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Spatial Navigation and Hippocampal Place Cell Firing: The Problem of Goal Encoding

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SYNOPSIS

Place cells are hippocampal neurons whose discharge is strongly related to a rat's location in the environment. The existence of such cells, combined with the reliable impairments seen in spatial tasks after hippocampal damage, has led to the proposal that place cells form part of an integrated neural system dedicated to spatial navigation. This hypothesis is supported by the strong relationships between place cell activity and spatial problem solving, which indicate that the place cell representation must be both functional and in register with the surroundings for the animal to perform correctly in spatial tasks. The place cell system nevertheless requires other essential elements to be competent, such as a component that specifies the overall goal of the animal and computes the path required to take the rat from its current location to the goal. Here, we propose a model of the neural network responsible for spatial navigation that includes goal coding and path selection. In this model, the hippocampal formation allows for place recognition, and stores the set of places that can be accessed from each position in the environment. The prefrontal cortex is responsible for encoding goal location and for route planning. The nucleus accumbens translates paths in neural space into appropriate locomotor activity that moves the animal towards the goal in real space. The complete model assumes that the hippocampal output to nucleus accumbens and prefrontal cortex provides information for generating solutions to spatial problems. In support of this model, we finally present preliminary evidence that the goal representation necessary for path planning might be encoded in the prelimbic/infralimbic region of the medial prefrontal cortex.

KEY WORDS

hippocampus, frontal cortex, unit recordings, place cells, spatial navigation, rat

1. INTRODUCTION

Twenty-five years ago, O'Keefe and Nadel /76/ put together critical evidence that the hippocampus carries out fundamental computations involved in spatial navigation. The core of this theory was provided by a discovery made a few years earlier. While O'Keefe and Dostrovsky /75/ were looking for the behavioral discharge correlates of neurons recorded from the hippocampus of freely moving rats, they were struck by the strong positional selectivity of some of the cells; their firing was so strongly correlated with the rat's location in the environment that they were named 'place cells'.

The discovery of place cells was an important step in understanding the neural basis of spatial processing since such cells provide ideal building blocks for implementing the capability to navigate.

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It is obvious that for a rat to solve a complex spatial problem, a problem that requires a representation of the environmental layout, an initial requirement is for the rat to locate itself. It is only once self-localization is achieved that planning a path toward a potential goal is possible. Performance in the water maze navigation task, in which the rat is demonstrably able to find rapidly a hidden platform using the array of available visual cues, is currently the prototypical illustrative example /55,63,113/.

Even though the spatial function of place cells is hardly disputable, their direct involvement in the generation of paths for navigation has remained controversial. At first glance, the connection between place cells and spatial memory is supported by the extensive lesion literature which reveals that damage to the hippocampus results in severe impairments in a wide variety of spatial tasks /35,64,71,83,85/. This conclusion is corroborated by more recent work in genetically modified mice with impaired long-term potentiation (LTP) and in rats after pharmacological blockade of LTP; in either case place cells are abnormal and there are corresponding performance deficits in navigational tasks /11,42,57,93,94/.

Unfortunately, there are other interpretations of the lesion data that render the support provided for the cognitive mapping theory less than convincing. For instance, the spatial memory deficits may result not from a loss of the representation of the current environment but instead could be due to a loss of the ability to store episodic memory that is crucial for performance /16,20,118/. The inherent difficulty of inferring function from gross or subtle lesion methods prevents us from gaining unambiguous answers via this method[1].

In this review we therefore take a different, more direct approach that attempts to relate spatial behavior to place cell discharge. The evidence we present confirms that there are close ties between the activity of single cells and the overall spatial behavior of the rat and therefore lends strong support for the direct involvement of place cells in navigational processing. Whether such processing is the main role of place cells, or just a particular case of a more general function is left for future work, but the spatial nature of place cell signals suggests at least that space is an important aspect of hippocampal function.

The strong spatial signals carried by hippocampal neurons do not mean, however, that the hippocampus is sufficient to accomplish all navigational functions. To the contrary, our review emphasizes a key aspect of navigation, the coding of the goal location, which appears to be more or less independent of the hippocampus, at least to the extent that no representation of goal within the hippocampus has yet been found. We intend to propose a model of the neural network responsible for spatial navigation that includes goal selection. After summarizing some of the main properties of place cells, we go on to present preliminary evidence that goal coding might depend on the interplay between several brain structures, and suggest that among these the prelimbic area of the prefrontal cortex is crucial.

2. FUNDAMENTAL PROPERTIES OF PLACE CELLS

The place cells phenomenon is seen when one monitors the activity of single pyramidal neurons in the CA1 and CA3 areas of the hippocampus and simultaneously follows the location of the rat as it moves freely in the experimental environment. Each place cell is intensely active only when the rat's head is in a cell-specific part of the environment (called the 'firing field'), and is usually silent elsewhere in the environment /64/. When rats are exposed for the first time to a new environment, place cells become active after a few minutes of exploration /7,29,117/. Once firing fields are established, their locations may be stationary for weeks or months /68,108/. In addition, place cell properties are very similar whether the rat is engaged in an explicit spatial learning task /78/ or during simple foraging in an open field /68/. Even though place cell discharge may be modulated by non-spatial variables /2,114,116/ or by the direction when on a linear track /59,66/, spatial location is by

[1] Beside the unavoidable problem of synaptic reorganizations that follow permanent lesions, interpretation of lesion-induced deficits is difficult because complex behavior is often the result of several, perhaps sequentially arranged processes. Therefore, the observable deficit may result from the loss of only one of these processes, with the others being undisturbed /1/.

far the best and most consistent correlate of their activity.

The location-specific nature of place cell activity is possible only if the animal extracts information about its environment. O'Keefe and Conway /73/ were the first to address experimentally the question of the sensory control of place cell firing. Using a T-maze inside a set of curtains, they first demonstrated that firing fields could be controlled by a set of four cues (a light, a card, a fan, and a buzzer) placed within a curtained 'controlled-cue' environment some distance off the maze arms. When the set of cues was rotated as a whole, firing fields rotated equally. Thus, distal cues manipulated by the experimenter were used by the place cell system to anchor location-selective activity. Control by explicit cues is also seen when only a single landmark is present. For example, Muller and Kubie /67/ recorded place cells in a cue-controlled environment in which the only intended orienting landmark was a salient cue card attached to the wall of the recording cylinder. To measure the control exerted by the card over firing fields, the card was rotated around the center of the cylinder in successive sessions. Under these circumstances, card rotation consistently resulted in equal rotation of firing fields. The implication is that the spatial firing of the cells is anchored to a reference frame provided by the wall card. Similar control was observed when the 2-dimensional card was replaced with three 3-dimensional objects set against the cylinder wall to form a triangular configuration, but not when the same objects were near the center of the cylinder /12,13/.

Although most experimental work has focused on the control exerted over place cell firing by visual information, other sensory cues may also be important. For example, firing fields remain relatively stable in the absence of visual information, provided olfactory cues on the floor are not scrambled /97/. Recordings from blind rats also suggest that tactile information is useful to anchor location-selective activity in a reference frame provided by slender objects /96/. Finally, clear evidence indicates that auditory cues can exert control over firing fields when visual information is removed (Kubie and Muller, unpublished observations).

Self-motion information also may be important in the absence of external cues /58,72,89,100/ or when such cues are unreliable /38,95/. To use self-motion information, the rat would update its position by tracking changes in position using signals derived from a variety of sources including the vestibular and proprioceptive systems and motor efference copy. A major problem with the use of such relative information is that it leads to unavoidable error accumulation. In the absence of recalibration, the total error may become so large that any self-localization becomes impossible. Difficulties with pure or nearly pure self-motion based positioning are confirmed by the finding that place cell discharge becomes spatially unreliable when external cues are severely restricted /97/.

To summarize, place cell firing is controlled by both external and self-motion (idiothetic) cues that interact with each other /38/ such that either type can be dominant in different circumstances. Nevertheless, distal visual cues seem to be of primary importance in the spatial control of firing fields /67,73/; motion-related cues might allow ongoing calculation of the rat's position without external reference, thereby reducing attention to external cues. Nevertheless, the rat still occasionally has to recalibrate its position to correct for errors, and the most usual basis for such recalibration is visual information /60,87/.

3. PLACE CELL FIRING AND THE CODING OF DISTINCT ENVIRONMENTS

Although place cell firing is characteristically stable in constant surroundings, it can be markedly different while the rat explores a different environment. Muller and Kubie /67/ recorded place cells in two differently-shaped apparatuses, a cylinder and a rectangular box, and found that the spatial firing patterns of most cells were greatly changed between the two environments. Generally, cells that fired in the two environments had fields that were very different in location, size, and shape and discharge rate. Other cells had fields in one apparatus but not in the other. This 'remapping' phenomenon suggests that each unique environment is represented by a distinct subset of hippocampal pyramidal cells; cells common to both

subsets have different firing fields. Although the development of a new set of firing fields may be very rapid, occurring in a matter of minutes /29,42, 117/, a slower time course is also possible /7,52/. Ultimately, however, place cells collectively provide information about both the rat's current environment and the rat's location within the environment.

The extent to which each environment is represented independently from other environments is an important issue. We recently explored an interesting case showing that two representations can be independent even when the represented environments are physically connected with a U-shaped runway that allows the rat to go from one environment to the other /81/. Place cells were first recorded while rats explored two boxes that differed in many ways, such as shape, color and floor texture. As expected, each place cell had a strongly different firing pattern in the two boxes. The crucial manipulation was to change one of the two boxes, causing a remapping of cell activity in the changed box. Despite this clear result, the spatial firing patterns of the same cells were in general unaltered in the other, unchanged, box (Fig. 1). We infer from this outcome that the hippocampal representation is local to the immediate surroundings; an independent map is formed for each apparatus and is activated only when the rat enters the represented apparatus. Thus, at least under the conditions used in this study, the hippocampal map appeared to be mainly activated and updated according to sensory data from the rat's current environment. These results suggest that place cell-based navigation is possible only within the currently perceived environment and that a switch of the map must take place for navigation to be correct in distant, undetectable portions of space.

4. PLACE CELL FIRING AND NAVIGATION

4.1. Precision and reliability of spatial coding by place cells

Beyond location-specific firing itself, what other evidence is there for a role of place cells in spatial learning and memory? One first issue is the accuracy of spatial encoding by place cells. Since every region of the environment accessible to the rat is represented with about equal probability, how precise is the information provided by the place cell

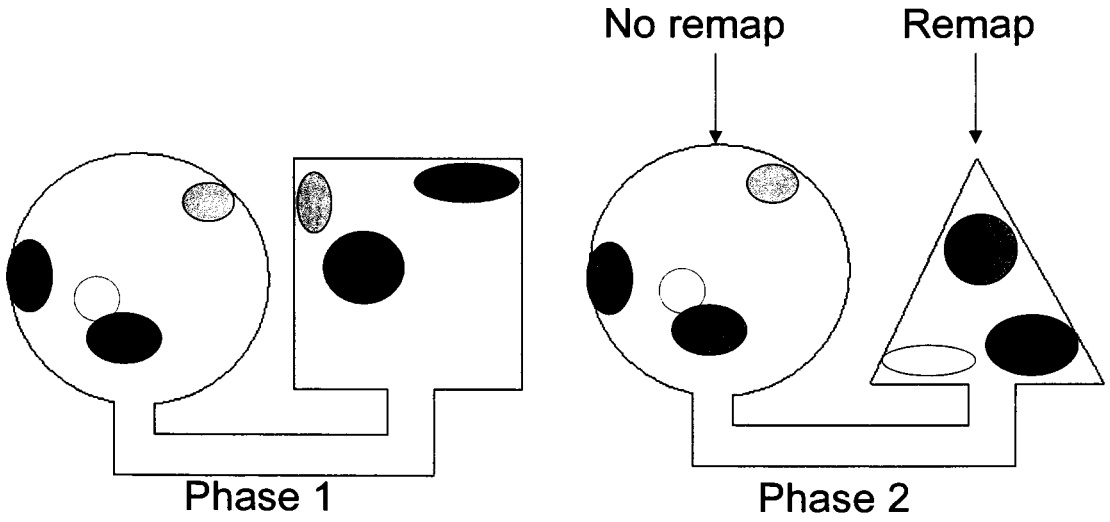

Fig. 1: After place cells are recorded while the rat explores two distinctly shaped connected boxes, one box is substituted. This change induces a local remapping of fields (shown as grey-shaded ellipses) in the changed box but discharge is mostly unaffected in the unchanged box even though the rat can freely commute between the two boxes. From /81/.

population about the rat's location within the environment? Current estimates of the number of place cells active for a specific apparatus is about 40% of the number of pyramidal cells. Since the number of pyramidal cells is roughly 500,000 per hippocampus, one imagines that many cells fire at each location traversed by the rat. Very basic interpolations of instantaneous firing for small numbers of simultaneously recorded cells allowed Wilson and McNaughton /117/ to reconstruct the rat's path with fair precision. With more sophisticated rules that take phase-coded firing into account /77/, Brown *et al.* /8/ were able to superimpose on the rat's actual path the calculated path knowing the instantaneous firing of just 16 simultaneously recorded place cells (see also Jensen and Lisman /39/). Thus, the ensemble activity of place cells is a good predictor of the rat's location. This prediction holds, however, better at the population level than the single cell level /27/, since the activity of individual place cells can be extremely variable from one run through the firing field to another, a phenomenon referred to as 'overdispersion' /19/.

4.2. Firing properties of place cells during navigation

If the firing of place cells relates in one way or another to oriented behavior, then one should expect differences in activity according to whether the rat is unambiguously engaged in navigation or simply moving in an apparently random fashion in space. Although there is some evidence at a structural level that hippocampal metabolic activity is greater during a spatial task than during a control task /6/, there are only hints that place cell firing is modulated by the rat's behavior. Thus, preliminary results seem to indicate subtle modifications of place cell firing during navigational behavior as opposed to foraging, in which the rat engages in random searching behavior for food (Fenton, personal communication; see also /79/). Comparisons of firing during navigation and foraging were done during performance of the 'place preference task' /92/ which was designed to allow place cell recordings during both behaviors. In this task, the rat has to enter a circumscribed, unmarked goal zone in a circular environment and stay there for a short period of time. A white cue card attached to the cylinder wall is the only spatial landmark the rat can use as a reference to find the goal zone. When the rat goes to the goal zone and dwells for a long enough time, an overhead dispenser is triggered to release a single food pellet. Since the released pellet can land anywhere in the cylinder, the rat has to leave the goal zone to find it. To receive another reward, the rat has to return to the goal zone. Because the goal is spatially dissociated from the wall card, the rat has to use a place strategy, in which the goal location is computed from its spatial relationship with the card (Fig. 2). Thus, each successful 'trial' consists of two steps, one in which the rat follows a path oriented towards the goal zone (goal-directed navigation) and another in which the rat follows a seemingly random trajectory while looking for the pellet (undirected foraging).

Comparing passes through the field during foraging and goal approach, subtle differences were seen in several characteristics of CA1 place cell firing. The clearest change during navigation was an increase of firing reliability or, in other words, decreased overdispersion /19/. The discharge rate was only marginally increased during navigation although cells fired more bursts than during foraging. The inference is that the positional signal of place cells is stronger during navigation than during foraging, as if the rat attends more to the current surroundings.

4.3. Relationship between the rat's spatial performance and place cell spatial firing fields

How intimately is place cell discharge related to behavior? In our view, probing this relationship requires concomitant analysis at the cellular and behavioral levels in normal animals after changes are made in the environment. The idea is simply that if the spatial information coded by place cells is important for spatial problem solving, then changes in the environment that result in changes of place cell firing should be reflected in the animal's choices. The next sections provide a brief review of studies based on this principle.

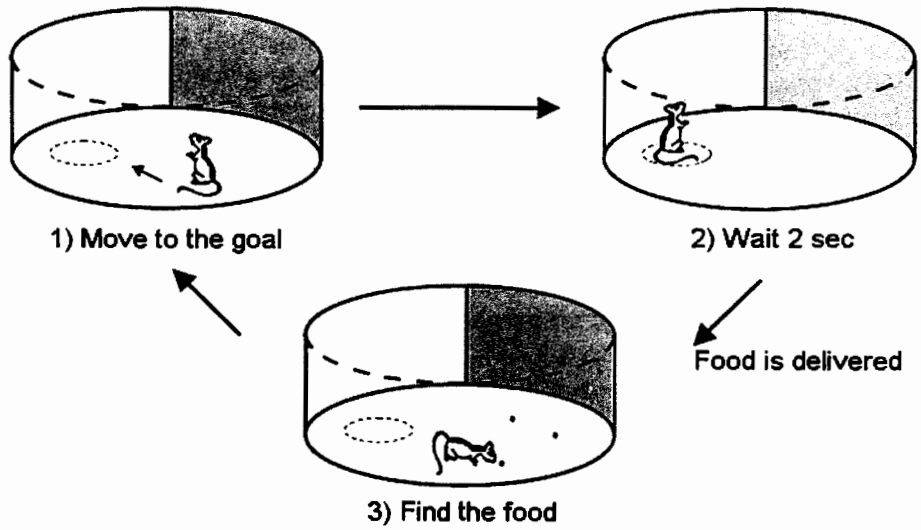

Fig. 2: Place preference task. The rat is required to move to a specific location relative to a cue card (goal-directed navigation) and wait there for 2 seconds. This triggers the delivery of a food pellet whose final location may be anywhere in the cylinder, thus requiring the rat to search for it (undirected foraging). From /92/.

4.3.1. Navigation data supporting the spatial mapping theory

O'Keefe and Speakman /78/ were the first to ask how well changes in place cell activity corresponded to changes in behavior. Rats were trained to go to one arm of a plus-shaped maze based on its location relative to a fixed set of extra-maze cues. On 'memory trials', these cues were removed before the rat was allowed to make its choice. When rats selected an arm in the absence of adequate information, the firing fields of place cells stayed in register with their behavioral choice, even when the rat chose the wrong arm /78/.

A second indication of a link between place cells and behavior is shown by progressive removal of available sensory information, which often resulted in a misregistration by ± 120° on a symmetric Y-maze of otherwise unchanged firing fields /51/. Rats were trained to perform a spatial alternation task on the Y-maze using for landmark information a prominent white card positioned midway between two of the arms. Several different cue manipulations including rotation or removal of the card could cause the angular position of firing fields to shift out of register by ± 120° from the position seen with the card in its standard position. In parallel with inconsistent field positions, alternation performance underwent a strong deterioration. The nature of errors, classified according to the required alternation sequence, indicated that the rats were disoriented. In addition, the direction of misregistration of firing fields often predicted which arms the rat would visit erroneously. Overall, the results suggest that inducing a mismatch between the environment and the hippocampal representation of the environment disrupts the rat's behavior, in clear agreement with the predictions of the spatial mapping theory.

The functional role of place cells was further investigated by looking at how the requirements of a navigational task determined the effects of disrupting their positional firing patterns /49/. The cognitive map theory predicts that integrity of hippocampal activity is critical for place navigation, but less important for cued (beacon) navigation behavior /80/. Thus, we looked at performance by normal animals in place and beacon navigation tasks after environmental manipulations that disturbed the relationship between the place cell representation and the cues used to solve the problems. The theory predicts that such disturbances will disrupt performance of place navigation but not of beacon navigation.

Place cells were recorded while rats performed the place preference task (see Section 4.2). To modify relationships between visible stimuli and place cell activity, we made 'hidden' or 'visible' 90° rotations of the card on the cylinder wall and, when present, independent rotations of the disk on the cylinder floor. Hidden rotations were made with the rat out of the cylinder and generally caused equal firing field rotations. Visible rotations were made with the rat inside the cylinder and very often did not cause fields to rotate /95/. Thus, hidden card rotations generally induced firing fields to stay in register with the goal location whereas visible card rotations generally induced firing fields to shift out of register with the goal location. When a card rotation did not induce field rotation, performance was greatly impaired if the task required place navigation to an arbitrary location relative to the cue (Fig. 3). In contrast, performance was altered to only a small extent when the animal had to go directly towards the cue card, and not at all when the cue was irrelevant to success because the goal was a disk on the floor that was moved independently of the cue card /49/. Thus, reorganizing the relationship between place cells and the environment affected performance in three highly matched tasks to an extent directly predicted by the navigational requirements of the task and, therefore, according to the cognitive mapping theory, to an extent predicted by the importance of place cells for solving the task.

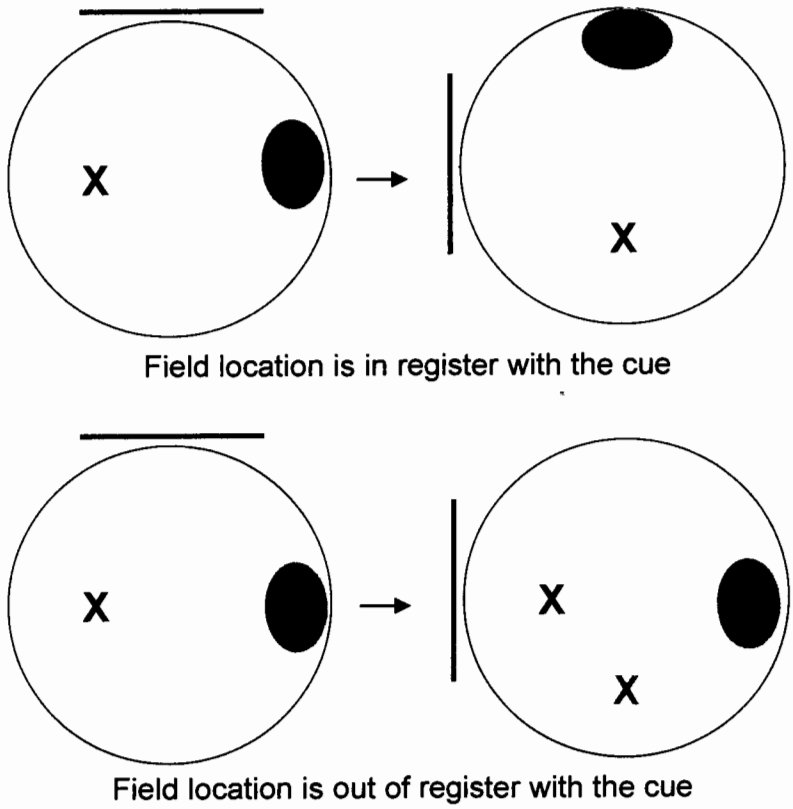

Fig. 3: When rotation of the cue is followed by corresponding rotation of the firing field (ellipse), the hippocampal representation is in register with the cue card (shown as a thick line outside the cylinder) and thus with the navigational task. The animal usually performs a correct search for the goal (location indicated by 'X'). When the firing field does not follow cue rotation, the hippocampal representation is misaligned with the cue. The rat performs the task poorly; it usually searches for the goal at a location consistent with the erroneous position of the firing field (black X), but inconsistent with the cue (grey X). From /49/.

4.3.2. Contradictory findings

The recent literature provides an interesting counter-example of the relationship between place cell firing and spatial performance /37/ (see also /33/). Place cells were recorded while rats had to solve a navigational task whose acquisition had been previously shown to depend on hippocampal integrity. The task required the rat to go to a specific corner in a square box in the center of a room richly provided with diverse cues. On each trial, the rat was first allowed to forage freely for rice grains scattered on the floor of the box, allowing place cell activity to be sampled everywhere in the box. Next, a tone was sounded to signal the availability of a food reward at the goal corner. Since the location of the goal corner was constant from one trial to another, a well-trained rat would immediately go to the correct corner to get a chocolate reward. At the outset, the arena walls and floor were black as they were during the extensive training period necessary to get the animals to solve the task reliably. Once the fields and behavioral performance was characterized in the black box, trials were conducted after the black box was replaced with a white box. In both boxes, the rat had to reach the same corner relative to the room cues. Although the change from a black box to a white box induced remapping for most place cells, navigational performance remained essentially intact /37/. Choice performance dropped from ~90% to ~70% correct, but this statistically reliable drop left performance in the white box well above the 25% chance level. Thus, rats could still perform correctly even though their hippocampal map was considerably disrupted by the change in the box color.

At first glance, this outcome is hard to reconcile with the idea that place cells drive navigation, but we would like to propose an alternative explanation that focuses on details of the rat's behavior. In this view, the initial solution of this task relies on a hippocampal representation of the box + laboratory. Once such a representation is built, however, the rat can switch to other strategies to perform correctly /80/. Therefore, once the rat knew how to go reliably to the goal corner in the study by Jeffery *et al.* /37/, it could begin to use a beacon strategy instead of a spatial strategy. In this view, the rat identifies a room cue that is directly 'behind' the goal corner and simply heads there. A solution method of this sort can be performed in the absence of a functional hippocampus /46,74,82/. In this study by Jeffery *et al.* /37/, reliance on a beacon strategy is encouraged by the variety of cues in the environment, by the simple geometric shape of the box, and finally by the extensive period necessary to train the rats to perform the task reliably.

We predict, in other words, that the same hippocampal damage that prevents the rat from learning the task /37/ would hardly affect performance after the 200 or more trials necessary to get to criterion /46/. If the hippocampus is no longer necessary for solution, remapping would not be expected to degrade performance in the task, much as misregistration of fields is not associated with poor performance when a beacon directly signals the goal /49/. Thus, we believe that the contradictory data reported by Jeffery *et al.* /37/ can be accounted for by the use of a beacon strategy by the rat.

4.3.3. Place cell firing during behavior in response to a spatial change

Preliminary exploration is necessary for rats to solve spatial problems, presumably because key information is gathered as the animal visits each part of a new environment /18,90/. The idea that information gathering is a fundamental function of exploration is strengthened by the finding that animals systematically re-explore modified portions of a familiar environment /86/. Re-exploration occurs regardless of whether the modification involves changes in the relative positions of objects inside an arena (spatial changes) or whether the modification involves substitution of a novel object for a familiar object (non-spatial changes). The occurrence of change-induced re-exploration implies the existence of a stored representation of the surroundings since behavior could not reliably be altered unless it were possible to compare the current situation to a previous situation. A key feature of re-exploration after spatial changes is that it is selectively reduced or eliminated by hippocampal lesions, whereas re-exploration after non-spatial changes is hardly affected /98/ but would probably be affected by lesions of perirhinal cortex /53,70,

111/. The implication is that the ability to recognize the arrangement (but not the identity) of objects in the arena depends on the stored hippocampal representation.

At the place cell level, remapping is a clear consequence of an animal's exposure to a strongly modified environment. It is, however, unclear how more subtle manipulations, such as object substitutions or rearrangements, might alter place cell activity. According to the effects of hippocampal lesions, spatial changes should modify the positional firing characteristics of place cells, whereas non-spatial changes should leave place cell activity unaffected.

To address this issue, we simultaneously monitored the rat's exploratory behavior while recording place cell activity after positional rearrangements of objects or after object substitution in a familiar environment /50/. Overall, the results confirmed our basic prediction since field modification was observed after spatial changes, but not after non-spatial changes. The modification, however, was limited in a very interesting way since it affected only the fields near the displaced objects; fields further from the objects near the apparatus wall were generally unaltered. We conclude that the layout of the apparatus and the objects themselves are coded separately (see also /24,91/). Interestingly, place cells failed to respond to object substitution, regardless of field location. This suggests that object identity is not the primary information signaled by place cell firing. Instead, objects appear to act as markers of specific locations, and their spatial arrangement is usually more important than their identities /13/.

In summary, there is a striking parallel between lesion and single cell data. Much as hippocampal lesions disrupt behavioral reactions to spatial changes, but hardly affect reactions to non-spatial changes, pyramidal cell activity is modified by a spatial change but is hardly affected by a non-spatial change. We take this overall correspondence as strong evidence that place cells are actively involved in re-exploration and thus in spatial processing.

4.4. Relationships between hippocampal cell firing and rats' performance in non-spatial tasks

Many unit recording studies indicate that hippocampal cells may do more than just encode the animal's position. For example, hippocampal cells recorded from rats performing a non-spatial version of the radial arm-maze task show activity changes associated with specific visual-tactile cues on the maze arms /120/. Similarly, in olfactory discrimination tasks, some hippocampal complex-spike cells show time-locked activity to various task-relevant behaviors, such as odor sampling and approach movements /17,116/. Such examples of non-spatial correlates of hippocampal pyramidal cell firing demonstrate the diversity of tuning of hippocampal pyramidal cells and suggest the complexity of the computations that might be performed by the hippocampus.

The likelihood that the hippocampus is involved in processing non-spatial 'relational' information does not, however, vitiate the idea that hippocampal neurons are components of an environmental map and are ultimately essential for the generation of navigation paths. The structure and anatomical connections of the hippocampus suggest that it is particularly well suited for processing information in a special way, and spatial processing may be a prototypical illustration of this mode, a specific instance of a wider set of functions. Thus, even if spatial processing does not capture the full function of the hippocampus, the strong relationships between place cell activity and spatial behavior underscore the idea that any reasonable account of hippocampal function has to include the processing of spatial information. This notion is further supported by the existence, in areas connected to the hippocampus, of cells also carrying powerful and complementary spatial signals (e.g., head direction cells /105-107/). Head direction cells share many properties with place cells including the ways in which they respond to external (mainly visual) and self-motion cues /44,107,115/. Interestingly, the activity of head direction cells correlates well with spatial behavior so that spatial choices are usually in register with the preferred firing direction of head direction cells /15/. Finally, the strong coupling of head direction cells and place

cells /44/ is highly suggestive of an integrated system dedicated at least partly to navigation.

5. NEURAL IMPLEMENTATION OF PLACE NAVIGATION: THE PROBLEM OF THE GOAL LOCATION

We have presented evidence that place cells contribute in an important way to the ability of rats to solve spatial problems. Accordingly, the neural machinery that allows an animal to select efficient and perhaps optimal paths through the environment should include the hippocampal place cell system as a key component. Nevertheless, the main signal carried by place cells, the rat's moment-to-moment location in its current environment, is not sufficient for the rat to compute paths. At least two other crucial kinds of information are necessary for it to be possible to compute complete paths, namely, a representation of the goal and of the sequence of movements to get from the current location to the goal. We now briefly describe two classes of solutions to how the goal and progress to the goal are represented.

In one class of solutions, the goal is somehow signaled by place cell activity and the hippocampus itself computes the optimal path[2]. In the second class of solutions, a larger network of structures solves the whole navigational problem such that each module in this system is dedicated to a specific aspect of spatial processing. After considering these possibilities we will present preliminary evidence in favor of the idea that spatial navigation requires a larger network and will emphasize the importance of medial frontal cortex and striatum.

5.1. Hippocampus-only models

Following the discovery of place cells, O'Keefe and Nadel /76/ proposed a model system, centered on the hippocampus, whose main role was to implement spatial navigation functions. Since then, several investigators have proposed schemes that rely on the fact that place cells and the hippocampal machinery can potentially provide the animal with all information required to compute paths through the environment. It is not in the scope of this short review to describe these models fully /110/ but it is useful to state their basics if only to say how they are lacking.

Hippocampus-only models assume that inputs to hippocampal place cells provide the information necessary to build place representations. They differ, however, in how such place information is used during goal-oriented navigation. Some models depend on topological relationships in which the rat gets from its current location to the goal by traversing a series of places along a previously experienced route /5,54,99,110/. In such models, the path is formed by using the properties of LTP. As the rat runs from its starting position to the goal during learning, place cells along the route fire in sequence so that synapses connecting place cells with adjacent fields are strengthened. When the rat is again at the starting point of such a sequence, the whole series of place cells can be replayed, thereby allowing the rat to follow the path from cell to cell so that it eventually gets to the goal. Models of this sort encounter serious difficulties when the rat (or robot) learns routes to two (or more) goals that cross since near the crossing the direction of further progress is ambiguous. Elaborations of path-following models can solve this difficulty /22/.

In a related model, exploration by the rat allows place cells to be linked by synapses whose strength represent in a general way the distance between their firing fields /69/. Thus, LTP-modifiable connections between place cells with fields that are close to each other would be strengthened because the cells fire in close temporal contiguity. In contrast, connections between place cells with widely separated fields would be weak because such cells cannot fire together. This encoding of distance is a consequence of connecting place cells by Hebbian-like synapses and could occur in the recurrent pyramidal cell to pyramidal cell connections in CA3. This model has the advantage that it does not rely on previously taken paths; it permits the animal to find an optimal path from any starting

[2] This does not mean that place cells contain all the information necessary to do the computation. In fact, many models assume that the complementary properties of place cells, head direction cells and other populations of cells in the hippocampus and para-hippocampal areas contribute to the generation of optimal paths /10,115/.

point to any goal location in a familiar environment.

Metric models also do not depend on following previously taken paths /9,10,112,119/. In such models, the rat is able to compute the vector that points from its current location to the goal by a change of activity in place cells whose firing fields are at the goal. It is possible to find a vector for each initial location so that the direction and distance to the goal can be computed from any starting point /110/.

In common to topological and metric models is that the representation of the goal location is directly assigned to place cell activity. This is a questionable assumption since there is little evidence that goal location in any way influences place cell activity. In particular, spatial firing patterns do not seem to undergo systematic changes when the goal is moved /51,102,109/. For example, in the absence of visual information, firing fields do not stay in register with the single arm of a symmetric Y-maze at whose end food is available even though this cue is sufficient to orient the animal /51/. Similarly, hippocampal place cell firing fields do not tend to occur in higher numbers near the goal zone in any of the three versions of the place preference task used to study how place cell activity is related to behavior /49/.

In contrast to these negative findings, there have been several reports that firing fields occur in excess numbers at goal locations /31,32,45/. Does such accumulation reflect a true representation of the goal or is it possibly due to methodological practices? In the cited studies, increased firing at the goal could be caused by reward-induced modulation of neuronal activity rather than by signaling of the goal location by place cells. In addition, in most experimental designs, the rat is required to spend more time in the vicinity of the goal than elsewhere in the environment. Since place cell firing is not zero outside firing fields, excess time in a certain location that happens to be the goal may cause an apparent excess of local activity. For example, in the place preference task, rats indeed spend more time in the zone designated to trigger food pellet release. Under these circumstances, the number of action potentials fired in the trigger zone appears elevated compared to other regions outside the firing field, but this is mainly because the time spent per unit area is lower elsewhere. Since each report of accumulation of fields near the goal involved preferred sampling of the environment near the goal, the issue of inhomogeneous sampling is crucial.

At present, our position has the following form. We cannot assert that goal location or anticipated arrival at a goal has no effect on place cell activity. Nevertheless, in the absence of more convincing evidence for such signals we assume that goals are not represented in this way. In part, our willingness to take this position depends on recent, *positive* evidence that goal location in fact influences the activity of cells in medial prefrontal cortex, a topic considered near the end of this paper.

5.2. Distributed models

The lack of goal representation in place cell firing suggests that such a representation exists in one or more other brain structures and therefore implies that the navigational system includes more areas than just the hippocampus. Distributed models differ according to the functions presumably served by each area but share the idea that navigation is separable into three processes /3,21,62/. In the first process, the map associated with the current environment is activated, thereby allowing self-localization. In the second process, the goal location is identified on the map and a decision is made about how to get to the goal. In the third process, locomotor commands that take the rat towards the goal are generated using information from the goal-location machinery.

We focus here on the model of Gaussier *et al.* /3,21/ since we use it as the framework for explaining some recent empirical findings. In common with virtually all models, its first component is presumed to include the hippocampal formation which is responsible for identification of the current environment and determination of the animal's position within this environment; together these are called 'place recognition'. The hippocampal formation also learns and stores (possibly in the recurrent connections of CA3) the set of places that can be accessed from each position in the environment that we may refer to as 'transition learning'. Such

learning relies on associations between current and adjacent locations, possibly via the strengthening of synapses between place cells with fields close to each other /69/ (Section 5.1). The outcome is a purely topological representation of space such that each place acts as an attractor that triggers the representation of nearby locations. The Gaussier model avoids assigning to place cells information about the motivational valence of the animal's current location or of neighboring locations. As a result, the search for optimal paths is shifted from the hippocampal module to the other components of the proposed navigational network.

The second anatomical component in the model is the prefrontal cortex which is thought responsible for encoding goal location and for route planning. Specifically, the prelimbic/infralimbic portion of the prefrontal cortex receives input directly from the ventral hippocampus /36/, some of whose pyramidal cells are believed to function as place cells although they occur with lower probability /88/ or have lower resolution /40/ than place cells in dorsal hippocampus. The hippocampal input may therefore provide positional information to the key portions of prefrontal cortex. Prelimbic/infralimbic cortex also receives input from the amygdala that may be the source of information about the reward value of different locations in the environment.

The third anatomical component of the Gaussier model is the nucleus accumbens (ventral striatum) that translates paths in neural space into appropriate locomotor activity that moves the animal towards the goal in real space. The nucleus accumbens gets hippocampal input via the subiculum and fornix /26,41/ but also receives afferents from prefrontal cortex, the amygdala, the hypothalamus and ventral tegmental area, the latter implying strong dopaminergic innervation. Importantly, cells in the nucleus accumbens respond both to spatial positional information and reward expectancy /48,101/. In contrast, cell discharge in the prefrontal cortex is mostly associated with temporary storage of information in memory /4,28,61/. Moreover, both prefrontal cortex and nucleus accumbens are tightly related to motor systems through connections with the ventral pallidum and dorsal striatum and the premotor/motor cortex, respectively.

The complete model assumes that the hippocampal output to the nucleus accumbens and prefrontal cortex provides information for generating solutions to spatial problems. Using elementary information about spatial transitions provided by the hippocampus, the ventral striatum can build simple sensori-motor sequences that select motor responses depending on an animal's immediate needs ('drives'). By itself, the hippocampal/striatal system allows only automatic performance of rewarded paths /80/ but cannot produce the complex, flexible action sequences required to achieve novel goals as in spatial navigation.

In contrast to the simple sequences possible with only the hippocampal plus striatal modules, the complex planning necessary for true navigation requires participation of the prefrontal cortex. By hypothesis, hippocampally supplied transition information from the entire environment is linked to each other in the prefrontal cortex so that it form continuous paths. In the language of graph theory, each atom of transition information from the hippocampus is an 'edge' that connects a pair of 'nodes', and the complete set of transition information forms an 'adjacency matrix'. The job of the prefrontal cortex is to build a path from the current location to the goal using the transition information from the hippocampus. Thus, a path is a set of linked transitions that represents a complex set of actions independent of specific goals as during latent learning. Because motivational signals are also available to prefrontal cortex from amygdalar inputs /34/, paths can be related to the animal's goal.

The model thus assumes that goals are represented by motivational nodes in the prefrontal cortex. Activation of these nodes progressively diffuses through the prefrontal graph of learned transitions leading to the goal allowing identification of the optimal/shortest path to the goal. Finally, the ventral striatum merges this prefrontal top-down information with hippocampal information about possible transitions from the rat's current location. If several transitions are possible, the prefrontal activity biases for the selection of the most relevant transition and the corresponding motor output and generates local progression towards the goal. By iteration, this process allows

for the execution of the shortest path to the goal. With regard to spatial navigation, the behavioral output of the three-module system is the production of smooth and direct paths oriented towards the goal location /3,21/ (Fig. 4).

5.3. Preliminary evidence for goal cells: A unit recording study of the prefrontal cortex

In the model proposed by Gaussier *et al.* /21/, spatial planning relies on the activity of a prefrontal network which associates places with their motivational valence and is therefore able to specify goals. If the model is correct, the firing of at least some neurons in the prefrontal cortex should reflect a combination of spatial and motivational correlates. This dual encoding is required to begin the hypothesized backpropagation of a motivational signal through the network to permit path building.

Recordings made during the place preference task /92/ (see Section 4.2.) strongly suggest the existence of goal cells in prefrontal cortex /30/. In the particular version of the place preference task that was used, the rat had to go to the 'trigger zone' inside a cylinder to cause release of a pellet. Rats were then observed to go reliably to the 'landing zone', the place underneath the feeder where released pellets first touched the floor. To actually eat the pellet, however, the rat had to forage around the cylinder area since the pellet scattered widely after dropping. Thus, there are two potential fixed goals in the cylinder, the trigger zone and the landing zone. Reward itself was, however, broadly distributed over the whole floor. This version of the place preference task makes it possible to disentangle the goal value of places from their reward value; firing in the trigger zone or the landing zone cannot be caused by the food reward itself since eating could occur anywhere.

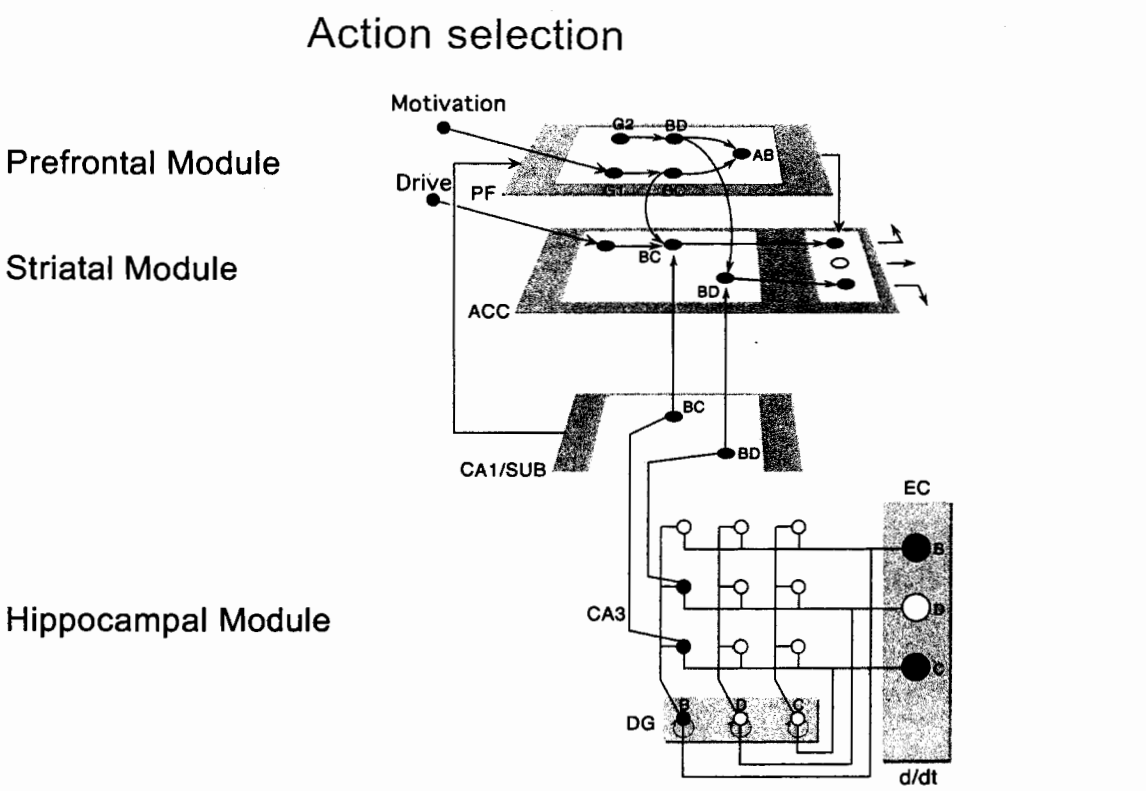

Fig. 4: A sketch of the model. In this architecture, CA3-CA1 learn transitions between places. Accumbens (ACC) and prefrontal cortex (PF) learn, store, and perform temporospatial sequences. Prefrontal activity produces a bias in accumbens activity, leading to the selection of the response most appropriate to the organism's current goal. Reprinted from Banquet *et al.* /3/ with permission.

The key finding of this study was that a substantial proportion (~20%) of cells in the prelimbic and infralimbic parts of medial frontal cortex had clear spatial correlates in the cylinder. This is remarkable since no evidence for delimited firing fields or even reliable regions of elevated firing was found when the rat had simply to forage for food in the cylinder /84/. Thus, prefrontal neurons are much more likely to display location-specific firing when the rat is engaged in planning than when it simply wanders about in the environment. A second important finding is that neurons with spatial correlates were more likely to be found in the prelimbic/infralimbic areas than in the more dorsal anterior cingulate area. This functional result is consistent with the distribution of anatomical connections from the ventral hippocampus which project to the more ventral aspects of the medial frontal cortex /36/. A third finding was that most (~75%) of the spatial firing fields of prefrontal neurons were found in the immediate vicinity of either the trigger zone or the landing zone (Fig. 5), the two fixed goal regions. Spatial correlates of this type seem strongly tied to the motivational valence of specific places. In short, neurons that discharge in this fashion have precisely the properties expected of cells encoding spatial goals, cells necessary for planning optimal paths in the environment.

It would not be surprising if neurons with similar characteristics can be found in other brain areas (e.g., the ventral striatum as suggested by Gaussier's model or the parietal cortex as suggested by other models /14/). Nevertheless we stress that they are not found in the hippocampus, but rather in a structure that is separately implicated in planning /25/ and has strong connections to the hippocampus. The finding of goal-related cells in prefrontal cortex provides a strong basis from which to conclude that spatial navigation relies on a dispersed, dedicated network that includes not only the hippocampus but also the head direction system, prefrontal cortex and at least parts of the striatum.

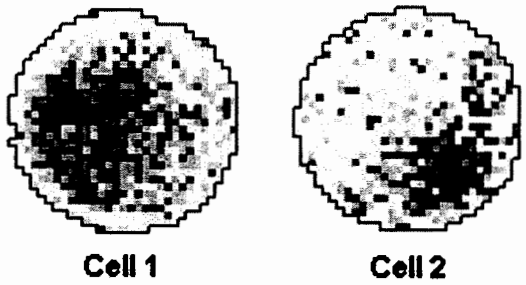

Fig. 5: Firing rate maps of two prefrontal cells showing high spatial selectivity for the trigger zone (left) and the landing zone (right). See text for details. From /30/.

6. CONCLUSION

In line with the original theory of O'Keefe and Nadel /76/, we believe that the basic properties of hippocampal place cells imply that they form part of an integrated neural system for spatial navigation; a key additional part is contributed by head direction cells /104/. The strong relationships between place cell activity and spatial problem solving indicate that the place cell representation must be both functional and in register with the surroundings for the animal to perform correctly in spatial tasks. The system composed of 'spatially tuned cells' (place cells and head direction cells) nevertheless requires other essential elements to be competent. In particular, we have focused on the need for a component that could specify the overall goal of the animal and could compute the path required to take the rat from its current location to the goal; we devoted much less attention to the need for an output mechanism that converts planning decisions into specific actions. The essential message in this paper is that preliminary evidence exists that the goal representation necessary for path planning might be encoded in the prelimbic/infralimbic region of the medial prefrontal cortex.

Even though our strong belief is that the hippocampal formation and prefrontal cortex are parts of a distributed neural network supporting complex spatial behavior, there are several unsolved issues that we raise briefly. One key question involves the possibility that the hippocampal formation does more than implement a representation of the rat's current environment and its location in that environment. For example, it is reasonable to ask whether signals from the prefrontal cortex and striatum are sent back to the

hippocampus. Such feedback could allow the rat to keep track of its whereabouts along the planned path. Although recent evidence shows that damage to the prefrontal cortex alters the properties of hippocampal place cell firing /47/, it is unclear how information from the frontal cortex reaches the hippocampal system. Similarly, recent work indicates that prelimbic frontal cortex is required for learning object-place associations /43/ whereas the hippocampus is necessary for long-term retention of such associations /23/. These findings are consistent with the role of the prefrontal cortex postulated above. They also suggest that in the long term the hippocampus eventually has access to information about the value of places, thus raising the interesting possibility that the nature of the place cell signal might change with time and experience.

In a different vein, the enhanced spatial organization of the discharge of both hippocampal place cells and frontal neurons seen when the rat engages in navigation compared to simple undirected exploration suggests that there are (at least) two modes of activity in these regions. Although our strong hypothesis is that the spatial signal seen in some frontal cortical cells represents the encoding of goals, it is more difficult to understand why place cell firing appears more organized during active spatial navigation. Although the two modes could reflect a different sort of attention to the spatial layout during foraging as opposed to more directed behavior, it could also be that the modes reflect fundamentally different forms of processing.

Lastly, even if place cells are truly involved in spatial navigation, they might contribute to other aspects of complex behavior, such as the storage of episodic memory as proposed by Eichenbaum *et al.* /16/, rapid learning /56/, or consolidation of recent memories /103/. In such models, it is usually assumed that the hippocampus is not necessary for long-term memory. So why is place cell activity persistent and reliable for weeks or months /108/? We believe that addressing these issues is necessary for achieving a full understanding of the function of the hippocampus and its place cells. It is our further intuition, however, that rapid progress in understanding the neural basis of navigation depends on solving the mystery of goal representation and the ways in which motivation is combined with what may be a system that is otherwise purely geometric.

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