Persistence, reticence, and opportunism of place-field activity in hippocampal neurons

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The experiments described here were done to determine if the nature of hippocampal place-cell activity is consistent with O'Keefe and Nadel's theory that the hippocampus serves as a cognitive map. The results indicate that place fields respond in ways similar to the animal's behavior in processing information from the environment. Both place fields and behavior are determined more by extramaze than by intramaze cues on the elevated radial-arm maze. The fields are opportunistic in selecting any information available to the organism. Like the behavior, the place-field activity is disrupted by lesions of hippocampal connections. The place-field activity is apparently so specific that the cells are virtually silent in most environments. Finally, the place fields are extremely stable for periods of time approaching the life of the organism in stable environments. Thus, the system appears to be well designed to serve as a cognitive map.

The studies discussed here were designed to test the viability of O'Keefe and Nadel's (1978) cognitive map theory of hippocampal function by examining the nature of hippocampal place-cell behavior. If the hippocampus is involved in spatial processing, then the place-field activity of hippocampal neurons should have certain attributes. They should have certain predictable relationships to the spatial behavior of the animal under a variety of conditions. Environmental manipulations that modify the animal's spatial behavior should produce parallel changes in place-field activity, and vice versa.

Under certain conditions, a rat's behavior when foraging on an elevated, open radial-arm maze is more controlled by the environmental "extramaze" cues than by the cues on the maze itself. That is, if one rotates the maze after the animal has made several choices, the animal avoids the places it has been relative to the room cues, but does not avoid the physical arms that it has traversed (Olton & Samuelson, 1976). If the hippocampus is the site of a cognitive map, then the place fields of hippocampal neurons should be determined by extramaze cues under the same conditions. Miller and Best (1980) showed that if the place field was located on a specific arm of the maze, and the maze was then rotated, the field persisted on the new arm rotated to the field's original position in the room; that is, it did not remain on the same physical arm in its new location with respect to the room.

Lesions of the major connections of the hippocampus, which produce deficits in spatial processing and behavior,

should also disrupt place-cell activity. Such was found by Miller and Best (1980), who showed that lesions of either the fimbria-fornix or the entorhinal cortex, both of which produce profound deficits in spatial behavior, also disrupt hippocampal place-cell activity. Recently, Shapiro et al. (in press) have replicated this deficit in place-field activity following fimbria-fornix lesions, and have shown that fetal brain implants that cause slight recovery of spatial behavior result in parallel recovery of the integrity of place-field activity.

Normally, when animals move about a familiar environment, they receive corroborating input from a variety of sensory modalities informing them of their location in the environment. Removal of the information from any one modality generally does not disrupt their behavior if the information from the remaining modalities is still corroborating. Such was also found to be the case with the place fields of hippocampal cells by O'Keefe and Conway (1978). Removal or movement of one cue did not disrupt the place fields, but rotation of the majority of room cues surrounding the rat caused a predictable relocation of the place fields. The fields maintained the same juxtaposition to the room cues as before relocation of the cues.

Hill and Best (1981) examined this same question in a slightly different manner. They reasoned that rats deafened and blindfolded should be more sensitive to intramaze cues than to extramaze cues. Their hippocampal cells still ought to have reliable place fields, but the fields ought to be more under the control of the cues located on the maze. Therefore, following maze rotation, the fields should remain on the same physical arm as before rotation, irrespective of the position of the arm in the

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room. Such was the case for 65% of the cells. However, the remaining cells had fields that persisted with respect to the room. They behaved the same as cells in animals receiving visual and auditory cues. Either the animals (and their place cells) were responding to other extramaze cues, such as odor, or something else was going on.

What if the information that was maintaining the persistence of the place fields in these deaf and blind animals was neither intramaze nor extramaze? What if it was intrahead? The possibility exists that even following the removal of exteroceptive cues, the animal could still maintain its bearing on the basis of information from its vestibular system. If such is the case, then disruption of the vestibular system should disrupt the spatial persistence of the place fields. To disrupt the vestibular system, we placed the animals in a towel and spun them both clockwise and counterclockwise in a horizontal and a vertical plane, about 20 rotations in each orientation.

The results of this experiment are shown at the top of Figure 1. Recall that, in these animals, if the maze was rotated and the animal was not spun, the field persisted in the same location with respect to the real world. The two upper-left panels in Figure 1 show a case in which the field was initially located on Arm 1. Following rotation of the maze, Arm 3 occupied Arm 1's position, and the field was located on Arm 3. However, if the rat was spun and the maze was rotated, then the field was maintained on the same physical arm as it had been before rotation and spinning. The top right panel of Figure 1 shows that following spinning the rat and rotating the maze, the field was still on Arm 3 in its new position. That is, the place-field activity did not go away, nor did the field move to an undetermined location. It remained constant with respect to the maze cues. Thus, the disruption of the field's persistence with respect to the real world was not due to a general disorientation of the rat or to emotional consequences of spinning.

The data show that when these animals had reliable information from their vestibular system, this information was used to determine the cell's place-field location. However, following disruption of the vestibular system, the fields were determined by intramaze cues, such as, perhaps, tactile or odor cues. But the animals did not know they were going to be spun on any specific session. On the initial session of the day, they did not know whether to attend to vestibular or intramaze cues to maintain their orientation. They must have perceived both. Yet when the vestibular system was disturbed, the fields were determined by maze cues. If the vestibular system was left undisturbed, the fields were not determined by the maze cues. Obviously, these cues were available to the animals all of the time, but when they were inconsistent with existing reliable vestibular cues, the maze cues did not determine the place fields.

Interestingly, the lower panels of Figure 1 show that when the animal was placed back on the maze the following day, the field was back in its original position (i.e.,
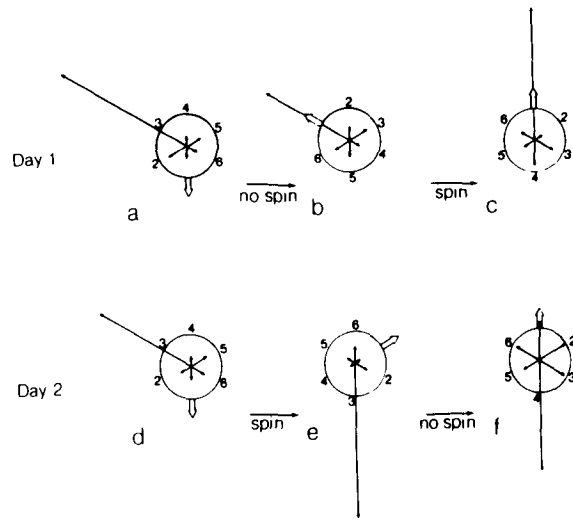

Figure 1. Vector representations of firing rates for a spatially persistent cell in a deaf and blindfolded animal on a six-arm radial maze. The length of each vector represents the mean firing rate for all visits to that arm in that spatial direction. The short, wide arrow designates the orientation of Arm 1 of the maze. Day 1: (a) During the initial orientation, the cell fires most rapidly on Arm 3; (b) following 120° clockwise maze rotation, the cell fires in the same room location, which is now Arm 1; (c) after the animal is spun and the maze is rotated an additional 60° clockwise, the cell continues to fire on Arm 1. Day 2: (d) During the same initial orientation as Day 1, the cell fires on Arm 3; (e) after the animal is spun and the maze is rotated counterclockwise 120°, the cell continues to fire on Arm 3; (f) after the maze is rotated an additional 60° counterclockwise (but the animal is not spun), the cell fires in the same room location.

Arm 3). When the maze was rotated counterclockwise and the animal was spun, the field stayed on Arm 3 in its new location. However, a later rotation of the maze, without spinning the animal, resulted in the field maintaining its immediately preceding position with respect to the external environment.

These results corroborate those of O'Keefe and Conway (1978) by further demonstrating that the brain is quite opportunistic in its use of the wide variety of sensory information available for maintaining registration of the position of the animal in space. Under most circumstances, the information from most, if not all, sensory inputs is consistent. But, obviously, the information from some modalities is more salient than that from others. When the more salient information is removed, or disrupted, the less salient information will be utilized. If the less salient information is inconsistent with the more salient information, it will not be utilized. However, the fact that it is not utilized does not mean it has not been registered. When we did not spin the animals, and thus their vestibular system was undisturbed, it appeared as if they were ignoring any local maze cues. However, if they had ignored the maze cues, then spinning should have totally disrupted the place fields, resulting either in no discernible fields or in fields in unpredictable locations.

If the hippocampus serves as a cognitive map, we would expect virtually all of the pyramidal cells to be place cells. Early studies of place-field activity found that almost every cell encountered in a particular environment had a place field in that environment (see O'Keefe, 1979, for a review of the early studies). This could mean that every hippocampal cell has a field in every environment it encounters. However, Kubie and Ranck (1982, 1983) found that some cells that showed reliable place-field activity in one environment were virtually silent in another environment. They also demonstrated that if the cell showed a certain level of background activity in an environment, then it would have a place field in that environment. These results revealed much greater specificity of place-field activity than had previously been thought. But the data could also mean that many hippocampal cells are not involved in spatial processing. They might be totally silent as the animal navigates around a familiar environment.

The fact that a cell could be silent in any environment recalled for us an observation made a number of years ago in my (P.I.B.'s) laboratory (Olmstead & Best, 1974). At that time, we isolated cells by lowering an electrode in an anesthetized rat until we isolated a good unit signal, and then cemented the electrode in place. After the animal arose from the anesthesia, behavioral testing commenced. However, in the awake animal, reliable isolated activity was found on only 10%–20% of the electrodes. It appeared that most of the cells were lost in the interim between implant and behavioral testing. However, when we reanesthetized the animals to make marking lesions at the end of the experiment, we occasionally recorded from the electrodes that had been silent in the awake animals. To our surprise, well-isolated cellular activity reappeared on most of those electrodes.

Recently, we decided to determine just how many cells were silent in any one environment (Thompson & Best, in press; Thompson, Kapur, Lacey, Salerno, & Best, 1985). To address this question, one has to have a procedure for driving the cells, in order to demonstrate that the electrode is resting close enough to a cell to pick up the electrical activity if the cell were active. A number of methods are possible: electrical stimulation of afferents and efferents, or local or systemic injections of appropriate pharmacological agents. The most reliable method is intraperitoneal injections of sodium pentobarbital. Similar results were obtained with a variety of benzodiazapine agonists.

The animals were first implanted with movable electrode bundles. On testing days, the rats were given a mild dose of pentobarbital (25 mg/kg), and the electrode bundle was advanced until a well-isolated cell appeared on one of the electrodes. The animal was permitted to recover from the anesthetic and was placed in one, two, or three testing environments for determination of place-field activity. The behavioral testing typically lasted more than 45 min. If no activity was seen in any of the environments, the animal was reinjected to determine if cellular activity

remained on the electrode. If no activity was found following the second injection, the data were not counted, since the cell could have been lost before behavioral testing.

Of the 273 cells isolated under pentobarbital, 218, or more than 80%, were silent on the elevated radial-arm maze. In addition, 63% were silent in all three environments tested. Expressed another way, only 20% of the cells tested in the radial-arm maze showed place fields or any spontaneous cellular activity there. Only 15% of the cells tested in a walled drum or in a rectangular walled chamber showed any activity there. As previously reported by Kubie and Ranck (1982, 1983), it was not possible to predict the location of a field in one environment, or the existence of a field at all, from the properties of the cell fields in another environment. Similarly, nearly every cell that fired in a specific environment had a place field in that environment.

Does the data then reveal that only a small proportion of the cells were processing spatial information? We think not. As the number of environments tested was increased, the number of active cells increased (see also Kubie & Ranck, 1983). Note that fewer cells had fields (or activity) in the box or the drum than in the maze, but that some of the cells that were silent in the maze revealed place fields in the other environments. Thus, if we added more and more environments, we would expect more and more otherwise silent cells to have place fields.

Finally, we will address the issue of the stability of place-field activity over time. If the cognitive map theory is correct, then the place field of a cell should not change over time in a constant environment. It has been well established for some time that these cells show changes in activity during learning experiences (Berger, Clark, & Thompson, 1980; Best & Best, 1976; Hirano, Best, & Olds, 1970). In fact, some of the papers in this session demonstrate that the place-field activity of these cells can be modified by various means.

Plasticity of hippocampal cellular activity, or even of place-field activity, need not be inconsistent with the cognitive map hypothesis unless one requires that the map is strictly of Euclidian space. However, the mapping system would be more adaptive in a Darwinian framework if it provided greater precision and differentiation with respect to those aspects of the environment that were more important to the animal's survival. The mapping system probably did not evolve to provide the Cartesian coordinates of the environment, but rather to help us navigate effectively from a safe home den to a watering hole to food sources, while avoiding places where we had experienced danger. Therefore, emotionally significant experiences could well modify a Darwinian map, if not a Euclidian one. Indeed, the map must provide us with an internal representation of the world, but not necessarily one that is precise in a Euclidian sense, or unchanging in a changing world.

Even if place cells show plasticity under changing conditions, there are certain conditions under which the fields
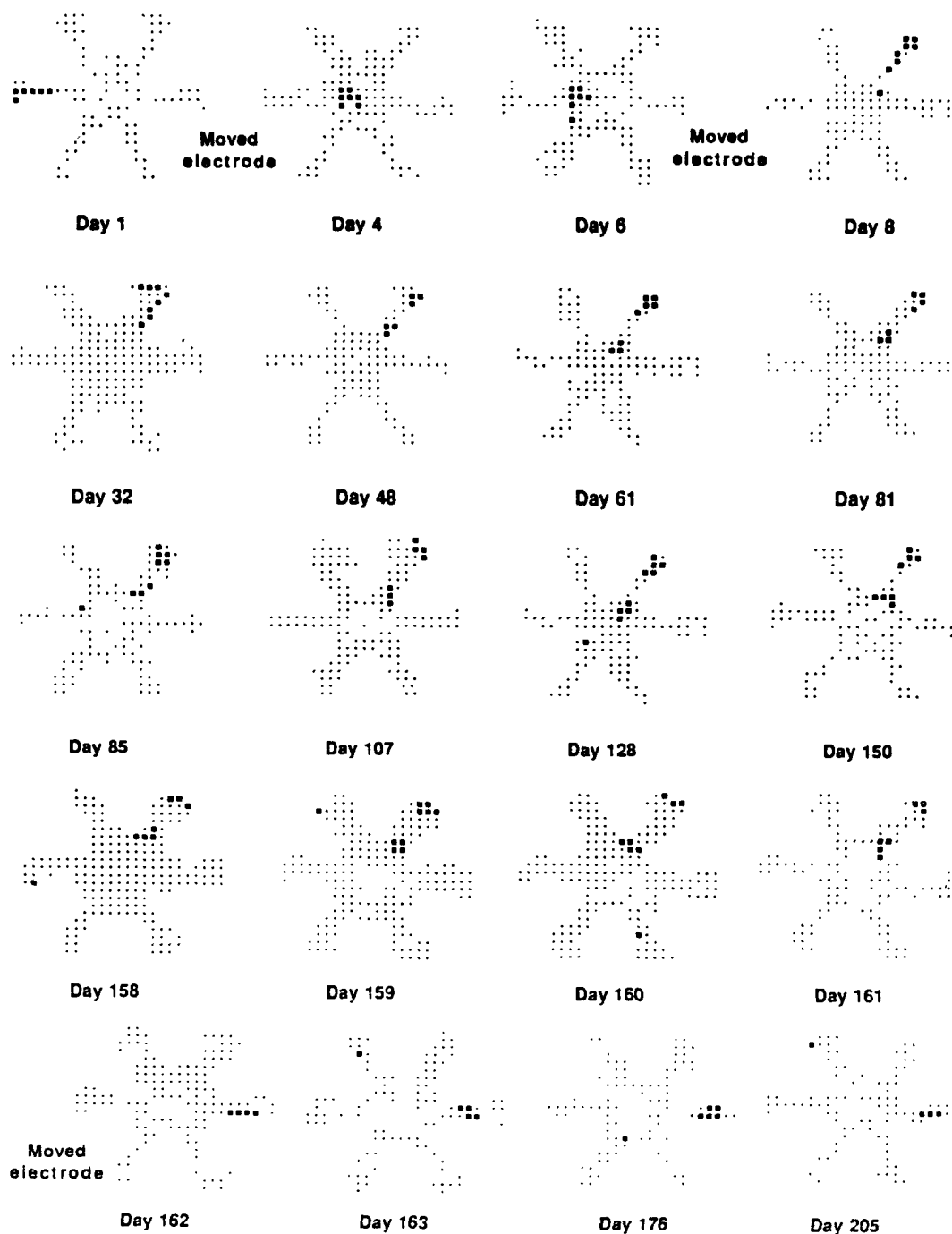
Figure 2. The place fields for the cellular activity isolated on a single electrode mapped on a six-arm radial maze. High firing rates are indicated by dark boxes, and background activity in all other places visited is indicated by small dots. On Day 1, the cell had a field on the left arm of the maze. The electrode was then moved approximately 30 μ, and on Day 4, a cell was found with a field in the central platform. The electrode was again moved following recording on Days 6 and 161. Note that when the electrode was moved, a cell with a new place field was found, but the place fields persisted in the same location if the electrode was not moved.

of these cells ought not change if the cognitive map theory is true. They should have stable fields in otherwise constant environments, relatively independent of the experiences the animal has outside of those environments. The final study we report here was an attempt to determine just how stable the fields can be for extended periods of time (Best & Thompson, 1984; Thompson & Best, in press).

When attempting to study long-term stability, there are a number of things that can happen to the cellular activity on any electrode over time. The electrode could move to a new cell, with a different field, or it could continue to record from the same cell over time, but the field of that cell could change. It would be very difficult to differentiate between these two possibilities. So if the cellular activity on an electrode shows a change in field location over time, the result gives us no information.

If the place field of the activity on an electrode is relatively constant over time, it could be due to the fact that the electrode is recording from the same cell, which has the same field, or it could be that the electrode moved to a neighboring cell with a similar field. The latter possibility, although less exciting, would still show long-term stability in the map. However, it is an unlikely outcome because of one very consistent finding. There is no topological relationship between the place fields of hippocampal pyramidal cells and the location of the cells in the brain. The close topological relationship between receptive fields in the peripheral sensory organs and the primary sensory areas in the central nervous system is not seen in the hippocampus. In fact, the location of the fields of neighboring cells are totally unpredictable. Whatever code is being used to translate place-field activity into a cognitive map, it does not appear to be topological.

In this study, a small light was mounted on the animal's head and an imaging device provided digitized coordinates of the animal throughout each session. Testing sessions for each unit lasted at least 45 min per day, at irregular intervals across as many days as the cell continued to show spontaneous activity. If spontaneous activity was not found, the electrode was advanced until a new unit was encountered.

Place fields were determined as follows. The coordinates of the animal's location were recorded periodically (every 0.25 sec) and each time the unit fired. The mean rate of activity was determined for each location on the maze by simply dividing the number spikes fired in each location by the amount of time spent there. Firing rates higher than three standard deviations above the overall mean firing rate were used to define the boundaries of place fields. In Figure 2, place fields are shown as large squares, whereas other explored areas in which firing rates were below criteria are shown as small dots.

In some cases in which a well-isolated cell with a reliable place field was isolated on a specific day, no activity was seen on that electrode during the following recording session. In every case in which well-isolated cellular activity was seen on the following session, the place field

of the cell remained in the same location as before. In no case did a switch in the location of the field occur in the following sessions. That is, in the following session, either no cellular activity appeared on the electrode, or the cell had the same field.

To date, we have recorded stable place-cell activity of over 5-days' duration on nine different cells. An example of long-term stability of the place field of a cell is illustrated in Figure 2. This figure illustrates the longest that we have been able to hold a cell and determine its place field. Note that the first cell encountered had a place field in the left arm, which was in the same location on Day 3. The electrode was then moved and a new cell with a different place field was encountered. The place field on this cell was stable for 153 days, until the electrode was moved again. Frankly, we do not intend to attempt a longer record.

Hippocampal neuronal activity has been found to change very rapidly in response to such a wide variety of manipulations that the hippocampus has been widely adopted as a model system for studying the effects of experience on the central nervous system. However, for a brain system to play an important role in experiential modification of behavior, changes in neuronal responsiveness must be maintained for periods of time appropriate to the behavioral needs of the organism. It is therefore not surprising to find stable representations lasting for periods approaching the life-span of the organism.

The activity of hippocampal pyramidal cells reported here meets the rather stringent requirements necessary for neural elements subserving cognitive mapping in the central nervous system. The place fields of the cells respond in ways similar to the animal's behavior in processing information from the environment. Both place fields and behavior are determined more by extramaze than by intramaze cues on the elevated radial-arm maze. The fields are opportunistic in selecting any information available to the organism. Like behavior, place-field activity is disrupted by lesions of hippocampal connections. Place-field activity is apparently so specific that the cells are virtually silent in most environments. Finally, the place fields are extremely stable for periods of time approaching the life of the organism in stable environments. Thus, the system appears to be well designed to serve as a cognitive map.

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