

of the molecular components KChIPs and DPPX? The discovery that DPPX interacts with Kv4 channels to form a critical component of  $I_{SA}$  is striking, but it also raises the possibility that, like KChIPs, DPPX has additional cellular functions.

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## Hippocampus and Memory: Can We Have Our Place and Fear It Too?

Theories of hippocampal function are often split into cognitive map theories and relational/episodic memory theories. In this issue of *Neuron*, Moita et al. (2003) show that hippocampal cells respond to the combination of spatial location and conditioned stimuli in a nonspatial fear conditioning task, suggesting a potential bridge between the competing theories of hippocampal function.

In 1978, John O'Keefe and Lynn Nadel proposed a theory that the hippocampus was the neural substrate of a cognitive map (O'Keefe and Nadel, 1978). Building on a long history of philosophical and psychological study on the concept of space, they argued that the hippocampus was the brain structure that constructed and mediated our perception of allocentric space (i.e., absolute space represented in world-based coordinates rather than body-centered, or egocentric, coordinates). This argument was based on two main lines of evidence: (1) animals with hippocampal damage had severe deficits in navigation tasks that appeared to require the use of a mental map of the environment (as opposed to tasks that can be solved using simple guidance or response strategies); and (2) recordings from hippocampal pyramidal cells in freely moving rats showed that these cells fired selectively in restricted locations in the environment. Although spatial mapping formed the core of the theory, O'Keefe and Nadel were well aware of the mne-

monic functions of the hippocampus, demonstrated most dramatically by the amnesic syndrome of patients with damage to the hippocampus and related areas in the medial temporal lobe. Thus, their theory was much richer than simply spatial mapping and navigation; they proposed that “the hippocampus is the core of a neural memory system providing an objective spatial framework *within which the items and events of an organism's experience are located and interrelated*” (O'Keefe and Nadel, 1978, p. 1; emphasis added). O'Keefe and Nadel explicitly had in mind a theory of episodic memory and flexible, context-dependent learning, with the spatial representation of the hippocampus acting as the essential, organizing framework of these types of memory.

In the years since the publication of their theory, much effort has been expended by many research groups to validate the essential spatial nature of hippocampal processing that was central to the theory (Best et al., 2001; Muller, 1996). Concurrently, other investigators emphasized the nonspatial aspects of hippocampal processing that were reflected in the global amnesia of hippocampal patients, and they described the function of the hippocampus in terms of declarative memory (in humans) or relational learning (in nonhumans) (Cohen and Eichenbaum, 1993; Eichenbaum et al., 1999; Squire, 1987). In recent years, episodic memory (a component of declarative memory) has received great attention as the function of the hippocampus. Overall, it appears that the field can be divided into two primary camps. The cognitive map proponents state that the hippocampus is essentially a spatial mapping system that is used to organize and remember the items and events of experience. In contrast, the relational learning/declarative memory/episodic memory proponents state that the hippocampus is a more general learning system important for encoding relationships between environmental stimuli and creating episodic memories; spatial representations naturally fall out of such a system but are not an essential part of it. The field is at somewhat of an impasse, because these theories make predictions that are very similar to each other, and therefore difficult to interpret objectively in favor of one view over the other. One's interpretation of the data tends to reflect one's preconceived notions, and many results interpreted in favor of one theory can easily and validly be reinterpreted in terms of the other theory.

A study by Moita and colleagues in this issue of *Neuron* provides a potential route out of this impasse. Moita et al. (2003) recorded the activity of CA1 pyramidal cells in the dorsal hippocampus of rats trained in an auditory fear conditioning task. Before training, they recorded the spatial firing fields (place fields) of the neurons as the rats explored the environment. The rats then underwent a number of trials in which a series of white-noise pips (the conditioned stimulus, or CS) was played, followed by periorbital shocks (the unconditioned stimulus, or US). A control group received the same number of white noise pips and shocks, but these stimuli were unpaired, such that the pips did not predict the delivery of the shock. The rats that received the paired CS-US training learned to freeze when they heard the pips, a classic measure of fear learning; rats that received the unpaired CS-US training did not learn to freeze to the pips. Pyramidal cell firing was recorded during all train-

ing trials, and Moita et al. show that before training, few cells responded to the pips. After training, however, rats that received the paired CS-US training and showed fear responses had many more cells that now responded to the pips. For the rats that had the unpaired training, there was no increase in the number of pip-responsive cells. Thus, this result is a clear demonstration of hippocampal responsiveness to nonspatial stimuli in a classic nonspatial learning task, supporting a relational theory of hippocampal function.

But wait a minute. Moita et al. next analyzed how the pip responsiveness of the cells related to the place fields that had been mapped in the prior session. They divided the training trials into those that occurred when the rat was in the place field of the cell and those that occurred when the rat was outside of the place field, and they found that the cell showed responses to the pips only when the rat was in the place field of the cell. Outside the field, the cell showed no response to the CS. Thus, the spatial location of the rat acted as a gate that allowed the cell to respond to the CS. In other words, the spatial representation that was constructed during the rats' initial exploration of the training environment incorporated the task-relevant stimuli into the representation. This sounds precisely like O'Keefe and Nadel's description of their overall theory. As discussed by Moita et al., this result may explain the role of the hippocampus in the context dependence of fear conditioning.

The finding that place cells can be modulated by nonspatial cues is not new. O'Keefe and Nadel (1978) reported the activity of "misplace" cells that fired in a certain location only when an unexpected object occupied that location or an expected object was absent. They also reported cells that responded only when the animal engaged in sniffing in a particular place. More recently, Wood and colleagues (1999) showed that in an olfactory discrimination task performed at nine different locations, a number of CA1 cells were classic place cells, while other cells were selective for particular odors. Many cells had both spatial and odor-selective properties. Although the constraints of their experimental design precluded Wood et al. from determining whether individual odor-related cells had a statistical interaction between their odor selectivity and spatial location, their population data suggest that the strength of the odor selectivity may have been spatially modulated. Wiebe and Staubli (1999) performed a conceptually similar experiment and showed nonspatial correlates of place cells in a match-to-sample task; however, their design allowed them to look for odor  $\times$  place interactions, and almost all of their odor-related responses were also significantly modulated by spatial location.

Thus, the literature is replete with examples of nonspatial correlates of hippocampal cells, and the recent results suggest that these nonspatial correlates may often ride on top of a spatial modulation signal. These results can be interpreted in terms of cognitive map theory, as originally proposed by O'Keefe and Nadel. They can also be interpreted in terms of relational learning theory, in that although these nonspatial tasks can make space irrelevant to the animal's ability to solve the task, one can never get rid of space, and thus spatial selectivity may naturally fall out of a relational learning system that automatically encodes the relationship be-

tween spatial cues. Although there may be some ways of eventually distinguishing the competing theories, perhaps this debate is no longer useful in driving the field. Experiments like that of Moita et al. and Wood et al. can be used as a starting point to take a more systems-oriented approach to hippocampal function; to understand the information flow from parahippocampal cortices through the entorhinal cortex, hippocampus proper, and back out through the subiculum; to understand the input/output functions of these areas; and to characterize the computations performed by each structure, including the CA subfields and dentate gyrus.

A number of intriguing avenues of investigation present themselves. Fear conditioning is an amygdala-dependent task, and the amygdala has stronger connections with the ventral hippocampus than with the dorsal hippocampus. Does the CS responsiveness that Moita et al. (2003) observed in dorsal hippocampus have its genesis in amygdala-ventral hippocampus interactions, with the dorsal neurons gaining this selectivity by virtue of the associational pathways along the longitudinal axis of the hippocampus? Alternatively, does the dorsal hippocampus acquire the CS responsiveness directly through the perforant path input from the entorhinal cortex? If so, are there separate channels that provide the spatial component and the CS-US components? Although entorhinal cortex neurons are known to exhibit spatial selectivity, recent data suggest that this spatial selectivity may be limited to the medial entorhinal area, with the lateral entorhinal area providing little or no spatial information (at least in terms of the superficial layers that provide the input to the hippocampus) (E.L. Hargreaves, L. Fu, and J.J. Knierim, 2002, *Soc. Neurosci.*, abstract). This dissociation suggests that perhaps the cognitive map, in terms of a more or less "pure" spatial representation, may arise from a set of anatomically interconnected areas comprising the postrhinal cortex, medial entorhinal cortex, and subicular complex. Another set of interconnected areas, comprising the perirhinal and lateral entorhinal area, may convey information related to nonspatial, behaviorally relevant task stimuli. Both the medial and lateral entorhinal cortex project to the hippocampus, where perhaps the "items and events of experience" encoded in LEA firing are integrated into a coherent spatial framework encoded by MEA firing. Under this scenario, one would predict that LEA neurons would respond to the CS and the US, MEA neurons would encode spatial location, and hippocampal neurons would encode the combinations of stimuli and locations. Alternatively, the entorhinal neurons may be the site where the CS-US associations are learned, and the CA1 responses recorded by Moita et al. merely reflect these properties that were generated upstream. Understanding the flow of information processing through the hippocampal formation, taking into account the increasingly detailed knowledge of anatomical connectivity between the hippocampus and the parahippocampal areas, may prove to be the best contribution that single-unit physiology can make to deciphering the ultimate function of the hippocampal system and related areas. Experimental paradigms like that of Moita et al. show promise toward understanding how the cognitive mapping functions of the hippocampus relate to

relational and episodic memory functions. Perhaps in the end, we can all have our cake and eat it too.

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