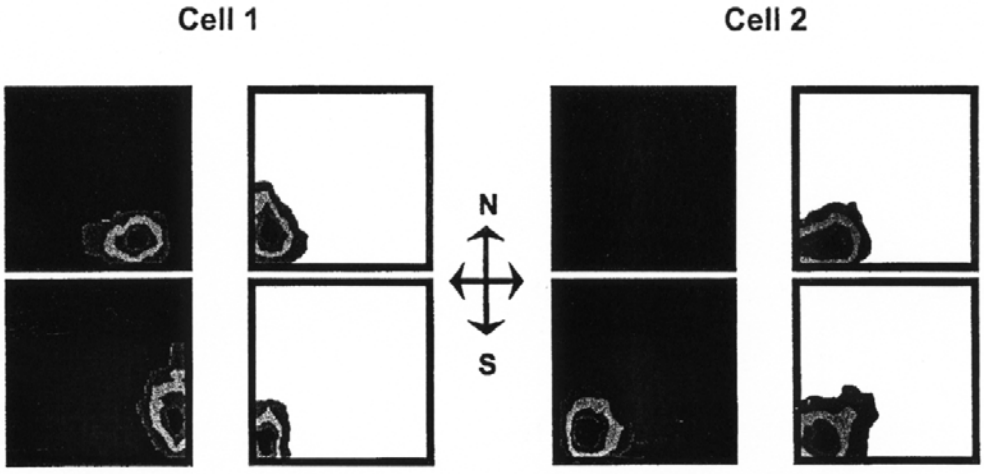

Fig. 7: Two cells that learned to discriminate the North from the South location of an environment when the environment was black, but which failed to discriminate the same two locations with remapped fields when the environment was white. The ability of single cells to discriminate with one field but not another suggests that the discriminative stimuli modulate the inputs governing a field, rather than modulating the whole cell. Adapted from Hayman *et al.* /31/.

previously weak input would only cause the cell to be even *more* active in one of the environments. It is possible in theory, though there is no evidence for this, that the potentiation occurs in inhibitory pathways, so that the discriminative cues acquire the ability to inhibit the cell in one or other environment. This does not, however, explain the behaviour of cells that lose their existing field in one environment but gain a different one in the other (like cells 3 and 6 in Fig. 2). Furthermore, LTP of feedforward inhibitory inputs has not, to our knowledge, been reported in CA1.

A more likely explanation for the loss of fields is that while inputs from discriminative stimuli are indeed strengthened, by LTP, this strengthening is counteracted by a simultaneous process that weakens the pre-existing inputs from the common stimuli. In other words, inputs that could previously drive the cell above its firing threshold by themselves lose the ability to do so, resulting in a functional weakening of these previously strong inputs. It is of some interest to ascertain what the rules are by which such a process could theoretically occur, based on some of the properties of synaptic plasticity that have been elucidated experimentally. Fuhs and Touretzky have begun to explore this issue using simulated neural networks /28/. They noted that ordinary Hebbian learning (strengthening due to co-activity), or a variant of it known as the Hebbian covariance rule (in which synapses are strengthened or weakened according to how much the presynaptic or postsynaptic neurons deviate from their mean firing levels), could not explain how fields could be lost in one of the environments. They had greater success with a synaptic learning rule known as the BCM rule, named after its inventors Bienenstock, Cooper and Munro /12/. In this rule the synaptic strengths are increased when the activity of the pre- and postsynaptic neurons exceeds a particular threshold and weakened when activity is below it. Crucially, this modification threshold varies according to the mean activity of both neurons, which prevents runaway scaling up or down of all the synapses. Thus, when the system is relatively quiet, the threshold gradually falls until it is low and even low neural activity can thus cause synaptic strengthening, which in turn nudges the cells' activity upwards. As the increasing synaptic strengths drive neuronal activity up to higher levels, the modification threshold also rises so that not all synapses are able to exceed it: those that do not become weakened. The concurrent strengthening of more active synapses and weakening of less active ones, together with a sliding modification threshold that is able to remain within the dynamic range of that particular system and keep the mean activity in a middle range, means that the strong and weak synapses are in essence 'pulled apart', and optimal pattern separation can thus occur. Fuhs and Touretzky showed that the BCM rule can account for some aspects of place cell discrimination: namely, the loss of a field in one of the two environments (the one in which the field was slightly weaker).

Can something like the BCM rule explain how place cells come to acquire location discrimination? This is not completely straightforward. According to the processes we postulated above, initially strong inputs to the place cell (from the box) become weaker, and initially weak inputs (from the distal cues) become stronger - the opposite to what happens in other pattern separation models. It is almost as if there is some process operating to normalise the total strength of synapses, so that as some synapses become stronger (presumably due to LTP), others, or perhaps the whole population, are collectively weakened by a small amount to compensate. Such balancing of synaptic changes has been observed experimentally and is referred to as synaptic scaling (see Turrigiano and Nelson for review /91/). Synaptic scaling allows the total activity of a neuron to be maintained within a set range, while preserving the distribûtion of synaptic strengths. Such a scaling mechanism operating in conjunction with LTP might explain how place cells learn to discriminate two environments: as inputs from the discriminative stimuli gradually increase in strength, the scaling process weakens the original inputs so that they are no longer able to drive the cell by themselves; henceforth, both the original inputs *and* the newly acquired discriminative inputs will be required to drive the cell to its firing threshold. We have diagrammed this postulated sequence of events in Figure 8.

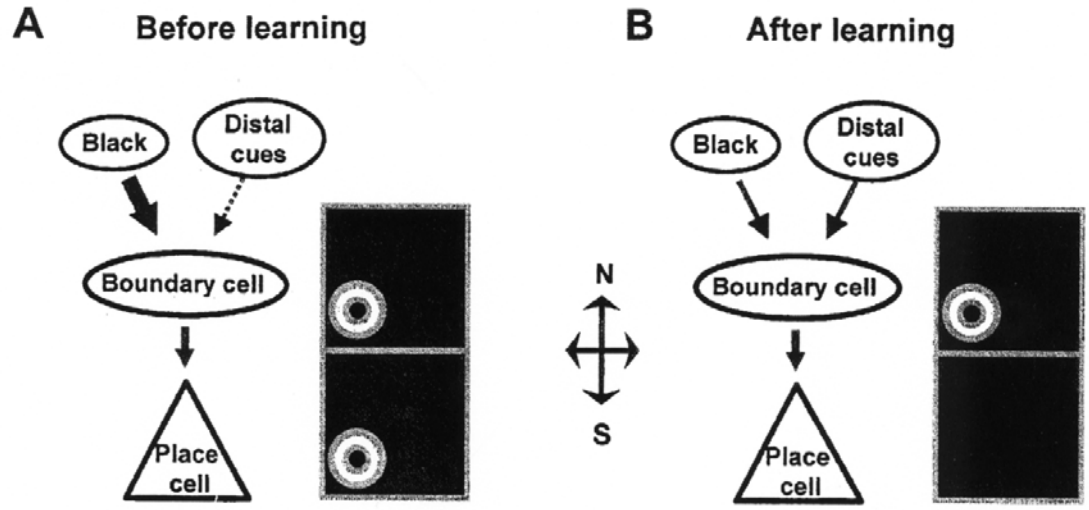

Fig. 8: Schematic diagram of how a place cell might come to acquire a discrimination between two environments. This models data from the experiment by Hayman *et al.* /31/ in which place cells learned to discriminate a North from a South location of a black recording box. Because of the independent modulation of fields that is described later, we assume that a particular field is specified by a boundary cell, which is in turn modulated by a set of inputs known as contextual inputs. **A.** Regardless of whether the box was in the North (upper) or South (lower) region in the room, this hypothetical place cell produced the same field. We assume that the boundary inputs specifying this particular field were in turn controlled by a set of contextual inputs indicating that the rat was in the black box. These context cues were initially sufficiently strong (thick arrow) to drive the cell by themselves. Although the cell also received weak inputs from the distal cues (dotted arrow), active when the box was in the North, these did not affect the cell's firing. Their activity did, however, co-occur with the cell's activity as driven by the black context cues, providing the necessary conditions for Hebbian strengthening. **B.** After repeated experience of the two locations, during which the distal cue inputs were repeatedly co-active with the cell, these inputs became stronger (solid arrow). Simultaneously, a homeostatic scaling process /91/ operated to weaken the pre-existing inputs. Now, a conjunction of the original contextual stimuli *and* the newly acquired distal cue inputs signalling that the box is in the North location are required to drive the cell to firing threshold. The cell thus only generates its field when the box is in the North.

Context-dependence of acquired discriminative inputs

The above processes may plausibly explain how a place cell can acquire discriminative responses to two similar environments, but they cannot explain how such acquired discrimination could be context-specific, as in the experiment by Hayman *et al.* described earlier /31/. For a given place cell to be able to express a discriminating field in one context and a non-discriminating one in another, like the cells in Figure 7, it is necessary to assume that the new inputs act at the level where the field is specified, rather than modulating the cell as a whole.

We have elsewhere suggested that fields can indeed be modulated independently of each other, by virtue of possessing independent sets of so-called contextual inputs /38/. According to our model, the inputs impinging on a place cell can be differentiated into so-called boundary inputs (after /30/), which produce a given field, and contextual inputs, which switch the field on and off (note that directional input is also important to orient the fields, see e.g. /39/). This model accounts for the interposition of a boundary cell between the inputs and the place cell that is shown in Figure 8. The boundaries of the environment determine which boundary inputs are active (and thus where the cell should fire), whereas the context inputs determine which, if any, boundary inputs are expressed by a cell in a particular environment. This hierarchical organization of the inputs thus allows the individual fields to be switched on or off independently

of one another. We suggest that when a discrimination is acquired, new items are added to the set of modulating context inputs. Since these interact with the field-generating inputs upstream of the place cell itself, the co-activity requirement for Hebbian modification ensures that only the active *field*, and not the active place cell as a whole, acquires the new inputs.

Thus, the principle of input specificity can be invoked to explain the context-specific acquisition of location discrimination (Fig. 9). In a familiar environment, the inputs specifying a given field have acquired new discriminative inputs, and have lost some of their pre-existing inputs (those from the common cues), so that a field will only form when both the common *and* the discriminative inputs are active. In the unfamiliar environment, on the other hand, a new set of contextual inputs is recruited that have not been previously active, therefore the cell can express its fields whether or not the discriminative stimuli are present. Because the discrimination learning required co-activity, the connections routed through the other boundary input sets (those activated by different contexts, not yet experienced by the rat and hence not yet active) did not change, and so the cell will remain non-discriminating in these contexts.

Processes recruited when place cells 'learn'

From the above, we can identify the following processes that may come into play during spatial learning by place cells /5/:

1. When an animal first enters a new environment, a random selection of place cells becomes active, each having the inputs necessary to specify a field. Evidence for this comes from the observation that studies in which synaptic plasticity has been manipulated, particularly the CPP study by Kentros *et al.* /44/ and the tetanization study by Dragoi *et al.* /23/, find that although the presence or absence of fields is altered, their initial existence and morphology appear normal. Thus, it does not seem, at least at present, that activity-dependent synaptic plasticity is necessary for the rapid establishment of fields on initial entry into the environment.
2. The co-activity of the now active place cells with the contextual cues specific to that environment causes a Hebbian strengthening (LTP) of the connections between the contextual inputs and the field-specifying (or 'boundary') inputs. This is supported by the ability of place cells to acquire discriminations between closely similar

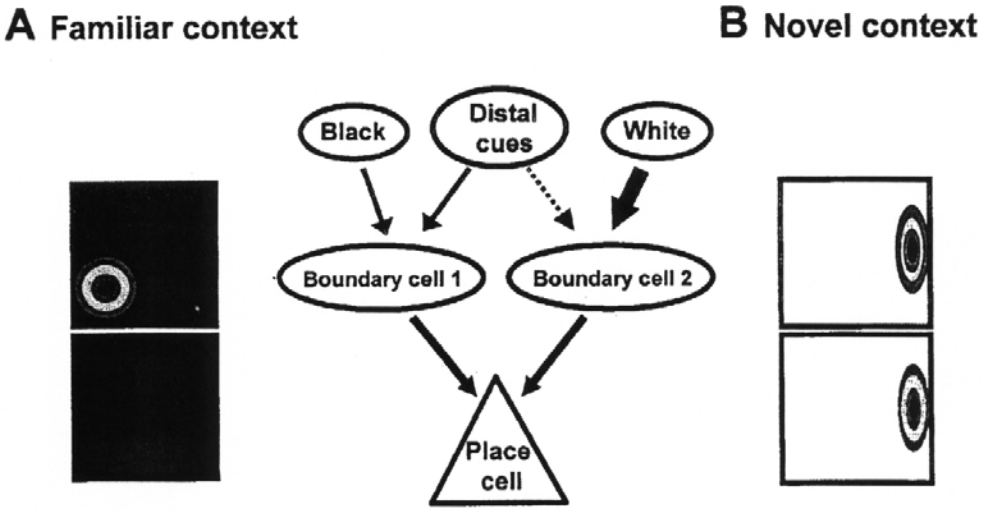

Fig. 9: Illustration of how an acquired location discrimination could be restricted to the learning context. **A.** After experience of the black box, synaptic strength changes have taken place as described in Figure 8, so that the cell now fires only when the box is in the location specified by the distal inputs. **B.** When the context is changed, a new set of inputs is now active. These inputs have not undergone strength changes and so the boundary input cell, and hence the place cell, is undiscriminating.

environments that were previously undiscriminated, implying that the information that differs between the environments (such as the colour of a cue card, as in the study by Bostock *et al.* /16/, the distal cues, as in the studies by Jeffery /36/ and Hayman *et al.* /31/, or the shape of the environment, as in the study by Lever *et al.* /47/) develops an influence it did not have previously. Establishment of long-lasting connections of this sort is probably NMDAR dependent, as evidenced by the finding of Kentros *et al.* that an NMDAR antagonist blocked stability of the fields for more than a few hours.

3. At the same time, there is a weakening of the link between these contextual inputs and the weaker or inactive field-specifying cells, perhaps by some kind of synaptic scaling process, so when the animal re-enters the environment in the future, these contextual cues will only elicit one field from the place cell. This weakening is inferred by the observation that discrimination appears to involve the loss of a field in one or other of the two environments, sometimes with development of a new field elsewhere (in the - less frequent - case of remapping by field shift).
4. Also at the same time, a weakening possibly occurs of the link between inactive contextual inputs and the field-specifying inputs, by heterosynaptic LTD, so that this cell comes to be driven *only* by the relevant contextual elements. It seems likely that this process, if it occurs, is also NMDAR dependent, since electrically induced LTD in the hippocampus is dependent upon NMDARs /48/.
5. Finally, with the learning of rewarded and punished locations in the environment, there may be a possible strengthening of the connections that associate certain places in the environment with the presence of goals (or, one assumes, aversive stimuli).

CONCLUSION

Experiments that have systematically manipulated the environment and/or the processes underlying LTP have provided several clues regarding the mechanisms of place cell plasticity. First, it seems likely that the basic place cell response is not dependent on the processes underlying LTP, since manipulations of plasticity rarely produce deformed fields. Rather it is the long-term characteristics, such as stability across days and across different contexts, that are selectively affected by such treatments. Long-term observational studies of place cell activity have revealed that the system is capable of incrementally acquiring discriminative information about different contexts, which has led to the proposal that place cells may be, among other things, a neural substrate for long-term incidental learning /47/. Experiments in which place cells are seen to diverge across environments and become more discriminative according to context show that place cells are able to encode more than pure spatial information. Instead, these observations support the idea, proposed many times previously /67,73/, that the hippocampus instantiates a richer representation than just the geometric parameters of a place.

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