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Hippocampal function in rodents

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Abstract

The hippocampus is crucial for the formation and recall of long-term memories about people, places, objects, and events. Capitalizing on high-resolution microscopy, *in vivo* electrophysiology, and genetic manipulation, recent research in rodents provides evidence for hippocampal ensemble coding on the spatial, episodic, and contextual dimensions. Here we highlight the functional contribution of newly described long-range connections between hippocampus and cortical areas, and the relative impact of inhibitory and excitatory dynamics in generating behaviorally relevant population activity. Our goal is to provide an integrated view of hippocampal circuit function to understand mnemonic computations at the systems and cellular levels that underlie adaptive learned behaviors.

Introduction

Since the 1950s, the hippocampus has been extensively studied in rodents as a powerful circuit model for learning about memory formation [1,2] and spatial navigation [3–6]. Hippocampal circuits have the remarkable ability to process multisensory information streams and collectively encode them as long-term memories. Such processing is crucial in our ability to recognize changing environments and alter our behavior to reflect these contextual changes.

Spatial and episodic memory of people, places, objects, and events is a critical functional output of the hippocampal circuit [1,7–9]. Early lesion studies suggested that the primary role of the hippocampus is the encoding of long-term memories, while the longer-term storage of these memories was believed to rely on cortical areas [10–12].

Episodic memory formation and recall require interactions between dorsal hippocampus with its neighboring entorhinal cortex (EC) [6,13,14] which processes multisensory information. The canonical model of this cortico–hippocampal circuit posits that hippocampus receives multisensory inputs from superficial layers of entorhinal cortex directly to both area CA1 (from Layer III, LIII of EC) and dentate gyrus (DG from Layer II,

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LII of EC). DG routes these sensory inputs via CA3 through Schaffer collateral synapses of the trisynaptic path to CA1 [15,16]. CA1 and subiculum send back processed memory output to the deep layer V of entorhinal cortex (Figure 1) as well as communicate with various other brain structures. In the last few years several new long-range circuit connections have been mapped to and from the hippocampus [17,18,19^{***},20^{***},21^{**},22^{**}]. These recent studies capitalizing on cutting edge circuit-specific imaging, electrophysiology, and optogenetic manipulations in rodent models reveal that hippocampal dependent acquisition, consolidation, and recall of memories require functional interactions with areas underlying sensory, executive, emotional, and reward processing.

In this review, we highlight how the organization and functional dynamics of hippocampal circuitry support hippocampal dependent functions and behavior such as learning, spatial navigation, and episodic memory. New-found interactions between cortico–hippocampal circuits and intra-hippocampal microcircuits can powerfully gate information flow to modulate the patterns and representation of sensory information in hippocampal ensembles.

Hippocampal ensembles—encoding episodic, spatial and contextual information

During episodic memory formation, the hippocampus integrates sensory, spatial, and temporal information through long-range and local circuit interactions. Representations of space, time, and context emerge as sequential patterns of activity in neuronal ensembles (Figure 2). Here, we define neuronal ensembles as groups of neurons that are co-active during behavior and reflect a functional property of the circuit. Manipulation of the ensemble activity leads to disruption of behavior.

Internally generated sequences

Internally generated sequences have originally been described as groups of neurons in dorsal CA1 with continually changing activity reflecting a behavioral function that is distinct from that driven by environmentally-controlled activity [23^{***}]. These sequences were demonstrated to exist during a two-arm alternation memory task where a rat has to alternate between running through the left and right arms of a figure eight maze to receive a reward while stopping to run on a wheel between transitions [23^{***},24^{**},25] (Figure 2). The sequential activity of neurons during the wheel-run delay phase where environmental cues remain fixed compared to those during maze-run was unrelated. Such task-phase specific cells were thereafter referred to as episodic cells to reflect their time-dependent and task-dependent firing in the absence of environmental changes—unlike place cells which depend on environmental inputs. Episodic cells (also referred to as time cells [26]) show theta oscillation dependence, overlap with place cells during spatial navigation [23^{***},24^{**}], and require input from the medial septum [27].

Episodic sequences in dorsal CA1 have also been observed in other memory-dependent tasks such as when a rat must make an object–odor association following a delay period to receive a reward [28]. During the delay period, neurons fire sequentially on repeated trials at distinct time points to ‘bridge’ the gap between key events such as object and odor

presentation. Furthermore, episodic (time) cells have been shown to integrate the distance traveled by the animal with different cells reflecting differing influence by distance integration when the speed at which the animal runs is varied [29].

In contrast to task-specific episodic sequences, sequential activity of hippocampal pyramidal neurons has also been imaged during self-guided motion in the absence of external memory demands or spatio-temporal constraints [30]. In these experiments, head-restrained mice were allowed to spontaneously run on a track. The sequential activation of neurons reflected the distance traveled by the animal such that only multiples of a fixed distance metric were represented as opposed to an absolute, continuous distance metric. Interestingly, some cells captured the temporal dynamics of the running epochs as described in the previous study above [29].

Spatially-dependent ensemble sequences

Research into place cells, the spatially-dependent ensembles in the hippocampus began with the first *in vivo* recording of hippocampal place cells in rats in 1971 [3]. Subsequent decades of work continued to expand on these findings and led to the discovery of phase precession [31,32] in hippocampal place cells and grid cells in the medial entorhinal cortex (MEC) [33,34]. The 2014 Nobel Prize in Physiology and Medicine recognized the importance of the discovery of place cells and grid cells. Place cells represent an ensemble of pyramidal neurons that form a cognitive map of space by increasing their activity at defined spatial locations of the animal referred to as place fields [3,35^{**},36,37], (Figure 2). Place cell activity is also organized temporally by theta oscillations and is dynamic in relation to theta phase. Individual place cells fire at progressively earlier phases of the theta cycle as the animal enters and traverses that cell's place field—a phenomenon described as phase precession [32,38^{*},39]. While the mechanism of phase precession is unclear, it may involve the recruitment of relatively faster firing neurons [38^{*}].

In animals running across space, strong theta oscillatory activity has been recorded in the hippocampus and is considered important for spatial navigation and long-term spatial memory acquisition. Theta sequences have also been demonstrated to predict spatial trajectory during reward-directed behavior [40]. In a reward-oriented spatial navigation task, place cells firing along the goal-directed trajectories were found to fire ahead of their place fields suggesting that they may participate in predictive behavior [40]. Theta-modulated sequential ensembles appear to be a scaffold for organizing neural activity supporting memory, spatial, and reward oriented behaviors.

The mechanism for generation of spatially tuned ensembles is a long-standing question in the field. While it is traditionally believed that MEC grid cells convey spatial information for the formation and stability of hippocampal place cells, experimental data suggests otherwise. Lesions to the MEC have a surprisingly minor impact on place fields [41^{**}], yet can disrupt phase precession of place cell ensembles in the hippocampus [42]. *In vivo* two-photon calcium imaging as well as intracellular recordings from place cells of the dorsal hippocampal CA1 area in head-fixed animals navigating a virtual environment have further confirmed previous electrophysiological findings regarding place cells [43^{**},44^{***}]. These studies not only offer subcellular resolution but also greater control of behavior and reveal

how spatially modulated activity is reflected in subthreshold membrane properties and intracellular Ca^{2+} across identified neuronal populations.

Near simultaneous two-plane imaging of the deep and superficial layers of CA1 pyramidal neurons reveals a functional separation whereby the superficial ensembles encode more stable place fields independent of behavioral demands [45]. Similar volumetric imaging of the CA1 pyramidal neuron soma and basal dendrites suggests that NMDAR-dependent dendritic Ca^{2+} spikes may precede spatially tuned somatic output to act as a predictive signal for place cell activity [46**]. Support for this idea comes from a series of *in vivo* intracellular recordings-based studies that show membrane potential ramps and dendritic plateau potentials (another way of describing dendritic spikes) are necessary for the prototypical place cell burst firing as a rat or mouse enters the place field of that cell [47***,48**]. These are similar to the membrane deflections observed in grid cells in MEC [49]. Furthermore, artificial somatic current injections of depolarizing steps [50**] as well as those mimicking propagated dendritic spike waveform are capable of converting ‘silent’ neurons into place cells tuned to the location of current injection [47***].

While the majority of research on place cell ensembles has been carried out in dorsal CA1, multi-unit recordings from neighboring area CA2 and CA3 also revealed place cell ensembles during spatial navigation [37,51–53]. Interestingly, place cells in CA2 had broader place fields relative to CA1 and CA3 place cells [54]. Functional separation of CA1 and CA2 has long been debated, but recent molecular, physiological and connectivity characterization [55–60] of CA2 pyramidal neurons establish CA2 as distinct from CA1. The recent discovery of neurons that show high activity during slow wave sleep and immobility states [61] – unlike sharp-wave ripple modulated CA1 place cells – suggests that computations in CA2 may reflect information about the animal’s current location in the absence of locomotion. CA2 has also been shown to be important for non-spatial function such as social memory [58] and shows a high density of oxytocin and vasopressin neuromodulatory receptors [59] making it an attractive candidate for future research.

Contextual ensembles

Studies above demonstrated that the hippocampus can represent spatial and episodic information in defined neuronal ensembles. However, whether hippocampal ensembles can also represent behaviorally-relevant contextual information was not well understood until recent studies, which optogenetically manipulated context-activated ensembles and revealed their importance in contextual learning [62,63]. Transgenically or virally driven channelrhodopsin (ChR2) expression under the control of activity-dependent immediate early genes such as c-Fos or Arc promoters enabled tagging of ‘co-active’ or functionally linked neuronal ensembles during distinct phases of behavior, such as learning and recall [62]. Labeled ensembles were subsequently reactivated with targeted photostimulation.

Ensembles in areas CA3 and DG have been shown to be involved in encoding of contextual representations [64]. Photostimulation of an optogenetically-activated DG ensemble in a fear context is sufficient for induction of fear memory recall in a neutral context [63]. Similarly, memory ensembles have also been reported in neighboring area CA3 where activation of a sparse ensemble network at highly-correlated nodes was sufficient to induce a fear response

in a neutral context [20***]. Interestingly, activation of these nodal points was driven by a novel group of excitatory projections from the anterior cingulate cortex [20***].

While both CA3 and DG appear to encode contextual representations, their ensemble representations differ. In a cue-mismatch double-rotation experiment where local cues along a circular track are rotated relative to the global reference cues surrounding the track, CA3 ensemble spatial firing fields follow either the local or global cues. This suggests that CA3 functions to maintain a stable representation of the environment in spite of subtle changes, consistent with a pattern completion function [65]. Unlike CA3, the DG shows increasing degradation within the represented ensemble as the mismatch between local and global cues increased, consistent with a pattern separation function [65].

While the cellular mechanisms underlying possible contextual discrimination in the DG are unknown, hyperexcitable newborn granule cells have been suggested to play an important role in this process [64]. Reactivation of memory ensembles is also differentially expressed in DG relative to CA3 such that reactivation in CA3 decreases following remote re-exposure [62].

The stability of memory ensembles as well as their anatomical distribution in the hippocampus is not well understood. Recently, freely-moving micro-endoscopy imaging experiments show that fear learning events in distinct contexts that occur within 5 hours of each other elicit Ca^{2+} activity in significantly overlapping CA1 pyramidal neuron ensembles. However, this overlap is significantly reduced when the fear learning events are separated by 7 days [66] (Figure 2). This suggests that neurons potentiated by previous activity are more likely to be recruited within subsequent memory ensembles. In addition to a temporal component governing ensemble overlap, the size and stability of neural ensembles also appear to be controlled, for example, in the DG by local dendrite targeting inhibitory circuits [67].

Hippocampal circuitry—functional role in ensemble coding and behavior

Long-range excitatory projection inputs

The canonical circuit model describes direct excitatory projections from the medial entorhinal cortex layer III (MEC LIII) that target the distal dendritic compartment of CA1 [68]. In addition, it describes excitatory projections from MEC layer II (LII) stellate cells that target DG and CA3. CA3 then indirectly routes this information to CA1 proximal dendrites through the Schaffer collateral synapses of the trisynaptic pathway.

Silencing of MEC LIII pyramidal neurons with tetanus toxin or optogenetically causes deficits in trace fear learning, but has a smaller effect on long-term spatial and contextual memory learning behavior [68,69]. While silencing of MEC LIII inputs decreases spatially modulated dendritic spikes and theta burst activity in CA1 place cells, CA1 place cell peak firing rate is only slightly reduced [47***,68].

A recent study shows that layer II (LII) MEC and LEC neurons also directly project to CA1. Interestingly, these LII pyramidal neurons (also referred to as island cells due to their

structural organization in relation to LII stellate cells) target predominantly local interneurons that drive feed forward inhibition upon CA1 pyramidal neurons [69]. As a result, they reduce the excitation provided by the MEC LIII pyramidal neuron inputs onto CA1. Optogenetic activation of LII inputs has opposing effects on LIII input activation and consequently decreases population spiking of CA1 pyramidal neurons and impairs trace fear learning [69].

The demonstrated involvement of MEC LII and LIII inputs in temporal association memory as well as the minor impact of their manipulation on long-term spatial memory and place cell activity [47^{***},68,69] is surprising given the canonical view that MEC conveys spatial information to CA1. These effects are significantly smaller compared to more non-specific MEC lesion studies in which place cell fields were partially degraded [41^{**},42,70] and long-term spatial memory was impaired [71]. Thus, excitatory inputs from MEC to CA1 alone cannot account for the formation of place cells [47^{***},68] and the central debate in the field regarding the causal relationship of how grid cells influence place cell activity remains unresolved. A recent review article challenges the long-held belief that grid cells are necessary for place cell formation and maintenance [72]. The authors propose that other cell types such as border cells, head direction cells, and inputs from the lateral entorhinal cortex are involved in place cell formation and that place cell formation is, more generally, driven by sensory inputs from the environment.

The role of excitatory inputs from the lateral entorhinal cortex (LEC), which are believed to carry non-spatial sensory information to the hippocampus, has not been explored with regard to spatial and contextual function. Interestingly, however, *in vivo* recordings from the LEC and MEC show preferential tuning to local sensory cues and distal visual/object cues, respectively, suggesting that place cell activity in the hippocampus may emerge from additional sensory information supplied by the LEC [73]. A recent study demonstrated the significance of long-range inhibitory projections from LEC to CA1 in contextual discrimination and novelty detection suggesting important roles for LEC inputs in shaping hippocampal function (see below). Furthermore, LEC neurons projecting to the hippocampus show prominent odor-selective tuning [74] consistent with previous findings on odor responsiveness in the LEC [75] and increased oscillatory coupling between LEC and the distal part of CA1 during an odor-dependent spatial task [76].

The DG receives strong, direct cortical inputs from LII of the lateral and medial entorhinal cortices and projects this integrated output to CA3. The vast population of DG granule cells shows relatively low excitability and strong feedforward and feedback inhibition giving rise to a highly dissipated and sparse output transformation for the EC spatial and sensory inputs [77]. There is also evidence for weak, but direct excitation, from the entorhinal cortex to area CA3 [78], although the behavioral function of these direct EC inputs to DG and CA3 is unknown.

Excitatory inputs from the anterior cingulate cortex (ACC) to dorsal CA3 and CA1 have recently been described [20^{***}]. Optogenetic activation of these inputs specifically to CA3 transiently increases freezing behavior during photostimulation in a neutral context that is otherwise non-aversive to control animals. Additionally, silencing of these inputs with

halorhodopsin during the fear memory recall phase decreases freezing behavior. This ACC-CA3 excitatory pathway facilitates the recruitment a sparse group of CA3 pyramidal neurons that are highly synchronized in their population activity specifically to the fear memory associated context after training.

In contrast to CA3, CA2 is strongly excited by direct inputs from EC LII [56–58] and weakly by CA3 [55]. Recent *in vivo* studies with multiunit recordings and Arc catFISH imaging show that direct EC sensory inputs can alter spatially tuned cells in CA2 independent of CA3 and DG input [79,80]. These results have led to an idea in the field that CA2 acts as the conduit for entorhinal cortical information arriving in CA1. However, it is unknown how silencing of CA2 may impact CA1 output or function.

Long-range inhibitory projection inputs

In addition to direct excitatory inputs, two recent studies have shown that both LEC [19^{***}] and MEC [81^{**}] send direct long-range inhibitory projections (LRIP) to CA1. Both of these studies [19^{***},81^{**}] demonstrate that the inhibitory inputs predominantly target local GABAergic interneurons in the hippocampus. By suppressing local feed forward inhibition to the distal dendrites of CA1 pyramidal neurons (Figure 3), LRIPs facilitate firing of dendritic spikes in these neurons [19^{***}]. Silencing of LRIPs reduces excitation and Ca²⁺ spikes in dendrites as well as prevents the induction input timing dependent plasticity at the soma (ITDP) [82,83].

Interestingly, two-photon calcium imaging in CA1 of the LEC LRIP axon terminals shows presynaptic Ca²⁺ responses evoked by sensory cues (such as light and tone) that are potentiated when such neutral cues are paired with aversive (airpuff) or rewarding (water) stimuli [19^{***}]. This finding implies that there are circuit operations occurring in EC that add contextual value to sensory signals being sent to the hippocampus and suggests LEC involvement in contextual associational learning that may depend on punishment or reward.

Furthermore, pharmacogenetic inactivation of LEC LRIPs during contextual fear learning decreases the ability of mice to discriminate between aversive and neutral contexts [19^{***}]. Additionally, these animals show a lowered discrimination index between novel and familiar objects in a hippocampal-dependent object recognition task. The increased freezing observed in both the conditioned and neutral contexts is indicative of the mice overgeneralizing fear memories. A similar overgeneralization of contextual fear memory is observed when nucleus reuniens inputs from the thalamus, which also target inhibitory neurons and pyramidal neurons in the distal dendritic layer of CA1, are selectively silenced [22^{**}].

Functionally, LRIPs may also modulate CA1 place cell formation and ensemble coding. As mentioned above, recent studies suggest that NMDA-gated dendritic Ca²⁺ spiking and associated plasticity can generate spatially selective CA1 place cells [46^{**},47^{***}]. Furthermore, *in vivo* EEG recordings show that these dendritic spikes which are involved in spatial tuning of place cells require coordinated activity from EC and CA3 [47^{***}]. Likewise, induction of LRIP-mediated dendritic spikes and input-timing dependent plasticity observed in acute slices in CA1 pyramidal neurons requires timed pairing of EC and CA3 inputs

[19***]. A previous study shows that optogenetic silencing of dendrite targeting somatostatin (SOM) interneurons in CA1 strongly increases burst firing of place cells [35**]. Physiological suppression of these dendrite-targeting interneurons by the LRIP could have a powerful effect on place cell burst activity. Therefore, disinhibitory gating of dendritic spikes and burst activity in CA1 pyramidal neurons by LRIPs may underlie the conversion of silent cells into spatially tuned place cells in a context dependent manner (Figure 4). This idea is further supported by the finding that MEC LRIP can modulate theta-related activity in hippocampal acute slices [81**] suggesting a role for these inputs in spatial navigation and memory. Examining the impact of silencing the MEC LRIP on place cell activity could help explain the differing results obtained from MEC lesion studies and pathway-specific silencing of MEC excitatory inputs.

Hippocampal excitatory projection output

The primary output from the hippocampus is from CA1 and subiculum. Classically, CA1 has been important for acquisition and recall of recent (within 24 hours), but not remote memories [84] (weeks to months based on long-term lesion studies). It is now clear, however, that CA1 is also required for remote memory recall [85] as demonstrated by recent temporally precise optogenetic silencing experiments. Transiently silencing CA1 during recall testing weeks after training impairs recall in a contextual fear learning task. Long-term optogenetic silencing of CA1, matching previous lesioning time intervals, interestingly shows intact remote memory recall due to the adaptive recruitment of anterior cingulate cortex [85] and retrosplenial cortex [86] as a long-term compensation mechanism.

The importance of hippocampal output in spatial coding was recently examined by a study that evaluated the impact of transient muscimol-induced silencing of dorsal CA1 on grid cell firing. This study revealed that CA1 inactivation disrupted the hexagonal firing pattern of grid cells [87]. In addition to the loss of grid firing fields, MEC neurons became more tuned to the rat's head direction. This study, in addition to some modeling studies [88,89], proposes that grid cell firing requires excitatory drive from hippocampal place cells and adds another level of complexity to our present understanding of grid and place cell interactions.

While dorsal CA1 is considered more critical for spatial memory and has been extensively studied in this context, the ventral hippocampus is thought to play a greater role in social and emotional memory by virtue of its direct connections with the amygdala, prefrontal cortex, and nucleus accumbens [90–93]. Interestingly, optogenetic silencing of excitatory projections from the ventral hippocampus to the medial prefrontal cortex (mPFC) during the cue-encoding phase, but not retrieval, impairs performance during a spatial working memory task [17].

Furthermore, a recent study demonstrated that information projected from the ventral hippocampus is sorted and packaged in a content-specific and target-specific manner.

This *in vivo* recording study used channelrhodopsin-assisted antidromic stimulation to target ventral CA1 neurons projecting differentially to prefrontal cortex, amygdala, and nucleus accumbens (nAC) during anxiety-related and reward-related behaviors. The largest number

of neurons that showed increased modulation of firing in anxiety-related spatial locations, such as open parts of an elevated maze, were those projecting to the prefrontal cortex [18]. Additionally, neurons tuned to reward locations during goal-directed navigation that showed increased activity projected preferentially to the mPFC and nAC, while those that showed decreased activity projected solely to the nAC.

Conclusion

The sparse nature of memory ensembles is emerging as a striking feature across multiple subregions of the hippocampus and indicates that a small group of active cells are not only sufficient to encode specific features of the internal and external environment, but can also drive recall and generate adaptively learnt behaviors. Although beyond the scope of this review, neuromodulatory input has been also shown to mediate feature selectivity in hippocampal microcircuits [21^{**},94,95]. Increasing experimental evidence suggests that a common mechanism allows hippocampal ensembles to flexibly shift their coding sequences to perform operations related to episodic, spatial, and contextual encoding. Rodent models will continue to serve as a powerful tool in our investigation of hippocampal function.

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Figure 1.

Information flow through the dorsal hippocampal circuit. Excitatory sensory inputs from LIII entorhinal cortex (EC) pyramidal neurons arrive at the distal dendrites of CA1 and CA2 pyramidal neurons in stratum lacunosum moleculare (SLM). EC LII stellate cells send direct inputs to dentate gyrus (DG). DG granule cells, in turn, project strong excitatory inputs to CA3 pyramidal neurons through the mossy fiber tract along with weaker excitatory inputs to CA2. Recurrently connected CA3 pyramidal neurons project to CA1 pyramidal neuron proximal dendrites in stratum radiatum (SR) through Schaffer collaterals (SC) and complete the classical trisynaptic path. CA1 pyramidal neurons provide the major excitatory output of the hippocampus and project back to entorhinal cortex to its deep layer neurons (LV) to complete the EC-hippocampal loop. This projection may be critical for sustaining grid cell firing patterns in medial entorhinal cortex (MEC). Not shown here the output paths of CA2 to cortical areas, CA3 to contralateral hippocampus as well as CA1 output paths to other cortical areas. SO, stratum oriens; SP, stratum pyramidale (cell body layer), SR, stratum radiatum (site of SC synapses), SLM, stratum lacunosum moleculare (site of EC input). Previously described classical excitatory circuits are in black.

New circuits highlighted in this review (numbered, excitatory inputs in blue and inhibitory inputs in red): (1) direct long-range excitatory projections from EC LII pyramidal neurons to CA1 that target local inhibitory neurons and indirectly inhibit CA1 pyramidal neurons – important for trace fear learning [69] (2) long-range inhibitory projections (LRIP) from EC that provide direct inhibition to local inhibitory neurons (red) in CA1 and act as a disinhibitory gate – important for discrimination between salient and neutral contexts as well novel and familiar objects [19***] (3) direct excitatory projections from the anterior cingulate cortex (ACC) to CA3 pyramidal neurons that mediate nodal recruitment of a highly synchronized sparse ensemble in CA3 during recall of contextual fear memories [20***].

Figure 2.

Hippocampal Ensembles. (a) Place cells (A, B, C, D) fire sequentially in CA1 during navigation on a linear track and encode spatial location by firing at designated place fields (faded boxes correspond to the place field of each neuron). (b) Similarly, episodic (time) cells fire sequentially in CA1 when an animal runs at a fixed location in the environment such as on a wheel of a two-arm delayed alternation memory task (lower panel). Such episodic sequences (A → B → C → D, upper panel) have been observed during spontaneous running as well as delay periods in goal directed tasks where the animal has to remember the location from which it entered the maze [23***]. When the delay period is extended, cells at the start (cell A) and end (cell D) of the sequence remain anchored to the temporal boundaries, while new cells may appear in the middle of the episodic sequences to fill in the contiguous gaps in time [96]. (c) Contextual memory ensembles acquired with micro-endoscopic imaging of GCaMP6-expressing CA1 pyramidal neurons in freely moving mice during contextual fear conditioning [66]. The association of a foot shock with a given contextual environment (Context 1) activates a subpopulation of CA1 pyramidal cells in red, while learning the association of the foot shock with a distinctly different contextual environment (Context 2) activates cells in green. Yellow signifies cells that show overlap in Ca^{2+} activity in both Context 1 and 2. A shorter time delay between the learning events (5 hours) produces a greater overlap between cells that show Ca^{2+} activity in both Context 1 and 2, while learning in Context 2 one week (7 days) after Context 1 engages Ca^{2+} activity in a distinct largely non-overlapping group of cells.

Figure 3. Circuit Dynamics of Long-range Inhibitory Projections (LRIPs) from Lateral Entorhinal Cortex (LEC) to CA1

(a) Confocal image showing GFP (green) labeled GABAergic projection axons in hippocampus, following unilateral viral injections in LEC. (b) Scheme showing functionally mapped disinhibitory circuit design of EC LRIPs and their target neurons in CA1. (c) Reconstruction of intracellularly filled neurons and GFP-labeled LRIP inputs to CA1. Whole-cell recordings were obtained from CA1 pyramidal neuron soma or dendrites (cyan, electrodes also in cyan). GFP-tagged LRIPs also express channelrhodopsin (ChR2) (green). Relevant inhibitory neurons located at the border of SR and SLM (magenta). (d) Electrophysiological recordings. (d1) Current recording of light evoked IPSC responses (light blue) from CA1 inhibitory neuron upon photostimulation of ChR2+ LRIP demonstrating that LRIP inhibit dendrite targeting inhibitory neurons in CA1. (d2) Voltage recording from distal dendrites of CA1 pyramidal neurons showing that when LRIPs are active, paired EC + CA3 stimulation (20 ms delay) elicits a large dendritic depolarization and long-lasting Ca²⁺ spikes (blue) due to disinhibitory gating by the LRIPs. Silencing the LRIPs prevents disinhibition as seen by the decrease in net depolarization and reduction in the number of dendritic spikes (red). (d3) Voltage recording from the CA1 pyramidal neuron soma. Repetitive pairing of EC and CA3 inputs via electrical stimulation induces input-timing dependent plasticity (ITDP) which produces a large potentiation of the CA3 SC-evoked post synaptic potential (PSP). Pharmacogenetic silencing of the LRIPs blocks ITDP. Adapted from [19^{***}].

Figure 4. Contextual Tuning of Long-range Inhibitory Projections (LRIPs) from Lateral Entorhinal Cortex (LEC) to CA1 and Postulated Role in Contextual and Spatial Function

(a) Design of an *in vivo* two photon imaging experiment to record the activity of LRIPs in dorsal CA1 through a cranial window in head-fixed awake mice during multimodal sensory stimuli presentation. (b) Time-averaged *in vivo* images of GCaMP6f⁺ LEC LRIP axons in SLM (green) with tdTomato-labeled CA1 interneurons (magenta). (c) PSTHs of the mean ($\pm$ SEM) $\Delta F/F$ Ca^{2+} signal from responsive ROIs to (c1) Aversive airpuffs (A) (c2). Neutral light (L) or (c3). Multimodal stimuli pairing airpuff + light (A + L) were randomly presented. These stimuli were chosen to simulate the animal's multimodal sensory experience and behavioral associations of sensory stimuli, respectively. (d) Plot showing the percentage (%) of responsive synaptic boutons after airpuff, light, and combined airpuff and light presentation. Note the supralinear increase in the Ca^{2+} signal and % of active boutons when airpuff and light stimuli are presented simultaneously. Adapted from [19***] (e) Model of how dendritic spikes and timing dependent plasticity underlie ensemble encoding. During learning, timed association of contextual and spatial sensory inputs from EC with intra-hippocampal inputs (CA3) to CA1 pyramidal neurons induce LTP in a subpopulation of cells (green) via supralinear dendritic spikes. Dendritic spikes provide environmental feature selectivity such as spatially tuning silent cells to place cells in a context dependent manner. These recruited cells compose the contextual memory ensemble (bottom, red) that is activated during recall. Alternatively dendritic spike firing and LTP induction stabilizes place fields of newly formed place cells upon subsequent navigation through their

corresponding place field locations. Dendritic spikes are also a suggested mechanism for context dependent place cell formation.

Model based on findings of [19***] and [47***].

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