

SPATIAL PROCESSING IN THE BRAIN: The Activity of Hippocampal Place Cells

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■ **Abstract** The startling discovery by O'Keefe & Dostrovsky (*Brain Res.* 1971; 34: 171–75) that hippocampal neurons fire selectively in different regions or “place fields” of an environment and the subsequent development of the comprehensive theory by O'Keefe & Nadel (*The Hippocampus as a Cognitive Map*. Oxford, UK: Clarendon, 1978) that the hippocampus serves as a cognitive map have stimulated a substantial body of literature on the characteristics of hippocampal “place cells” and their relevance for our understanding of the mechanisms by which the brain processes spatial information. This paper reviews the major dimensions of the empirical research on place-cell activity and the development of computational models to explain various characteristics of place fields.

INTRODUCTION

When humans and other complex animals move about the environment, they naturally form representations of their experiences. These representations permit them to recall what happened, when it happened, and where it happened. This review addresses the study of brain mechanisms for processing the “where” of experience. Because space appears to exist as a mental construct, how then is it constructed in the brain? How would a brain be organized such that representations of space would emerge from its operation? What forms of brain activity could we observe that would provide evidence for brain mechanisms of spatial processing? The current review focuses on the study of place-field activity of hippocampal neurons in freely behaving animals and the implications of this research for the nature of spatial processing in the brain. The first part of the review describes the empirical study of place-field activity of hippocampal neurons. The second part describes the

use of computational models to understand the mechanism of place-field activity in particular and spatial processing in general. For additional information about hippocampal place cells and current theories of hippocampal function, the reader is referred to a recent special issue of the journal *Hippocampus* (Vol. 9, number 4, 1999) and to a recent book by Redish (1999).

The internal representation of the “where” of experiences could take many forms at the formal conceptual, cognitive level, as well as at the basic cellular neurobiological level. The nature of that representation is of critical importance for developing navigational strategies. A number of formal strategies can be used for effective navigation, such as dead reckoning, path integration, or the formation of cognitive maps (see Redish 1999). The consequent ability of the organism to navigate effectively depends on the nature of those internal representations. For example, birds with hippocampal lesions can migrate accurately many miles by using dead-reckoning processes, but they get lost in their local neighborhood because they lack the ability to form cognitive maps (Bingman & Yates 1992).

In the 1930s and 1940s, when American behavioral psychology was dominated by stimulus-response or stimulus-stimulus explanations of behavior, Tolman proposed that animals do not learn to complete maze tasks solely on the basis of stimulus-response relationships. He believed that “In the course of learning, something like a field map of the environment gets established in the rat’s brain” (Tolman 1948). Such maps represent the environment as a configuration that allows the subject to navigate flexibly from any given location. They free organisms from the confines of fixed stimulus-response interactions with the environment and allow them to anticipate the existence of important stimuli from a distance. For instance, they provide organisms with the capacity to take various novel paths to avoid locations in the world where predators have been encountered and to approach distant locations known to contain food, water, shelter, or mates. Although the idea of cognitive maps was dismissed by the behavioral mainstream in the 1950s (see Restle 1957), some investigators continued to see in animal behavior strong evidence for the existence of internal representations of space or cognitive maps (Hebb 1961).

The Discovery of Place Cells

The first demonstration of an internal representation of space in the brain was presented by O’Keefe & Dostrovsky (1971), who reported that the activity of some cells recorded in the hippocampi of freely behaving rats was closely related to the locations of these animals in an open field. These so-called “place cells” fired maximally when an animal was in a rather small, well-defined region of the environment, the “place field,” and were virtually silent when the animal was elsewhere. Even though the behavior of the place cells was quite remarkable, only 10.5% (8 of 76) of the cells studied showed place field activity.

In 1973, Ranck reported a comprehensive study of the relationship between hippocampal cellular activity and various behaviors. He found that there are two

distinct classes of cells in the hippocampus; cells with complex spikes, which were known to be pyramidal cells (the primary output cells of the hippocampus) and the more rapidly firing theta cells, which were later shown to be interneurons (Fox & Ranck 1975, 1981). Ranck's (1973) study found that the activity of individual hippocampal complex-spike cells fell into a small number of discrete classes, each with a very specific relationship to various aspects of an animal's behavior. He also found that theta cells fired faster during locomotion, when the hippocampal EEG was in the theta frequency band. However, his study found no close relationship between cellular activity and an animal's location in the environment. In a later study, originally planned to further analyze the relationship between cellular activity and various behavioral categories, 16 of 18 complex-spike cells showed place-field activity. Five theta cells fired faster during locomotion but showed no obvious relationship to a rat's location (Best & Ranck 1975, 1982). The nature of the place-field activity was so compelling that, when naïve observers examined videotapes containing images of the behaving rat and the oscilloscope record, they had no difficulty identifying the place-field activity of the cells.

O'Keefe (1976) next published a study reporting on the activity of 50 hippocampal neurons, 26 complex-spike cells that exhibited place-field activity, and 16 cells that had the electrophysiological and behavioral characteristics of Ranck's theta cells. A subsequent study by O'Keefe & Conway (1978) demonstrated that the place fields of hippocampal complex-spike cells were affected in predictable and logical ways by various environmental manipulations. They recorded units as rats performed in an open T-maze in a room containing four salient extramaze stimuli: a light, a fan, a white cue card, and a noise generator. For all place cells, rotation of the distal cues was accompanied by rotation of the place fields. Furthermore, although removal of any two distal stimuli had a negligible effect on place-cell activity, removal of any three stimuli typically caused the place fields to disintegrate. These early reports began to stimulate the study of place-field activity in other laboratories and provided compelling evidence that the hippocampus plays a central role in spatial processing. An example of the place field activity of a hippocampal neuron is illustrated in Figure 1.

The Cognitive-Map Theory

The discovery of place cells, coupled with the results of several hippocampal-lesion studies, led O'Keefe & Nadel (1978) to propose a theory that the hippocampus serves as the neural substrate for cognitive maps. They further proposed that hippocampal place cells are the basic units of the map. According to this theory, an environment is represented by a collection of place cells, each of which represents a specific region of space. The specific configuration of place cells provides an internal representation of the environment that affords an animal knowledge of its position relative to important locations. Whereas the classical sensory systems are designed to process egocentric space, that is, the location

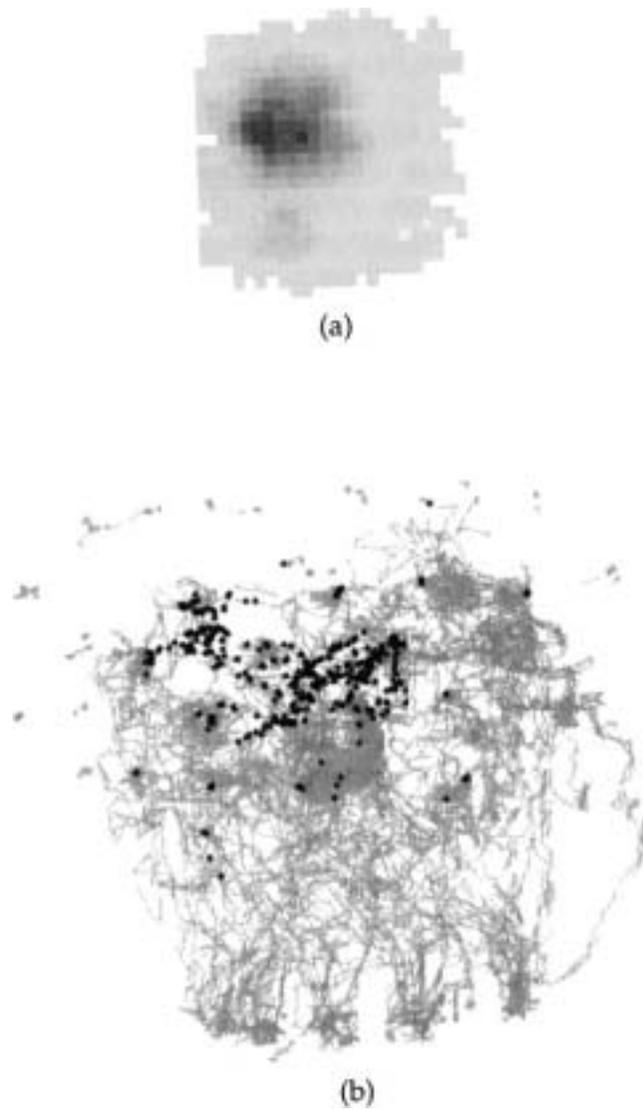


Figure 1 A. Place field in a small enclosed arena in which rats foraged for food that was randomly dropped in the arena. *Darker shading* indicates areas in which a higher rate of firing was seen. B. Place field in a large open arena. *Dots* indicate location of the animal when a spike was fired. *Gray lines* indicate trajectory of the animal. [From Figure B.6 of Redish 1999, with permission of author and publisher (copyright 1997, MIT Press). Data courtesy of D. Nitz, K. Gothard, B. Skaggs, K. Moore, C. Barnes, and B. McNaughton].

of stimuli with respect to the receptors and the organism, the hippocampus, according to the cognitive-mapping theory, encodes allocentric space, the location of the organism with respect to important places in the environment. Thus, the nature of the information that causes place cells to fire in their place fields must affect the organism's awareness of its location in the environment such that it can engage in the appropriate locomotor behavior to navigate effectively to another location. This information comes not only from the configuration of exteroceptive stimuli, but also from the vestibular system and other proprioceptive systems, as well as from already existing representations of space in the organism's memory.

This theory also predicts that lesions of the hippocampus and related structures should cause learning, memory, and performance deficits on behavioral tasks that require cognitive-mapping strategies, while having little or no effect on behavioral tasks that do not require spatial cognitive processing. A discussion of the hundreds of studies on the effects of hippocampal lesions on spatial behavior goes beyond the scope of this review. Suffice it to say that the overwhelming majority of these studies support the cognitive mapping theory, but several do lend support to other interpretations of hippocampal function. For a thorough review of the lesion literature, see Redish (1999).

WHAT INFORMATION DETERMINES WHERE PLACE CELLS FIRE?

After the initial characterization of place cells and the development of the cognitive-mapping theory, researchers began to address questions regarding the nature of the information that drives place-cell firing. For instance, does a particular sensory modality dominate in determining place-cell activity, or are a variety of types of sensory information equally weighted? As might be expected, research addressing this issue has revealed that the answer to the question is complicated. Distal visual cues, when present, appear to provide the preferred source of information used to support place-cell activity. Other forms of external sensory information, such as olfactory, auditory, and local visual cues, can influence place-cell activity. Additionally internal proprioceptive and vestibular systems can provide self-motion or "idiothetic" cues that influence place-cells (Knierim et al 1998). Furthermore, under some circumstances, distal, proximal, and idiothetic cues interact to determine place-cell activity.

Distal Visual Information Can Influence Place-Cell Firing

A number of studies have shown that distal sensory information can exert a strong influence on place-cell activity. O'Keefe & Conway (1978) addressed this problem by rotating the distal cues around a stationary open maze. As discussed above, under such circumstances, place fields rotate with the distal cues. Another way

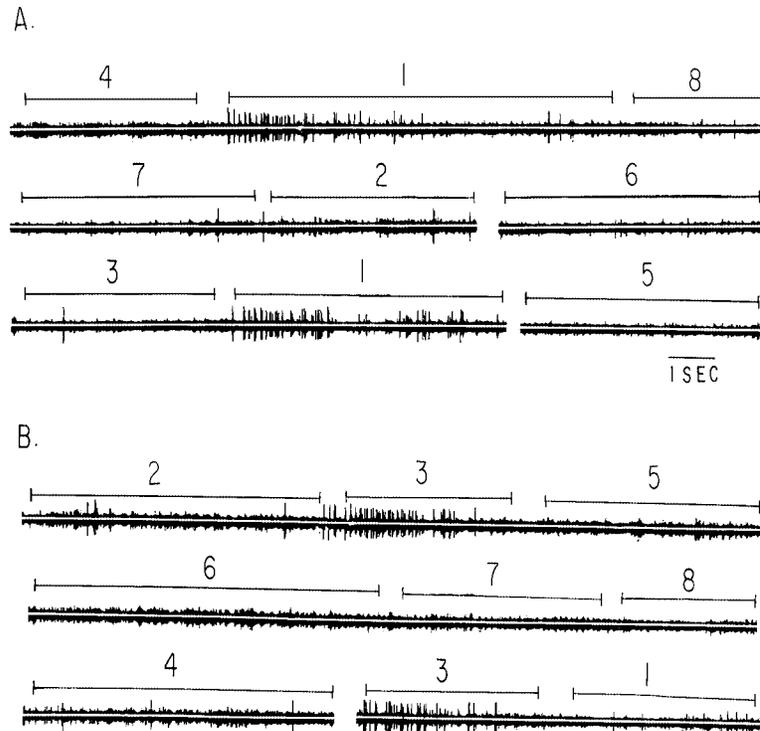


Figure 2 Oscilloscope trace of the activity from a unit in the dorsal CA1 region of the hippocampus as the animal traversed an eight-arm radial arm maze. The numbers represent the arms of the maze. *A.* The maze is in the initial position. Place field is on arm 1. *B.* The maze has been rotated 90° , such that arm 3 is now in the position originally occupied by arm 1. The place field is now on arm 3. (From Figure 8 of Miller & Best 1980, with permission of authors and Elsevier Scientific. Copyright 1980.)

to investigate the relative influence of distal and proximal cues on place-field activity is to rotate a symmetric maze in the fixed environment. When place fields are located on an elevated, open radial-arm maze and the maze is subsequently rotated, the place fields remain in the same positions relative to the room and not on the same physical arm of the maze (Olton et al 1978, Miller & Best 1980; see Figure 2).

Subsequent work has demonstrated that, of the various types of distal information, stable distal visual cues exert a particularly powerful influence over place-cell firing. Muller & Kubie (1987) demonstrated that a single visual cue, a white card attached to the inside wall of a cylindrical arena, could exert almost total control over the location of place fields. Rotations of the card were accompanied by equal rotations of the place fields. Removal of the card did not alter the size or shape of the fields, but did cause the fields to move to new positions (Muller & Kubie 1987).

Thus, once established, the location of place fields can drift in the absence of stable distal cues to anchor them.

Hetherington & Shapiro (1997) recorded place-field activity while subjects moved about in a square recording chamber with cue cards on three of the four walls. Rotation of the cues led to concomitant rotation of the place fields. Removal of individual visual cues altered both the size of the place fields and the within-field firing rates of the cells. Place-field size and within-field firing rates were decreased by removal of a cue located near the place field, but they were increased by removal of a cue located far from the field. Thus, individual visual cues influence place fields, and the degree of influence depends on their proximity to the place field.

Distal visual cues can lose their control over place-cell activity if the rat learns that the cues are unstable. Jeffery & O'Keefe (1999) recorded activity from place cells as rats foraged for food on a platform located in a curtained enclosure containing a single, prominent visual cue. After the locations of place fields were determined, the cue was moved to a new location. When rats were not able to see the experimenter move the cue, the place fields rotated with the cue. However, when rats were able to see the experimenter move the cue, place fields did not reliably rotate with the cue. Similar findings have been reported in other studies (e.g. Knierim et al 1995).

Proximal Sensory Information Can Influence Place-Cell Firing

Although stable distal cues, when present, exert a powerful influence over place-cell firing, a number of studies suggest that under certain conditions place-cell activity can be influenced by proximal cues. Muller et al (1987) investigated the impact of introducing novel, salient proximal cues to an environment on place-cell firing. Introduction of a barrier into the place field typically caused the field to disappear. This occurred even if the barrier placed in the field was transparent. Introduction of the barrier to a portion of the environment outside the place field exerted little impact on activity of the cell.

Cressant et al (1997, 1999) also found that proximal cues located outside a place field exert little influence over place-cell firing. The authors placed three objects near the center of a cylindrical chamber that contained a single distal visual cue. When the positions of the objects were rotated, firing fields remained fixed relative to the distal cue. When the objects were moved against the walls of the cylinder, they exerted powerful control over place-cell firing; that is, they then acted as distal cues.

Shapiro et al (1997) recorded activity from hippocampal place cells while rats traversed a four-arm radial arm maze located in the center of a four-sided curtained enclosure. A prominent visual cue was located on each curtain, and each arm of the maze contained a unique combination of tactile, visual, and olfactory information. After the place fields had been established, a trial ensued in which distal cues were rotated 90° in one direction and proximal maze cues were rotated 90° in the opposite direction. The fields of some cells rotated with the distal cues, while

many other fields rotated with the proximal cues. In another condition, the relative positions of distal and proximal cues were scrambled. Some fields moved with particular proximal stimuli and some with particular distal stimuli, and some cells fired maximally only when the proximal and distal cues were oriented in a particular way relative to one another. Thus, place-cell activity can be controlled by distal or proximal cues or by a combination of the two.

Place-Cell Activity in the Absence of Visual Information

A number of studies suggest that visual information is often neither necessary nor sufficient to govern place-cell firing. Hill & Best (1980) found well-defined reliable place fields in rats that were both deafened and blindfolded as the subjects traversed a six-armed radial maze. After maze rotation, the place fields of the majority of the cells rotated with the physical apparatus. In the absence of visual and auditory information, place fields for those cells were determined by proximal cues on the maze. In one-third of the cells, place fields remained stationary with respect to the real world after maze rotation. Because these subjects were receiving no visual or auditory information, it appears that they were relying on idiothetic information to track changes in location in an internal map of the environment. The subjects were later removed from the maze and spun to disrupt their vestibular system. After spinning, the place fields rotated with the physical apparatus, indicating that, in the absence of reliable idiothetic information, the place-field locations were now determined by proximal cues on the maze.

Save et al (1998) also examined place-cell activity in animals that did not have access to visual information. Place cells were recorded from both normal, sighted rats and rats that were blinded shortly after birth. Recording took place in a cylindrical arena containing three objects (a wooden cone, a plastic cylinder, and a bottle of wine) near the wall of the apparatus. When the objects in the arena were rotated, place fields from both groups rotated with them. However, in blind rats, place-field activity did not begin until at least one of the three objects was approached and explored by the animals. In contrast, for sighted animals, place-field activity typically began during the subject's first pass through the field. The place fields recorded from animals bereft of visual information were similar to those recorded from sighted animals, but were defined by interactions with proximal stimuli.

The Influence of "Intrahead" Variables on Place-Cell Firing

It has become clear that place-cell activity is influenced by a variety of intra-head variables, besides pure idiothetic information, such as the animal's memory and motivational state. Under certain circumstances, these intrahead variables can override the influence of external sensory information on place-cell firing. For instance, when rats are placed in an environment in the presence of room lights, turning the lights off does not disrupt the locations of place fields. However, when the rats are placed in the environment in the dark, many cells develop new place

fields, the majority of which persist when the room lights are turned on (Quirk et al 1990). Such evidence strongly suggests that, in some cases, an animal's recent experiences in an environment can exert a more powerful influence on place-field firing than presently available stable distal cues.

Additional studies suggest that place-cell activity can be influenced by an animal's experiences in an environment. Breese et al (1989) recorded unit activity as rats navigated on a platform that contained five watering cups, only one of which contained water. When the position of the cup containing the water was shifted, the place fields of some cells shifted in the direction of the rewarded cup. Similarly, Markus et al (1995) observed that changing the nature of the search strategy that subjects needed to retrieve food reward on an open platform, from random to directed searching, caused a relocation of place fields in approximately one-third of the cells. The dramatic effect of behavioral task and/or location of reward on the location of place-cell firing stands in stark contrast to the stability of place fields in constant environments. In unchanging environments, place fields have been found to remain stable for ≤ 153 days (Thompson & Best 1989).

A recent study by Skaggs & McNaughton (1998) also demonstrates that intra-head cues influence place-cell firing. The authors recorded place-cell activity while rats shuttled back and forth between two virtually identical boxes that were connected by a corridor. The subjects first foraged for food in one box (box A) and then moved via the corridor to the other box (box B). If external sensory information alone controlled the location of place fields, then cells with place fields in box A would have place fields in the same relative locations in box B. Generally, this was not the case. Cells with fields in box A often had firing fields in box B, but the fields were typically in different locations.

It is possible that the two environments were different enough that subjects could distinguish between them. However, in a second daily recording session, the relative positions of boxes were switched. The subjects were placed in box B, which was now located in box A's position. If subjects recognized the two environments as distinct, then the place fields should have moved with the particular boxes. In no case did the place fields move with the boxes. Similar findings were recently reported by Tanila (1999) using two identical environments connected by a hidden door.

The obvious question that arises from the findings described above is how were subjects able to distinguish between the two environments if they were virtually identical? The most likely explanation is that subjects were aware that they were leaving one environment and entering another based on self-generated motion information or idiothetic cues, and they were therefore aware that the environments differed. Thus, the findings clearly indicate that (a) current external sensory information alone does not control place-field locations and (b) idiothetic information plays a role in governing place-cell activity.

Further evidence that hippocampal place cells are not merely sensory neurons but are highly influenced by various intrahead variables was provided by O'Keefe & Speakman (1987). The authors trained rats on a radial-arm maze to

select a goal-arm that was defined by its location with respect to a set of salient distal cues. The set of cues was rotated to a different position before each trial. Subjects rapidly learned to choose the correct goal-arm, and the activity of most of the place cells rotated with the cues. On some (memory) trials, the cues were removed before subjects were allowed to choose the goal arm. Most of the time, the rats chose correctly, and the place fields remained constant relative to the now absent cues. So, even in the absence of the cues, the subject's memory of the room layout was sufficient to maintain both the accuracy of choice behavior and the location of the place fields. On some memory trials, the animal chose the wrong arm. On these trials, the locations of the place fields were far from random. Their locations were highly predictable based on the location of the arm that the subject chose as the goal arm. In other words, the cells fired when animals evidently thought they were in the place fields. These results indicate that the place cells are not merely responding to exteroceptive sensory input, but are instead important components of a coherent allocentric cognitive map.

Interaction Between “Intrahead” and Distal Visual Cues

As detailed above, there is mounting evidence that information from idiothetic cues influences place-cell activity. A few recent studies have recorded place-cell activity in instances in which information from idiothetic cues was incongruent with information from distal visual cues. For instance, in the study by Jeffrey & O'Keefe (1999) described above, place-cell activity was examined when a prominent distal visual cue was moved either in clear sight of subjects or out of the subjects' views. When subjects were unable to see the visual cue being moved, place-field locations rotated with the cue. When subjects were able to see the cue being moved, place fields did not consistently rotate with the cue. Such evidence suggests that, when the subjects were unaware that the cue was moved, the visual cues dominated over idiothetic information in determining place-field locations, but when the subjects were aware that the cue was unstable, idiothetic cues dominated.

Similar findings were reported by Knierim et al (1998), who recorded place cell activity as rats foraged in a cylindrical apparatus located in the center of a curtained enclosure bearing a single, prominent visual cue. After place fields were initially characterized, the apparatus was rotated abruptly by either 45° or 180°. Place-field locations remained under the control of the distal visual stimulus when the apparatus was rotated 45°. Responses to the 180° rotation were variable. In some instances, distal visual cues continued to define place-field locations, whereas in other cases, complete remapping of hippocampal place fields occurred (i.e. place fields disappeared, and new firing fields emerged). Such findings suggest that, when the mismatch between idiothetic information and distal visual information is small, external visual cues govern place-field locations. However, for many place cells, when the mismatch between idiothetic information and distal visual information is large, neither source of information completely controls place-field activity, and the cells form new fields.

A similar experiment was conducted by Rotenberg & Muller (1997), except that the distal visual cue, rather than the apparatus, was moved by various amounts in the animal's presence. If the cue was rotated in increments of 45° , place fields rotated with the cue, but if it was rotated by 180° in one move, the place fields retained their original positions. If the 180° rotation was followed by four 45° rotations, the place fields did rotate with these smaller movements, so that a return to the original cue configuration left the fields 180° out of phase with their original positions. The results again support the hypothesis of competitive control of place fields by external and idiothetic cues.

In another experiment, Gothard et al (1996b) studied the effect of mismatch between visual cues and idiothetic estimates of position via path integration. The animals were trained to run from a movable start box to a fixed food box at the other end of a linear track and then return to the start box. While a rat was running to the fixed box, the start box was moved up the track by various amounts so that the return journey was shortened. Recordings showed that place fields fired at fixed distances from the start box on the outward journey and return journeys. During shortened return journeys, if the box had been moved a small distance, the place fields moved gradually up the track to compensate. However, if the box was moved a great distance, the place fields jumped abruptly to correct the mismatch between the perceived and expected positions. The authors saw this as evidence that place fields are controlled competitively by idiothetic and external cues. Under these circumstances, the idiothetic cues actually appeared to dominate unless there was a large mismatch between idiothetic and external cues, which triggered a correction based on external cues.

Normally, external information and idiothetic information are congruent as an animal navigates in an environment. The above studies reveal the relative importance of different types of information by dissociating external and internal information. Although both external and vestibular information are easily disrupted or dissociated from each other and external information can be easily eliminated, it has been difficult to eliminate vestibular information. To determine whether the absence of vestibular information would reduce the consistency of hippocampal place coding, Knierim et al (2000) recorded place-cell activity in rats during flight on the space shuttle. They found that the place fields on a three-dimensional track were as robust in the weightless environment as in earth gravity.

Ensemble Characteristics

Recent technical advances in recording and analysis techniques have permitted the development of procedures to record unit activity from many electrodes and from many cells on the same electrode. Thus, one can now record from an ensemble of many neurons simultaneously in an individual behaving animal and can examine the relationship among the activity of individual units in the ensemble. An example of simultaneous recording from five individual neurons is illustrated in Figure 3. Using this approach, Wilson & McNaughton (1994) recorded the activity

of up to 89 place cells simultaneously from individual animals during spatial tasks and slow-wave sleep. Cells that had overlapping place fields in the awake state also tended to fire together during slow-wave sleep, indicating enhanced synaptic connectivity between them and providing indirect evidence for Hebbian plasticity. This plasticity can lead to the emergence of cell assemblies that code for specific environments and capture the topology of these environments because the connection strength between place cells becomes inversely related to the distance between their place fields. Such assemblies can provide a means for localization (Samsonovich & McNaughton 1997, Redish & Touretzky 1998), prediction (Blum & Abbott 1996, Gerstner & Abbott 1996), and efficient navigation (Muller & Stead 1996). One consequence of associative, temporally asymmetric Hebbian learning (Levy & Steward 1983) between place fields would be an experience-dependent, asymmetric expansion of place fields as the animal explores an environment. The existence of this phenomenon was verified experimentally by Mehta et al (1997). Wilson & McNaughton's work on place-cell reactivation during sleep was refined and extended by Skaggs & McNaughton (1996) and Kudrimoti et al (1999), who verified the dependence of the effect on experience and showed that it does not occur during "REM" (rapid-eye-movement) sleep.

Remapping Due to Dissonant Cue Configurations

A very noticeable feature of hippocampal place codes is that, when sensory cues are dramatically disrupted or the animal is moved to a new environment, the result is an almost complete reconfiguration of place codes (Bostock et al 1991). Wilson & McNaughton (1993) recorded from ensembles of hippocampal place cells while animals experienced a dramatic change in their environment. Animals foraged for food in an environment consisting of two identical boxes, A and B, separated by a partition. Cellular activity was first recorded as the animals were familiarized with box A. Then the partition was removed, and the animals were allowed to move around in both boxes. Eventually the partition was replaced, and the animals were confined again to box A. Between 73 and 148 neurons were recorded in each animal. The ensemble place code for the novel part of the environment (box B) was initially quite noisy but stabilized after 10 min of exploration. The opening of box B and experience in it did not alter place fields in box A. Only a fraction of the cells in the recorded population showed place fields in each box, and, for those cells, fields in box B were distinct from fields in box A. The authors concluded that the activity of ~140 place cells provided sufficient information to localize an animal's position to within 1 cm, indicating that the place code is extremely redundant. These results suggest that the hippocampal place cells provide a reliable, robust, and plastic distributed code for the animals' positions in familiar and novel environments.

Tanila et al (Tanila et al 1997a, Shapiro et al 1997) used the ensemble approach to examine the impact of a dramatic reconfiguration of distal and proximal cues on place-cell firing. In these experiments, distal and local cues were rotated in opposite

directions (double rotations), scrambled, or removed, and ensembles of place cells were recorded. In the double-rotation experiment, place cells responded in one of many ways: Some remained consistent with distal cues while others went with the local cues, and others lost their fields or acquired new fields. However, discordant responses were more common in older animals than younger ones, which tended to remap completely (Tanila et al 1997a,b). Repeated double rotations increased the incidence of complete remapping and reduced that of partial remapping. When cues were scrambled or removed, place cells tended to remap or remain consistent with a subset of cues. These results led the authors to conclude that place cells encode a hierarchical representation of the environment with different cells tied to a broader or narrower subset of cues.

Results like those discussed above suggest the presence of global cognitive maps rather than collections of unconnected place cells. Kubie & Muller (1991) speculated that CA3/CA1 place cells might be configured into self-supporting cell assemblies, each corresponding to a cognitive map. This idea was later developed into the notions of reference frames (Gothard et al 1996a, McNaughton et al 1996, Redish & Touretzky 1996, 1998), charts (Samsonovich & McNaughton 1997), and latent attractors (Doboli et al 2000; see below). Several researchers have recently performed experiments to study reference frames in more detail.

Gothard et al (1996a) studied behavioral correlates of CA1 pyramidal cells in a spatial task in which reward locations in an open cylindrical environment were consistently indicated by a pair of local landmarks. These landmarks were moved relative to distal cues from trial to trial, but they retained their position relative to each other. Numerous cells were recorded simultaneously from each animal. The authors discovered four distinct classes of cells: (a) place cells that depended on location with respect to the distal cues; (b) goal/landmark cells that fired close to the reward location or the landmarks, independently of their position in the environment; (c) cells that fired only upon entering or leaving the start box; and (d) cells that coded conjunctively or disjunctively over more than one of these dimensions. The authors concluded that the hippocampus had constructed multiple representations of the environment, each with its own frame of reference, and the appropriate ones were activated in different situations.

THE RELATIONSHIP OF THE HIPPOCAMPUS TO THE REST OF THE BRAIN

If the hippocampus serves as the substrate for the cognitive map and place cells represent the basic units of the map, then not only should disruption of the hippocampus selectively disrupt spatial behaviors that rely on a functioning cognitive map, but disruption of inputs to the hippocampus should disrupt both spatial behavior and place-field activity. Furthermore, there should be some evidence of spatially related neuronal activity in some of the areas of the brain that are connected to the hippocampus. As mentioned above, a large number of studies have

demonstrated that lesions of the hippocampus or its connections with the rest of the brain produce deficits in a wide variety of spatial tasks, while leaving performance on a variety of nonspatial tasks unaffected.

The Effects of Lesions of Hippocampal Afferents on Place-Cell Activity

A number of lesion studies have been conducted to determine the influence of afferent inputs on hippocampal place-cell activity. Of the many structures providing input to the hippocampus, the two regions most critical to hippocampal function appear to be the medial septum and entorhinal cortex. The medial septum projects rhythmically bursting GABAergic and acetylcholinergic fibers to the hippocampus via the fimbria-fornix. These fibers synchronize the activity of hippocampal neurons, giving rise to the hippocampal theta rhythm (Ylinen et al 1995). The hippocampus receives its major cortical input from the entorhinal cortex (Jones 1993). The entorhinal cortex projects to the hippocampus via the perforant path and provides the hippocampus with highly processed sensory information (Lopes da Silva et al 1990).

Lesions of the medial septum or entorhinal cortex or their projections to the hippocampus disrupt the hippocampal EEG and impair spatial memory (Partlo & Sainsbury 1996, Marighetto et al 1998). It therefore seems reasonable to expect that such lesions should also disrupt hippocampal place-cell firing. Interestingly, lesion studies have produced mixed results. Entorhinal lesions virtually abolish place-field activity in hippocampal neurons (Miller & Best 1980). Fimbria-fornix lesions reduce the precision of place-field activity by increasing the rate of activity outside the field and increasing the field size. They also change the nature of the external stimuli that influence field locations. As in blindfolded and deafened rats, the locations of place fields in lesioned animals are more influenced by the local intramaze cues than by the distal room cues (Miller & Best 1980, Shapiro et al 1989).

In contrast to the dramatic effects described above, a number of other studies have revealed much more subtle effects of damage to afferent systems on place-cell activity. Mizumori et al (1989) recorded place-cell activity during reversible septal inactivation via tetracaine. Whereas septal inactivation disrupted the activity of CA3 place cells, it did not alter the activity of CA1 place cells. These findings indicate that place-cell activity in CA1 occurs independently of normal input from either the septum or CA3. A study by McNaughton et al (1989) indicates that place-cell activity in CA3 and CA1 is not dependent on information flow along the classic trisynaptic loop. Colchicine lesions were made in the dentate gyrus, destroying roughly 75% of dentate granule cells. Dentate lesions impaired performance in a variety of spatial tasks, but produced relatively minor changes in the firing properties of place cells recorded from both CA3 and CA1. A recent study by Leutgeb & Mizumori (1999) suggests that the impact of septal lesions on place-cell activity correlates with the impact of septal lesions on spatial memory. Place-cell activity was recorded after subjects received excitotoxic lesions of the

septum. Damage to the septum impaired spatial working memory but produced only mild effects on place-cell firing. Lesions did not disrupt spatial specificity (i.e. ratio of in-field firing to out-of-field firing), but they did increase the variability in place-field activity from trial to trial. The magnitude of the lesion effect on the variability was related to both the size of the lesion and the impairment in working memory. Interestingly, whereas the place fields of intact animals remapped or new fields were developed when a subject was placed in a new environment, place fields of animals with lesions were much less likely to remap in the new environment. Such findings suggest that septal lesions reduce the flexibility of place-cell activity.

The Role of the NMDA Receptor in the Formation of Stable Place Fields

Recent studies have demonstrated that NMDA receptor-mediated synaptic plasticity plays a role in the formation of normal place fields. McHugh et al (1996) examined place-cell activity in a line of genetically engineered mice known as CA1 knockout (CA1-KO) mice. In these animals, the gene encoding the NMDA1 receptor is missing exclusively in CA1. Long-term potentiation (LTP) at Schaffer collateral-CA1 synapses does not occur in hippocampal slices from these animals, and they show significant acquisition deficits in the water maze (Tsien et al 1996[P1], Wilson & Tonegawa 1997). Interestingly, despite the fact that CA1-KO mice exhibit deficient LTP and impaired spatial learning, CA1 pyramidal cells in these animals continued to exhibit salient location-specific increases in activity. The size of the place fields for these cells are roughly one-third larger than fields in wild controls, but the fields remain stable for periods of ≥ 1 h. The firing rates of cells with overlapping place fields are also far less correlated than in normal controls, suggesting that the quality of the spatial information leaving the hippocampus might be diminished in these animals. Thus, deletion of the NMDA1 receptor from CA1 leads to subtle changes in the general characteristics of place cells, but does not block the formation or maintenance of place fields over a ≥ 1 -h period.

Additional studies have investigated the effects of widespread NMDA receptor blockade on place-cell activity in normal lab rats. Kentros et al (1998) found that NMDA receptor blockade by 3-[(\pm)-2-carboxypiperazin-4-yl]propyl-1-phosphonate, a competitive NMDA receptor antagonist, did not disrupt activity in place fields that were established before drug administration, indicating that NMDA receptor activation is not needed for the maintenance of previously established place fields. When drug-treated subjects were placed in a novel environment, new place fields emerged and persisted for ≥ 1.5 h. However, fields formed under 3-[(\pm)-2-carboxypiperazin-4-yl]propyl-1-phosphonate were not present when subjects were returned to the environment the following day, indicating that NMDA receptor blockade prevented the long-term stabilization of the fields. Further research (Shapiro & Eichenbaum 1999) revealed that NMDA receptor blockade can prevent even the short-term stabilization of place fields. As before, when

drug-treated animals were placed in a novel environment, new place fields were formed. However, when the room lights were turned off for 5 min and then turned back on, place fields in drug-treated animals moved to new locations.

The Location of Cells with Spatial Properties

Most of the studies of place-field activity discussed above have concentrated on pyramidal cells in the CA1 and CA3 regions of the dorsal hippocampus. Place cells are also found in ventral hippocampus (Poucet et al 1994). However, fewer cells in ventral hippocampus have place fields, and the fields tend to be less spatially selective than dorsal cells (Jung et al 1994).

Although theta cells are generally assumed not to have spatial properties, they have been found to fire at slightly differential rates in different locations in the environment. However, their fields are very large, sometimes encompassing >50% of the test environment, and the modulation in rate by location is not at all as great as their modulation by movement (Kubie et al 1990). Granule cells in the dentate gyrus, which provide inputs to CA3 and CA1 pyramidal cells, also have been found to have spatial properties. Their fields show slightly more spatial specificity than theta cells, but nowhere near the spatial specificity of pyramidal cells (Jung & McNaughton 1993).

Cells exhibiting location-sensitive activity have been recorded in other areas of the brain that are connected to the hippocampus. In no studies have cells been found which have spatial specificity approaching that of hippocampal pyramidal cells. Cells with spatial properties have been found in entorhinal cortex (Quirk et al 1992, Barnes et al 1990), parasubiculum (Taube 1995b), and subiculum (Phillips & Eichenbaum 1998, Sharp & Green 1994, Sharp 1997). Whereas the locations of the place fields of hippocampal pyramidal cells are unrelated in different environments, the relative locations of firing fields recorded from subicular cells are maintained when the subject is moved from one environment to another; that is, if a subicular cell fired near the north wall of one arena, it will also fire near the north wall of a second arena. Sharp (1999) suggests that cells in the subiculum, in concert with cells in the entorhinal cortex, form generic or universal maps that are used to represent multiple environments. Novel combinations of input from the generic map and input regarding sensory information from the environment give rise to the location-specific firing of hippocampal pyramidal cells.

Many cells in postsubiculum, called "head direction cells," are very active when the rat's head is oriented in one direction in the horizontal plane and fire more slowly as the head moves away from the preferred direction. This directional specificity is found in all parts of the environment and is independent of the nature of the environment, the animal's location, or the orientation of the animal's head relative to its body (Ranck 1985, Taube et al 1990a,b). Typically head direction cells are under the control of distal stimuli, like place cells, and have different preferred directions in different environments. Head direction cells have also been found in anterior thalamus (Taube 1995a, Blair & Sharp 1995). Under conditions that

disorient the rat's sense of direction, the stability of hippocampal place cells and thalamic head direction cells are strongly coupled (Knierem et al 1995). It appears that the strength of external stimulus control over both place cells and head direction cells depends on the rat's learned perception of the stability of the stimuli.

Cells in the medial and lateral septum do not show spatial specificity nor do cells in medial prefrontal cortex, a target of CA1 cells of the temporal hippocampus (Poucet 1997).

COMPUTATIONAL MODELING AND SYSTEM LEVEL THEORIES

As the sensory, perceptual, and contextual dependencies of place activity have become clearer, so has the need for a more subtle and complex systemic understanding of the hippocampus's role in spatial processing. Computational models have been developed to explore and refine various theories of spatial processing in the hippocampus. Because of their computational nature, these models allow researchers to explore ensemble dynamics under a variety of simulated circumstances. The remainder of this review discusses computational-modeling studies of hippocampal place cells.

Place-Field Models

The first detailed computational model of the hippocampal place-cell system was developed by Zipser (1985, 1986). Zipser (1985) used a two-layer, feed-forward neural-network model to show how place fields could emerge from information about a small set of visual landmarks/cues. Sharp (1991) presented a particularly simple and insightful model for landmark-based place fields. The model uses a feed-forward neural network with a sensory input layer and two processing layers of competitive units. The model is able to produce very realistic place cells and can even account for the different degrees of directionality seen in place fields in open environments (Muller et al 1987) and arm mazes (McNaughton et al 1983). Another model for the emergence of place fields was reported by Shapiro & Hetherington (1993), who use the back-propagation algorithm to train a three-layer neural network with input neurons tuned to visual landmarks. More recently, O'Keefe & Burgess have developed a detailed computational model for the dependence of place fields on visual cues (O'Keefe & Burgess 1996, Burgess & O'Keefe 1996). This model, which constructs place fields from Gaussian firing fields tuned to individual cues, is able to replicate a variety of results from cue manipulation experiments.

The Role of Learning in the Place-Cell System

Several authors have considered the possible role of LTP in place representations. Using a model of CA3 with detailed, multicompartment neurons, Wallenstein &

Hasselmo (1997) have shown that LTP in the recurrent excitatory connections and selective modulation of GABA B inhibition by the theta rhythm spontaneously produce place tuning in the CA3 cells. Kubie & Muller (1991) suggest that, due to the associative and temporal characteristics of LTP, synapses between pairs of CA3 cells should, over time, come to reflect the distance between the cells' place fields. This effectively encodes the topology of the environment in the system architecture. Muller & Stead (1996) demonstrated quantitatively that the information in such a "cognitive graph" can be used by a conventional shortest-path algorithm to discover short cuts between arbitrary locations in a familiar environment.

LTP between CA3 place cells can also help in learning routes by strengthening associations between consecutively activated cells along frequent routes. Experimental studies (Wilson & McNaughton 1994, Mehta et al 1997, Kudrimoti et al 1999) have shown strong evidence that sequences of hippocampal-activity patterns elicited during spatial navigation are indeed learned by the system. Such learning can be useful in goal-directed navigation, and this has been considered in several computational models of the hippocampus (Blum & Abbott 1996, Gerstner & Abbott 1996, Samsonovich & McNaughton 1997, Redish & Touretzky 1998).

Models of Navigation

The first model of hippocampally guided navigation was developed by Zipser (1986), who used his place-field model (Zipser 1985) as the basis of two computational models for landmark-based navigation such as that seen in the Morris water maze (Morris et al 1982). The first of these models associates goal directions to directional place fields by using Hebbian learning. The goal is first encountered through random search, and its direction is tracked thereafter by idiothetic update. The second navigation model by Zipser (1986) is much more abstract, building a transformation matrix that maps any landmark conjunction to a goal location.

An early model by O'Keefe (1991) uses an approach similar to Zipser's, that is, casting the navigation problem into a coordinate transformation framework. The model addresses how a global, allocentric cognitive map can be used to guide navigation via transformation to egocentric coordinates. Similar models by McNaughton et al (1989) and McNaughton & Nadel (1990) investigate whether a CA3-like recurrent network could use LTP to learn associations between current location, motor actions, and the resulting locations, thus performing path integration (Mittelstaedt & Mittelstaedt 1980). Hetherington & Shapiro (1993) also proposed a recurrent neural-network model that learns to produce a sequence of location codes from a starting location to the indicated goal location.

Burgess et al (1993, 1994) presented a connectionist model of the hippocampal system comprising place cells, subicular cells, and goal cells. In the model, the subicular cells develop large place fields via LTP on the synapses from the place cells. In the course of exploration, the goal cells become estimators of the animal's distance and direction from the goal(s) and are used to determine motor commands during navigation. The model makes use of the phase precession effect—firing at

successively earlier phases of the theta cycle as the animal moves through the cell's field (O'Keefe & Recce 1993; see below).

Wan et al (1994a,b) hypothesized that the place code provides a mechanism for maintaining consistency between an animal's sensory and idiothetic perceptions of location and direction in a familiar environment. In their model, the place code, the visual input, and the head direction signal are associated in a local-view system, which can reset the head direction based on the place and visual signals if the animal becomes disoriented. The visual input can also reset the path integrator if the latter becomes incorrect due to disorientation or drift. Elaborations of these models have been developed by Redish & Touretzky (1997a,b, 1998) using an explicit connectionist implementation with attractor networks for localization, path integration, and head direction coding. A detailed account of the theory underlying this model is presented by Touretzky & Redish (1996).

Several other models of navigation based on hippocampal place codes have been reported in the literature. Recce & Harris (1996) proposed a model that uses the hippocampus as an auto-associative memory, which stores cortical cognitive maps by using place cells and is used to complete cortical representations during navigation. Blum & Abbott (1996) modeled a CA3-like network of place cells that uses temporally asymmetric LTP (Levy & Steward 1983, Gustafsson et al 1987) to learn routes towards a specific goal. Work by Gerstner & Abbott (1996) provided theoretical analysis of this model and also extended it by allowing the possibility of multiple goals by introducing a goal-dependent modulation of the place fields. Sharp et al (1996; see also Brown & Sharp 1995) hypothesized that directed motion is controlled by cells in the nucleus accumbens that receive input from hippocampal place cells and from the head direction cells in the postsubiculum and the anterior thalamic nucleus. The paper also presented a comprehensive model of head direction cells in the postsubiculum and the anterior thalamic nucleus. Recently, Foster et al (2000) proposed a model of navigation in the water maze by using the principle of temporal difference learning (Sutton 1988). Another model developed by Arleo & Gerstner (2000) views CA3/CA1 place cells as providing basis functions for the construction of goal-dependent reward surfaces for guiding navigation. As in the model by Foster et al (2000), a temporal-difference procedure is used to learn directed navigation. The authors have implemented their model using an actual robot, and they demonstrate that the model works effectively for a number of realistic situations.

Reference Frames

The issue of reference frames has been of great interest recently, motivated by experiments showing that place codes can remap in certain situations (Quirk et al 1990, Bostock et al 1991, Gothard et al 1996a,b; Barnes et al 1997). Redish & Touretzky (1997a,b, 1998) proposed that the reference frame for an environment is instantiated in a preconfigured attractor network of head direction cells whose activity becomes associated with the place code. Different attractors in the

head direction network correspond to different reference frames. A comprehensive model by Samsonovich & McNaughton (1997) also hypothesized that reference frames are implemented via continuous, stimulus-dependent attractors called charts. The CA3 is proposed as the location of these charts. The function of the place code, according to this model, is to maintain consistency between exteroceptive and idiothetic place estimates. A detailed mathematical analysis of the chart model was presented by Battaglia & Treves (1998). Another recent attempt to model reference frames is the latent attractor model of Dobioli et al (2000). This model hypothesizes that the dentate gyrus-hilus system functions as an attractor-based biasing system that imposes a contextual element on CA3/CA1 place-cell activity. An accessible overview of attractor-based models of hippocampal place coding was provided by Tsodyks (1999).

Other Issues Addressed by Modeling

Several other aspects of hippocampal place representations have been explored through computational modeling. Brunel & Trullier (1998) used LTP of synapses between CA3 pyramidal cells to explain the observation that place cells are non-directional in open environments but show directionality in constrained ones (Markus et al 1995). A similar approach was used by Arleo & Gerstner (2000).

The precession of place-cell firing relative to theta phase as an animal moves through the cell's field (O'Keefe & Recce 1993, Skaggs et al 1996) has been modeled variously as arising from asymmetric interactions between place fields (Tsodyks et al 1996), attentional dynamics during each theta cycle (Burgess et al 1994, Burgess & O'Keefe 1996), interplay between attractor dynamics and path integration (Samsonovich & McNaughton 1997), and partial replay of previously learned routes (Wallenstein & Hasselmo 1997). However, the phenomenon is still not fully understood.

Finally, modeling has also been used to quantify the information content of place firing. Skaggs et al (1993) used information theoretic arguments to measure the information in single spikes. Subsequently, several researchers have studied whether a moving animal's position can be determined accurately from the ensemble activity of a place-cell subpopulation by using template matching (Wilson & McNaughton 1993), Bayesian estimation (Zhang et al 1998), and reconstruction based on inhomogeneous point processes (Brown et al 1998). All of these studies have demonstrated that place cells provide a very accurate and redundant distributed coding of an animal's position.

Modeling has contributed significantly to the current understanding of spatial processing in the hippocampus. However, the models have been most useful in evaluating system-level hypotheses, and they have not yet yielded definitive answers to the main questions they address: How are place fields formed? How are they stabilized? and What are they used for, and how? Nevertheless, computational models remain an extremely powerful way to explore large-scale theories of hippocampal function.

CONCLUSIONS

Hippocampal neurons exhibit robust changes in firing that are highly correlated with an animal's location in the environment. O'Keefe & Nadel (1978) suggested that these neurons, which they labeled place cells, form the basic units of Tolman's cognitive maps, with each cell representing a particular region of space and a collection of cells representing an entire environment. Presumably, as an animal moves through the world, the changing activity of hippocampal place cells provides information to the rest of the brain regarding the animal's current location in allocentric space. Despite the compelling nature of place-field activity and the effects of hippocampal lesions on spatial navigation, there is considerable evidence from lesion and recording studies that the concept of a cognitive map might not totally capture the function of the hippocampus and that place cells might represent far more than locations in space.

Hippocampal lesions have been found to cause disruption in some explicitly nonspatial tasks, for which a cognitive-mapping strategy appears to be irrelevant. Such lesions disrupt Pavlovian trace conditioning and performance on certain nonspatial "working-memory" tasks (Rawlins et al 1993) and tasks that require nonspatial configural or contextual processing (Wiener et al 1989, Sutherland & Rudy 1989). In humans, hippocampal lesions disrupt formation of new episodic memories (Squire 1992). Other studies have shown a close relationship between hippocampal pyramidal-cell activity and factors other than the rat's location in space (Eichenbaum et al 1987, Hampson et al 1993). For instance, hippocampal neurons show well-defined reliable conditioned responses in Pavlovian conditioning paradigms (Berger et al 1980, McEchron & Disterhoft 1999). Such evidence suggests that perhaps the hippocampus is involved in a more general fundamental process, of which cognitive mapping is a specific example.

Although the exact nature of the contribution made by the hippocampus to cognition is still uncertain, the importance of the extraordinary discovery of place-field activity and of the development of the comprehensive cognitive-mapping theory is undeniable. The discovery of place cells has dramatically impacted the study of the role of the hippocampus in behavior and has produced a significant paradigm shift (Kuhn 1970) in the study of brain mechanisms of behavior. The data gathered over the past 30 years of place-cell research have yielded profound insight into the nature of the neural mechanisms underlying the "where" of experience.

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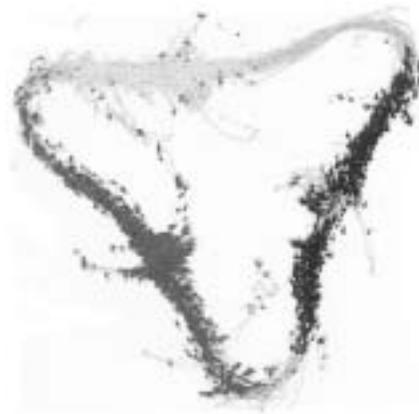


Figure 3 Map of the place fields of five simultaneously recorded units on an elevated triangular maze. The light gray trace represents the rat's path as it traversed the maze. The dots in each color indicate the locations in which each of the five cells fired. (Data courtesy of C Barnes & B McNaughton.)