

Commentary

Hippocampal cellular activity: A brief history of space

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In relativity, there is no real distinction between space and time coordinates, just as there is no distinction between two space coordinates.

Stephen W. Hawking (1)

“Space and time coordinates are only the elements of a language that is used by an observer to describe his environment,” said Sachs nearly 30 years ago (2). In modern physics, space and time are nothing but names, forms of thought, words of common usage, constructions of our minds (3). Even though we cannot know for certain whether space and time really do exist physically, we do know that they exist as mental constructs. If they exist in the mind, then the questions for the neuroscientist are: How are they constructed in the brain? How would a brain be organized such that these concepts would emerge from its operation? What forms of brain activity could we observe that would provide evidence for brain mechanisms of spatial or temporal processing?

In the 1930s, when the central theme of American behavioral psychology was that all forms of knowing and understanding in rats and humans were merely the result of complex S-R or S-S conditioning, Tolman and his students insisted that rats and humans formed cognitive maps of their environments as they navigated to find food, water, or sex partners (4). Although the idea of cognitive maps was dismissed by the mainstream (5), some investigators continued to consider the persistence of position habits or spatial hypotheses in animal experiments as strong evidence for the existence of an internal representation of space or a cognitive map (6). Contemporary cognitive scientists like Tulving and Madigan (7) hold a somewhat sardonic view of this controversy, “Place-learning organisms, guided by cognitive maps in their heads, successfully negotiated obstacle courses at Berkeley, while their response-learning counterparts, propelled by habits and drives, performed similar feats at Yale.”

The first evidence for the existence of cognitive maps in the brain was dramatically demonstrated by O’Keefe and Dostrovsky, who reported in 1971 that the activity of a few cells in the hippocampus of freely behaving rats was closely related to the animal’s location in an open field (8). These so-called “place-cells” fired maximally when the animal was in a rather small, well-defined region of the environment, the “place-field,” and were virtually silent elsewhere. The initial response to O’Keefe and Dostrovsky’s report was somewhat skeptical (9). However, since that first report, a large number of studies from several laboratories have corroborated the basic finding and have examined the properties of these neurons under a wide variety of conditions. It is very difficult to convey in words the compelling nature of place-field activity. Even the oscilloscope traces or false color rate maps presented in many of the manuscripts fail to capture the distinctly close relationship between the activity of the place-cell and its typically very small and circumscribed place-field. The same cell that fires over 20 times a second inside its place-field can be very quiescent outside of the place-field, often firing less than once a minute.

In an environment in which a cell has no place-field, the cell can be essentially silent for long periods of time, upwards of an hour (10, 11).

The discovery of place-cells led O’Keefe and Nadel (12) to propose that the hippocampus serves as the cognitive map. They further proposed that hippocampal place-cells, now known to be pyramidal cells, the main output cells of the hippocampus, are the basic units of the map (13, 14). According to the 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 the animal knowledge of its position relative to important locations. Though many important questions remain unanswered, the past 25 years have witnessed great advances in our understanding of the nature of place-cell activity. The work of Fenton and Muller (15) reported in this issue of the *Proceedings* represents one such advance.

The original investigations by O’Keefe and colleagues suggested that the animal derives its location in the environment from its position relative to a number of distal, or extramaze, cues. The place-cells fire in the same locations relative to distal room cues despite rotation of the platform on which recording takes place. Further, rotation of the distal cues generally is accompanied by concurrent rotation of the place-fields. Under most conditions the locations of the fields do not appear to be determined by any single distal cue in the environment. Only radical changes in the layout of the recording environment are capable of disrupting the location-specific firing of the cells (8, 16).

Subsequent work has addressed questions about the nature of environmental information that permits the animal to know its location in space. Is a particular sensory modality dominant for an animal to determine its location, or are a variety of types of sensory information equally weighted? It appears that stable visual cues, when present, provide the preferred source of information used to support place-cell activity. When only one salient visual cue is present, it can exert control over the location of a place-field. Rotations of that cue are accompanied by rotations of the place-field (17). When a small set of proximal maze cues and distal wall cues are provided, visual cues still predominate, and the size of the place-fields and the within-field firing rates of the cells can be predictably and reversibly altered by the removal of individual visual cues (18).

In the absence of visual information, it appears that subjects can use whatever information is available to attempt to locate themselves in the environment. Hippocampal place-cells are found to have well-defined, reliable place-fields in blindfolded and deafened rats on a radial arm maze. Following maze rotation, the place-fields of the majority of these cells rotate with the physical apparatus rather than remaining fixed with respect to distal room cues. Thus, in the absence of visual and auditory information, those place-fields are determined by proximal cues on the maze. Several other cells show place-

fields that are not bound to intramaze stimuli. These place-fields remain stationary with respect to the real world following maze rotation. These subjects receive no visual or auditory information, so it appears that they are relying on internal data, such as vestibular or proprioceptive information, to track their location in their internal map of the environment. When that internal information is disrupted by spinning the animals, the place-fields also are disrupted (11).

The activity of place-cells is not determined simply by the nature of the sensory information impinging on the animal at the time it is in the place-field. Place-cells are not merely sensory neurons, exclusively under the control of stimuli currently in the environment. If rats are placed in the environment in the presence of room lights, when the lights are turned off, the location of the place-fields and the in-field firing rates are dramatically unaffected by darkness. However, placing the subjects in the already dark environment significantly impacts the firing properties of many cells. Moreover, the majority of cells that show altered firing when placed directly into the darkened environment continue to exhibit the altered firing when the room lights are turned on. Thus, under certain conditions, place-field activity can be more strongly influenced by the animal's recent experiences than by current external stimuli in the environment (19).

Further evidence that hippocampal place-cells are not merely sensory neurons, but are highly influenced by various "intra-head" variables, is provided by O'Keefe and Speakman (20), who 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 the beginning of 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 trials the cues were removed before subjects were allowed to choose the goal-arm. Most of the time, the rats were capable of choosing 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 specific firing of the place-cells. On other trials, when the cues were removed before placing the subjects on the maze, choice accuracy obviously fell to chance. However, on these trials the locations of the place-fields were far from random. Their locations were highly predictable based upon the location of the arm that the subject chose as the goal-arm. The cells fired when the animal evidently thought he was in the place-field (20).

If place-cells provide specific information about the animal's position in the environment, one might expect the location of a place-field, and the cell's firing rate within that field, to be consistent over long-term periods of time in an unchanging environment. In support of O'Keefe and Nadel's theory, the locations of place-fields have been shown to be extremely stable for long periods of time in constant environments. Under certain conditions, place-fields have been found to remain stable for weeks and months, in one case up to 153 days (11).

If hippocampal place-cells are the substrate of the cognitive map, then lesions of the hippocampus should selectively disrupt spatial behaviors that rely on a functioning cognitive map, and lesions of inputs to the hippocampus should disrupt both spatial behavior and place-field activity. A large number of studies in the literature 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. In fact, hippocampal lesions actually facilitate performance on some tasks for which a cognitive mapping-based strategy would be disadvantageous, such as tasks in which the animal must ignore room cues to find the reward (21–23).

Despite the compelling nature of place-field activity, and the effects of hippocampal lesions on spatial navigation tasks, 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. 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 performance on certain nonspatial "working memory" tasks (24) and tasks that require nonspatial configural or contextual processing, such as occasion setting tasks, in which one stimulus indicates whether another stimulus will be reinforced (25, 26).

Studies of the effects of lesions of hippocampal connections on place-cell activity have not produced a clear picture. If the hippocampus serves as the substrate for the cognitive map, and place-cells represent the basic units of the map, then lesions that disrupt performance on spatial tasks also should disrupt the location-specific firing of place-cells. Some studies have found reliable effects of fimbria-fornix and entorhinal cortex lesions on place-field activity. Entorhinal lesions virtually abolish place-field activity in hippocampal neurons (11). 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 location. As in blindfolded and deafened rats, the locations of the place-fields in lesioned animals are more influenced by the local intramaze cues than by the distal room cues (11, 27). However, a number of studies on the effects of lesions of the medial septal nucleus, dentate gyrus, and various hippocampal regions have failed to find reliable changes in the nature of place-field activity (28, 29). The reasons for these failures are not clear. Perhaps the pathways of information-flow through the hippocampus are different than we thought, or the effects of lesions are more subtle than expected, and thus require more sensitive behavioral methods.

Although place-field locations are known to be consistent over time, not much is known regarding the activity of place-cells within the place-fields themselves during consecutive visits. If place-cells carry information regarding only the animal's location in the environment, the firing rate observed during any given pass through the field should closely resemble the rates observed during previous passes through the field. In contrast, Fenton and Muller (15) observed that firing rates frequently differed from those predicted by previous visits. They observed a high level of variability in the firing rate, which significantly exceeded that predicted by their statistical model. They concluded that the firing rate of a place-cell during a pass through its place-field cannot be predicted from the firing rate of that cell during previous traverses (15). This excessive variance is perhaps another indication that pyramidal cells process information other than the animal's absolute position in the environment.

As previously mentioned, place-field activity can be influenced by the nature of an animal's experiences in an environment. For example, in an environment containing multiple watering cups, only one of which contains water, changing the location of the water is sufficient to shift the location of the place-fields in the the direction of the water source (30). Also, changing the nature of the search strategy that subjects are required to use to retrieve food reward (i.e., from random to directed searching) can result in relocation of place-fields (31). Place-cell activity also is affected by the direction and velocity of the animal's movement (32). Other studies have shown a close relationship between hippocampal pyramidal cell activity and factors other than the rat's location in space (33–35). In rabbits, hippocampal neurons show well-defined, reliable conditioned responses very early in conditioning, before the elaboration of conditioned behavioral responses (36, 37).

The results of the last 25 years of research indicate that the hippocampus is intimately involved in the processing underlying the formation of Tolman's cognitive maps. However, the effects of hippocampal lesions on nonspatial performance, coupled with the nonspatial correlates of hippocampal pyramidal cell activity, suggest that cognitive mapping is not the only function of the hippocampus. Perhaps the hippocampus is involved in a more general fundamental process, of which cognitive mapping is a specific example. Although the Cognitive Mapping Theory might require some minor revisions, it has stood the test of time. To date, there is no better explanation for the profound effects of hippocampal lesions on spatial navigation, or for the compelling phenomenon of hippocampal place-field activity.

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