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CA1 pyramidal cell diversity enabling parallel information processing in the hippocampus

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Abstract

Hippocampal network operations supporting spatial navigation and declarative memory are traditionally interpreted in a framework where each hippocampal area, such as the dentate gyrus, CA3, and CA1, consists of homogeneous populations of functionally equivalent principal neurons. However, heterogeneity within hippocampal principal cell populations, in particular within pyramidal cells at the main CA1 output node, is increasingly recognized and includes developmental, molecular, anatomical, and functional differences. Here we review recent progress in the delineation of hippocampal principal cell subpopulations by focusing on radially defined subpopulations of CA1 pyramidal cells, and we consider how functional segregation of information streams, in parallel channels with nonuniform properties, could represent a general organizational principle of the hippocampus supporting diverse behaviors.

The hippocampus is a structure within the medial temporal lobe, playing key roles in spatial navigation and episodic memory[1–6]. Principal neurons in the hippocampal trisynaptic circuitry (dentate gyrus (DG)–CA3–CA1) fire spatially modulated spikes whenever the animal traverses a particular area of the environment (the ‘place field’), forming a neural representation of space and supporting spatial navigation and episodic memories[7–10]. Theoretical and experimental studies suggest that learning and memory may be produced by the activity of discrete groups of neurons[11–18], and various forms of synaptic and intrinsic plasticity between principal neurons are thought to direct memory-coding ensemble formation[19–21]. Until recently, hippocampal mnemonic processing has been often interpreted in a framework of random synaptic connections between large, homogeneous populations of principal neurons in each hippocampal area. Indeed, informative computational models of memory have been developed using a framework consisting of uniform principal cell populations within each hippocampal area[14,18,22–24].

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Competing interests

The authors declare no competing interests.

However, a major limitation of this framework is that it has difficulties explaining how a single circuit can reliably process and store memories acquired under dramatically different learning conditions. For example, within the domains of spatial and episodic memory alone, the hippocampal circuit supports primarily spatial (for example, goal-directed), temporal associative (for example, trace fear), or contextual (for example, contextual fear) learning, with each form of learning being associated with distinct encoding, retrieval, and consolidation states and depending on a varying degree of available extrinsic (sensory) and intrinsic (intrahippocampal) information[4,22,25–29]. Therefore, understanding how the hippocampal circuitry consisting of homogenous populations of principal cells can be reconfigured on demand to support such diverse memory processes and how learning-related new information is stored while preserving old information remain major challenges. While a common conceptualization of the systems-level organization of memory is that different types of memory are mediated by distinct neural systems performing a high degree of parallel processing, this concept is much less established at the cellular and microcircuit levels within memory circuits[30]. The hippocampal circuit architecture can, in principle, afford several parallel circuits to carry out these multifarious mnemonic operations. Indeed, there is increasing evidence suggesting that there are dual (spatial and nonspatial) input streams into the hippocampus[25,31–33] and that these two streams remain relatively segregated. The main question is, however, whether these parallel information channels represent uniform or nonuniform computational modules (Fig. 1). Uniform modules would perform essentially similar transformations on different afferent signals and send processed information to different downstream targets. Alternatively, the nature of the input–output transformation itself could be different, with nonuniform modules constituting the parallel circuits. In the latter case, components making up the parallel circuits might be different between channels and thus executing nonidentical transformations on the incoming nonidentical signals carried by the different afferents to the hippocampus.

In this review, we focus on recent results that collectively support an emerging framework in which the hippocampus is comprised of heterogeneous principal cell populations constituting several distinct, nonuniform parallel circuit modules that are independently controlled and affect different behaviors, enhancing the computational flexibility and capacity of the hippocampal circuit. We first discuss evidence for principal cell heterogeneity at the genetic and developmental levels, and then highlight how principal cell heterogeneity is reflected in biased local microcircuits serving particular output pathways. Next, we discuss evidence that increasingly ties principal cell and microcircuit heterogeneity to distinct behaviors. We keep our primary focus on radial heterogeneity in the CA1 area but also highlight evidence that principal cell heterogeneity appears to exist along multiple axes across the hippocampal formation. We close by formulating outstanding questions that will need to be addressed in order evaluate the relevance and implications of this ‘multichanneled’ framework for hippocampal memory operations.

Topographically defined radial subdivisions of CA1 pyramidal cells

Area CA1, with its widespread projections[34,35], is a key output node of the hippocampal memory circuit. However, a number of additional functions have been proposed for CA1, including novelty detection, input comparison, and enrichment of hippocampal output,

potentially by redistributing information from CA3 across a greater number of output neurons[18,24,36–38]. As a potential correlate to the multifarious functions suggested for the CA1, it has been increasingly recognized that CA1 pyramidal cells (CA1PCs) exhibit a significant degree of heterogeneity, which could support the emergence of nonuniform parallel circuit modules. In particular, a clear morphological subdivision between deep and superficial CA1PCs exists along the radial axis (i.e., from the ventricles to the pia, perpendicular to the CA1PC layer), a feature noted by early anatomists[39] and observed in diverse species[40]. Beyond the positional distinction between superficial and deep CA1PCs (Fig. 2a), there are radial differences in the timing of neurogenesis due to the inside-out pattern of hippocampal development (Box 1 and Fig. 2b). Likely related to their different birthdates and associated differences in genetic programs, superficial and deep CA1PCs differ in molecular, structural, physiological properties (Fig. 2), as well as in connectivity (Fig. 3).

Box 1

Development of the CA1 pyramidal cell layer

The rules governing hippocampal and neocortical development are similar but not identical. In rodents, PCs in the CA regions are generated in the ventricular zone, and then migrate toward the pial surface (the hippocampal fissure), ultimately settling into the hippocampal plate, the future PC layer[137]. Hippocampal laminar formation takes places in an inside-out pattern, in which earlier-born cells form the deeper part of the PC layer, whereas the later-born neurons pass the older cells and settle in the more superficial part, as in the neocortex[138–140]. However, in contrast to the relatively straight path of the radially migrating neocortical neurons, hippocampal cells migrate toward the hippocampal plate obliquely at first, followed by a more conventional radial route[141]. In addition, neocortical migrating neurons typically proceed using a single radial fiber as scaffold, whereas migrating future hippocampal pyramidal neurons use multiple radial glial fibers and migrate considerably more slowly[137]. Furthermore, clonally related CA1 neurons are distributed in a more horizontal manner, not in a well-defined vertical column as in the case of neocortical PCs[109]. The obscuring of the basic inside-out pattern may be related to the ongoing horizontal expansion of the relatively thin hippocampal plate during development, which may make it difficult for clonally related cells to be strictly vertically aligned[137]. It should be noted that postmitotic cells can migrate tangentially from one to another radial glia even in the neocortex[142], and it is possible that the difference in dispersion is related to the more tortuous path taken by radial glia in the hippocampus. In spite of variations to the basic radial migration scheme, neurons born at the same time in the CA1, CA3, and DG connect preferentially with each other and show similar gene expression patterns[100], laying the foundations for parallel information-processing channels.

In addition to the well-known lamina-specific neurochemical differences (for example, calbindin and zinc expression in superficial CA1PCs), a recent study demonstrated transcriptional gradients along the radial axis[41] (Box 2 and Fig. 2c,d), which could manifest in cell-intrinsic differences in protein expression and functional properties. Indeed,

differences in CA1PC morphology and intrinsic electrophysiological properties have been found along the radial axis (Fig. 2e)[42–44], with distinct molecular regulatory mechanisms and downstream effects on learning and memory[45]. Moreover, much of this heterogeneity in the radial direction is expressed along with spatial gradients following the other principal axes of the hippocampus, the dorsoventral (reviewed in ref. [46]) and proximodistal axes (reviewed in ref. [47]).

Box 2

Spatial distribution of gene expression profiles within the CA1PC population

Transcriptional mRNA profiling studies[41,143–147] reveal a high degree of gene expression heterogeneity within the CA1PC population. These transcriptional differences are most prominent along the dorsoventral axis of the hippocampus, but they are also present along the proximodistal and radial axes: for example, a recent study using next-generation RNA sequencing reported that 265, 33, and 71 genes are expressed differentially along the dorsoventral, proximodistal, and superficial–deep axes, respectively[41] (Fig. 2c,d). That most of these transcriptional differences also manifest at the protein expression level[41] and comprise genes with known functions (for example, transcriptional factors, voltage-gated channels, receptors, and auxiliary subunits) indicates that gene expression differences are fundamental in producing variability in connectivity, morphology, physiology, and connectivity and that these gene expression differences ultimately underlie differences in behavioral functions of CA1PC subpopulations. These experiments[41,143,148] indicate continuous transcriptional gradients without prominent subdomain organization along the hippocampal dorsoventral axis (cf. refs [147,149]). Transcriptional profiling approaches will be invaluable for identifying novel marker genes for anatomically or developmentally defined CA1PCs subpopulations, informing targeted perturbations (for example, CRISPR–Cas gene editing) to causally test their functionality during hippocampal operations.

CA1PC heterogeneity and local microcircuits

How do the heterogeneous CA1PCs integrate into the hippocampal circuit? Are all PCs controlled by essentially identical GABAergic microcircuits, or do the interneurons nonuniformly target specific subpopulations of CA1PCs? Data from various neocortical areas reported lack of both preference[48,49] and selectivity[43,50–56] by interneurons for different postsynaptic populations. In the CA1, fast-spiking, parvalbumin-expressing basket cells (PVBCs) provide unitary synaptic currents almost three times larger in deep compared to superficial CA1PCs in both the dorsal and ventral CA1[43]. The larger synaptic currents exert more effective control of action potential discharges and originate from a denser PVBC innervation of the deep CA1PCs (Fig. 3a). Furthermore, the differences extend to local recurrent excitatory connections as well, with superficial CA1PCs innervating PVBCs with three times higher probability compared to deep cells (Fig. 3a). Thus, PVBCs receive more excitation from superficial CA1PCs but deliver stronger inhibition to deep CA1PCs. The biased inhibitory and excitatory microcircuit organization between the heterogeneous PCs

and PVBCs sets up preferential lateral inhibition from the superficial to the deep layer (Figs. 1b and 3a).

At the level of individual cell pairs, PVBCs form unitary connections with similar probability and strength with superficial cells regardless of whether superficial CA1PCs provide excitatory inputs to the PVBC, and similar organization was observed for deep CA1PCs as well[43]. This is in contrast to neocortical excitatory– inhibitory motifs, where synaptic connections between pairs of excitatory cells and fast-spiking interneurons differ depending on whether the connection was reciprocal or present only in one direction[56]. Interestingly, while PVBCs on average evoke larger unitary inhibitory events in deep cells, the location of the CA1PC somata in itself is not a perfect predictor of the synaptic current amplitude[43]. The latter property is likely to be related to the lack of a neocortex-like strict radial migration for CA1PCs (see Box 1), and it may also reflect differential long-distance projection targets of CA1PCs from within the same layer (Fig. 3b). Such distinct perisomatic inhibitory interactions between separate output channels may critically contribute to the sparse and distributed structure of network activity.

Asymmetric connectivity between radial CA1PC subpopulations and PVBCs[43] (Fig. 3) provides one compelling piece of evidence for the existence of biased excitatory–inhibitory microcircuits in the hippocampus that could dynamically regulate routing of information between CA1PCs subcircuits, possibly depending on area-specific activity patterns and computational tasks[57]. In the CA1, where the level of recurrent excitatory connectivity between CA1PCs is low, the extent to which inhibitory microcircuits can dynamically segregate information flow between parallel circuit motifs is a particularly relevant question. Therefore, it will be important determine whether other inhibitory cell types[58–61] are also differentially interconnected with distinct CA1PC subpopulations. For instance, interneurons that innervate dendrites[62–65] or axon initial segments[66–69] may also show preference for CA1PC subgroups to exert subcircuit-selective regulation of input integration and spiking output generation, respectively[66–70].

Functional heterogeneity of CA1PC in the context of behavior

To what degree are these radial differences between CA1PC populations relevant to behavior? Regionally specified heterogeneity along the dorsoventral and proximodistal axes has been found to be an important contributor to different forms of learning and memory[27,46,71– 80]. Recent studies indicate that differences along the radial axis also translate to similarly meaningful differential roles in supporting behavior. A recent study using silicon probes demonstrated that deep CA1PCs are more active and more likely to form place fields than superficial neurons and that deep neurons can shift their firing-phase preference depending on brain state[81], lending support to a model in which the sublayers can differentially communicate with downstream targets. Importantly, studies using various in vivo electrophysiological recording techniques report a bias in the recruitment of radially defined CA1PCs during hippocampal sharp wave-ripples (SPWRs), with superficial cells firing earlier, more, and more consistently during these events[81–84], in agreement with the notion that superficial and deep CA1PCs form functionally heterogeneous groups in vivo (Fig. 4).

The questions of spatial remapping dynamics and the evolution of sublayer-specific activity over the course of learning were addressed using Ca^{2+} imaging in head-fixed mice, demonstrating that superficial CA1PCs formed spatial maps that were more stable than deep CA1PC maps[85]. Moreover, superficial maps more reliably discriminated contexts at both the single-cell and population levels than deep maps. Because place-map dynamics are affected by learning and task demands[86–89], chronic two-photon functional imaging during a multiday head-fixed goal-oriented learning task was used to assess differences in coding between the sublayers[85] (Fig. 4a). In this learning task, deep CA1 neurons were more stable than they were during a random foraging task. Furthermore, place cell representation of the goal by deep CA1PCs was more predictive of performance on the task than was representation by superficial neurons (Fig. 4a,c). Thus, one may speculate that, through separate output channels, the superficial CA1 sublayer conveys a more stable spatial map of the environment while the deep sublayer represents dynamic features, such as reward location, to support learning, providing a potential solution for the stability–plasticity dilemma of memory networks. Consistent with this reasoning, a recent study using silicone probe recordings showed[90] that firing fields in a subset of deep CA1PCs are more tightly linked to the location of individual sensory stimuli (i.e., landmarks on the navigation belt), while the superficial layer contained CA1PCs that were more likely to represent a global spatial context. Together, these studies on radial CA1PC subdivisions provide strong support for a conceptual framework in which hippocampal output neurons are parsed into parallel nonuniform subcircuits, supporting distinct cognitive functions.

Another important question concerns the differential afferent and efferent connectivity of heterogeneous CA1PC groups that would support the formation of parallel nonuniform subcircuits. Recent studies suggest that this is indeed the case for direct excitation from the entorhinal cortices. The medial and lateral entorhinal cortices (MEC and LEC, respectively) provide dual input streams into the hippocampus[31], with the MEC providing predominantly spatial information and the LEC providing primarily nonspatial information to CA1PCs[31–33]. In this pathway, MEC and LEC project to different parts of CA1 along the proximodistal axis, leading to differential recruitment of PCs along this axis during spatial and nonspatial tasks[47,75,76,78,80,91,92]. A recent study[93] found that these two inputs also activate the radial CA1PC sublayers differentially (Fig. 3a) and that this differential innervation varies as a function along the proximodistal axis. That is, the MEC drive is strongest in proximal CA1 (toward CA2), whereas the LEC drive is strongest in distal CA1 (toward subiculum). In proximal CA1, strong MEC and weak LEC inputs favor deep CA1PCs, whereas in distal CA1, strong LEC and weak MEC inputs prefer superficial CA1PCs.

These results provide a potential circuit mechanism for the findings that deep CA1PCs are more likely to have place fields during spatial navigation[81,85], due to the stronger excitation of deep CA1PCs by MEC inputs, at least in the proximal part of CA1. The increased stability of superficial place maps[85]—where proximal cues and landmarks are more relevant—is also consistent with the preferential innervation of superficial CA1PCs by LEC. These results demonstrate that CA1PC diversity along the radial and proximodistal axes are interrelated, in that changes along one axis can vary as a function of position along the other axis. The stronger direct excitatory drive from LEC to superficial CA1PCs suggests that this

subcircuit may play a preferential role in processing nonspatial information during learning. Indeed, calbindin-immunopositive CA1PCs, which are predominantly located in the superficial sublayer, receive stronger LEC inputs and exhibit more selective spiking responses to odor cues during olfactory associative learning, and their optogenetic inactivation slows learning[94] (Fig. 4b,c).

Among other intrahippocampal afferents, CA2 pyramidal cells provide stronger excitatory inputs onto deep compared to superficial CA1PCs (Fig. 3a)[95]. This biased intrahippocampal excitatory connectivity may play a role in the differential recruitment of radial CA1PC subdivisions during hippocampal network activities (for example, SPWRs; see below).

In addition to distinct afferents, heterogeneous CA1PCs may differ also in their efferent connectivity (Fig. 3a). Indeed, as the main hippocampal output neurons, CA1PCs can route distinct behavior-contingent information selectively to different target areas[35]. Therefore, a critical question concerns the extent to which the observed differential relationship of CA1PC subpopulations to behavior is attributable to differences in efferent connectivity between CA1PC subpopulations. Recent studies have provided compelling evidence for such selective routing of information to downstream targets via projection-specific CAPC subpopulations. For example, anxiety-related, goal-directed, and SPWR-related firing are selectively increased in CA1PCs projecting to the prefrontal cortex, nucleus accumbens, and in triple-projecting neurons (targeting the prefrontal cortex, amygdala, and nucleus accumbens), respectively[96]. Further, CA1PCs projecting to the nucleus accumbens shell from the ventral hippocampus, preferentially located in the deep sublayer, play a necessary and sufficient role in social memory[97]. Similarly, CA1PCs projecting to the basal amygdala mediate contextual fear behavior, whereas CA1PCs projecting to the central amygdala mediate context-dependent fear memory retrieval[98].

These results demonstrate the presence of functionally dedicated and anatomically segregated neuronal circuits supporting behavioral-contingent regulation of fear learning by the environmental context. These studies, by convincingly demonstrating that anatomically defined subcircuits can route behavior-specific information to distinct targets, have started to reveal important features of how output neurons interact with target structures, which may represent general organizing principles across the hippocampus. Furthermore, the hippocampus could interact with downstream targets via multiple parallel pathways[98], exhibiting functional dissociation during hippocampal-dependent learning between these processing streams. Interestingly, while these studies demonstrate the presence of anatomically segregated CA1PC population outputs, they also indicate the existence of CA1PCs with multiple projections[96,99], which may coordinate the expression of inference and generalization of mnemonic processes.

Summary and outlook

Taken together, the evidence from radially defined CA1PC subpopulations suggests that the hippocampus comprises several distinct, parallel, nonuniform subcircuits that are independently controlled and affect different behaviors. By relating principal cell diversity with function in each hippocampal area, we can better understand how the hippocampus is

capable of supporting multifarious operations during navigation and learning. Functional investigations of parallel, nonuniform circuit modules assembled from developmentally, genetically, and anatomically defined subpopulations of principal cells and their inhibitory partners across the hippocampus hold the potential to assign behavioral relevance to parallel processing units among principal cells. In order to test the hypothesis concerning parallel, nonuniform subcircuits further, we outline several outstanding questions below.

Open questions about heterogeneity of principal neurons in the hippocampus

How many parallel subcircuits are there in the CA1 area, and what is their impact on the information transfer and storage capability of the hippocampal network?

The functional segregation of CA1PCs along the superficial–deep, dorsoventral and proximodistal axes, accompanied by spatial differences in gene expression (Box 2) and specific behavioral roles of target-specific CA1PC subpopulations[46,47,96–98], implies the existence of a multiplicity of parallel, nonuniform hippocampal subcircuits. However, an even larger and finer-grained array of segregated parallel subcircuits may exist in relation to timing of embryonic neurogenesis, as indicated by evidence that CA3 pyramidal cells (CA3PCs) form selective interconnections with their birthdate-related partners in the CA1[100,101]. The existence of ‘parallel-connectivity channels’ between temporally matched subpopulations in CA3 and CA1 suggests the presence of an extrinsic patterning mechanism capable of parsing the CA1PC population into functionally related subunits. A prediction of this framework is that neurogenesis-related CA3 and CA1PCs might exhibit similar spatial tuning during spatial navigation. Such a mechanism is not without precedent: for example, radially arranged ‘sister cells’ in the mouse visual cortex, derived from the same radial glial cell, preferentially form synaptic connections and show similar stimulus selectivity[102–105]. Given the large number of potential parallel subnetworks, it will be important to gain quantitative modeling insights into the relationship between the degree of functional granularity of CA1PCs and the overall information transfer and storage capabilities of the hippocampal network. Computational studies[18,106–108] analyzing the impact of structured connectivity in the CA3-to-CA1 projections suggest that the efficacy of information transfer depends on both the ratio of CA1 to CA3 cells and the scale of spatial correlation of the CA3 representations. The presence of selectively interconnected CA3 and CA1PCs may help to prevent information loss within segregated channels while having relatively minor effect on the overall information transfer and storage capacity of the network.

How do biased excitatory–inhibitory microcircuit motifs emerge?

A related question concerns the emergence of biased hippocampal microcircuits between heterogeneous PC subgroups and GABAergic interneurons. Are they formed during development or are they principally shaped by activity-dependent plasticity mechanisms? A role for developmental processes has been recently demonstrated in the formation of preferentially interconnected fast-spiking basket cells and the CA1PC subgroups[109], where clonally related sister CA1PC pairs do not preferentially form synapses with each other but fast-spiking cells provide common GABAergic synaptic inputs selectively to sister CA1PCs.

Such preferential innervation of clonally related CA1PCs could underlie the observed synchronous activity in sister cells and indicate that the foundations of the biased excitatory–inhibitory local network motifs are at least partly established during development. In agreement with the latter notion, early-born pioneer PCs in the deep CA3PC layer operate as assemblies in the developing hippocampus and later become powerful single units able to influence network dynamics[110]. While developmental programs are likely to play an instructive role in setting up biased connectivity, recent evidence indicates that hippocampal inhibitory circuits undergo a wide range of experience- and learning-related[111–114] plasticity, indicating that biased excitatory–inhibitory microcircuit motifs may be remodeled in vivo[19].

How do CA1PC subnetworks relate to hippocampal-dependent behaviors?

Recent studies demonstrated that stable and labile place coding elements, segregated along the CA1 radial axis, show distinct in vivo physiological properties and differentially predict learning of rewarded spatial locations and show that these elements are differently interconnected through GABAergic circuits[43,81–83,85,90,94]. These results, together with other studies on the dorsoventral and proximodistal axes of hippocampus (reviewed in refs [46,47]), raise questions about the nature of relationships between PC subcircuits and hippocampal-dependent behaviors. What are the roles of these subnetworks during distinct forms and phases of hippocampal learning behaviors? Can we assign specific behavioral functions to developmentally defined, topographically organized, or target-specific subgroups of PCs during spatial, temporal associative, or contextual learning? Would these subgroups play equally important roles in memory encoding, retrieval, consolidation, and extinction stages associated with particular forms of learning, or would they support specific behavioral functions? Relatedly, are these subcircuits differentially engaged during distinct behavioral-state-dependent network activity patterns (for example, theta oscillations and SPWR events)? Investigations into these questions will require both correlational analyses of population dynamics of identified PC subgroups during learning behaviors and selective manipulations of PC subpopulations during distinct forms and stages of hippocampal-dependent behaviors.

What is the relationship between parallel processing streams and ‘preconfigured’ functional subpopulations of CA1PCs?

The hippocampal memory code is sparse at both the single-cell and population levels[115], which is implicated in ensuring high capacity memory encoding and in reducing interference in associative memory[14,18,24,115]. However, the mechanisms that govern the selection of the actual subset of active PCs in a given environment remain unknown. The simplest scenario would be a random allocation of place cells[116] to maximize the separation of neuronal representations in different environments (‘pattern separation’ or remapping[117–119]). However, recent experiments challenge this model, demonstrating that firing rate distributions of CA1PCs are skewed (log-normally distributed)[120], the firing activity of each cell is largely preserved across behavioral states[120], and hippocampal PCs may even be, at least in part, preselected for activation[121,122]. Other results also indicate that high-firing-rate, diffusely firing neurons may form a stable ‘backbone’, over which plastic low-firing-rate cells ‘learn’ to encode for highly specific aspects of the environment[123]. A similar mechanism may help explain how new experiences integrate with stable memories, allowing

for flexible updates of cognitive maps. Therefore, it will be important to characterize the developmental origin, anatomical identity, molecular profiles, and connectivity of these functionally defined CA1PCs subpopulations to determine the contribution of various patterning mechanisms to the allocation of activity across cells during distinct behavioral states, as well as to various forms and stages of learning.

Do parallel subnetworks exist outside area CA1?

Heterogeneous principal cell subpopulations appear to exist elsewhere in the hippocampal formation, possibly related to the birthdate-related formation of parallel channels discussed above[100,101,124]. For example, subicular pyramidal neurons can be divided into two classes based on morphological, electrophysiological, extrahippocampal projection, and plasticity properties[125], and deep CA2PCs play distinct roles in initiating SPWRs[126]. Gene expression in CA3PCs displays prominent laminar specificities[127], and CA3PC morphological and intrinsic physiological properties vary along the main axes[128,129], as well as with regard to the extent of mossy fiber innervation of individual CA3PCs[130]. The identification of a subpopulation of early-generated, deep CA3PCs with ability to synchronize adult network activity[110] is consistent with developmentally derived radial differences. Sparse input from granule cells (GCs) to CA3PCs could foster the formation of segregated GC–CA3PC subcircuits through the selective innervation of CA3PCs by GCs born during matched time windows during embryonic[100] and adult[131] neurogenesis. Because the DG is formed according to an outside-in developmental rule (older cells are located closest to the pial surface, i.e., the fissure) that is opposite the inside-out pattern of other cortical areas (Box 1), a testable prediction is that DG PVCBs should preferentially innervate mature (early-born) superficially located granule cells, while receiving preferential recurrent excitation from the younger (late-born) GCs located deeper in the GC layer (closer to the hilus). Such an arrangement would suggest a principal role of developmental programs—the timing of neurogenesis—as opposed to mere anatomical position, in the formation of biased excitatory–inhibitory microcircuits (Fig. 3).

Are biased hippocampal subcircuits differentially sensitive to diseased conditions?

Research into the functional organization of heterogeneous hippocampal PC populations will also yield valuable insights into abnormal circuit function in neurological and psychiatric disorders. Future studies into disease-related mechanisms must take into account the fact that random sampling of cells from the highly heterogeneous PCs is likely to miss subpopulation-specific alterations that may be important in abnormal circuit functions. Indeed, deep and superficial PCs differ in their sensitivity to insults (reviewed in ref. [40]), and recent data indicate that they may also be differentially involved in the generation of abnormal activity patterns[84]. Application of modern research tools to understand the genetic, molecular, structural, and functional differences between PC subpopulations in normal and disease-related conditions is expected to bring new insights into the parallel processing functions of hippocampal circuits and their roles in disorders.

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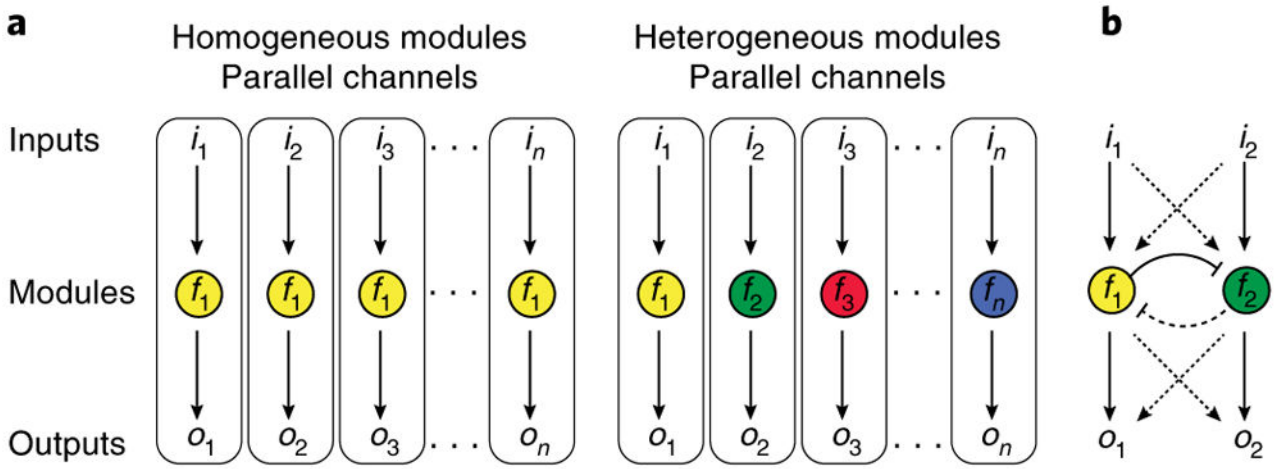

Fig. 1. Hypothetical nature of parallel channels

a, Left: schematic diagram illustrating hypothetical parallel information-processing channels, where each homogeneous module (f_1) performs essentially similar operation on the inputs. Right: for heterogeneous modules ($f_1 \ldots f_n$), each information-processing channel performs a different operation on the distinct inputs. Each module can be thought of as a microcircuit consisting of particular principal cell and GABAergic interneuron subpopulations, with the principal cells receiving distinct afferents and projecting to different downstream target brain areas. i_1–i_n, inputs; o_1–o_n, outputs. **b**, Schematic representation of parallel circuits consisting of heterogeneous modules with inhibitory interactions between the modules, with potential for a certain degree of overlap between specific afferent inputs and efferent outputs. The inhibitory interactions can be asymmetric (see Fig. 3).

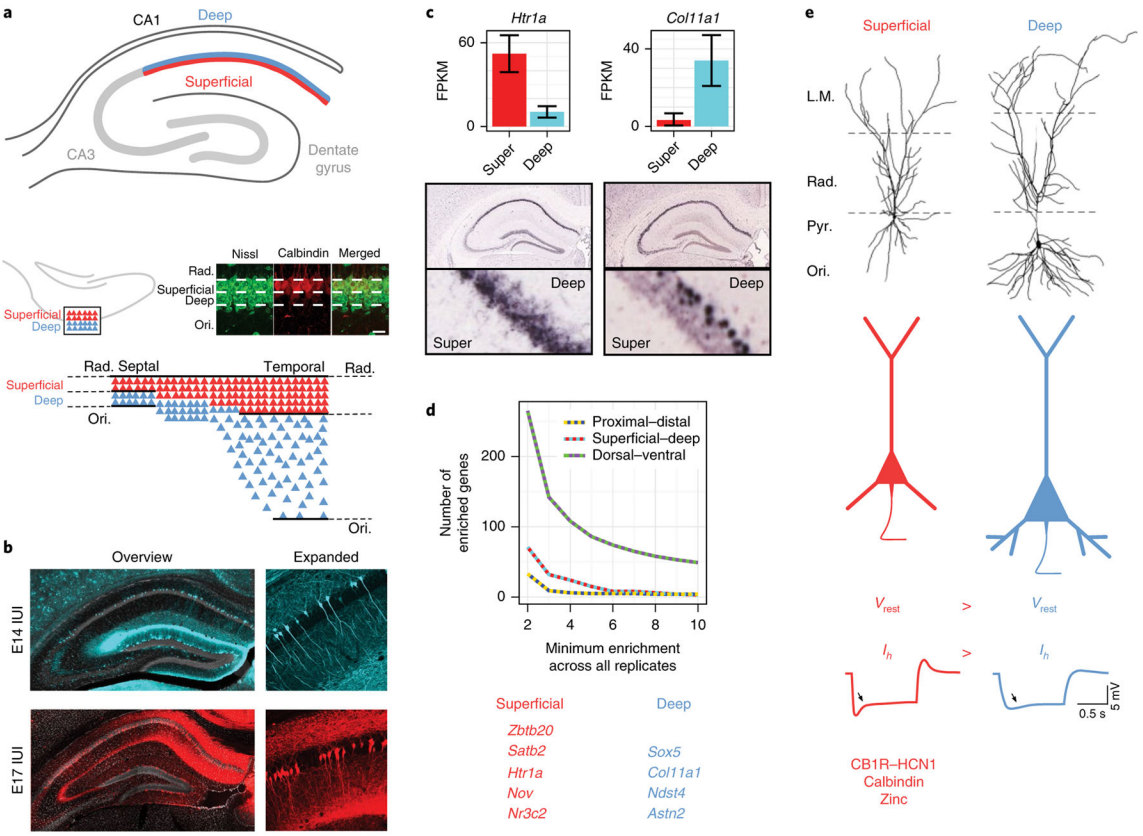

Fig. 2. Developmental, genetic, morphological, and intrinsic electrophysiological differences between radially defined CA1PC sublayers

a, Top: schematic illustrating coronal section of the hippocampus with major subregions. Middle left: schematic drawing illustrates the deep (blue) and superficial (red) subdivisions of the CA1 somatic layer. Middle right: calbindin expression in the superficial sublayer in the septal CA1. Scale bar, 20 μm. Rad., stratum radiatum; Ori., stratum oriens. Bottom: differences in the cellular compactness and width of the deep and superficial CA1PC sublayers along dorsoventral axis of the hippocampus. Adapted from ref. [43], Cell Press. **b**, Superficial and deep CA1PCs are generated in different time-windows during embryonic neurogenesis: in utero intraventricular injections (IUI) of tdTomato-expressing adeno-associated virus at embryonic day 14 (E14, cyan) and E17 (red) label deep and superficial CA1PCs, respectively. Pyramidal cells of the densely packed superficial layer in CA1 arise approximately 2–3 d after those of the deep layer, on average. **c**, Two example marker genes for superficial and deep sublayers identified with RNA sequencing (top) and cross-validated with in situ hybridization (bottom); gene-expression values (top) are expressed in fragments per kilobase of exon per million fragments mapped (FPKM). Super, superficial. **d**, Top: the number of enriched genes as a function of the minimum enrichment across all replicates using bulk RNAseq. Note that the dorsoventral axis exhibits the most robust gene-expression differences, but there are many enriched genes across both the superficial–deep and proximodistal axes as well. Bottom: examples of genes enriched in the superficial and deep sublayers. Differences in gene expression may relate to functional differences between layers: calbindin-deficient mice and mice with deletion of the gene encoding the

transcription factor Zbtb20, which controls calbindin expression, demonstrate deficits in hippocampal-dependent learning and LTP[132–134]. Zbtb20 expression is maintained throughout adulthood in superficial CA1PCs, and its expression is mutually exclusive with that of Sox5, a marker of deep CA1PCs[135]. Images in **b**–**d** adapted from ref. [41], Cell Press. **e**, Morphological and intrinsic electrophysiological differences between superficial and deep CA1PCs. Top: representative camera lucida drawings of a superficial CA1PC and a deep CA1PC. L.M., stratum lacunosum-moleculare; Rad., stratum radiatum; Pyr., stratum pyramidale; Ori., stratum oriens. Deep cells have larger soma and more complex basal dendrites (adapted from ref. [43]). Note that Li et al.[93] reported that calbindin-expressing CA1PCs, primarily located in the superficial sublayer, have more complex apical dendritic arborizations (not shown). Middle: superficial CA1PCs exhibit a more strongly depolarized somatic resting membrane potential (V_{rest}) and a larger somatic *h*-current that mediates a depolarizing sag (indicated by arrow) during hyperpolarizing current pulses. Bottom: examples of superficial CA1PC-biased signaling pathway, calcium-binding protein, and a divalent ion. *H*-current, a major regulator of dendritic excitability and synaptic input integration, is larger in superficial CA1PCs, and recent results indicate that tonic activity of postsynaptic cannabinoid type 1 receptors (CB1R) maintains the amplitude of I_h through a dedicated molecular pathway[45] in these cells. HCN1, hyperpolarization-activated cyclic nucleotide-gated channel.

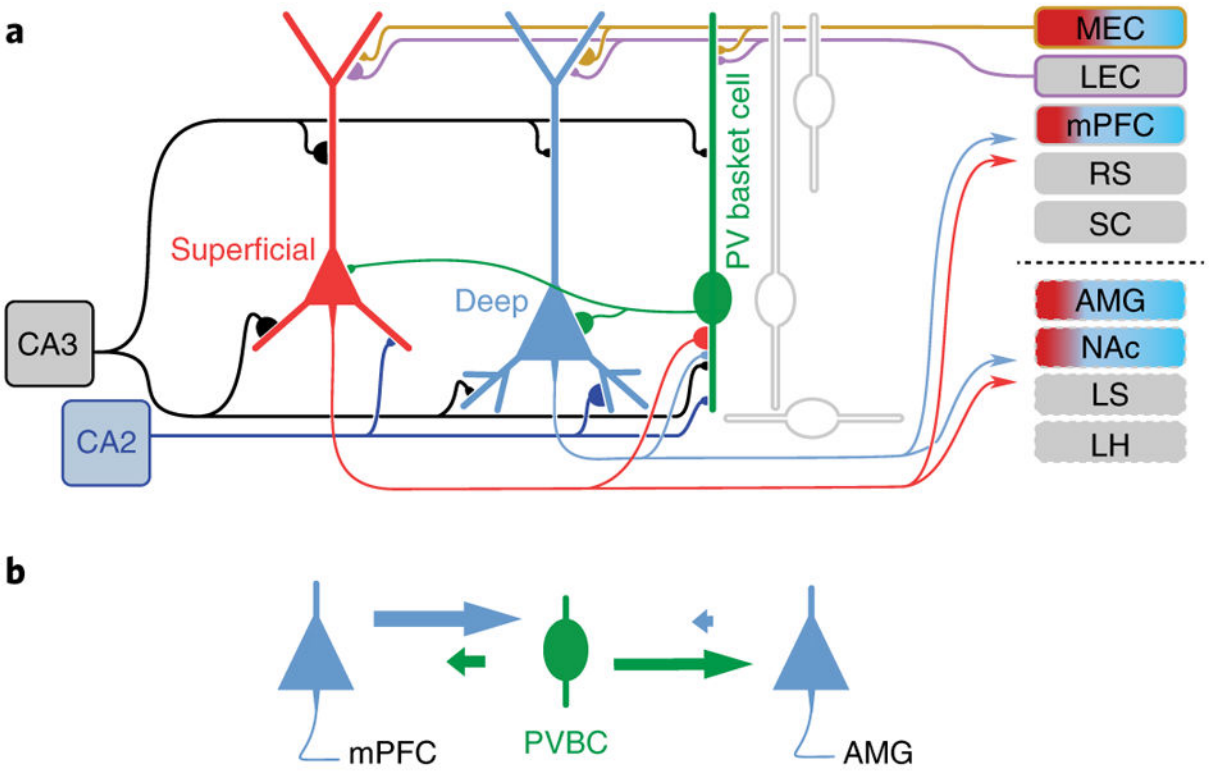

Fig. 3. Biased microcircuits and afferent–efferent connectivity of superficial and deep CA1PCs

a, Deep CA1PCs receive stronger feedforward excitation from MEC and from hippocampal area CA2, while superficial CA1PCs receive stronger excitatory drive from LEC. CA3 Schaffer collateral excitation is stronger in calbindin-positive, superficially located CA1PCs. Note that proximodistal differences in cortical innervation between radial sublayers have also been reported[93,94] (not shown). PVBCs (green) provide stronger perisomatic inhibition onto deep CA1PCs and receive stronger excitation from superficial CA1PCs. Despite the stronger innervation of deep CA1PCs by area CA2, which is important for SPWR initiation[126], deep CA1PCs participate less reliably in SWPRs compared to their superficial counterparts[81,82]. One possible explanation is that CA2PCs may also recruit feedforward inhibition via PVBCs, which can in turn preferentially suppress deep CA1PCs during SPWRs. Biased microcircuit connectivity of other GABAergic interneuron types remains to be determined (open gray symbols). Among these, the second major basket cell class that provides perisomatic innervation to PCs, the regular-spiking cholecystokinin-positive (CCK) basket cells, did not show a preference for either the deep or superficial CA1PCs in mice[43], although they appeared to provide stronger innervation to superficial PCs in rats[82]. Superficial and deep sublayers provide output both to cortical and subcortical (divided by horizontal dashed line) target areas. mPFC, medial prefrontal cortex; RS, retrosplenial cortex; SC, subicular complex; AMG, amygdala; NAc, nucleus accumbens; LS, lateral septum; LH, lateral hypothalamus. For some of these efferent projections, the soma locations of CA1PCs have been mapped, showing unbiased (for example, MEC) or deep-biased (for example, mPFC) localization of projection neurons. For other cortical and subcortical targets (gray), the precise sublayer distribution remains to be determined. **b**, Schematic

representation of the biased, nonuniform interaction between AMG-projecting and mPFC-projecting CA1PCs via PVBCs. Adapted from ref. [43]. Deep AMG-projecting CA1PCs receive inhibitory inputs three times larger compared to neighboring deep-layer mPFC-projecting CA1PCs. In turn, the differentially projecting CA1PCs from the same (deep) layer provide highly biased innervation to PVBCs, so that the CA1PC population that receives less basket cell inhibition provides stronger excitation of these interneurons. The net result of this microcircuit organization could be that discharges by the mPFC-projecting deep CA1PCs will preferentially enhance the inhibitory drive onto the AMG-projecting cells, a feature that is broadly consistent with the differential activity patterns during fear extinction[136].

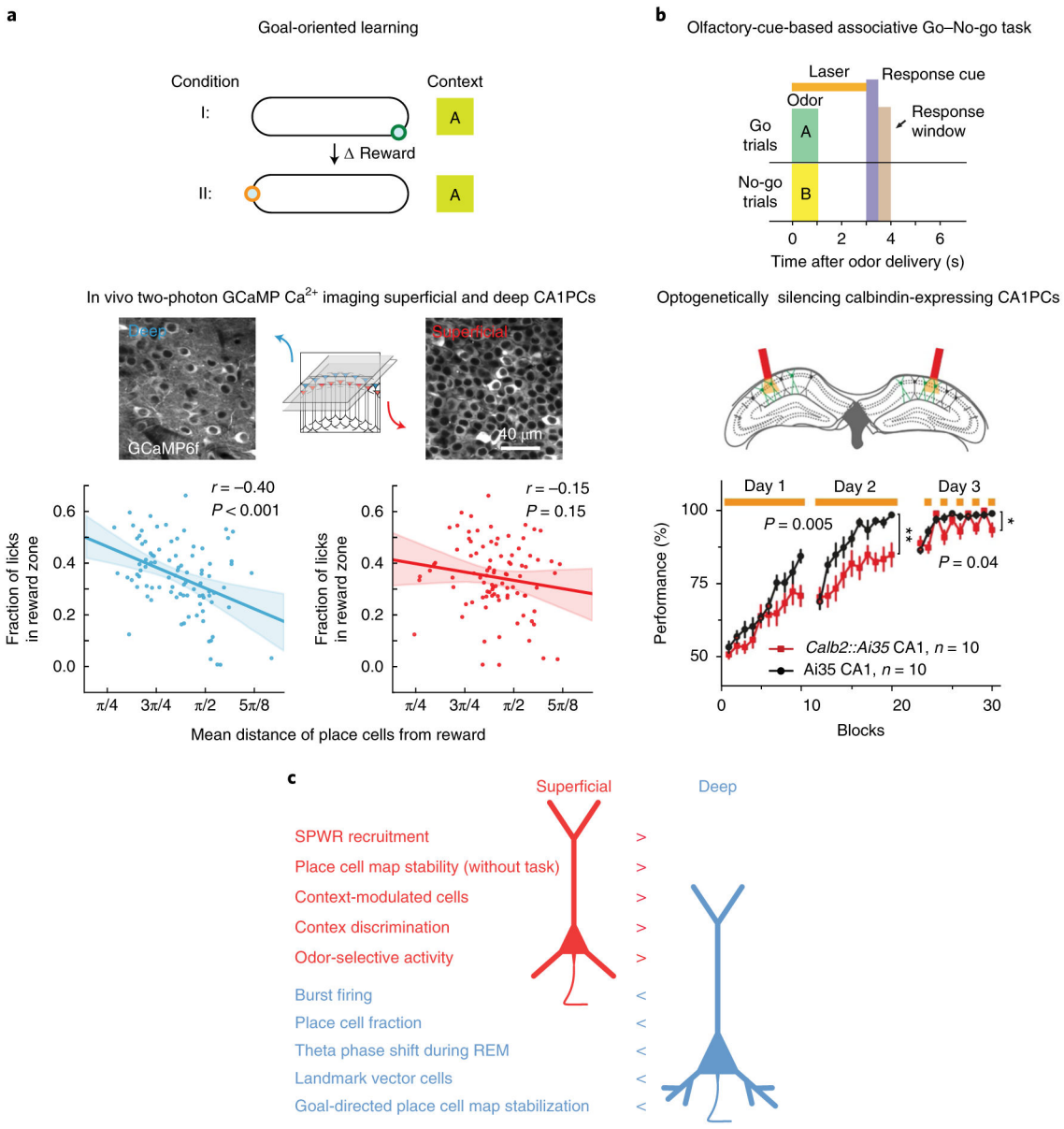

Fig. 4. Differential behavioral functions of radially defined CA1PCs subpopulations

a, Two-photon Ca^{2+} imaging of superficial and deep sublayers during a head-fixed goal-oriented learning task in mice. Top: schematic of the goal-oriented learning task. Head-fixed mice searched for an unmarked reward zone by running on a cue-rich circular treadmill belt, and water rewards were administered only when the mice licked operantly within the goal zone (circled). At the end of Condition I, the reward was moved to a new location of the belt, and the experiment was repeated (Condition II). The same multisensory context (A) was maintained in both conditions. Middle: simultaneous two-photon imaging of Ca^{2+} sensor GCaMP6f in deep and superficial sublayers of dorsal CA1 using a piezoelectric crystal. Time-averaged image sequences from a representative recording session. Planes were separated by 25 μm. Bottom: fraction of licks in reward zone, the behavioral output measure of learning, plotted against the mean distance of deep (left) and superficial (right) place cells

relative to the reward. Individual points represent single recording sessions. Dashed line indicates the linear fit, with the 95% confidence interval shaded. A significant relationship was observed between learning performance and mean distance of place cells in the deep sublayer, but not in the superficial sublayer, indicating that goal-directed reorganization ('reward zone enrichment') of deep place cell maps is predictive of learning performance. Adapted from ref. [85], Cell Press **b**, Top: model of the olfactory cue-based associative Go–No-go task. Middle: schematic of bilateral optogenetic silencing of calbindin-expressing (green) CA1PCs (in *Calb2-IRES-Cre::Ai35* mice) in the dorsal hippocampus. Bottom: optogenetically suppressing activities of calbindin-expressing CA1PCs impairs associative learning. Adapted from ref. [94], Nature Publishing Group **c**, Comparison of some in vivo physiological properties of superficial and deep CA1PCs.