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Heterogeneity in hippocampal place coding

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The discovery of place cells provided fundamental insight into the neural basis by which the hippocampus encodes spatial memories and supports navigation and prompted the development of computational models to explain the emergence of their spatial selectively. Many such works posit that input from entorhinal grid cells is critical to the formation of place fields, a prediction that has received mixed experimental support. Potentially reconciling seemingly conflicting findings is recent work indicating that subpopulations of pyramidal neurons are functionally distinct and may be driven to varying degrees by different inputs. Additionally, new studies have demonstrated that hippocampal principal neurons encode a myriad of features extending beyond current position. Here, we highlight recent evidence for how extensive heterogeneity in connectivity and genetic expression could interact with membrane biophysics to enable place cells to encode a diverse range of stimuli. These recent findings highlight the need for more computational models that integrate these heterogeneous features of hippocampal principal neurons.

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Introduction

Decades of research point to a critical role for the hippocampus in supporting declarative memory and spatial navigation [1–3]. The profound memory deficits observed in patient H.M. after bilateral hippocampal resection, combined with subsequent animal and human work, solidified the importance of hippocampal processing in episodic and semantic memory [1,2]. In parallel, a significant leap forward in understanding the neural basis by which the hippocampus supports spatial navigation occurred with the discovery of place cells in multiple regions of the hippocampal formation [4]. Place cells initially appeared to represent an animal's instantaneous location in an environment, as they were observed to fire in one or few restricted spatial locations that strongly correlated with an animal's current position. However, consistent with the posited role of the hippocampus in memory, subsequent work has increasingly demonstrated that many place cells also encode features beyond current position such as past and future spatial trajectories [5,6], goal locations and distance to a goal [7••,8••], the position of other animals or objects [9,10], odors [11,12], tactile cues [14], time elapsed [15–17] and the temporal order of items or events [18]. In hippocampal sub-region CA1, the focus of this review, these features are encoded heterogeneously, with different subsets of place cells responding to spatial or non-spatial features, combinations of these features, or different features across different tasks (e.g. [16,19••]). These heterogeneous coding features allow CA1 place cells to represent the broad range of stimuli necessary for building episodic memories of unique events while simultaneously supporting navigation through local environments.

Given the established importance of the hippocampus in memory and navigation, significant experimental and computational efforts have focused on uncovering the mechanisms that generate place cell feature selectivity. Seminal computational models of classic location-modulated CA1 place cells describe how inputs from upstream regions could combine in a feed-forward manner to yield place-specific tuning [20–22]. One cortical region that has been studied extensively in this context is the entorhinal cortex, which provides the primary source of cortical input to the hippocampus. The entorhinal cortex is subdivided into two primary functional regions: the lateral portion (LEC), which encodes non-spatial, contextual features such odor or objects and the medial portion (MEC), which encodes features associated with the location of an animal with respect to its environment and serves as a prime candidate to drive the spatial component of the hippocampal place code [23–26,27•]. Within MEC reside a number of functionally distinct, spatially modulated cell types that include grid cells that fire in periodic spatial locations, border cells that increase their firing rate near environmental boundaries, head direction cells that fire when an animal faces a particular direction and spatial cells with stable non-geometric spatial firing patterns [24–26,27•]. Initially, research focused on the hypothesis that input from grid cells with different phases and spatial scales could sum via a Fourier synthesis mechanism to yield a single downstream place field [20]. As these models often conceptualized CA1 place cells as a relatively homogenous population, it is perhaps not surprising that experimental evidence in support of the grid-to-place model has been mixed [28].

Traditionally, heterogeneity in place cell coding properties has been ascribed to differential connectivity with upstream input regions. For example, the preferential targeting of proximal CA1 by MEC and distal CA1 by LEC is thought to underlie the proximal-distal transition from pure place to more contextual coding and more recent works have shed light on how differences in the coding features of place cells in deep versus superficial CA1 layers might reflect differences in afferent connectivity [29]. Adding potential sources of place cell heterogeneity, however, recent studies have highlighted key roles for single-cell biophysics in gating place cell responses and RNA-sequencing analyses have revealed a greater amount of genetic variability amongst CA1 pyramidal neurons than previously appreciated [30••]. How this diversity in circuit connectivity, biophysics and gene expression interact to contribute to place coding remains incompletely understood. Here, we outline how recent discoveries have shifted the dialogue regarding the mechanisms governing the formation of place fields. We first present a subset of experimental findings with seemingly contradictory findings regarding how MEC grid cell inputs contribute to place cell codes and consider how a closer inspection of input or functional heterogeneity amongst place cells may help reconcile these results. We then more broadly discuss new evidence for how differences in connectivity, biophysical properties and genetic profiles could intersect to yield the heterogeneous nature of hippocampal coding and include proposals for how future work can address these new complexities regarding place cell generation.

Heterogeneity in the functional coding features of inputs can shape place fields

While studies indicate an important role for LEC [31], as well as other brain regions, in driving features of the hippocampal place code, we will focus our initial discussion on how MEC inputs shape CA1 place coding, as recent work has made significant traction in addressing this topic (Figure 1). Shortly after the discovery of grid cells, several computational models proposed that grid cell inputs could give rise to the firing features of place cells in CA1 [20,32–35]. This hypothesis however, has been met with mixed experimental support. Congruent with the hypothesis were the observations that 'global remapping', in which place field locations change across environments, occurs in tandem with rotation or translation of the grid pattern [36] and that the increase in place field size along the longitudinal axis of CA1 parallels an increase in the spatial scale of grid cells along the same axis [24,37]. However, early electrolytic and pharmacological manipulations probing the general impact of MEC inputs to CA1 yielded varying results [38–40], potentially due to variability in the extent of MEC impacted by a given manipulation. Thus, recent works have aimed to utilize more temporally precise, reversible manipulations and target specific genetically or functionally defined MEC cell-types. These studies have primarily focused on the role of MEC inputs in determining two cardinal features of the place code: the organization of place maps across environments (i.e. global remapping) and the spatial precision (i.e. field size) of place maps.

Confirming that MEC plays a key role in shaping place cell responses, both transient optogenetic inactivation and chemogenetic depolarization of MEC evoke place cell remapping [41•,42]. However, causally linking remapping to changes in the activity of specific MEC cell-types remains a formidable goal as, presently, there are no genetic markers by which to distinguish these functional cell-types. Nonetheless, to more directly examine the role of grid cells in hippocampal remapping, several studies have leveraged the observation that medial septum inactivation disrupts grid activity while minimally affecting other types of spatially modulated cells in MEC [43,44]. In two such works, septal inactivation did not strongly impact previously formed CA1 place fields or prevent the formation of stable place fields in a novel environment, casting doubt on the necessity of grid activity in generating or maintaining established place fields. However, in another study in which rats explored larger spatial environments, septal inactivation resulted in disorganized activity in the majority of place cells, save for a few neurons with fields near environmental boundaries [45]. Potentially reconciling these disparate findings is the possibility that different types of functionally defined MEC cells drive different subpopulations of place cells, and the proportions of these subpopulations sampled or activated could vary across experimental conditions. For example, border cells may provide stronger drive to place cells with fields near environmental boundaries, whereas grid cells could exert a greater influence on place cells far from environmental boundaries, where the animal has access to fewer landmark cues. Such dissociation could explain why the impact of septal inactivation was greater in a large environment in which proximal cues were less readily available. Additional support for the idea comes from the time-course of the development of stable place representations: early during post-natal development, when mature border but not grid activity is expressed [46], place maps provide more accurate information about the edges of an environment; later in development, stable grid cell activity and informative place maps across the entire environment emerge concurrently [47].

In addition to remapping, another feature of the place code is its spatial precision, or place cell field size. Whether MEC, or grid cells specifically, contribute to the size of place fields has been controversial. Fourier synthesis models of grid-to-place transformations predict that removal of small versus large scale grid cell inputs should have opposing effects downstream, increasing or decreasing the size of place fields, respectively [20]. Yet, while many grid-to-place cell models predict that only