What do grid cells contribute to place cell firing?

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The unitary firing fields of hippocampal place cells are commonly assumed to be generated by input from entorhinal grid cell modules with differing spatial scales. Here, we review recent research that brings this assumption into doubt. Instead, we propose that place cell spatial firing patterns are determined by environmental sensory inputs, including those representing the distance and direction to environmental boundaries, while grid cells provide a complementary self-motion related input that contributes to maintaining place cell firing. In this view, grid and place cell firing patterns are not successive stages of a processing hierarchy, but complementary and interacting representations that work in combination to support the reliable coding of large-scale space.

Spatially modulated firing in the hippocampal formation

The medial temporal lobes, and hippocampus in particular, have long been implicated in episodic and spatial memory function in humans and animals respectively [1–3]. Early *in vivo* electrophysiology studies, seeking to identify the behavioural or cognitive correlates of neural activity in this region, established that the firing of principal cells in rodent hippocampus is primarily determined by the location of the animal [4]. These 'place cells' are typically active in a single area within a given environment – the corresponding 'place field' (Figure 1A) – and have been hypothesised to support a cognitive map of known locations in rodents, and episodic memory in humans [3]. Decades of subsequent research have attempted to establish the sensory stimuli and neural mechanisms that support their rapidly expressed, highly specific and spatially stable firing patterns. During this time, several other spatially responsive cell types have been identified in the hippocampal formation (Box 1). The next to be discovered were head direction cells, which encode the head direction of the animal in the horizontal plane independently of location [5–7]. More recently, grid cells – which exhibit periodic

spatial firing fields that form a triangular lattice covering all environments visited by an animal (Figure 1B) [8] – were identified in the medial entorhinal cortex (mEC), a principal input to the hippocampus (Box 2). Finally, boundary vector/border cells (hereafter referred to as boundary cells) – which fire at a specific distance and direction from environmental boundaries (Figure 1C) – were identified in subiculum [9,10], parasubiculum [11], and mEC [11,12].

Following the discovery of grid cells, several theoretical studies established that place fields could be generated by combining grid firing patterns with different spatial scales [13–24], and grid cell input has subsequently come to be considered the primary determinant of place cell firing (e.g., [25]). However, recent studies have challenged this view by demonstrating that place field firing patterns are largely unaffected by an absence of stable grid cell activity. Here, we briefly review the properties of spatially responsive cells in the hippocampal formation, describe theoretical models of the grid cell to place cell transformation, evaluate the evidence for and against these models, and present an alternative view. In this view, place field firing patterns are primarily determined by environmental sensory inputs, including boundary cells (Box 3) [26,27] to encode locations within specific spatial contexts, whereas grid cells provide a highly efficient and context-independent spatial metric for path integration and vector navigation. Thus, grid and place cells do not represent successive stages of a processing hierarchy, but rather provide complementary and interacting representations that work in combination to support the reliable coding of large-scale space.

Place cells

Place cells, most often studied in rats, are typically complex spiking pyramidal cells of the CA3 and CA1 hippocampal subfields [4,28]. CA1 and CA3 place cells generally exhibit a single place field, but sometimes several in larger environments [28,29]. In addition, granule cells in the dentate gyrus (DG) can exhibit several, smaller place fields [30]. Place fields are established rapidly in a novel environment [31–33] and remain stable between visits to an environment [34] while slowly evolving over longer timescales [35,36]. Place cells are present throughout the dorsoventral axis of the hippocampus, but place fields are larger towards the ventral pole [37–39]. Place cell activity is typically observed during translational movement, which is associated with 5–10 Hz theta oscillations in the local field potential (LFP) [40]. During these periods, place cells
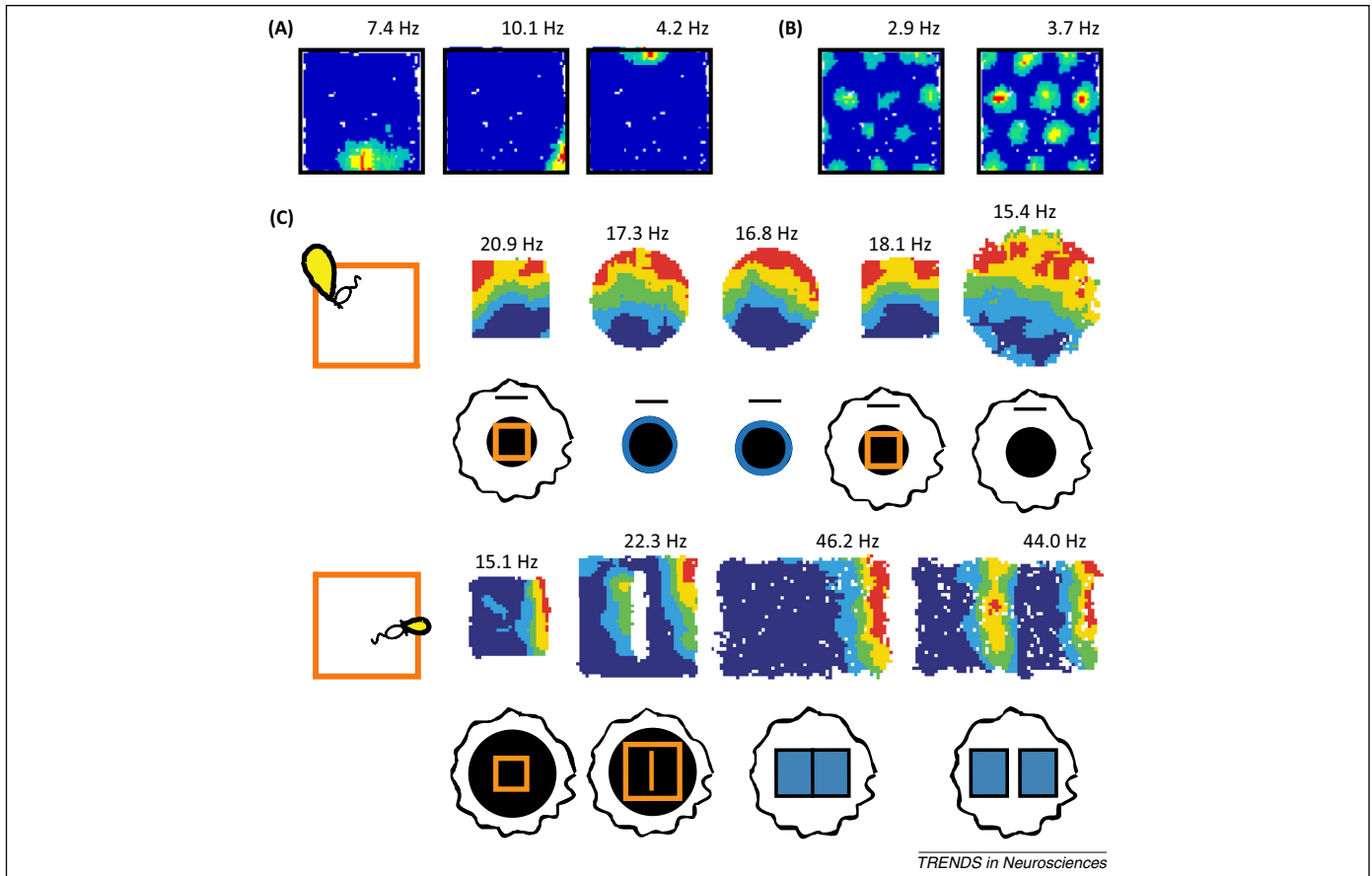
Figure 1. Spatially modulated firing in the hippocampal formation. **(A)** Firing rate maps for three simultaneously recorded CA1 place cells (adapted from [68]). **(B)** Firing rate maps for two simultaneously recorded grid cells in dorsal medial entorhinal cortex (mEC) (adapted from [68]). **(C)** Putative tuning curves (left panel) and firing rate maps for two subicular boundary cells recorded in multiple environments, illustrating the constant relationship between their firing fields and local borders within each environment (adapted from [10]). Superscript indicates peak firing rate.

Box 1. Other spatially modulated cell types of the hippocampal formation

In addition to place and grid cells, the hippocampal formation contains several other spatially modulated cell types, including head direction cells [5–7], boundary cells [9–12], and cells that encode object locations [99,100].

Head direction cells, initially identified in the subiculum but subsequently throughout the Papez circuit, encode the animal's head direction in the horizontal plane, independent of location (Figure 4A) [5,6]. Head direction cells maintain their firing orientation in the dark, suggesting that they can be updated on the basis of self-motion [7]; and rotate coherently with grid and place cells when distal visual stimuli are moved, suggesting that they become coupled to sensory input with experience [53,62].

Boundary cells of the subiculum [9,10], parasubiculum [11], and mEC [11,12] fire whenever a boundary is at a particular distance and direction from the current location of the animal, independent of head direction, and exhibit a second firing field at the same distance and direction to additional boundaries placed within a familiar environment (Figure 1C) [9–11]. These cells also maintain their firing patterns in darkness and rotate with polarising visual stimuli, coherently with head direction and grid cells [10,11].

Neurons in the lEC typically fire in response to non-spatial cues such as odour [101], but rarely show stable spatial tuning in an open field [102]. However, they can encode the relative distance and direction to the current or previous location of specific objects within an environment, and provide an equivalent level of spatial information to cells in mEC under these conditions (Figure 4B) [99,100].

exhibit theta phase precession – that is, their firing phase relative to theta is negatively correlated with the distance travelled through the place field [41,42].

What factors are known to modulate place cell firing? First, evidence suggests that place fields are controlled by local boundaries, as firing often occurs at fixed distances from boundaries in one or more allocentric directions across geometrically deformed versions of an environment (Figure 2A) [26,27,43,44], and secondary firing fields often develop in the same position relative to a new boundary placed into the environment (Figure 2B) [27,35]. Second, it is believed that place cells receive inputs reflecting self-motion [44–49]. For example, when environmental and self-motion cues are put in conflict, firing field locations of a significant proportion of place cells are specifically influenced by movement related information [26,43–45]. Third, place cell responses are oriented to distal visual cues. For example, if a polarising visual cue in a circular environment is rotated, then the positions of place fields within that environment rotate correspondingly (Figure 2C) [50–52], coherent with head direction cell responses [53]. Proximal sensory cues can also exert some control over place cell firing [50,53,54]. Finally, not all place cells are active in all environments. Although approximately 90% of principal cells in the dorsal hippocampus can exhibit place fields, only 15–50% do so in any given environment [32,43,55], and there appears to be