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Research Report

Time and space in the hippocampus

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A B S T R A C T

It has been hypothesized that one of the functions of the hippocampus is to enable the learning of relationships between different stimuli experienced in the environment. These relationships might be spatial ("the bathroom is about 5 m down the hall from the bedroom") or temporal ("the coffee is ready about 3 min after the button was pressed"). Critically, these spatial and temporal relationships may exist on a variety of scales from a few hundred milliseconds up to minutes. In order to learn consistent relationships between stimuli separated by a variety of spatial and temporal scales using synaptic plasticity that has a fixed temporal window extending at most a few hundred milliseconds, information about the spatial and temporal relationships of distant stimuli must be available to the hippocampus in the present. Hippocampal place cells and time cells seem well suited to represent the spatial and temporal locations of distant stimuli in order to support learning of these relationships. We review a recent computational hypothesis that can be used to construct both spatial and temporal relationships. We suggest that there is a deep computational connection between spatial and temporal coding in the hippocampus and that both serve the overarching function of learning relationships between stimuli—constructing a "memory space."

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1. Introduction

The modern era of research on hippocampal function began with Scoville and Milner's (1957) identification of the hippocampus as critical to memory in humans. Subsequent pioneering studies that sought the basis of hippocampal memory function in the firing properties of hippocampal neurons revealed the existence of "place cells", neurons that fire when a rat occupies a particular location in its environment (O'Keefe and Dostrovsky, 1971). This observation, plus studies showing selective deficits in spatial learning following hippocampal damage, inspired the notion that the hippocampus supports memory by creating a cognitive map of the physical environment into which memories are encoded (O'Keefe and Nadel, 1978). Decades of research since then have sought to characterize the organization of the cognitive map. Recent research in this direction has focused on how the hippocampus and neighboring interconnected structures supports navigation through space (McNaughton et al., 2006; Moser et al., 2008), indicating this line of research is losing sight of the well established more general role of the hippocampal system in memory (Eichenbaum and Cohen, 2014). Here we will review some of the key features of

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hippocampal place cells and suggest that they reflect a more general mechanism of temporal as well as spatial organization of events, and that this broader function is the basis of hippocampal function in memory.

1.1. Coding across space and time in the hippocampus

The hippocampal place code provides an exquisitely detailed representation of the animal's location in allocentric coordinate system at multiple spatial scales (Wilson and McNaughton, 1993; Solstad et al., 2008). Eichenbaum (2001) hypothesized that the spatial map in the hippocampus is a special case of a more general function in representing relationships among all of the task-relevant stimuli, including both spatial and non-spatial variables (see also Eichenbaum et al., 1999). If the hippocampus captures relationships among stimuli separated by macroscopic quantities of space and time, and if plasticity depends on simultaneous activation within a fixed temporal window, there must be some way to bridge these gaps. Put another way, if the hippocampus is to facilitate learning of a relationship such as, "these nuts are stored 20 cm from the big oak tree" or "the shock will come 5 s after the tone" then it must have some facility to represent these relationships. At the location where the nuts are being stored, the hippocampus must have some ability to describe the distant location of the oak tree; at the time the shock arrives the hippocampus must have some way to represent that a tone was experienced a certain time in the past. Once the relationship of the distant stimulus is represented, it is relatively straightforward to associate that representation to the other stimulus—the nut in the spatial example or the shock in the temporal example. In this way, the spatial and temporal representations can be used to cue the response. For instance, when the animal is 15 cm from the oak tree, the similarity between the current spatial representation and the stored representation can cause activation of the representation for the nuts. Similarly, if one is looking for nuts, nuts may be used as a cue to recover the spatial representation coding for "20 cm from the oak tree."

1.1.1. Spatial coding reflects spatial relationships to distant stimuli

These considerations suggest that the neural activity in the hippocampus at a particular time is not solely, nor even predominantly, caused by the stimuli available in the environment at that moment. For instance consider the experiment performed by Gothard et al. (1996). They trained a rat to run back and forth on a linear track. Each of the journeys along the track started from a goal box. Across journeys the location of the box was moved relative to the track and the room coordinates. On journeys away from the box, place cells fired at a constant distance from the start box, moving across journeys relative to the room frame. Consider a place cell that fires 50 cm from the start box. Because the location of its firing is controlled by the box, this means that a stimulus that was experienced perhaps several seconds in the past—the box—controls firing of the cell in the present. Moreover, because the phenomenon also holds in the dark (Gothard et al., 2001), we can be certain that the firing in this experiment is not dependent on the animal being able to see the

goal box from its current location. Burgess and O'Keefe (1996) observed similar control of firing in a two-dimensional environment; as the shape of the enclosure changed, place fields in the center of the environment changed location to maintain their relationship to one or more of the walls of the environment (see also Hartley et al., 2000; Barry et al., 2006; Lever et al., 2009).

These place cells are apparently not coding for a place *per se* but a spatial relationship relative to a landmark, or set of landmarks. That is, a place cell in the Gothard et al. (1996) experiment is not coding for a location, but rather something more like "50 cm from the goal box"—a spatial relationship. Note that without establishing stimulus control, simply observing that a place cell fires in a particular location within an environment provides no information about the stimulus and relationship (or relationships) that it is being used to represent (Fig. 1).

1.2. Temporal coding may reflect temporal relationships of temporally remote stimuli over long time scales

The principle that currently available stimuli do not control hippocampal firing should also inform non-spatial firing as well. A large body of evidence suggests that the hippocampus constructs temporal and sequential relationships in addition to spatial relationships (e.g., Bunsey and Eichenbaum, 1996; Clark and Squire, 1998; Westmacott and Moscovitch, 2001). It is clear that neural activity supporting memory changes gradually over long periods of time. Although there are examples of some cells in the MTL that respond to non-spatial stimuli currently being perceived, such as the celebrated "Jennifer Aniston" cells (Quiroga et al., 2005), these cells coexist with other cells that show very slowly changing activity. Fig. 2 illustrates this phenomenon in recordings from human epileptic patients during performance of an item recognition experiment using pictures of faces and scenes (Howard et al., 2012; Viskontas et al., 2006). Note that the cells
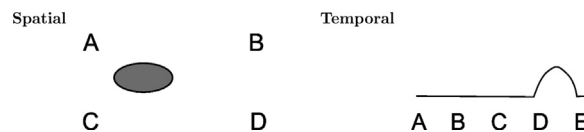

Fig. 1 – Firing of hippocampal cells must be controlled by events distant in space and time. Left: A place cell fires in a location within an environment with four landmarks, A B C D. It is unclear whether the cell fires because it is SE of A, SW of B, NE of C, NW of D, or any conjunction of those variables. In order to determine this, it would be necessary to systematically move the landmarks and establish control over the cell's firing. Right: A cell fires during a temporal sequence of events A B C D E. It is not clear whether the cell fires because D has just been presented, because it is one time step after C was presented, or because it is two time steps after B was presented. If the sequence is consistent and well learned it is also possible that the cell is firing because E is predicted. In order to determine which of these relationships is responsible for the cell firing, it would be necessary to present the stimuli many times in many different orders to establish stimulus control of the firing.