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Heterogeneity in hippocampal place coding

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Abstract

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.

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

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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 inactivation of dorsal MEC should increase place scale, increases in place scale appear to occur regardless of where along the dorsal–ventral axis MEC is pharmacologically inactivated [48]. In contrast, neither optogenetic inactivation of MEC nor inactivation of medial septum inactivation affect place scale [44,49]. However, an important consideration is that, at present, nearly all experimental investigations into the impact of grid cell activity on the scale of place representations have involved the inactivation of MEC. Moreover, as noted in the previous paragraph, a growing body of works suggests that distinct subpopulations of place cells may be driven by inputs that convey different functional firing features. The difference in the function coding features of inputs to place cells could underlie the seemingly conflicting reports of how MEC inputs influence both CA1 remapping and the size of place fields. Consistent with this idea, recent work discovered that increasing grid scale through targeted knockdown of HCN1 channels reduced long-term place field stability in a sub-population of CA1 place cells and simultaneously expanded the size of CA1 place fields, with the magnitude of this impact dependent on the distance of a given place field from the nearest environmental boundary [50••]. Thus, it is important to keep in mind that experimental design, such as the availability of proximal or boundary related sensory cues, can have highly variable effects on the coding features of CA1 place cells, and caution should be exercised when drawing conclusions regarding generalizable mechanisms. In addition, consideration should be given to the fact that input from CA1 also influences MEC coding and that this feedback likely plays a critical important role in how MEC inputs then drive CA1 coding [51].

Additional sources of heterogeneity that influence place cells formation and coding features

Many computational models of place field formation have traditionally conceptualized pyramidal cells as a relatively uniform functional population that receives similar types of inputs. Yet, the varied responses of place codes to MEC manipulations, as reviewed above, points to functional heterogeneity in place cells. Some of this heterogeneity can be attributed to heterogeneity in the functional coding features of the inputs place cells receive. In addition, however, a growing body of evidence has revealed that gene expression, morphological characteristics, local and long-range connectivity and intrinsic biophysical properties all vary among hippocampal pyramidal cells, often in a topographically organized manner [8••,30••,52,53•]. Such organization suggests that different sub-regions of hippocampus may play district roles in behavior. Indeed, the graded contributions of place cells to spatial versus emotional or contextual processing along the dorsal–ventral and proximal–distal axes have been the focus of much experimental work (for review see

[52,54]). Here, we discuss new evidence for heterogeneous topographies across the radial axis and discuss the implications this may have on features of the place code.

Layer-specific differences in place cell coding features—Determining the layer of recorded place cells can be challenging using conventional electrophysiology, but recent advancements in silicon probe electrodes and optical imaging have successfully confronted this issue [55]. These approaches revealed differences in the firing characteristics of place cells located within deep (closer to stratum oriens) versus superficial (closer to stratum radiatum) layers (Figure 2). For example, deep cells display greater amounts of bursting and are more likely to have place fields [56], whereas superficial cells are more depolarized during sharp wave ripple events [53•]. These differences in firing properties extend to their functional coding features. In a recent study in which head-fixed mice navigated on a cue-enriched treadmill, superficial cells remained more spatially stable over time compared to deep cells [8••]. This long-term instability in deep cell place fields may reflect their unique state-dependent coding features. For instance, when the attentional demands of the task increased, only the spatial stability of deep cells increased, and the stability and precision of deep cells were more strongly modulated by the distance of their place field from the reward zone [8••]. Consistent with these findings, a second study using a similar paradigm reported that superficial cells fired in unique spatial locations across contexts, while deep cells encoded individual landmarks across different contexts [57•]. The ability of deep cells to dynamically encode the environment based on landmark or state-dependent variables may serve an adaptive purpose as the activity of deep, but not superficial, cells has been shown to significantly predict task performance [8••].

What mechanisms could account for the distinct firing properties and functional coding features of deep versus superficial place cells? Differences in afferent connectivity likely contribute: deep CA1 place cells receive stronger excitation from CA2, superficial CA1 place cells receive stronger excitation from CA3 [53•], and the extent of MEC and LEC drive to CA1 varies across both the radial and transverse axes (Figure 1) [58,59]. However, it is also possible that differences in single-cell intrinsic biophysical properties and the genetic expression profiles that underlie such biophysics contribute. For example, a signaling pathway by which activation of cannabinoid type-1 receptors enhances the magnitude of the hyper-polarization activated cation current (I_h) was recently reported to act exclusively in superficial, but not deep pyramidal cells [60]. I_h, in turn, strongly impacts both long-term potentiation and the temporal summation of synaptic inputs [61]. Thus, the differential modulation of I_h through endocannabinoids could render deep versus superficial subsets of cells more sensitive to specific inputs or combinations of inputs.

The contribution of single cell biophysics and intra-hippocampal computation to place responses—Recent works have also made strides toward identifying the algorithms by which heterogeneous inputs are transformed into place representations. Advances in intracellular recording techniques have made it possible to directly measure the synaptic inputs received by CA1 place cells and the biophysical properties that may gate their responses. In any given environment, only a fraction of principal cells develop place fields, while the majority remain ‘silent’, firing no or very few action potentials. Distinct

subsets of principal cells are then active in different environments, enabling place cells to generate non-overlapping population representations of different spatial contexts [62]. What determines which cells are active and which remain silent in a given environment presents a puzzling question. While not entirely understood, recent whole cell recordings of active versus silent cells have begun to provide insight into the mechanistic underpinnings of this coding feature. The subthreshold membrane potential of an active place cell (which represents its net input at the soma) varies in a hill-like fashion as a function of location, while that of a silent cell is essentially flat [13••,63,64]. On its own, this finding could support a model in which simple summation of spatially modulated input is followed by a thresholding processes, driving place cells to either fire in a spatially restricted manner or remain silent. In such a scheme, silent cells would receive either spatially homogenous or weak input. Yet, several observations challenge such a model. Each CA1 pyramidal neuron is thought to receive spatial input at thousands of synapses across its dendritic compartments [65]. Simple summation of these inputs would likely result in multiple membrane potential peaks across space rather than the unimodal hill typically observed, and silent cells would still be expected to have membrane potential peaks, albeit smaller ones that did not reach threshold [64]. Additionally, differences in the intrinsic biophysical properties of active and silent cells appear to predict the initial establishment of a place field. Before exposure to a novel environment, cells that go on to form place fields are more prone to burst in response to current injection and during exploration the firing thresholds of active cells are significantly lower than those of silent cells [63]. Perhaps the strongest argument against the simple summation hypothesis is that injection of uniform positive current can instantly convert silent cells into active place cells that are indistinguishable from typical place cells in their subthreshold membrane potential profiles [64] (Figure 3).

This would suggest that the inputs to silent cells are sufficient to drive the formation of a place field and membrane potential hill but only in the presence of additional depolarization [64]. For example, inputs to silent cells may encounter dendritic filtering, which can reflect topographically organized dendritic ion channel expression patterns [66,67], or intrahippocampal gating mechanisms, such as feedback inhibition [68•], that would prevent these inputs from reaching the soma. This gating mechanism, however, could be overcome by strong depolarizing events capable of inducing plasticity. Supporting this idea, the repeated injection of large membrane depolarizations at a consistent track location can artificially induce the formation of a place field in a formerly silent cell [13••]. As many place cells receive excitatory inputs from neural populations that vary their representations with time, such as neurons in CA2 [69], or behavioral state [70•], a subset of CA1 neurons may thus be primed to form place fields in any given environment. The long-term stabilization of the place code for a given environment would then depend on plasticity, which could involve regenerative dendritic spikes or plateau potentials—large calcium-mediated complex spike events [13••,63,71•]. This idea is consistent with newer research indicating that plateau potentials are not necessary for the formation of fields but contribute to their long-term stabilization [72•]. Variability in place cell stability seen, for example, in superficial versus deep layers could then arise from differences in single-cell biophysics that render the conditions for a plateau potential induction more or less favorable.

Heterogeneity in the genetic identity of place cells—In addition to diversity in inputs and biophysics, new work has revealed extensive diversity in the genetic identity of hippocampal pyramidal cells along axes that were previously thought to contain uniform genetic cell populations [30••]. While variability is seen across all axes of hippocampus, that across the dorsal–ventral axis is the largest and, strikingly, comparable in magnitude to that distinguishing different classes of pyramidal neurons (i.e. CA1 and CA3). Differences also emerge when considering the efferent targets of neighboring cells: for example, neurons located within the same dorsal–ventral pole but with projections to different brain regions (i.e. nucleus accumbens or amygdala) exhibit pronounced variation in gene expression [30••]. This is especially intriguing in light of work showing that different classes of interneurons target specific CA1 subpopulations that differ in their outputs [73]. Thus, the long-range output targeting of hippocampal cells presents another feature that may vary together with afferent inputs, local inhibitory circuitry and genetic and biophysical profiles to define unique and possibly independent functional neuronal subpopulations (Figure 3). Interestingly, genetic expression differences do not seem to define discrete cell types but rather emerge as continuous gradients [74]. This could enable cells with otherwise overlapping input and outputs to encode a larger continuum of features. How exactly genetic diversity shapes place cell responses remains an area of ongoing investigation. For example, the levels and distribution patterns of ion channels or receptor expression could vary between cells to differentially alter the excitability of their dendritic segments. This could render some subpopulations more tuned to specific inputs and not others. Moreover, such expression patterns could change across time, motivational state or task demands, altering which features a given pyramidal encodes depending on context. Whether such changes occur and the events that trigger them could be interesting avenues for future research.

Conclusions

While initially conceptualized as a homogenous cell population, CA1 place cells in fact show incredible heterogeneity, allowing them to represent the broad range of stimuli required to encode rich episodic memories and environmental spatial features that create the neural foundation for successful navigation. The last several years have brought important insights into how diversified sets of inputs, biophysics and genetic profiles contribute to the heterogeneity in the place code. Understanding how these features interact to generate features of the place code will be critical for future work. Combined, new data support a model in which subpopulations of pyramidal neurons form distinct networks differentially driven by a complex interaction of their unique biophysical or genetic profiles and heterogeneous inputs. These developments demand that future experimental work consider this heterogeneity when interpreting the results of manipulations to the place cell populations and that computational work attempt to integrate a more heterogeneous perspective when modeling place cells. The continued development of new hypotheses regarding how subpopulations of place cells that share similar input, biophysical, genetic or long-range projection profiles organize within hippocampus, generate unique neural codes and drive behavior will enable a deeper understanding of how hippocampal place cells shape our cognitive experience.

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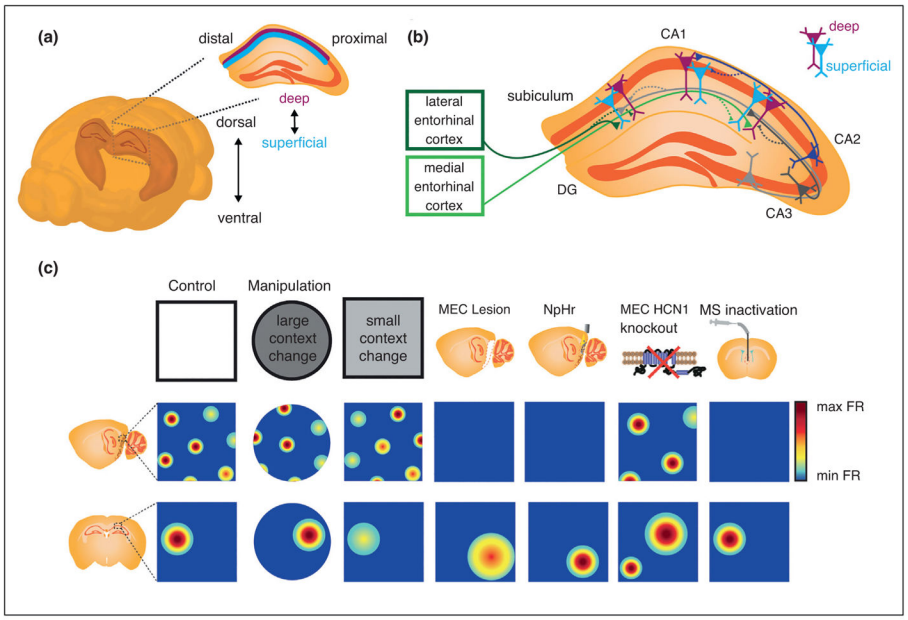

Figure 1.

Heterogeneous place cell responses arise, in part, from varying inputs. **(a)** Schematic of a mouse brain. The shaded area depicts the CA regions of hippocampus, with the inset depicting a coronal section of dorsal hippocampus. The three cardinal axes of CA1 are: dorsal to ventral, proximal (closer to CA2) to distal (closer to subiculum), and deep (closer to *stratum oriens*) to superficial (closer to *stratum radiatum*). Images created from the Brain Explorer 2, Allen Brain Atlas and modified from [30••]. **(b)** Topographical organization of hippocampal inputs has been observed across all axes of hippocampus. Depicted here are a subset of the inputs known to display topographical organization across the radial or proximodistal axes of CA1. Solid lines with larger arrows indicate stronger drive, while dashed lines with smaller arrows indicate weaker drive. CA2 more strongly excites deep CA1, while inputs from LEC and MEC preferentially drive distal, superficial CA1 and proximal, deep CA1, respectively. Input from distal CA3 more strongly drives proximal CA1, and input from proximal CA3 more strongly drives distal CA1 [75]. CA3 input elicits depolarization of superficial CA1 and hyperpolarization of deep CA3 [53•]. Additional inputs display topographical organization across the longitudinal axis (not shown). For example, dorsal and ventral entorhinal cortex (EC) predominately innervate dorsal and ventral CA1, respectively, and via the EC, dorsal hippocampus receives more input from anterior cingulate and retrosplential cortex, while ventral hippocampus receives more input from infralimbic and prelimbic cortices [52]. Modified with permission from [58]. **(c)** Illustration highlighting experiments in which changes in grid cell representations were associated with altered place cell activity. The top panels depict the experimental condition or type of manipulation. The middle and bottom panels depict the impact on grid and place cell activity, respectively. From left to right: Control recordings in a white rectangular arena; Large changes in environmental context resulted in realignment of the grid pattern and global remapping of place cells [36]; Smaller changes to environmental context altered to varying degrees the firing rate of individual grid nodes and induced rate remapping in place cells [27•]; Lesions of MEC that eliminate grid activity have largely resulted in increased

place field size (similar effects were seen following muscimol inactivation of MEC, not shown) [38,40,76]; Optogenetic inhibition of MEC greatly reduced grid cell firing and drove remapping in place cells without impacting field size; MEC-specific knockout of HCN1 channels increased the scale of both grid and place cell representations (particularly amongst place fields located far from environmental boundaries) and decreased place cell stability [50••]; Inactivation of medial septum (MS) largely eliminated the periodicity of grid cell firing patterns, with the impact on place cells including minimal effects on stability and large disruptions in the spatial coding of all place cells save those with fields near boundaries [44,45,49,76].

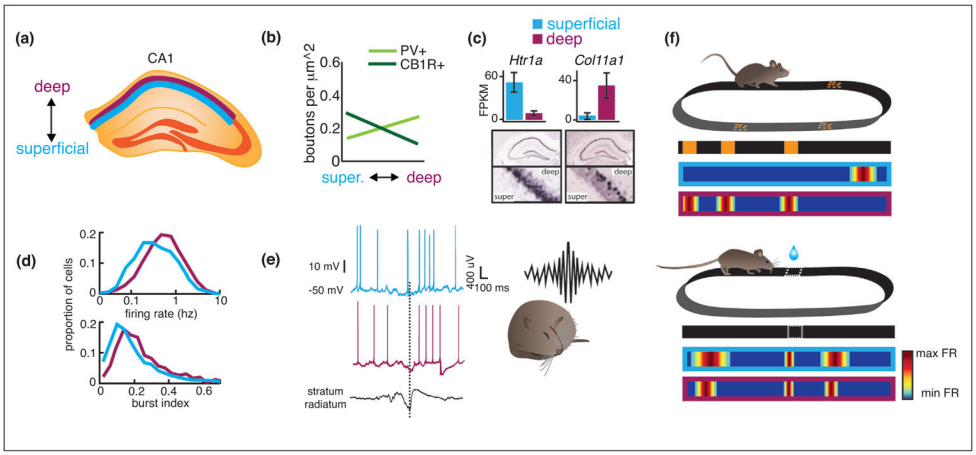

Figure 2.

Place cells are a highly heterogeneous cell population. **(a)** Variation in place cell connectivity, gene expression, coding features and recruitment during behavior is observed across all axes of hippocampus. We focus here on the radial axis. Superficial (blue) and deep (purple) layers of CA1 are depicted in a coronal section of dorsal hippocampus. **(b)** In addition to differences in long-range inputs (shown in Figure 1b), perisomatic inhibition by different classes of basket cells varies across the radial axis. For example, innervation by parvalbumin positive (PV) interneurons is strongest within deep layers and decreases toward superficial layers. The opposite is true of cholecystokinin (CCK) positive interneurons, which most strongly innervate superficial layers. Data modified from [53•] with permission. **(c)** While gene expression varies most significantly across the dorsal–ventral axis of hippocampus, gradients are also observed across the radial axis. Shown are two examples of novel genes recently found to preferentially express in superficial (Htr1a) or deep (Col11a1) layers. FPKM: fragments per kilobase of exon per million fragments mapped. Data reproduced with permission from [30••]. **(d)** Basic firing characteristics including firing rate (top) and burst firing (bottom) differ between pyramidal neurons in superficial and deep layers. Data reproduced with permission from [56]. **(e)** Superficial and deep pyramidal neurons differentially participate in sharp-wave ripples: pyramidal neurons tend to be depolarized, while deep pyramidal neurons tend to by hyperpolarized. Data modified from [53•] with permission. **(f)** Superficial and deep pyramidal neurons show unique coding properties and play different roles in behavior. *Top:* Mice ran on a linear treadmill enriched with local cues. Superficial neurons were more prone to fire in a single, unique location across an environment, whereas a subpopulation of deep neurons encoded specific landmarks across multiple environments. Schematic modified from [55]. *Bottom:* Deep cells were more strongly impacted by an animal's behavior on a task in which the mouse navigated to an unmarked location along a treadmill belt to receive reward [8••]. In both deep and superficial layers, place cells with fields located closer to the goal location were more spatially precise than those with fields located far from the goal, but this relationship was stronger amongst deep place cells. In addition, the stability of deep, but not superficial, place cells was increased across days when animals performed the attentional task (data not shown).

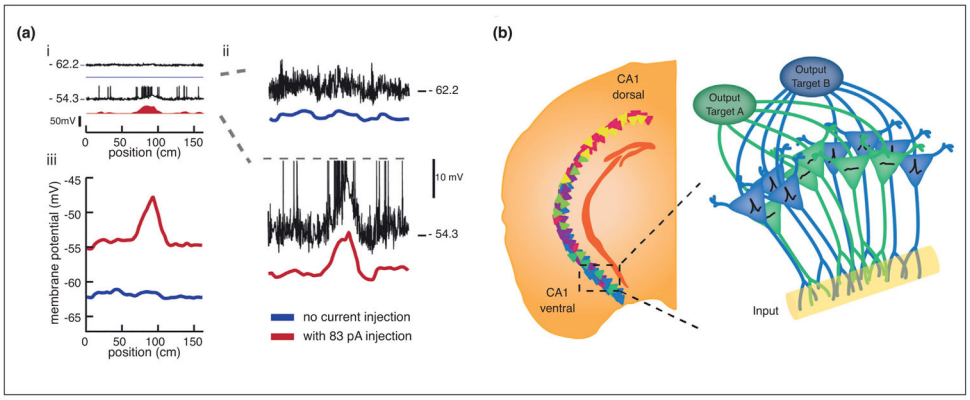

Figure 3.

Heterogeneity in biophysical properties, genetic expression profiles and connectivity interact to shape place responses. **(a)** 'Silent' pyramidal neurons can be converted into place cells by injection of uniform depolarizing current, highlighting a potential role for intrinsic biophysics in gating place responses. **(a_i)** Whole-cell recordings were made from CA1 pyramidal neurons as a rat traversed an oval-shaped track [64]. Linearized position is shown. Top: the membrane potential (black) and firing rate (blue) of silent CA1 pyramidal neuron before injection of positive current. Bottom: the membrane potential (black) and firing rate (red) of the same neuron during injection of positive current. **(a_{ii})** Closer view of the membrane potential (black) and mean subthreshold membrane potential (color). Spikes have been truncated (gray dashed line). Note the emergence of a hill-shaped ramp in the subthreshold membrane potential during injection of positive current. **(a_{iii})** The average membrane potential for all laps before (blue) and during (red) current injection. Note that the membrane potential is relatively flat on laps prior to the current injection, with no indication of where the field will emerge upon depolarization. Figure modified with permission from [64]. **(b)** Schematic showing the possible interaction between several sources of place cell heterogeneity. *Left*: Cartoon illustrating genetic variation across the longitudinal axis. The colors of the cells represent pole-specific marker genes in dorsal (warm colors) or ventral (cold colors) CA1. Figure modified with permission from [74]. *Inset:* within the ventral CA1 pole, pyramidal neurons with similar output projections share similar gene expression patterns. Cartoon depicts a hypothetical scenario in which two different subpopulations are excited to differing degrees upon receiving a shared input. Differences in the genetic profiles of these subpopulations lead to differential expression of ion channels and receptors that renders one subpopulation (blue) more sensitive to the particular input than another subpopulation (green).