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Current Opinion in Neurobiology

A local circuit-basis for spatial navigation and memory processes in hippocampal area CA1

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Abstract

The hippocampus is a multi-stage neural circuit that is critical for memory formation. Its distinct anatomy has long inspired theories that rely on local interactions between neurons within each subregion in order to perform serial operations important for memory encoding and storage. These local computations have received less attention in CA1 area, the primary output node of the hippocampus, where excitatory neurons are thought to be only very sparsely interconnected. However, recent findings have demonstrated the power of local circuitry in CA1, with evidence for strong functional interactions among excitatory neurons, regulation by diverse inhibitory microcircuits, and novel plasticity rules that can profoundly reshape the hippocampal ensemble code. Here we review how these properties expand the dynamical repertoire of CA1 beyond the confines of feedforward processing, and what implications they have for hippocampo-cortical functions in memory formation.

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Current Opinion in Neurobiology 2023, **79**:102701

This review comes from a themed issue on **Neurobiology of Learning and Plasticity 2023**

Edited by **Muming Poo** and **Thomas John McHugh**

For complete overview of the section, please refer the article collection - Neurobiology of Learning and Plasticity 2023

Available online 4 March 2023

https://doi.org/10.1016/j.conb.2023.102701

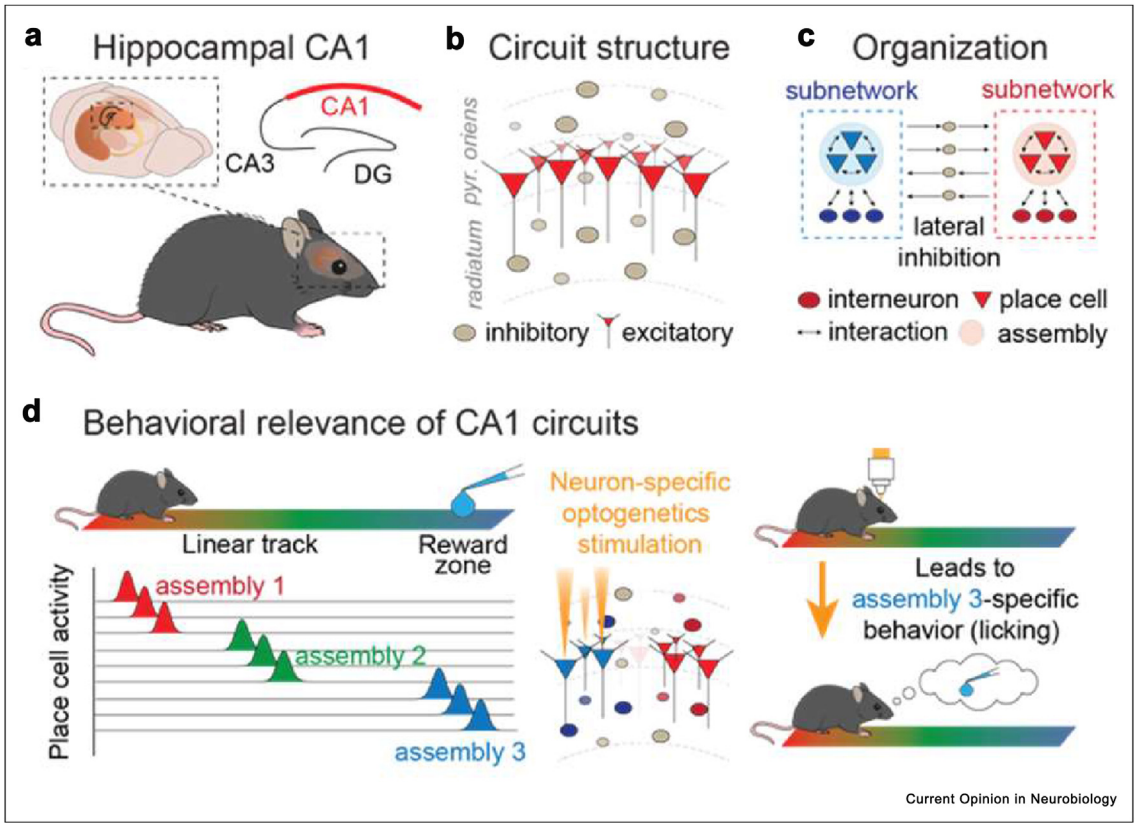
Blurb: Local circuits actively shape the functional organization of hippocampal area CA1 and its computational role in memory formation, properties that have now been measured with increasing fidelity *in vivo* through innovations in large-scale population recordings and precise optogenetic interventions.

Introduction

Deciphering the link between the physical and dynamical organization of neural circuits is critical for understanding the function of individual brain regions, and for how those functions may drive behavior. The hippocampus plays an important role in the joint processes of learning and memory. Its serially connected regions (Figure 1a) are thought to perform operations enabled by the distinct organization of their local circuits. In the dentate gyrus (DG), the hippocampal input region, excitatory granule cells transform cortical signals into a sparse code that decorrelates similar input patterns [1,2]. This pattern separation is thought to reduce memory interference and to consequently increase memory capacity, enabled by a strong network of recurrent inhibitory circuits that enforce a low coding level and promote competition between granule cells [3]. Granule cells then project to CA3, where prominent recurrent connections between excitatory pyramidal neurons are believed to support attractor dynamics that can retrieve memory patterns from incomplete cues [4] ("pattern completion"). Information from CA3 is then conveyed to CA1, the canonical output node of the hippocampus and its interface with the rest of the brain. Unlike in CA3, anatomical studies have found only sparse connectivity between the excitatory pyramidal cells of CA1 [5] (10-fold lower than in CA3, and 100-fold lower than in sensory cortices). Theorists have subsequently ascribed various roles to CA1 based on feedforward characteristics, such as increasing the coding level or information content of recalled CA3 patterns [6], or performing comparative actions [7,8] such as novelty detection [9].

However, new experimental approaches and computational insights have enabled recent work that challenges this limited view of CA1 function. We hypothesize that CA1 circuits are ideally positioned to extract memory patterns from the CA3 storage site at the cellular level, by comparing CA3 signals to current sensory features provided by direct entorhinal inputs, and to subsequently amplify those patterns locally at the circuit-level to form behaviorally-relevant cell assemblies that can interact and influence downstream circuits. Here we review the growing evidence for CA1 performing these

Figure 1



a. Anatomy of the mammalian hippocampus. **b.** Hippocampal region CA1 is organized into several layers (stratum oriens, pyramidale, radiatum/lacunosum) populated by excitatory pyramidal cells and inhibitory interneurons. **c.** Excitatory and inhibitory interneurons are specifically connected to form cell assemblies that interact through lateral inhibition. **d.** Hippocampal CA1 assemblies carry behavioral functionality.

operations. We discuss how local CA1 circuits may intrinsically support the formation of cell assemblies, manifesting as strong functional interactions (through both excitatory and indirect inhibitory connectivity motifs, regulated mono/poly-synaptically or through gap junctions) between excitatory neurons. These dynamics are extensively regulated by numerous local circuit GABAergic interneurons [10], whose actions are now being delineated in the behaving animal (Figure 1b). In conjunction with novel plasticity mechanisms in CA1 [11] acting as comparative detectors of multiple input pathway activity, these circuit features have the potential to rapidly reshape the structure of hippocampal output, impacting downstream processing and, ultimately, behavior.

Understanding CA1 function by probing local circuit organization

Hippocampal circuits are often examined through the prism of spatial behaviors in rodents. During exploration, excitatory neurons in the hippocampus are selectively active at specific locations along the animal's trajectory. Populations of these 'place cells' collectively depict the entire environment, forming representations of ongoing experience that are thought to support spatial learning and navigation [12] and more generally to form a substrate for episodic memory [13]. These responses have been studied extensively in dorsal CA1, whose anatomical position is most amenable to both cellular- and network-level recordings in the hippocampus during behavior (Figure 1a). Recent work has advanced our understanding of how representations form in CA1, how circuit elements interact with one another, and of the ways that CA1 activity may be functionally relevant for memory-guided behavior. These studies highlight the fact that local circuits in CA1 provide an important constraint on activity dynamics at the level of both single neuron and population responses.

Local network interactions are often described within the framework of "cell assemblies" (Figure 1c), groups of neurons that exhibit coordinated activity and which have long been thought to underlie many cognitive processes [14]. In the hippocampus, cell assemblies are believed to be the building blocks needed to encode and retrieve memories [15,16]. Co-activity in these

assemblies can emerge by synchronization of input patterns [17–19], or by more local interactions between circuit elements [20,21]. Since CA1 lacks strong recurrent collaterals, it has been assumed that the coordination between its excitatory neurons is inherited from upstream circuits. However, it is increasingly clear that this view is incomplete, and recent experiments combining recordings of CA1 place cells with optogenetic perturbations of local circuits provided strong evidence that local operations in CA1 actively shape neural tuning [22], population coordination, and behavior. Focal light activation of pyramidal cells using micro-LED in mice navigating a linear track led to robust effects across the population, such as persistent firing rate changes and scrambling of existing place cell representations (termed remapping [23]). Remapping was not specific to the stimulated location, as place cells did not necessarily appear or disappear around that area, but rather unveiled preexisting dynamics [24], such as weak firing rate already present at the location of what would later become the spatial receptive field of the neuron. These findings show that local interactions between place cells exist beyond those inherited from their inputs and that individual neurons in CA1 do not operate as independent coding units. Another study used an all-optical system to functionally identify pyramidal neurons based on their spatial tuning and activate these neurons using targeted two-photon optogenetic stimulation. It demonstrated that the co-activation of as few as ~15 CA1 pyramidal cells with nearby place fields is sufficient to modify animals' spatial behavior [25] (Figure 1d), potentially due to functional excitatory interactions between CA1 pyramidal neurons that could amplify the responses. In these two studies, light-assisted activation of pyramidal cells did not specifically induce the creation of new, stable place fields in the targeted neurons, likely due to the low titer of power used to limit or prevent activating non-targeted neurons. Nevertheless, these results suggest that functional interactions between neurons could amplify the effect of stimulation throughout CA1 networks to the extent that it produces a behavioral response. This interaction may be enabled by broadly-connected interneurons. For example, in sensory cortices, large behavioral responses were achieved when manipulating putative interneurons, whose lateral connectivity allows them to effectively amplify perturbation effects throughout a network [26]. Consequently, a large body of work has recently delved deeper into the interactions between excitatory and inhibitory neurons [27,28].

CA1 has been a historical hotbed for the discovery of new interneuron subtypes [29]. Inhibitory interneurons are far less numerous than their excitatory counterparts, which has hindered experimental access in the past. New imaging techniques are overcoming these challenges and now allow for measurement of subtype-specific impacts of inhibitory circuits on hippocampal coding [30–34]. Recent studies have demonstrated that interneurons exert many circuit-level controls on CA1 activity, such as tuning the size of excitatory ensembles [35,36], coordinating population responses [37,38], and maintaining a balance of multiple input streams [39]. While inhibitory interneurons in CA1 have long been appreciated for their control over the fine-timing of excitatory spike patterns [40], they have also recently been implicated in shaping the rate code of place cells [41,42]. One recent study examined the functional interactions between place cells and their synaptically-connected interneurons, and showed that inhibition can stabilize the location of place fields after they form [41]. It also demonstrated that dynamic and plastic interactions between inhibitory and excitatory neurons can amplify spatial representations from single neurons to multi-neuronal assemblies, a scale relevant for behavior (Figure 1c).

While principal neurons and interneurons appear to be non-randomly connected, it is unknown whether this organization is achieved with learning by experience-dependent structural changes, or if it is a deterministic feature of the circuit. Earlier studies pointed towards the latter scenario, and demonstrated that intricate architectures that originate during development [43,44]. Furthermore, anatomical and lineage analysis in CA1 showed common inhibitory synaptic inputs regulating the synchronous synaptic activity between clonally-related pyramidal cells [45]. In addition, inhibitory "hub" neurons with widespread axonal arborization were found to orchestrate network synchrony during the development of hippocampal networks, and they maintain a powerful impact on CA1 ensembles' synchronization throughout adulthood [46–48]. Consistent with this idea, the emergence of functional representations and oscillatory signatures in CA1 appears to be independent, to some extent, of experience, as it develops gradually during early postnatal weeks [49–51].

Single-cell plasticity under local circuit control promotes rapid formation and transformation of CA1 ensemble code

Clearly, CA1 activity is not a simple function of its inputs. Rather, afferent information is actively transformed by local circuits, which likely structure cell assemblies that drive behaviors [25,36]. Our understanding of these processes often derives from studies of animals in familiar environments or behavioral tasks, but CA1 is a highly plastic circuit. It is equally important to understand the role that these local circuit motifs play during learning in new experiences. This is particularly critical given the unique and powerful plasticity rules that have recently been discovered through recordings of CA1 pyramidal neurons, which can rapidly and dramatically alter the feature tuning of these neurons. Here we discuss how local network interactions and cellular plasticity rules can interact to powerfully

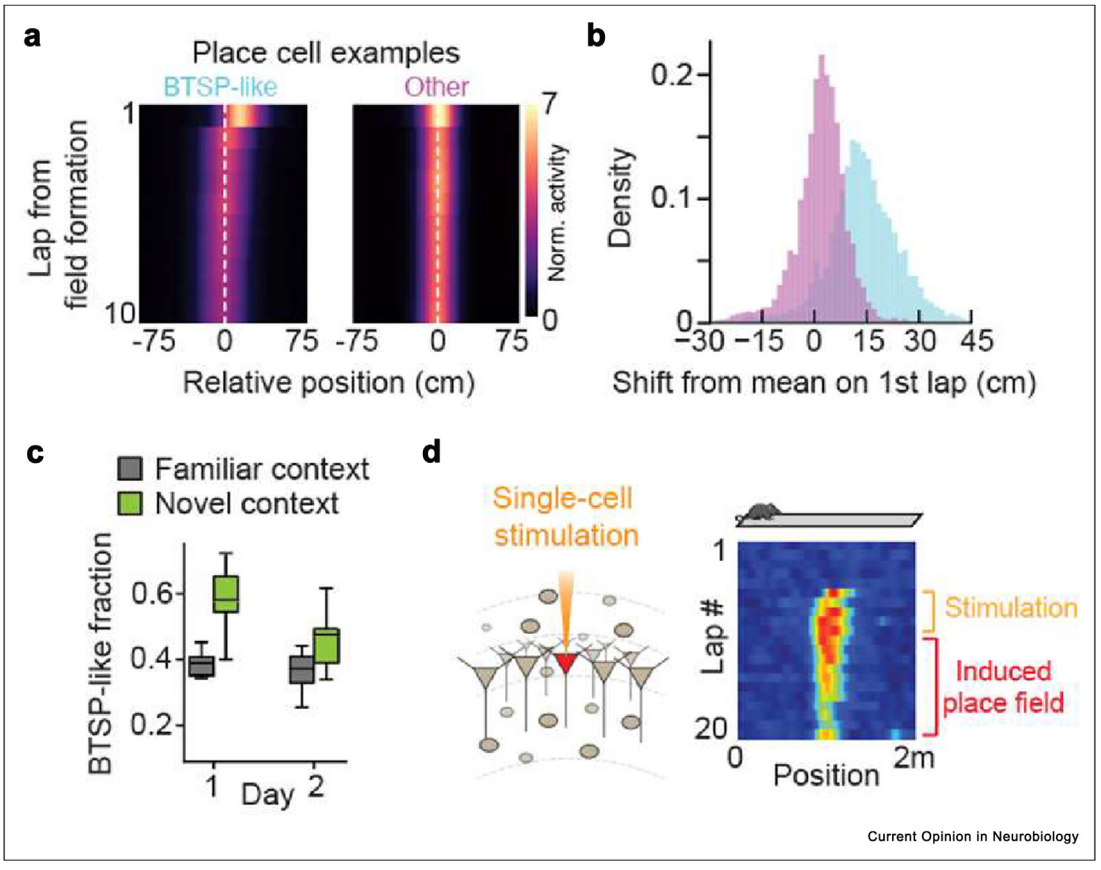
reshape ensemble coding in CA1 during learning and ultimately influence behavior.

Most excitatory inputs on a CA1 pyramidal neuron originate from CA3 and from layer 3 neurons of the entorhinal cortex (EC). These inputs target different dendritic compartments [52]. Electrophysiological work *in vitro* has shown that the temporal overlap of these pathway activations can generate large plateau potentials that produce widespread calcium influx into the cell and long-term synaptic potentiation [53]. In a pair of landmark studies using whole-cell recordings in awake behaving mice, it was shown that plateau potentials are sufficient for place field formation, and that place fields can be synthetically "induced" at arbitrary locations by artificially triggering a plateau potential via current injection [54,55]. Strikingly, the plasticity rule inferred from this process was shown to potentiate inputs that are active within a seconds-long window around the time of the plateau potential [54]. In that regard, this "behavioral-timescale synaptic plasticity" (BTSP) appears different from traditional spike time-dependent plasticity rules [56] (Figure 2a).

Complementary experiments have concentrated on the dendritic mechanisms at play during place field formation and maintenance. Evidence suggests that localized activity in individual dendritic branches predicts the location of future place fields [57]. Furthermore, dendritic activity across the arbor of existing place cells was found to be tightly linked to the stability and precision of the place field [58], and may reflect co-activation of spatially clustered synaptic inputs [59]. These dendritic mechanisms are thought to operate gradually over the course of many place field traversals, in stark contrast with plateau-mediated field formation, which produces rapid, cell-wide changes in synaptic potentiation (Figure 2b). Relatedly, a recent study of CA1 pyramidal cells found that high levels of dendritic co-activity during sharp-wave ripple events can promote the stabilization of spatial tuning during subsequent exploration [60].

It is possible that these two plasticity mechanisms are differentially recruited for distinct behavioral demands. For instance, initial representations of new environments may be rapidly encoded to support the formation of context-specific memories [61], which may then be

Figure 2



a. Field location as a function of lap traversal for two representative place cells. A signature of BTSP-like mechanisms is the field's backward shift after formation (left). **b.** On the first lap of field formation, place activity can be tens of centimeters ahead of where the field will eventually stabilize. **c.** BTSP-like place fields are more prevalent upon exposure to novel contexts, and decay with experience. **d.** Hippocampal place cells can be optically induced by optogenetics stimulation at any given location, when the density of stimulated neurons is extremely sparse.

subsequently refined by slower processes with further experience [62]. A dynamic learning rate would be highly valuable for CA1, as it could support the fast and selective construction of novel representations to support adaptive behavior, for example, by memorizing a rewarded location in a new environment [36]. Indeed, a recent study presented strong evidence that place field formation in novel environments is largely consistent with plateau-mediated plasticity mechanisms, and that the probability of these events decays with familiarity [61] (Figure 2c). Similar effects have also been seen in place fields located near rewarded locations when animals experience a new spatial reward learning task [63], which could reflect a general tendency to recruit rapid plasticity mechanisms during novel or salient events. Given that BTSP induces a large reconfiguration of a cell's synaptic weight profile, it is possible that these events could destabilize network representations over time as they overwrite prior memory traces. This is kept in check likely by the strong regulation of BTSP induction by local inhibition [36] (see paragraph below) but it is possible very salient events or large-scale artificial induction BTSP could strongly impact existing representations of related memories, interference effects that can be measured in future experiments. The presence of rapid mechanisms like BTSP though may also contribute to the highly labile nature of hippocampal representations in general, which are known to drift over relatively fast timescales [64].

This experience-dependent regulation of plasticity rules might arise from the regulation of CA1 circuits by modulatory inputs originating outside of the hippocampus. For instance, subcortical cholinergic neuromodulation can promote plasticity of dendritic excitability in CA1 pyramidal cells [65], and the activity of catecholaminergic projections from the locus coeruleus was shown to modulate the density of place fields near rewarded locations [66]. Neuromodulation is traditionally associated with arousal [67] and novelty detection [68] in the hippocampus, and thus could be at play during the formation of plateau potentials and rapid learning that is observed upon exposure to new environments [61]. Finally, subcellular mechanisms can shape place field specificity and maintenance, such as intracellular processes that mediate calcium release and underly dendritic computations [69].

Locally, inhibitory circuits exert myriad effects at the cellular and network level [27,31] that could selectively open windows of heightened synaptic plasticity in active dendrites [57]. Recent work has also shown that local inhibitory tone can critically regulate place field formation. Using a novel all-optical approach, recent studies have optogenetically induced place fields while simultaneously recording CA1 networks via calcium imaging [36,41,69] (Figure 2d). This "optogenetic place field induction" fails when tens of neurons are stimulated simultaneously [36], which suggests that stimulation of a larger ensemble drives disproportionately elevated recruitment of local inhibition, thus suppressing the dendritic excitation needed to effectively potentiate inputs [35,70]. Induction of a larger population could be achieved by pharmacogenetic suppression of local inhibition [36], and those results are consistent with other experiments that stimulated populations of excitatory neurons in CA1 but failed to induce spatially restricted remapping [22,24,25]. Given prior studies that demonstrate changing inhibitory tone during new experiences [31], connections likely exist between inhibitory networks and observed changes in place field formation during novelty and reward learning [61,71]. However, additional experiments will be needed to mechanistically connect these processes. Thus, it will be important to continue to explore and broadly apply novel techniques such as targeted optogenetic and molecular manipulations of neuronal plasticity underlying place field formation, which can be harnessed to modify hippocampal representations via targeted plasticity and therefore to study the consequences on spatial memory and behavior.

Implication for interactions with other brain regions

The hippocampus is a central component of the brain's episodic memory system, and continuously interacts with other circuits involved in executive functions, long-term memory storage, and regulation of internal states. While the mechanisms of circuit communication between brain regions is an open question [72,73], the organization of local CA1 circuits may provide clues to the consequences of hippocampal outputs to downstream processes.

Temporal coordination is a candidate mechanism for enabling dialogues between hippocampal and extrahippocampal neural populations. Since neurons integrate inputs over short periods of time, the synchronization of activity in presynaptic neurons is more likely to evoke action potentials in a downstream target. Ensembles of place cells in CA1 with shared spatial selectivity are thus well-positioned to transmit information to an external reader. Local circuits in CA1 can facilitate the development of cell assemblies with shared selectivity, such that an individual place cell can functionally recruit between 10 and 20 pyramidal neurons to represent the same spatial location [41]. It is possible that neurons with shared tuning are not only locally coupled in CA1, but also share common synaptic targets in downstream regions. While such connectivity requires future investigation, the formation of local subnetworks may originate during development [40,43] which could also underlie their wiring and integration with long-range circuits. This organization would be beneficial, given that it is the coordinated activation of

groups of correlated cells, rather than individual place cells, that can drive behavior such as movement toward a physical location, indicating that cells must work in concert to influence downstream circuits and behavioral output [25,36].

Within this framework, local CA1 circuits could also play a role in segregating information processing and routing these processes to specific downstream regions. Functional heterogeneity along anatomical axes has already been shown to shape CA1 circuit organization, enabling parallel information-processing functions [74—77]. Previous studies have shown that local inhibitory microcircuits, especially those composed of parvalbumin-expressing basket cells, exert selective actions not only to pyramidal neurons from specific anatomical compartments, but also to those with specialized long-range projection targets [78]. Therefore, local circuits may be integral to larger, multi-regional circuit organizations, one of which might allow CA1 to route distinct behavior- and task-related information to different brain regions. Although most studies along this line of reasoning have focused on projections from the ventral hippocampus [79], dorsal CA1 has been implicated in forming distinct circuits for the encoding and retrieval of fear memories [80].

The CA1-entorhinal cortex (EC) pathway is particularly important, since the EC is both the main input to the hippocampal system and one of its main output targets [52]. It is notable that place cells in the hippocampus arise before grid cells in the EC during the maturation of the CA1-EC system [44], and this directionality carries functional importance throughout adulthood for maintenance of grid pattern periodicity [81]. Although grid cells exist in all strata of the medial EC, they are less prominent in layer 5 [82], which receives the majority of CA1 inputs. Thus, it is unlikely that grid responses result directly from input arriving from converging place cell subnetworks. However, CA1 may constantly interact with the EC through direct and indirect pathways to continuously compare external sensory signals arriving from the cortex with representations stored internally in the hippocampus, allowing for detection of changes in experience structure and subsequently for the updating of representations. Further investigations will be required to test this hypothesis and to deepen knowledge about the microcircuit organization of the EC that conveys and transforms CA1 inputs in EC5 to other layers.

Conclusion

In summary, we have reviewed recent evidence that local circuits endow CA1 with considerable capabilities to support the mnemonic and navigational functions of the hippocampus. The unique plasticity mechanisms allow CA1 pyramidal neurons to rapidly reconfigure and adapt to changing environments or other salient features. These plastic responses are the resulting expression of temporal overlap of pathway activation, in CA3 and EC, thought to carry distinct mnemonic functions.

The cellular-level response is subsequently amplified by local circuit connectivity patterns to generate cell assemblies suitable for driving behavioral output by interacting with downstream circuits in other parts of the brain. The intricate organization of CA1 inhibitory networks, which tightly regulate neuronal feature tuning and the genesis of coordinated responses at the population level, is foundational to these mechanisms.

While navigation has traditionally served as a model system to study hippocampal circuits, the hippocampus is also unquestionably involved with the processing of more classically defined associative memories. Nevertheless, place cell representations in the spatial domain will help reveal general connectivity and plasticity mechanisms that provide the scaffolding for other functions such as episodic and social memory. More generally, a deeper mechanistic understanding of the local circuit determinants of hippocampal activity is of critical importance for health-oriented research, as it may accelerate the development of targeted strategies against memory-related behavioral impairments.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

T.G. is supported by 1K99MH129565 from the National Institute of Mental Health (NIMH). A.L. is supported by R01MH124047 and R01MH124867 from NIMH, and by RF1AG080818 from the National Institute on Aging (NIA).

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