Studies of the hippocampal cognitive map in rats and humans

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The function of the mammalian hippocampus is one of the most widely debated issues in neuroscience. Interest in this structure began with the observation by *Scoville* and *Milner* [56] that an epileptic patient, HM, who underwent bilateral resection of his medial temporal lobes, awoke from his surgery with a profound and permanent anterograde amnesia. Because of the prominence of the hippocampus within the medial temporal lobe, Scoville and Milner identified damage to this structure as the likely cause of the amnesia, and suggested, therefore, that the hippocampus has a crucial role in memory formation.

The proposal that a focal brain structure might play a role in memory aroused great interest, as an extensive series of lesion studies, performed by *Lashley* over many years, had apparently found that no one brain structure appeared to be essential to learning [26]. Finding an animal model of medial temporal lobe amnesia proved, however, to be a remarkably difficult problem. Lesion studies in rats and monkeys found no apparent deficit in the ability to learn a variety of standard laboratory learning tasks [10, 25]: hippocampus-lesioned animals were, for example, unimpaired on simple classical and operant conditioning tasks, and showed no discrimination deficits in any sensory modality. Since an animal model is an essential prerequisite for studying brain function at a neuronal level, this failure to see »amnesia« in animals was highly problematic.

Things took a step forward in the early 1960s, when *Olton* and colleagues showed that rats with hippocampal lesions were profoundly impaired in their ability to learn a simple spatial task, the radial maze [50]. This finding opened to the door to a field of enquiry that promised (and still promises) to shed light not only on mechanisms of animal learning, but also on the neurobiology of human memory. The basic observation made by *Olton* was that hippocampus-lesioned rats could not learn a foraging task in which they had to collect food from the end of each arm of a multi-arm radial maze without missing arms or going into any arm more than once. *Olton* suggested that the function of the hippocampus might be to provide an on-line store of information that was unique to a given trial. For example, to solve the radial maze task the animal

would need to remember which arms it had already visited, and update this information after each new arm visit. This type of memory would, according to *Olton's* conceptualisation, essentially consist of a hippocampus-based »list« containing information about the identity of each arm (perhaps labelled by its association with some prominent cue in the room) together with information about whether it had been visited yet. *Olton* gave the name »working memory« to this kind of continually revised list memory, and suggested that the reason for HM's amnesia was that without this working memory store, information could not be transferred to long-term memory for future recall.

In 1978, *O'Keefe* and *Nadel* proposed an alternative explanation for the lesion-induced radial maze deficits in *Olton's* rats [48]. Their suggestion was motivated by *O'Keefe's* discovery in the hippocampus of single cells that fire selectively in certain regions of the environment [47] (see below). *O'Keefe* named these cells place cells, and suggested that their activity collectively contributes to the formation of a »cognitive map«, a neural representation of the environment that animals could use in navigation. *O'Keefe* and *Nadel* suggested that *Olton's* rats could not solve the radial maze task because they lacked a cognitive map and therefore could not uniquely identify each arm. According to their proposal, the arms could only be distinguished on the basis of the whereabouts in the room, and that without a cognitive map with which to do this, the rats would have no mechanism for knowing which arms they had visited and which they had not. *O'Keefe* and *Nadel's* view contrasted with Olton's assumption that the arms could be identified by means of local cues that signposted each arm. The resolution of this dichotomy was provided in the early 1980s by *Morris*, who devised a watermaze task [39] that can apparently only be solved using a cognitive map. *Morris's* findings are discussed below.

THE COGNITIVE MAP

The concept of the cognitive map dates back to *Tolman*, who suggested in 1948 that some kinds of goal-finding behaviour in rats can only be solved by the use of an internal map-like representation of space, rather than as a set of stimulus-response associations [61]. In *Tolman's* classic experiment, he trained rats to find a goal via an indirect route, and then altered the maze so that the indirect route became blocked but they now had the opportunity to follow either a direct route or one of a number of other decoy routes. The rats chose the direct route more often than would be expected by chance, suggesting that they knew in which direction the goal lay even though they had never travelled that way before (Figure 1). Since this behaviour was novel to the animals,
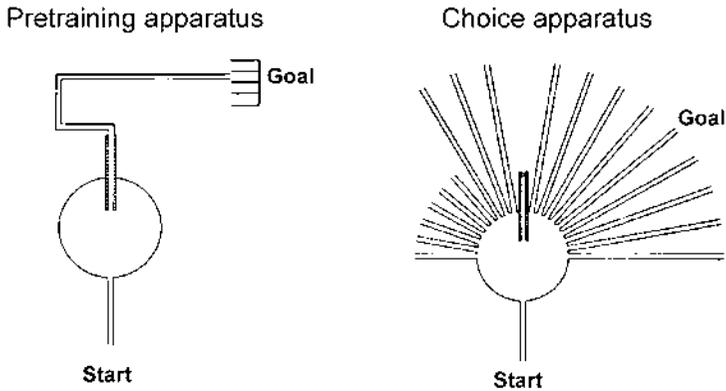
Pretraining apparatus

Goal

Start

Choice apparatus

Goal

Start

Figure 1: Tolman's sunburst maze (adapted from [61]). In the pretraining phase (left diagram), rats were trained to follow an indirect path between a start point and a goal. In the choice phase (right diagram), the original path was blocked and the rats given a number of alternatives from which to choose. The animals chose the arm leading in the direction of the previously-learned goal (labelled »goal«) significantly more often than by chance, even though this route was novel.

their expression implied that they had not been learned over a series of stimulus response pairings, but rather that the animal had been able to consult some internal, higher-level representation of the environment – a map – in order to determine which way to go (Fig. 1).

Tolman's cognitive map hypothesis met a great deal of resistance at the time he proposed it, because the dominant paradigm in psychology was then (and remained for many years) the behaviourist doctrine that all behaviour is composed of assemblages of stimulus-response elements. *Tolman's* suggestion that some kinds of behaviour could not be explained in this way was largely ignored. However, *O'Keefe* and *Nadel's* 1978 influential book, The Hippocampus As a Cognitive Map [48], resurrected *Tolman's* hypothesis with a carefully laid-out analysis of almost all the extant spatial learning literature, suggesting that not only was *Tolman* right about the existence of a cognitive map, but that such a map might occupy a specific region of the brain (the hippocampus). Their hypothesis was supported not only by behavioural data, but also by physiological data suggesting that single neurons in the hippocampus exhibited activity that could not be explained on the basis of simple associations between sensory inputs and the neuronal responses. They also showed that the performance deficits of animals with hippocampal lesions could plausibly be accounted for by assuming that they were impaired in spatial learning.

Shortly after the publication of *O'Keefe* and *Nadel's* book, *Morris* demonstrated that rats could navigate in a situation devoid of local landmarks [38], in a way that could not apparently be explained by stimulus-response learning. In his now-classic watermaze task, a rat is placed into a pool of water (usually 2 m in diameter) in which is hidden a slightly submerged escape platform (Figure 2). The water is made opaque with milk powder or paint, so that the platform cannot be seen. On their first trial in the watermaze the rats swim randomly in the pool until they encounter the platform by chance. On subsequent trials, however, provided the platform remains in the same location the animals learn to swim directly to it and so escape from the pool. If the platform is moved randomly from trial to trial then the rats never learn to find it, confirming that it is undetectable to the senses. Because there are no local cues in the pool to guide navigation, the task can, according to Morris and others, only be solved by using a mental representation of the spatial location of the platform, constructed using the cues in the room outside the pool (»extramaze cues«) (a cognitive map). This interpretation of the watermaze is now widely accepted, and the belief of most spatial learning researchers is that animals indeed possess a higher-order representation of space, which contains not only the landmarks in an environment but also some kind of information about how these landmarks are related to each other (Fig. 2).
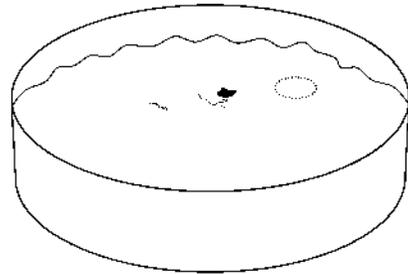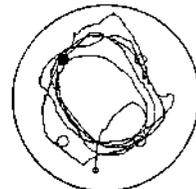

Figure 2: The Morris watermaze. A rat is placed in a tank of opaque water and learns to swim to a hidden platform (dotted circle). Since there are no local cues to guide the rat, it must learn the location of the platform based on cues in the room outside the pool. The lower diagrams (adapted from [55]) show the search path of a normal rat and a rat with a hippocampal lesion, when allowed to search for the platform in an empty pool for 60 sec. The normal rat concentrated its search in the place where the platform had been whereas the lesioned rat circled apparently aimlessly.
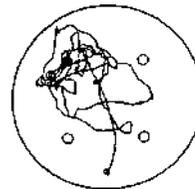
Search path of normal rat   Search path of rat with hippocampal lesion

THE HIPPOCAMPUS AS A COGNITIVE MAP?

There is now a vast body of literature that implicates the hippocampus as the brain region critical in representing the spatial information necessary to solve cognitive mapping tasks. The earliest studies found that rats with hippocampal lesions could not solve tasks like T-maze alternation. Following the publication of *O'Keefe* and *Nadel's* book, many studies have tested hippocampal rats on a variety of spatial tasks and almost all find a deficit. The most widely known and highly-researched finding is that rats with hippocampal lesions are unable to solve the watermaze task [37], although they have no difficulty with a land-mark-cued analogue of it (in which the correct platform location is signposted by one of two visual cues).

Studies of other species have also found evidence of a role for the hippo-campus, or its homologue, in spatial behaviour. A comparative study of two species of meadow vole, one sexually dimorphic for spatial behaviour and one not, found a relationship between hippocampal size and spatial behaviour [19]. In the polygamous species, males range more widely and perform better on laboratory spatial tests than females, whereas in the monogamous species, both sexes show similar spatial ability. Males in the polygamous species have a relatively larger hippocampus than the females, whereas males and females in the monogamous species do not differ. Even more remarkably, food sto-ring birds, who have to remember the spatial locations of their food caches (sometimes numbering many hundreds) over the course of the winter, show a relative increase in the size of the avian homologue to the hippocampus [6]. Since birds and mammals last shared an ancestor 250 million years ago, this suggests that the spatial mapping function of this area of the brain evolved long ago and has been relatively preserved, testifying to its important adap-tive value.

Investigations of spatial mapping in humans have provided less clear-cut evidence for a spatial function of the hippocampus, but this picture is slow-ly changing. Part of the difficulty lies in the fact that human patients with bilateral [p1] temporal lobe damage show such a profound episodic amnesia that it is difficult to perform sophisticated tests of cognitive mapping on these subjects. Such tests as have been conducted in the past, however, tended to show relatively preserved ability in tabletop spatial tasks such as the Corsi blocks task [28]. Nevertheless, in the last few years a number of studies have suggested that while small-scale spatial tasks may be preserved following temporal lobe lesions, navigation in large-scale space (that is, space which can be walked through) may be impaired. *Maguire*, for example, tested pati-

ents with unilateral temporal lobectomy on a virtual reality task in which they viewed a videotape made by a camera operator who walked through the two intersecting main roads of a small town [29]. After viewing the videotaped trip, the subjects were then asked to draw a sketch map of the layout of the town. Temporal lobectomy patients produced very degraded maps compared to control subjects, with the worst maps being produced by those with right-sided lesions. Despite this deficit, the patients themselves had never reported or even noticed problems in navigation.

Functional neuroimaging studies also find that the human hioppocampus plays a role in spatal behaviour, though the picture is more complex than for rodents. In follow-up study to the one described above, *Maguire* conducted functional imaging tests of normal subjects performing the same virtual reality task, and found activation of the right hippocampus, and of the parahippocampal gyri (adjacent to the hippocampus) bilaterally [30]. In a further study, London taxi drivers were scanned using positron emission tomography as they imagined driving well-learned routes through London streets [31]. Activity in the right hippocampus was increased in this imaginary navigation task when compared with control, non-spatial tasks. Structural MRI studies of a different cohort of taxi drivers showed a relative increase in the size of the posterior hippocampus (homologous to the dorsal, most spatially important part of the hippocampus in rats) [32]. Even more intriguingly, a positive correlation was found between the size of this area and the length of time spent as a taxi driver. This finding is important because it suggests that frequent practice of a spatial mapping task might actually cause structural changes in the hippocampus, such as an increase in the dendritic arbour or increased neurogenesis (since the dentate gyrus in the hippocampus is known to undergo experience-dependent neurogenesis [24]). Other functional imaging studies also report increased activity of the hippocampus and surrounding region in virtual navigation tasks [2].

Taken together, these and a large number of studies conducted in the past 30 years seem to point towards the fact that the mammalian and probably also avian hippocampus play a role in the representation of place, if not other things too. But how is this »map« actually constructed in the brain? Is it really a higher-order cognitive representation, as *Tolman* suggested, or does it merely provide a sophisticated means of forming elemental associations between stimuli, as many behaviourists have claimed? To answer these questions, it is necessary to examine the fine structure of the underlying neural representation.

PLACE CELLS AS UNITS OF THE COGNITIVE MAP

O'Keefe's finding in the late 1960s that individual hippocampal neurons show spatially localised activity was one of the most important discoveries in cognitive neuroscience in the past several decades, because it seemed to point to the existence in the brain of an abstract, high-level cognitive representation. While single hippocampal neurons had previously been recorded in behaving animals, these experiments involved behavioural tasks in which the spatial behaviour of the animals was highly stereotyped. The firing correlates of the cells were usually therefore attributed to aspects of the behaviour, rather than to the location of the animal per se [53]. When *O'Keefe* began recording from freely foraging animals, however, it became obvious immediately that a large number of the cells responded primarily to the location of the animal in space, regardless of its actions. Figure 3 shows an example of a place cell, recorded as a rat foraged for 4 min in a 60 x 60 cm square box. It can be seen that whenever the animal entered the Northwest region of the box the cell became active, whereas in the rest of the box it remained virtually silent. This region of heightened activity is called the cell's place field, analogous with receptive fields of simple sensory neurons (Fig. 3).

A

Figure 3:
A: The firing of a hippocampal place cell. Single hippocampal cells were recorded from the hippocampus of a rat as it foraged for 4 min in this 60 x 60 cm square box. The path of the rat is shown by the grey line, and the individual spikes fired by the cell are shown as small black squares, superimposed on the place where the rat was at the moment the cell fired. It can be seen that this cell preferred to fire when the rat was in the Northwest corner (direction is shown by the compass rose).

B
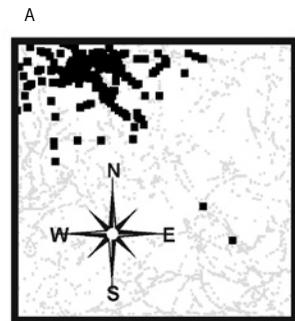
B: A head direction cell recorded from the post-subiculum (adapted from [15]). The x-axis indicates the 360 degrees of compass direction, and the y-axis the firing rate of the cell in each direction. This cell fired maximally when the rat's head was pointing at about 210 degrees (i.e. approx. Southwest).
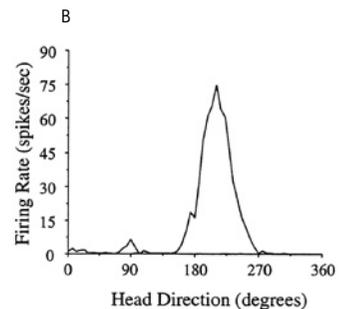
The very obvious spatial firing correlates of place cells represent one of the clearest physiological correlates of cognition so far discovered. Knowing how these cells form their spatial representation would represent the first description of how »knowledge« is represented in the brain, and for this reason, place cells have attracted an enormous amount of research in the past 30 years. Determining how the hippocampus receives sensory information and converts it into a map-like representation of space will be enormously important in understanding both the informational principles and the biochemistry underlying cognitive representation.

According to the behaviourist doctrine, which dominated psychology for several decades, behaviour is built up from sets of simple stimulus-response elements, and it follows that the neural basis of behaviour should also be composed of such elements. In other words, there should not be a complex internal representation mediating the steps between sensation and action (no »black box«) and any representation of space should also be composed of stimulus-response elements. By this view, then, place cells should have relatively simple sensorimotor firing correlates. However, a large number of experiments conducted in many laboratories in the past 30-odd years have shown that place cells do not respond to any particular simple sensory stimulus, or even to a simple combination of such stimuli.

To take an example, a place cell recorded in an open arena will fire when the rat is in the location of its field regardless of which way the animal is facing, even though the visual environment looks entirely different in the different directions. Similarly, place fields remain intact even if the environment is plunged into complete darkness, provided the animal was in the environment at the onset of darkness [52]. Rotation of a subset of polarising landmarks in an otherwise symmetrical environment causes place fields to rotate, but the fields persisted if these cues were removed [20, 45, 49]. Furthermore, when rats were enclosed behind an opaque barrier and slowly rotated, their place fields upon release were found to have rotated too [20]. Since the environment (and hence sensory stimuli) outside the rat had not rotated, the rotation of the place fields cannot be explained by any simple stimulus-response association.

Instead, it seems that the cells respond to a higher-order combination of stimuli. In particular, it is gradually becoming apparent that the cells use some kind of metric, such as a representation of distance and direction, which is an abstract concept not allowed under the behaviourist doctrine. The picture is rather complicated and only just beginning to be understood, but the main categories of information seem to be as follows:

(1) Geometric cues
(2) Directional cues
(3) Context cues

These kinds of input, and their interactions, are discussed below.

HOW DO PLACE CELLS »KNOW« WHERE TO FIRE?

Given that a place cell fires when the rat is in a particular place, how does a place cell »know« where the rat is at a given moment? One of the most important determinants of place cell firing appears to be the distance of the rat to some of the walls of the immediate environment. *O'Keefe* and *Burgess* recorded place cells in a box, with movable walls, that could be varied in size and shape between a small and large square, or between rectangles oriented north-south or east-west [46]. They found that each place cell responded by »following« a subset of the walls, the specific walls being almost invariably those closest to the location of the firing field. On the basis of these results, they proposed that each cell has its own preferred combination of walls, and fires maximally when the rat is at the optimal distance from that particular subset of walls. They and others [16] have also shown that the cell determines how far away the walls are by a combination of visual information and information about how far and in what direction the rat had travelled since last touching one of the walls. This movement-tracking capacity is known as path integration [36], and it may play an important role in supporting the spatial representation in the gaps when immediate sensory cues are unavailable.

As well as geometric information about the distance of the walls, the place cells also need information about which way the environment is oriented. Since place fields in a symmetrical environment are not themselves symmetrical, there must be some source of polarising information that tells them which wall is which so that, for example, a cell with a field in the Southwest corner of the environment will be able to distinguish this corner from the three other, identical corners. When a polarising landmark is present the cells apparently can use this as a directional indicator, since, as mentioned above, rotation of this landmark usually causes all the place fields to rotate in unison [40]. However, even without a polarising landmark the fields usually remain orientated and therefore must have some other source of directional information. A considerable body of evidence now suggests that this information is provided by the »internal direction sense« of the rat, maintained as it tracks its movements through space. This was shown by the experiment mentioned earlier in which the rat's internal sense of direction was manipulated by enclo-
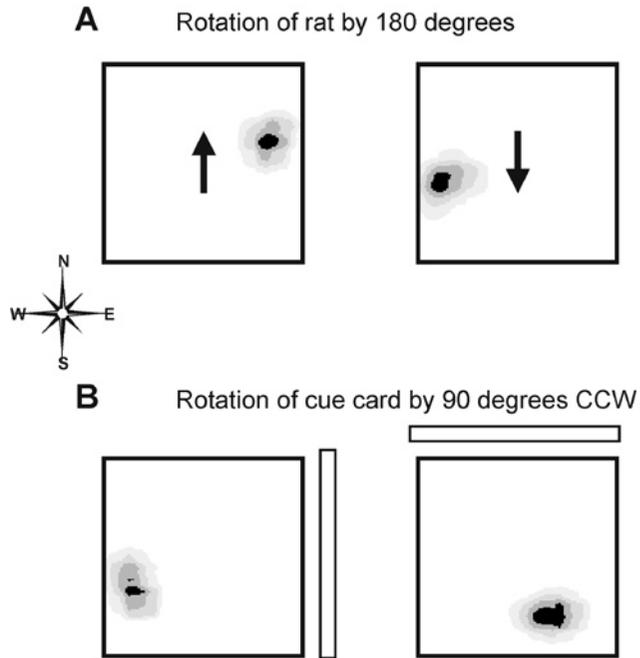
Figure 4: Directional influences on the orientation of place fields. Place cells were recorded as a rat foraged in a 60 x 60 cm square box. The area within the box where the cell preferred to fire is shown by the firing rate contour plot (black = maximum rate).
A: Under baseline conditions the cell fired when the rat was in the vicinity of the East wall. The direction of the rat's presumed sense of »North« is indicated by the black arrow. The rat was then confined under a cover on a platform inside the box and rotated slowly by 180 degrees, so that its sense of North would correspond to actual South. Now, upon release and further foraging, the place cell fired when the rat was near the West wall.
B: Addition of a large visual cue (a spotlit white card, indicated by the thin rectangle) did not change the firing location of this cell. However, when the cue card was rotated 90 degrees counterclockwise, the cell rotated its firing field through the same angle. Thus, place cells can use either the rat's internal sense of direction or an external directional reference, in conjunction with the geometry of the environment, to localise their firing.

sing the rat in a confined space, and then rotating the rat very slowly, so that it became re-orientated with respect to the outside without realising that this had happened [23]. When the rat was released and allowed to forage again, the place fields were found to have rotated by the same amount, suggesting that the rat's (now inappropriate) belief about which way was North was influencing the place cells too (Fig. 4).

How does information about direction reach the hippocampus? The »sense of direction« is probably mainly controlled by vestibular and proprioceptive information [41], telling the cells how the orientation of the rat changes from

moment to moment. Additional sources of movement information (which is ? sometimes known as idiothetic) include optic flow of the visual field as the rat turns its head, and copies of motor efference commands sent to the spatial system from the motor system. Together, these information sources tell the place cells how the rat has moved since the cells last had the opportunity to orientate themselves using visual cues. It is likely, though not yet proven, that these different sources of directional information are pieced together by a network of structures known as the head direction system [59], which surround the hippocampus and feed into it via the entorhinal cortex.

Geometric and directional information are important for driving place cells but do not, by themselves, account for all the place cell phenomena seen in the laboratory. In particular, they do not explain a phenomenon known as »remapping«, in which the cells reassemble their fields in an entirely new representation in response to a non-spatial (i.e., non-geometric and non-directional) change to the environment. An example of remapping occurring after the environment was changed from black to white is shown in Figure 5. In this example some of the cells stopped firing, some began firing where they previously were silent, and one cell developed a different field in the white box from the one it had in the black box. When remapping occurs it often seems to involve the entire population of place cells, leading to the belief of many investigators that the cells have collectively decided that the rat is in a new environment. Whether the rat itself »thinks« it is in a new environment remains unanswered at present (Fig. 5)
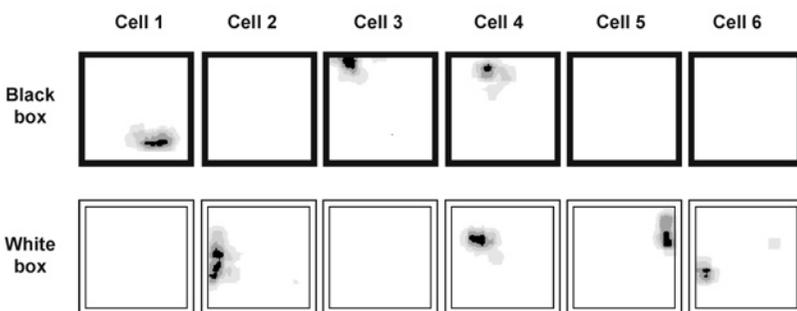

Figure 5: Contextual influences on place fields. Place cells were recorded as a rat foraged in a 72 x 72 cm square box (for clarity, the cells are shown in individual panels). The upper row shows the place fields of the cells when the box was black. The lower row shows the place fields when the box was changed to white. Cells 1 and 3 stopped firing altogether, and cells 2, 5 and 6 began firing where they were silent previously. Cell 4 shifted its firing field (in this case, only slightly). Thus, the location of the place fields was determined not only by the geometry of the box but also by the additional contextual information available.

Remapping phenomena show that as well as using purely geometric inputs, place cells are able to use context information to tell them which environment they are in (and therefore, as we shall see below, which set of geometric inputs they should respond to). Context cues may include features of the environment such as its colour or odour. They may also, however, include more abstract features such as the expectations the rat has about what is going to happen in that environment. For example, *Markus* et al. found that place cells would remap in the same environment when the rat switched tasks between random foraging and goal-directed search [34]. Similarly, *Wood* et al. found that place cells would remap along identical parts of a well-learned route depending on whether the rat, which was required to alternate turns at the end of the path, was expecting to turn left or right [64]. These findings show that place cells receive highly processed information pertaining to the current situation, as well as information about spatial location per se. As we shall see below, such a capacity is useful for a system that is designed to encode the elements underlying complex, event-based memories.

Our experience of the world around us is unitary, in that we know we are either in Place A or Place B and there is rarely any ambiguity. We might intuitively expect, therefore, that the internal representation of space would have a similarly unitary character, with the collective activity of the cells unambiguously signalling spatial location. The finding of context-induced »complete« remapping (i.e. changes in firing by the entire population of place cells) has long suggested such a unified representation. However, such a view has had to be revised in the light of the findings in recent years that remapping need not always involve the whole population of place cells but may affect only a subset of them. Such behaviour raises the alternative possibility that the »cognitive map« may not be a coherent and rigid structure, like a grid map, but may instead be a distributed set of overlapping representations that can encode not only spatial location, but also other aspects of an animal's experience.

The first experiment to »break apart« the cognitive map, and show that place cells do not always act collectively, was the deformable-box experiment of *O'Keefe* and *Burgess* [46], mentioned earlier. In this experiment, it was found that moving the walls of a small box apart to make larger boxes caused some cells to shift their fields, as if they were »following« the moved wall, while other fields appeared to remain anchored to some of the walls. This suggested that each cell received information about the distance and direction of the rat to a subset of the walls, and that different cells received information about different subsets. This finding was somewhat surprising, as previous studies had suggested that changing the shape of an environment

would normally cause the place cell population as a whole to »remap« [40, 62]. These earlier findings may in fact have been caused by the propensity for place cells to remap following changes in context. *O'Keefe* and *Burgess's* experiment showed that if the changes were subtle and restricted to geometry, complete remapping does not occur, and the cells appear to respond to individual stimuli (or collections of stimuli).

A number of subsequent studies have also found that place cells need not act as a unified whole, if the changes made to the environment are sufficiently subtle. *Tanila* et al. found that [58] rotation of a subset of cues in a radial environment caused some cells to rotate their fields to follow, while others did not. *Skaggs* and *McNaughton* found such »partial remapping« (i.e. change in firing pattern of only a subset of cells) when a rat was allowed to walk back and forth between visually identical but spatially separate (adjacent) recording boxes. We have also found partial remapping between adjacent but identical environments [21]. We found that the ability of cells to discriminate two visually identical environments seems to develop over time, suggesting that the cells acquire new inputs, either from the locomotion of the rat or from the room outside the recording area, that allow them to distinguish one environment from the other. *Lever* et al. have reported a similar phenomenon when an environment is gradually deformed between a square and a circle [pers. comm.]. As discussed below, we have also found partial remapping in response to context changes too. The existence of such partial remapping phenomena suggests that the »cognitive map« is not a rigid structure, so much as a collection of individual units (in other words, the »map«) is highly distributed.

INTEGRATION OF SENSORY INPUTS BY PLACE CELLS

How do place cells piece together the various sources of information that impinge on them from the outside world? It is not yet known how the directional and geometric inputs are combined. However, a picture is beginning to emerge for the interaction between contextual and spatial inputs. It is clear from the remapping phenomenon that context inputs must somehow tell a place cell which geometric inputs to respond to, but how?

Several experiments show that the context information is probably associated with the geometric inputs before this information reaches the place cell. Take the well established example of a cell that has one place field in a black box, and a different place field in a white box (e.g., the cell shown in Figure 6 A). This cell must have received two sets of geometric inputs, one set to specify each field. If the context signal arrived at the cell independently of

A   B

Figure 6:
A: A place cell that shifted the location of its firing field when the box was changed from white to black.
B: This »biconditional« behaviour is most easily explained by assuming that the geometric inputs are colour-coded, so that the inputs driving the cell in a given field are only active when the box is the appropriate colour.
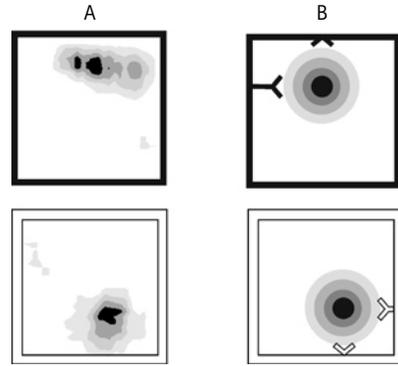
Black (familiar) box   White (novel) box

Figure 7: A spatial discrimination acquired by a place cell in one context is not transferred to a different context. Place cells were recorded in two adjacent environments, one North and one South (direction is indicated by the compass rose). After cells had begun to detect the change (evidenced by the altered firing fields in the two locations) the box was changed to white. Cells showed contextual remapping, firing differently in the white box from the black box, but no longer fired differently in the two locations. This suggests that the discriminating spatial inputs that were learned by cells in the black condition were not effective in driving the cell in the white condition – in other words, the newly acquired spatial inputs were »colour-coded«.
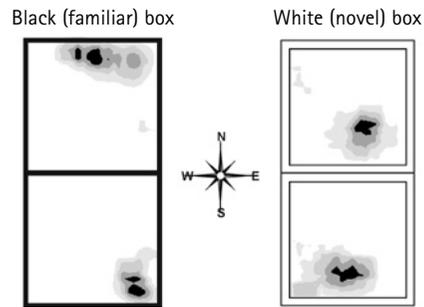
the geometric inputs, then the effects of the two kinds of information (geometric and contextual) should be simply additive and the cell should fire in both places in both environments. In fact, however, the cell fires in Place A in Context 1 and Place B in Context 2, but never in Place B in Context 1 or Place A in Context 2. This pattern of response is technically known as »biconditional« (because a given pattern requires the simultaneous satisfaction of two conditions (that the rat be in the right place and that the box be the right colour). It has long been known from work in neural networks that such patterns cannot arise from any linear combination of inputs arriving independently at the cell. Rather, the combinations must be generated upstream of the cell. In other words, the geometric inputs must somehow arrive at the cell with the relevant context information already associated with them (Figure 6 B).

In a recent experiment, we have taken this line of enquiry a step further, by manipulating spatial and non-spatial cues independently, and have again found that context information is probably »attached« to the spatial inputs be-

fore reaching the place cell. Partial remapping was induced by allowing a rat to forage in two identical adjacent environments, one North and one South, until some place cells had acquired the ability to detect the difference. This implies that spatial inputs had developed onto the discriminating cells that told them which environment was North and which South. The colour of the boxes was then changed from black to white. Now, the cells had new fields (produced by contextual remapping). Figure 7 shows that the same cells that could discriminate North from South in the black box could no longer do so in the white box (in other words, they failed to transfer a previously-learned discrimination to a new context, even though the spatial inputs remained the same. Again, this suggests that the spatial inputs, carrying information about North vs. South, did not arrive at the cell independently of the colour information (Fig. 7).

The above results imply that spatial inputs seem to arrive at the cell with context information already attached. Does this mean that a structure upstream of the hippocampus makes some decision about which context the rat is in, and labels the geometric inputs accordingly? The answer is (apparently) not. In fact, it appears that each place cell receives its own private subset of context information, with different cells receiving different messages.

We recorded place cells in environments that were varied between two »colours« (black and white) and two odours (lemon and vanilla) [1]. Remapping was found to colour, odour, or both. However, interestingly, in these environments the remapping was usually only partial – in other words only some of the cells remapped following a given change (e.g. from a black lemon to a white vanilla box). Furthermore, different cells remapped differently. Some cells would alter their firing in response to changes in colour while other cells, simultaneously recorded, would change only in response to odour. Some cells would only fire when a specific combination of colour and odour cues were present. The upper cell in Figure 8, for example, would only fire when the box was both lemon-scented and white, while another cell would only cease firing when the box was vanilla and white. Most intriguing of all were cells that would fire to one colour/odour combination, or the other, but not to cross-combinations, like the cell in Figure 9. As we saw earlier, such biconditional patterns can only arise if the relevant inputs are combined before they reach the cell. In other words, within-context interactions must, like the interactions between context and geometry, occur upstream of a given place cell. This means that each cell encodes a specific subset of contextual cues, and that the activity of the population as a whole reflects the particular configuration of cues that characterises a unique context.
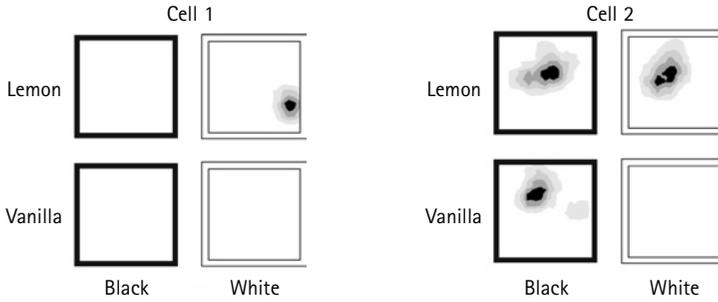
Figure 8: Interaction between subsets of context inputs to place cells. Cells were recorded as rats foraged in an environment that was either black or white, and scented with either vanilla or lemon. Cell 1 in this example only fired in response to one odour/colour combination, whereas cell 2 only didn't fire in one odour/colour combination.
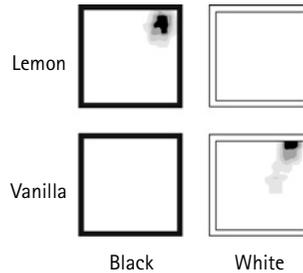
Figure 9: A biconditional response pattern. This cell had the same field when the environment was black and lemon-scented or white and vanilla-scented but not in either of the other two combinations. This pattern of responding could only arise if the black and lemon inputs were combined upstream of the cell.

The above findings reveal several things about the hippocampal representation of space. First, partial remapping phenomena show that place cells act as individuals, rather than as a collective. Second, the inputs that drive place cells must be combined before they reach the cell, perhaps in a structure upstream from the cells, such as the dentate gyrus or entorhinal cortex. And finally, context information is not a global signal but appears to be conveyed differently to different place cells. This, in theory, allows them to make unique combinations of context cues that allow the population as a whole to make subtle context discriminations. Thus, rather than representing a »place«, the hippocampus as a whole may be better specialised to represent a unique context, or »situation«. This is a facility that would theoretically be vital to a structure important in episodic memory, a point that will be discussed below.

THE HIPPOCAMPUS – SPACE, CONTEXT OR EPISODIC MEMORY?

One of the most puzzling anomalies in the hippocampal literature has been the persistent finding that while hippocampal lesions in the so-called »lower« mammals produce a predominantly spatial deficit, in the »higher« mammals,

and especially in humans, the defect appears less spatial and has a pro-nounced mnemonic component. Humans with hippocampal damage show severe defects in episodic memory while often reporting few problems in na-vigation per se.

Many investigators have suggested that rather than constructing a cogni-tive map, the hippocampus performs a higher-order function of which spatial learning is merely one particular kind. Such higher-order functions as have been proposed include the formation of configural representations of stimuli [54], relational learning [11], contextual learning [17], declarative memory formation [57] and many others. What these alternative ideas mostly have in common is the assumption that the hippocampus functions to construct an elaborate representation from a collection of simpler sensory stimuli. Some of these ideas have been difficult to test (e.g. relational learning, because of the difficulty in specifying exactly what a »relation« is) while others have tur-ned out simply to be wrong (e.g. configural learning theory, for which it has been since shown that animals with hippocampal lesions are unimpaired in learning configural tasks [8, 13]). One of the most robust, however, has been the idea that the hippocampus constructs a representation of »context« which is used not only in navigation, but also in the storage of representations of events that happened in that context.

Context is a higher order concept than space, because not only does it in-clude the geometric components of location, it also includes other, non-spatial aspects of »place« that serve to differentiate one situation from another. Such a representation is of enormous adaptive importance to an animal. For example, a physical place such as a meadow needs to be represented in, say, a rat's brain very differently in one context (e.g., midday in the summer) than in another (e.g., midnight in the winter). Not only does an animal need to know the phy-sical whereabouts of objects, it needs to represent the fact that, say, the usual water supply may have dried up, in the former situation, or that there might be hungry predators around, in the latter situation. When an event occurs in the animal's life, it needs therefore to encode in its memory not only the place, but also the situation that pertains at the time. This is particularly important for areas where the animal spends much time, like its home territory, where many events may occur in the same place.

Several investigators have suggested that perhaps the hippocampus en-codes context rather than space per se. A context theory of hippocampal function was first proposed by *Hirsh* [17], who suggested that the structure functioned to hold, offline, information pertinent to a learning task that was not actually part of the sequence between stimulus and response. An example

Hirsh gave was hunger, acting as a contextual cue to tell an animal whether to turn left (towards food) or right (towards water) on a T-maze. In *Hirsh's* formulation, however, almost any cue could be a contextual cue, leading to the prediction that hippocampally lesioned animals should not be able to learn conditional discriminations.

In fact, animals with hippocampal lesions are capable of learning conditional tasks [9]. Nevertheless, the proposal that the hippocampus might have a preferential role in processing context continued to gain supporters. Following on from the cognitive map theory, *Nadel* and *Willner* [44] proposed that that the same brain system that subserves place learning (i.e., the hippocampus is also responsible for context learning). They argued that the context is as crucial an attribute of a place as its geometric layout. In support of their proposal, the Blanchards had previously shown that rats could learn to fear a place that had been associated with shock, and that hippocampal lesions abolished that fear [3]. *Nadel* and *Willner* suggested that rather than being collections of stimuli that behave like the explicitly conditioned stimuli in classical conditioning tasks, contextual cues are bound together in map-like representations by the hippocampus, so that they can be used to retrieve the appropriate CS-US associations. Further support for the role of the hippocampus in learning context has come more recently from studies showing that animals with hippocampal lesions are impaired in context-learning tasks such as fear conditioning [51, 63]. Our findings that place cells collectively can represent constellations of contextual stimuli lends further support to the idea that context is at least as important an attribute of its function as is space per se. But what about memory? How does a putative role for the hippocampus in representing spatio-temporal context explain the findings in human temporal lobe amnesics?

Nadel and *Moscovitch* [42] have attempted to link context to memory by suggesting that the hippocampus constructs a representation of context which forms links with sites in the neocortex that represent other to-be-remembered aspects of experience. By this view, the hippocampus forms an »index« (a concept introduced by *Teyler* and *DiScenna* [60]) which points to the places in the neocortex which store the actual memories. When an animal experiences an event, the elements of the event (e.g. what happened, and when) activate sites in the neocortex, whereas the »when and where« of the event remain encoded by the hippocampus. In order to reassemble all of the elements of the remembered experience, the spatio-temporal context must be reactivated. In the absence of a hippocampus, the fragments of episodic memory that remain distributed in the neocortex are unable to be re-connected, and the memory

becomes irretrievable. In this way, the original spatial representation function of the hippocampus has become, through evolution, intimately bound up with the representation of events.

The notion of the hippocampus as a structure for representing and storing context is appealing because it accounts for many physiological and psychological findings. A literature is accumulating now to suggest that animals with hippocampal lesions are unable to show certain kinds of context-based learning [7, 18, 33, 51, 63] (though not under all circumstances – see [12, 14, 35]). Somewhat intriguingly, animals with hippocampal lesions are unable to solve a non-matching task when the items to be compared are configured as »contexts« (i.e., sufficiently large) but can do so when the exact same items are configured as objects (made smaller) [4]. Furthermore, place cell remapping in response to a context change does not impair navigation per se [22], suggesting that these cells cannot be simply explained as grid elements in a map. Rather, it seems that the cells encode additional aspects of the environment that serve to uniquely identify it not only as a place, but also as a situation, whose significance to the animal encompasses many more dimensions than the three of ordinary space. A representation of situation would, in theory, be the ideal framework on which to overlay a representation of events (episodic memory) and it may well be that the mammalian hippocampus has evolved to do just this.

SUMMARY

The human hippocampus has long been linked with the formation of autobiographical memories, and yet studies in both humans and animals have suggested that its role may also be in the representation and recall of spatial location. A challenge for hippocampal researchers is to reconcile these superficially divergent explanations of hippocampal function.

Recent evidence suggests that the hippocampus, rather than representing space per se, may be more involved with the representation of context (a context which incorporates space but which also includes non-spatial attributes of a situation such as the expectations of the animal). *Nadel* and colleagues have suggested that such a representation of spatial and non-spatial context may be an essential underpinning of an episodic memory system [42, 44], since events are best recalled when the context in which they occurred is re-established [5, 27, 43]. Our experiments with place cells, described in the present chapter, show that the place representation in the hippocampus is not unitary, but can be broken down if aspects of the context are manipulated

independently of each other. This finding lends support to the idea that the hippocampus is better described as a representor of context than as a straight-forward map.

The ability to represent context independently of space would give an animal the ability to remember not only where an event happened, but also under what circumstances (a vitally important function for an animal that spends much of its time in the same place, but where context-specific events often occur. The human facility for autobiographical (or episodic) memory may have evolved within the framework for such a representation, explaining why context is such a powerful retrieval cue for episodic memories, and also why loss of hippocampal function in conditions such as Alzheimer's dementia often manifests itself initially as a deficit in navigation.

Understanding the physiological underpinnings of the context represen-tation may open the door to treatments targeted at memory disorders such as Alzheimer's disease or post-traumatic stress disorder. Furthermore, it may reveal some general principles of other cognitive representations, and thus begin to illuminate the biological foundations of cognition.

ACKNOWLEDGEMENTS

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