

Sources of the spatial code within the hippocampus

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Abstract

Neurons in the hippocampus are thought to provide information on an animal's location within its environment. Input to the hippocampus comes via afferents from the entorhinal cortex, which are separated into several major pathways serving different hippocampal regions. Recent studies show the significance of individual afferent pathways in location perception, enhancing our understanding of hippocampal function.

Introduction and context

Considerable research on the hippocampus focuses on the phenomenon of 'place cells', neurons that provide an internal spatial map of an animal's environment. This map acts as the mental foundation on which episodic memories are engraved, such as the memory of a recently taken path or where an important event took place. Place cells were originally defined as neurons in the rat that appear maximally active when the animal occupies a particular location within its environment [1,2]. The population of place cells responds differentially to different locations. Determining the source of place cells' spatial signal has been the goal of numerous laboratories over the past 40 years. In addition to the place cells of the hippocampus, many neurons in the postsubiculum and deep layers of the medial entorhinal cortex (MEC) display activity strongly correlated with the orientation of the animal's head [3,4]. These 'head-direction' cells may serve as an internal compass for navigation. Studies of the spatial correlates of hippocampal neuronal activity have revealed how certain types of information enter the hippocampus and are processed within it. Recent advances have enhanced our understanding of the nature of these inputs - specifically, how they might contribute to the spatially selective firing of place cells.

As the entorhinal cortex supplies the hippocampus with most of its input [5], understanding the anatomy of this

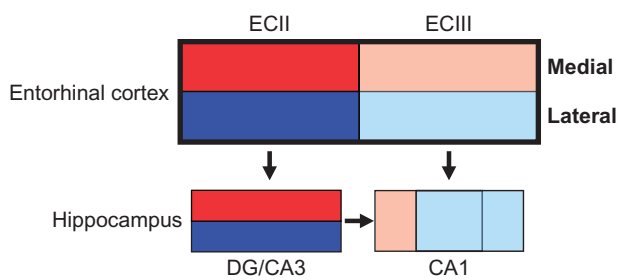
input is central to understanding hippocampal function. Two layers of the entorhinal cortex provide major projections to the hippocampus. Layer II (ECII) projects specifically to the dentate gyrus and to region CA3 of the hippocampus (Figure 1). The dentate gyrus sends connections to CA3, which sends most of its projections to CA1. Entorhinal layer III (ECIII) bypasses the dentate gyrus and region CA3 and projects exclusively to region CA1. The same septo-temporal levels of the entorhinal cortex and CA1 are involved in reciprocal connections from CA1 back to the deep layers of the entorhinal cortex (layers V and VI).

The entorhinal cortex is further divided into medial (MEC) and lateral (LEC) regions. These are distinct regions, with different single-cell physiologies and different targets within the hippocampus. The medial ECIII projects to parts of region CA1 that are more proximal to CA3 [5,6], whereas the lateral ECIII targets cells more distant from CA3 (Figure 1). Thus, a key question has been what kinds of afferent information arrives from ECII compared with ECIII, and from the MEC compared with the LEC.

Major recent advances

To determine the role of direct ECIII input to region CA1 Brun *et al.* [7] recorded place cells in region CA1 after completely disconnecting CA3 and CA1. This effectively

Figure 1. Schematic diagram of the general organization of entorhinal cortex input to the hippocampus.



Entorhinal cortex layer II (ECII, on the left in bold color) projects to the dentate gyrus (DG) and region CA3 in the hippocampus. Layer III (ECIII, on the right in pale color) projects mainly to region CA1. Blue and red coloring reflect the organization of medial (red) and lateral (blue) entorhinal input to DG/CA3 and CA1. Note that input from the medial entorhinal cortex (red) targets portions of CA1 closer to DG/CA3, whereas lateral entorhinal cortex (blue) targets regions further from DG/CA3. Region CA3 densely targets CA1 neurons, whereas DG only targets cells in CA3.

blocked the indirect information loops from ECII via the dentate gyrus, and left only direct ECIII-to-CA1 connections intact. The authors report no significant abnormalities in the spatial receptive fields of CA1 place cells (place fields) as rats traversed an open arena. In contrast, a reduction in the spatial specificity of CA1 place fields was found after a selective lesion of ECIII neurons [8]. Together, these results emphasize the importance of direct ECIII input to normal place-cell function.

To distinguish differences between lateral versus medial entorhinal input, Hargreaves and colleagues [9] recorded in both areas in the open field. They found cells with strong spatial modulation in the MEC but not in the LEC. Concurrent work in the MEC revealed the intriguing phenomenon of 'grid cells' [4,10-12]. In contrast to place cells, which fire when a rat is at a single, particular, location, a grid cell fires when a rat is at any of multiple different locations in the environment that are distributed in a hexagonal array. These results indicate that the MEC may convey spatial information, whereas the LEC encodes information about objects and items [9,13].

The discovery of grid cells has driven a range of recent research. Several models have been proposed to explain how MEC grid cells might provide a basis for driving hippocampal place-cell activity [14-17]. These models are supported by data showing that hippocampal place cell populations acquire new spatial representations (i.e. remapping) concurrent with simultaneous changes in the spatial phase and orientation of entorhinal grid cells [11]. In addition to grid-cell input to the hippocampus, a context signal [18] (concerning landmark configuration or

behavioural requirements) could account for remapping of place cells while the orientation, phase and spacing of the grid cells remain consistent with each other. A separate input of this sort to place cells could drive the experience-dependent expansion in grid-cell dimensions that is associated with changes in environment boundaries [19].

If the entorhinal cortex grid cells provide the input for place cells, one would predict a scaling of the sizes of the spatial receptive fields of place cells (spatial scaling) along the dorsal-to-ventral axis of the hippocampus similar to the spatial scaling of grid cells [10]. Such spatial scaling was indeed demonstrated recently in the hippocampus [20], in which remarkably large firing fields (up to 10 meters long) were found in the ventral hippocampus. The largest firing fields are consistent with very large grid receptive fields found in the ventral regions of the entorhinal cortex [21].

Questions about the input that causes grid cells to fire and the mechanism that generates the firing pattern have been addressed by models that effectively simulate grid-cell firing patterns. These models are of two competing types. One is the 'oscillatory interference model' [22,23]. This proposes the interaction of oscillations that occur at slightly different frequencies, causing a beat frequency equal to the difference of the frequencies. In this model, grid cells depend on input from head-direction cells, consistent with the selective input from areas containing head-direction cells to medial, but not to lateral, entorhinal cortex. Modulation of oscillation frequency by cells sensitive to head direction and running speed, reported to have been found in the postsubiculum and hippocampus, can cause interference which results in a two-dimensional pattern of grid-cell firing. This model generates a realistic representation of both grid-cell firing and the phenomenon of theta-phase precession [22], and is supported by experimental data showing theta-phase precession in grid cells in ECII [12]. Theta-phase precession is the observation that, as an animal moves through the firing field of a place cell or grid cell, spikes in the electroencephalogram (EEG) gradually shift from late to early phases of theta-frequency oscillations [12,24]. The model also accounts for the change in time course of theta-phase precession observed in the large firing fields in ventral entorhinal cortex and hippocampus [22,25].

The oscillatory interference model also predicts that changes in spatial scaling in grid cells along the dorsal to ventral axis of the MEC [4,10] arise from differences in the intrinsic oscillation properties of neurons [2,22]. This prediction is supported by intracellular data showing differences in membrane potential oscillation frequency and resonance along the MEC dorsal to ventral axis

[23,26,27]. Other experimental data support predictions of this model in regard to changes in intrinsic spiking frequency [28] and decreased theta-rhythm frequency in novel environments [29].

The experimentally observed absence of theta-phase precession in grid cells of ECIII [12] suggests that some grid responses do not arise from oscillatory interference, but might arise from 'attractor dynamics'. In attractor dynamic models, excitatory synaptic feedback between entorhinal neurons in the presence of background inhibition causes a subset of these cells to fire as grid cells [14,30]. Published attractor dynamic models of grid cells do not yet simulate theta-phase precession, but can account for the activity of grid cells apart from precession. These models can account for recent ECIII data showing discrete, rather than continuous, scaling of grid cells at different dorsal to ventral positions [19].

Future directions

Future studies should resolve important remaining questions about the entorhinal input to the hippocampus. For example, more extensive data is needed to understand the type of information supplied by the LEC - in contrast to the strongly spatially coded information supplied by the MEC. Future studies could also test for differences in spatial specificity of firing within CA1 that is associated with the segregation of medial input to CA1 cells closer to region CA3 and lateral input to cells more distant from CA3.

More data are needed to select between possible mechanisms of grid-cell firing, in order to test further predictions of the oscillatory interference model versus those of attractor dynamic models. Both these proposed mechanisms might contribute to grid-cell firing, or they might be supplemented by other physiological properties, including the time course of spike-frequency adaptation [31] or the frequency of stable persistent spiking [32,33].

A remaining issue is whether MEC cells are providing the hippocampus with rigid spatial information or with a more flexible representation that can allow the hippocampus to disambiguate information about distinct episodic memories. Lesion studies have shown that the MEC is necessary for spatial navigation [34]; however, it is not clear how the MEC participates in non-spatial episodic encoding. One recent study has shown that some cells in the MEC can distinguish between sequences on a T-maze alternation task [35].

Models of oscillatory interference using phase reset [22,32,36] (that is, restarting of oscillations) can account

for context-dependent (that is, task specific) firing [32,36] of both entorhinal neurons [35,37,38] and hippocampal neurons [39-42]. Future studies can test the predictions of these models to determine whether the same mechanisms contribute to both regular spatial firing and to context-dependent firing in specific tasks.

The full circuit of grid cells, place cells and head-direction cells provides a continuous code of spatial location and movement direction that has been used to effectively model the episodic encoding and retrieval of spatial trajectories [33,43]. In other words, this circuit forms the memories of where animal has been and supports the recall of these previously taken paths. The anatomical and physiological data on the interactions between these regions provide a detailed functional perspective on potential circuit-level mechanisms of episodic memory.

Abbreviations

EC, entorhinal cortex; ECII, layer 2 of the entorhinal cortex; ECIII, layer 3 of the entorhinal cortex; EEG, electroencephalogram; DG, dentate gyrus; LEC, lateral entorhinal cortex; MEC, medial entorhinal cortex

Competing interests

The authors declare that they have no competing interests.

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