



Learning from inhibition: Functional roles of hippocampal CA1 inhibition in spatial learning and memory

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Abstract


Hippocampal inhibitory interneurons exert a powerful influence on learning and memory. Inhibitory interneurons are known to play a major role in many diseases that affect memory, and to strongly influence brain functions required for memory-related tasks. While previous studies involving genetic, optogenetic, and pharmacological manipulations have shown that hippocampal interneurons play essential roles in spatial and episodic learning and memory, exactly how interneurons affect local circuit computations during spatial navigation is not well understood. Given the significant anatomical, morphological, and functional heterogeneity in hippocampal interneurons, one may suspect cell-type specific roles in circuit computations. Here, we review emerging evidence of CA1 hippocampal interneurons' role in local circuit computations that support spatial learning and memory and discuss open questions about CA1 interneurons in spatial learning.


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Abbreviations

BTSP, behavior timescale synaptic plasticity; CR, calretinin; VIP, vasoactive intestinal polypeptide; SST, somatostatin; AAC, axo-axonic chandelier; PV, parvalbumin; CCK, cholecystokinin; CB, calbindin; VGAT, vesicular GABA transporter.

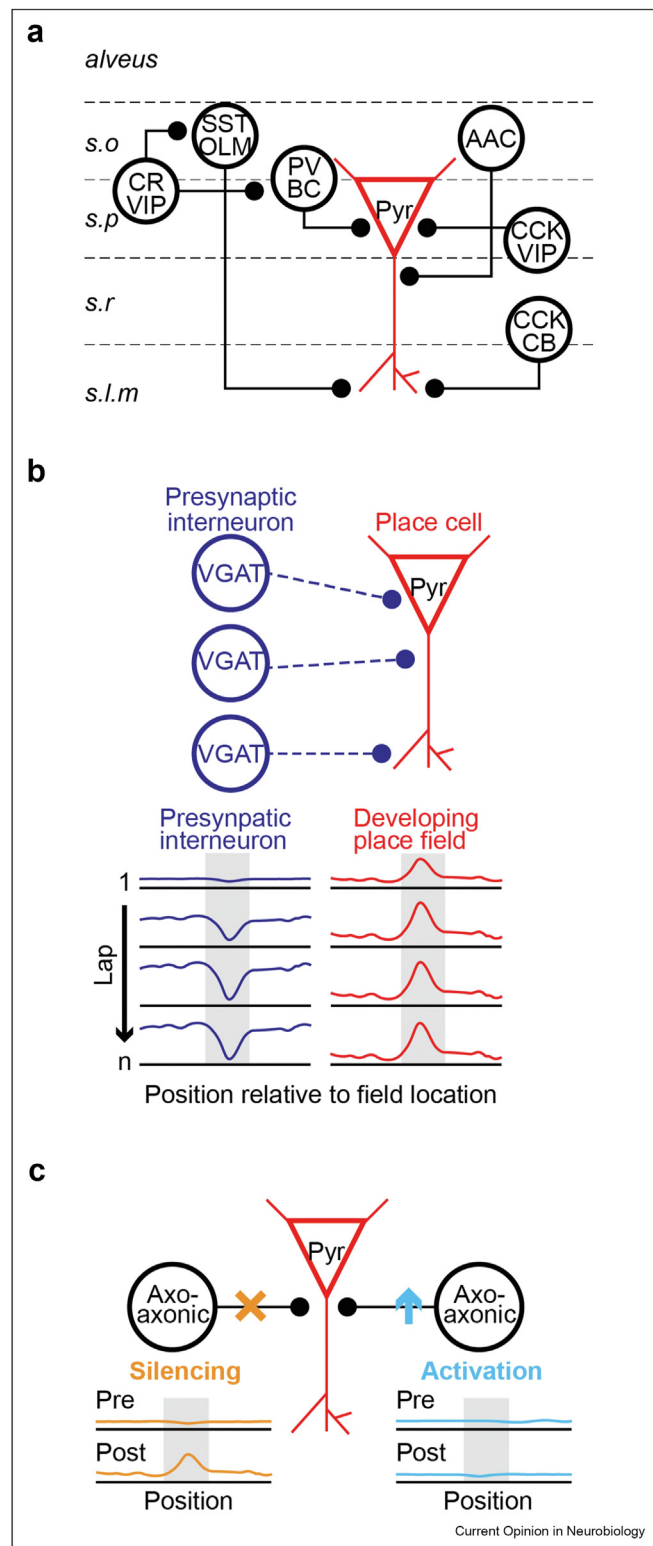
Main Text

Learning is the process by which an animal acquires knowledge or skills through experience. This process

includes forming neural representations of novel information which are initially stored for short-term access and then stabilized into long-term memory through the process of consolidation [1]. The hippocampus is essential for rapid learning and consolidation of spatial and episodic memory, or memories of events [2–4]. Hippocampal excitatory pyramidal cell activity is thought to represent the internal perception of the external environment such as one's position in space-time dimensions and associations between external stimuli relevant for task performance [5–13]. Inhibitory interneurons strongly influence brain functions required for memory-related tasks and are known to play a major role in many diseases with common symptoms of memory impairment [14–20]. While genetic, optogenetic, and pharmacological interventions have shown that hippocampal interneurons play essential roles in spatial and episodic learning and memory [14,20–22], exactly how interneurons affect local circuit computations during behavior is an active area of investigation and debate. Recent studies have revealed significant functional heterogeneity in spatial and contextual selectivity, as well as heterogeneity in temporal dynamics of various interneurons, suggesting cell-type specific roles in circuit computations [23–25]. Indeed, interneuron subclasses in CA1 not only exhibit transcriptomic heterogeneity, but also target different cell-types and cellular compartments in CA1 (Figure 1a) [26–28].

Here we review the emerging role of hippocampal interneurons in circuit computations for spatial learning and memory and open questions about interneurons in learning. In this review, we focus on recent articles investigating the main hippocampal output region CA1 using recording and manipulation of select neuronal populations during hippocampus-dependent spatial navigation tasks. While one of the primary established roles of interneurons is the generation of neural oscillations, this has been reviewed elsewhere and therefore will not be the focus here [29–36]. Recent studies have shown that CA1 interneurons exhibit previously underappreciated feature selectivity that is relevant for spatial learning and memory [37,38]. Growing evidence suggests that this selectivity for features—whether it be a specific location, type of information, or context—may be attributed to specific subclasses of interneurons [23].

Figure 1



Inhibitory roles in place field formation and maintenance. (a). Simplified diagram of CA1 interneuron subclasses and their inhibitory synaptic targets on a pyramidal cell (Pyr.) with circles and triangle illustrating the location of the cell body of the interneuron and pyramidal cell, respectively. Calretinin (CR)- and vasoactive intestinal polypeptide (VIP)-

Thus, we review how interneuron roles in computations for learning and memory are actively being rewritten by recent findings investigating cell-type-specific inhibitory populations during behavior.

Formation and maintenance of place codes

When an animal navigates an environment, hippocampal pyramidal cells develop location-specific receptive fields, or place fields, where they preferentially fire action potentials when the animal is in a specific part of the environment [13]. Place cells have been studied extensively as an elegant example of how neural firing patterns develop to form internal representations of the external world [39,40]. Some studies have shown that place fields tend to cluster around reward zones [6,10,41–43], consistent with the idea that they prioritize behaviorally relevant locations over less important ones. Recent work has shown that place cells are causally involved in goal-directed behaviors [44]. For example, optogenetically stimulating groups of place cells that typically fired when animals were at a rewarded location led mice to lick at an unrewarded location, behaving as if they were at the reward location [44]. Thus, it is important to understand how interneurons affect place field formation and maintenance because place fields are relevant for memory-guided navigation.

The role of inhibitory interneurons in place field formation and maintenance is currently debated in the field. On one hand, one study showed near uniform inhibitory firing across spatial positions in CA1 of head-fixed navigating mice [45]. Under uniform inhibitory firing, spatial modulation of excitatory cells is thought to arise primarily from spatially specific excitatory

expressing interneurons inhibit dendritic-targeting O-LM cells that primarily express somatostatin (SST), as well as soma-targeting parvalbumin-expressing basket cells (PVBC), thereby disinhibiting pyramidal cells. Basket cells co-expressing cholecystokinin (CCK) and VIP target the soma of pyramidal cells, whereas CCK and calbindin (CB)-expressing interneurons typically target the dendrites. Axo-axonic chandelier (AAC) cells primarily target the axon initial segment. Note that the diagram focuses on interneurons described in this review and is not a comprehensive overview of hippocampal inhibitory circuitry. (b). Prior work shows that spatially selective reduction in inhibition is not required for new field formation but may be important for stabilization and maintenance of new fields. Top, several types of inhibitory interneurons that synapsed onto a pyramidal cell were identified and targeted by their expression of vesicular GABA transporter (VGAT). The inhibitory neurons included multiple cell-types with multiple possible synaptic target locations. Bottom, no change in presynaptic inhibition was found prior to the lap where a new place field formed, but as the place field stabilized, the presynaptic interneuron developed “inverse” spatial selectivity such that it fired less than baseline levels at the postsynaptic pyramidal cell’s place field location [37]. (c). Spatial selectivity in place cells is inducible with cell-type-specific reduction in inhibition. Optogenetic activation or silencing of axo-axonic cells targeting the axon initial segment of the pyramidal cell led to place field remapping in vivo during behavior [51]. Specifically, optogenetic silencing led to induction of new, persistent place fields at the photostimulated location. In contrast, optogenetic activation led to no significance change in the number of place fields at the stimulation site although rare pre-existing place fields were suppressed.

inputs or strengthening of excitatory synapses, requiring little spatially-specific inhibitory input [46,47]. On the other hand, spatial selectivity in CA1 interneurons has been previously reported in varying degrees [38,48–50], and some have speculated that location-specific release of inhibition at least partly contributes to the spatial tuning of place cells [48]. Other studies that have examined CA1 excitatory and inhibitory responses to spontaneously developed or optogenetically induced place fields in head-fixed behaving mice have reported seemingly conflicting findings [23,37,51–53]. Below we highlight recent empirical data investigating the role of interneurons in place field formation and maintenance.

A recent study reports a role for CA1 interneurons in place field maintenance [37]. This study by Geiller et al. (2021) elucidated interneuron effects on place fields in mice by using *in vivo* single-cell electroporation combined with monosynaptic retrograde tracing and optogenetics to identify synaptically connected cells *in vivo* [37]. The authors retrogradely labeled neurons presynaptic to an electroporated starter pyramidal cell and found that over 90% of the presynaptic inputs were from local inhibitory interneurons. Given this observation, the authors then expressed a genetically encoded Ca^{2+} indicator in all inhibitory interneurons using the VGAT-Cre mouse line, followed by electroporation of a starter pyramidal cell in CA1. This approach allowed for calcium imaging of functionally coupled pyramidal cells and interneurons in head-fixed mice running on a belt decorated with different tactile cues and licking for randomly delivered water rewards. Strikingly, while there was no detectable reduction in the activity of presynaptic interneurons during spontaneous place field formation, presynaptic interneurons showed “inverse” spatial selectivity once newly formed place fields stabilized, with strong reduction in firing at field locations of the starter pyramidal cell (Figure 1b). These findings contrast with prior work that showed inhibitory inputs are spatially uniform and contrast to theories that reduced inhibition is required for place field formation [45]. The discrepancy in spatial selectivity of interneurons between different studies may be due to the cells included. Geiller et al. specifically examined interneurons that were presynaptic to cells with place fields in the current environment and these cells may have higher spatial selectivity than other interneurons, for example, those that synapse onto cells without a current place field. Additionally, differences in the behavior paradigm (like randomly delivered reward versus reward delivered in specific parts of the track), may affect the animal’s use of position-specific cues leading to differences in spatial selectivity of interneurons.

In contrast, another study suggests CA1 interneurons do play a key role in place field formation, but these effects

may be interneuron subtype specific. Dudok et al. (2021) show that disinhibition by axo-axonic chandelier cells, which target the axon initial segment of pyramidal cells, can induce place field formation [51]. In this study, the authors created a new genetic mouse line to specifically target and optogenetically manipulate CA1 axo-axonic chandelier cells [51]. This work found axo-axonic cells inhibit firing activity of pyramidal cells in awake behaving mice. Both optogenetic activation and silencing of axo-axonic cells led to remapping of place fields. Interestingly, optogenetic silencing induced new place fields near the photostimulation site that persisted during post-photostimulation laps while optogenetic activation did not change the total number of place fields (Figure 1c). Thus, location-specific reduction in axo-axonic cells’ firing may be sufficient to generate place fields at that location. Together, the findings of Dudok et al. and Geiller et al. suggest that spatially organized activity of interneurons plays a key role in the development and maintenance of hippocampal representations of spatial experience with the exact role dependent on the interneuron subclass.

Indeed, spatial selectivity in CA1 interneurons differs between interneuron subclasses, or interneurons that have the same molecular markers, like parvalbumin, but differ in their morphological classification, like basket cells and bistratified cells [23]. Geiller et al. (2020) used three-dimensional 2-photon calcium imaging and molecular verification by immunohistochemistry to survey several subclasses of CA1 interneurons simultaneously recorded in behaving head-fixed mice. This study found that many interneuron subclasses showed spatial selectivity, although the degree or stability of modulation varied by subclass. For example, spatial selectivity was more stable across sessions for parvalbumin-positive basket cells than for somatostatin-positive interneurons, although they both had similar spatial modulation. Given the diversity in interneuron responses, inhibitory populations likely contribute significantly to spatial representations that are typically thought to be represented by excitatory populations with significant spatial modulation. Indeed, Geiller et al. (2020) found that the animal’s current position was decoded above chance levels from CA1 interneuron activity alone although decoding performance was better with CA1 place cells than with interneurons only.

Beyond the development of individual place fields, Rolotti et al. (2022) suggest that local feedback inhibition may control the size of the excitatory population to represent a specific location [52]. This is analogous to the previously reported role of dentate somatostatin interneurons in controlling the size of fear memory ensembles [54]. In this study, Rolotti et al. used a tamoxifen-dependent Cre virus and Cre-dependent excitatory opsin ChRmine to achieve sparse opsin

expression across CA1 subpopulations in head-fixed mice running on a treadmill for randomly delivered water rewards. By varying the dose of tamoxifen injected in each mouse, the authors titrated the fraction of opsin-expressing CA1 pyramidal cells, while co-injection of GCaMP6f allowed for imaging calcium dynamics of the entire CA1 excitatory population. Rolotti et al. found that most single neurons could be optogenetically induced to develop place fields at the stimulation location that lasted at least 24 h post-stimulation. Thus, new place fields may require strong enough excitatory drive above a certain threshold. Indeed, they showed that the percentage of pyramidal cells that were stimulated to fire together affected the efficacy of place field induction at the stimulation location [52]. Stimulation of fewer cells together due to lower opsin expression density led to a higher induction of place fields at the stimulation location compared to mice with higher opsin expression density. The authors then reasoned that a larger stimulated excitatory subpopulation might be more likely to recruit local interneurons, providing lateral inhibition onto nearby CA1 pyramidal cells. As a result, place fields could be more difficult to induce due to this lateral inhibition. Consistent with this hypothesis, the number of activated excitatory cells in a subpopulation was increased by chemogenetically suppressing local inhibition with inhibitory DREADDs specific to interneurons. Similarly, McKenzie et al. (2021), which used relatively low-power stimulation of CA1 pyramidal cells in head-fixed behaving mice, observed induction failures at the stimulation site perhaps due to larger recruitment of interneurons than place field induction via intracellular recordings [53]. These experiments suggest that interneurons play a key role in a competitive mechanism by which some pyramidal cells are selected to be part of a neuronal assembly while other pyramidal cells are suppressed and excluded [55,56]. Such groups of neurons firing together during an experience would then strengthen their connections which is thought to be the basis of memory formation [57,58].

Interneurons have been hypothesized to play a key role in developing and refining spatial codes thus improving the signal-to-noise of such coding [59]. These recent studies support this hypothesis and refine it by showing that specific functions vary by interneuron subclass. Together, these studies point to a model in which interneurons refine spatial codes in multiple ways. First, the activity of some spatially modulated interneurons can decode animal location [23]. Second, presynaptic interneuron activity exhibits an inverse relationship with new place field activity to maintain sharp and stable place fields [37]. Third, while interneurons disinhibit high firing cells at their place field locations, interneurons also suppress low firing pyramidal cells such that cells with inadequate excitatory drive do not participate in an assembly [52]. Thus, these studies suggest that interneurons increase spatial coding signal-

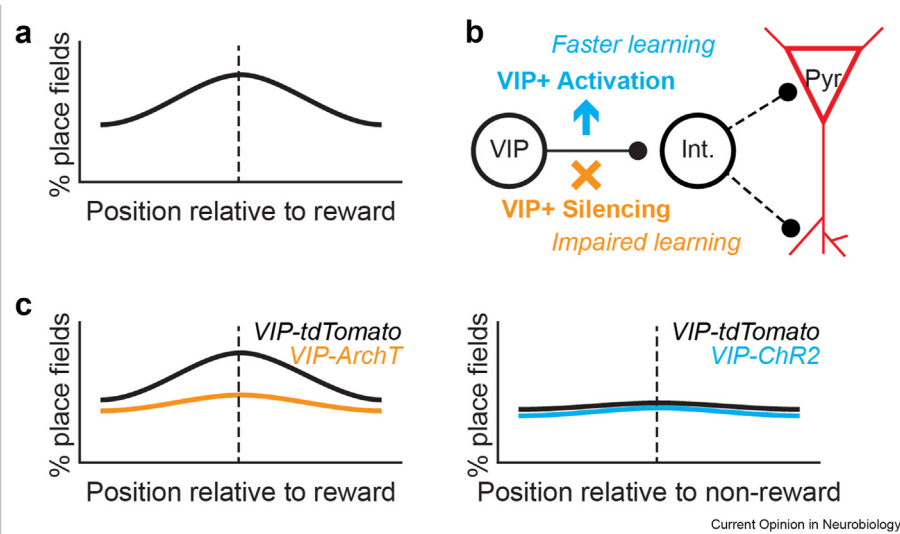
to-noise to stabilize new memories and suppress low or unstable excitatory activity with their exact roles differing by cell-type. The notion of cell-type-specific spatial selectivity in interneurons is further supported by cell-type-specific plasticity mechanisms discovered in CA1, including at glutamatergic synapses onto interneurons and at inhibitory synapses onto excitatory pyramidal cells [60–63]. Spatially-selective interneurons may also play a role in behavior timescale synaptic plasticity (BTSP) in which excitatory cells exhibit extended periods of subthreshold depolarizations over behavioral (seconds) timescales, although this has traditionally been attributed to excitatory inputs [47,64]. Furthermore, spatial selectivity that seems to be driven by excitatory inputs may have an inhibitory component. Previous *in vitro* work has shown that the efficacy of inhibition depends on the distance to adjacent excitatory inputs on the same hippocampal dendritic branch, while excitatory and inhibitory drives are also balanced across dendritic branches [65]. This within-dendrite inhibitory influence over excitatory inputs may contribute to spatial selectivity of excitatory inputs. Future work is necessary to determine which plasticity mechanisms contribute to different phases of spatial learning.

Learning goal-directed navigation

The hippocampus is essential for rapid learning, whether after a single experience or a few minutes [2–4]. While recent articles described above examined place field formation and maintenance as a model of memory formation, place field formation occurs even when animals explore open fields and does not necessarily require animals to express their learning via behavioral changes [39]. To study learning-related behaviors explicitly, a few recent studies have shed light on the role of interneurons in circuit function as animals learn to find new goal locations [66,67]. These studies have examined neural inputs and connections as well as place fields that tend to cluster around reward location (Figure 2a).

Interneuron-targeting interneurons, which ultimately disinhibit pyramidal cells, were recently discovered to play a key role in goal-directed spatial learning in the work by Turi et al. (2019) [66]. This study focused on CA1 vasoactive intestinal polypeptide (VIP) positive interneurons, a subset of interneurons that primarily target parvalbumin- or somatostatin-expressing interneurons [68,69], and ultimately release pyramidal cells from perisomatic or dendritic inhibition. After verifying that these VIP interneurons were indeed disinhibitory on CA1 pyramidal cells *in vitro* and *in vivo*, the authors virally expressed GCaMP6f in the dorsal CA1 region of VIP-Cre mice to observe chronic Ca^{2+} activity in head-fixed mice running on a treadmill. The authors first found that VIP interneurons could be separated into two groups based on whether they were

Figure 2



Inhibitory roles in learning goal-directed navigation. (a). Place cells overrepresent behaviorally relevant locations such as reward zones and, while place fields tile the entire environment, more place fields cluster around these important locations. (b). Vasoactive intestinal polypeptide (VIP)-expressing interneurons target other interneurons (Int.) that provides either perisomatic or dendritic inhibition onto pyramidal cells (Pyr.). In a recent study investigating a local CA1 disinhibitory circuit in goal-directed learning, optogenetically activating VIP interneurons (light blue) was found to induce faster learning of a new reward zone, as demonstrated by increased licking near the reward location [66]. Optogenetic silencing (yellow) led to impaired learning in the same goal-directed navigation task. These findings suggest that new goal learning (and its behavioral expression) is mediated by local inhibition and disinhibition of pyramidal cells. (c). Left, consistent with these behavioral changes in B, optogenetic silencing of VIP neurons led to a reduced proportion of place cells with fields near the goal (yellow, inhibitory opsin ArchT in VIP interneurons). Right, in contrast to the observed behavioral effects, VIP optogenetic activation (light blue, excitatory opsin ChR2 in VIP interneurons) did not lead to observable changes in the proportion of goal-representing place cells. These results suggest that transient release of pyramidal cells from local inhibition is necessary, but not sufficient, to induce learning-dependent neuronal reorganization.

positively or negatively modulated by speed. Upon training in a behavioral task that required the mice to learn to lick at a specific location, the firing of both VIP interneuron groups was modulated by proximity to reward, but in opposite directions. Interestingly, this reward modulation was not observed if the mice did not have to learn the task as in random foraging conditions. The authors then tested the hypothesis that disinhibition of CA1 pyramidal cells is necessary for overrepresentation of goal location by place cells during learning and subsequent improved performance. To do this, Turi et al. virally expressed either the opsin channelrhodopsin or the opsin archaerhodopsinT in CA1 of VIP-Cre mice to optogenetically activate or silence, respectively, CA1 VIP interneurons in mice learning a new reward location. In support of their hypothesis, the authors found that optogenetic silencing of VIP interneurons reduced the number of place cells near goal locations as well as the rate of learning measured by licking earlier as animals approached the reward location (Figure 2 b,c). Mice learned significantly faster than controls when CA1 VIP interneurons were optogenetically stimulated near the reward location, even if it did not affect CA1 pyramidal cell reorganization. Based on these results, the authors concluded that disinhibition

mediated by VIP interneurons is necessary, but not sufficient, for learning-dependent reorganization of CA1 pyramidal cells.

Prior work has shown that the strength of connections between pyramidal cells and interneurons rapidly reorganize during spatial learning [67]. Dupret et al. (2013) found that rats rapidly learning new goal zones in an otherwise familiar environment had learning-dependent changes in the strengths of putative monosynaptic connections between pre-synaptic excitatory place cells and post-synaptic inhibitory cells in CA1 [67]. This study showed that putative pyramidal-to-interneuron connections alter input weight distributions following learning, with the direction of change dependent on whether the assembly represented new learning. Pyramidal assemblies that represented newly learned goal locations strengthened their connections to post-synaptic interneurons that preferentially fired when the new map was expressed. Conversely, these same pyramidal assemblies weakened their coupling to interneurons whose firing was more correlated with the old map. Furthermore, the changes in connection strength were more likely to occur around rewarded locations compared to unrewarded locations, even though

pairing events were observed in all locations [67]. These findings indicate that local pyramidal-to-inhibitory circuits reconfigure dynamically based on both learned information and their affiliation to the map of relevance, and thus may contribute to outputting learned behavior. While this study was unable to differentiate between different subclasses of interneurons, it would be important for future work to determine whether and how cell-type-specific changes in connection strengths drive new learning [23].

Together these studies show that CA1 interneurons develop learning-dependent changes important for goal-directed behavior. First, interneurons alter firing responses to specific spatial cues that predict reward, with the magnitude and direction of response modulation varied by subclass. Second, interneurons rapidly reorganize over learning by redistributing their synaptic weights onto nearby neurons. Ultimately, interneuron changes in firing activity and synaptic strength lead to stable representation of newly learned locations directly relevant for task performance.

Functional outcomes of inhibitory deficits in disease

Interneurons are sensitive to disease states and deficits in inhibitory activity are likely to lead to network dysfunction due to their powerful influences on neural circuits [70–72]. Multiple studies have shown abnormal inhibitory activity of multiple subclasses in several animal models of Alzheimer's disease (AD), revealing common pathophysiological mechanisms [19,73–78]. Furthermore, abnormal GABAergic inhibition is observed in depression, autism spectrum disorder, and Down syndrome, suggesting the sensitivity of inhibitory neurons to disease and potential common inhibitory mechanisms across multiple pathological conditions [79–81]. Recent studies using *in vivo* electrophysiology in animal models of disease have demonstrated the need for subclass-specific investigation of interneurons that may affect different aspects of spatial learning and memory. Paterno et al. (2021) using the *Cntnap2* KO mouse model of autism showed reduced inhibitory transmission *in vitro* by parvalbumin-expressing interneurons onto CA1 pyramidal cells in KO mice, which also had impaired performance in spatial object recognition and object congruence tasks [82]. This model also had layer- and frequency-specific deficits in gamma phase-amplitude coupling, which could be directly related to deficits in subclass-specific transmission at inhibitory synapses. In another study, Chung et al. (2020) found that in mice injected with toxic amyloid beta oligomers, optogenetically activating CA1 parvalbumin- or somatostatin-expressing interneurons restored peak gamma or theta power, respectively, to normal levels *in vivo*, albeit during anesthesia [83]. The optogenetic manipulation also led to resynchronization of pyramidal cell spiking relative to gamma or theta

oscillation, respectively. While this study did not examine mice during task performance, it would be of interest to consider interneuron subclass-specific rescue of frequency-specific oscillations during spatial memory-guided behavior. Similar to these observations, our study using the 5XFAD genetic mouse model of AD and a virtual reality spatial navigation task found fewer and shorter sharp-wave ripples in AD mice, which correlated with a significant reduction in the strength of putative interneuron-onto-pyramidal neuron monosynaptic connections in CA1 [84]. These studies suggest that interneurons are involved in memory impairment in multiple models of disease either by disrupting oscillations or driving network imbalances and hyperactivity. Considering recent studies revealing the diversity and specialization of inhibitory populations and their roles for spatial coding and memory formation described above, interneuron dysfunction likely plays more direct roles in memory impairment, however empirical data for the specific roles of interneurons in circuit dysfunction in disease models is lacking.

Current gaps in knowledge

Together these recent studies reveal previously unappreciated spatial selectivity in some interneuron types which in turn increases the signal-to-noise ratio of spatial codes and enables learning [23,37,51,52]. We must also keep important experimental limitations in mind when considering these findings. First, several studies have made clever use of induced place fields [37,52,53]. However, these place fields are generated artificially so may differ in their inputs or structure than naturally occurring place fields. Second, many of these studies were performed in head-fixed mice. This approach enables complex imaging and electrophysiology, but limits vestibular inputs to animals among other limitations [85]. Third, optogenetic stimulation can have many unintended side effects [86]. Fourth, imaging of hippocampus often includes extensive damage to overlying cortex which may affect hippocampal functions or animal behavior since interactions between hippocampus and cortex are involved in cognition [87–89]. Even with these limitations, these studies have provided key insights into interneuron roles in spatial coding.

These findings raise several key questions. First, it remains to be examined whether inhibitory interneurons are crucial in selecting specific assemblies over others to represent or respond to particular experiences. Second, the specific plasticity mechanisms at play in the development of interneuron spatial selectivity and in changing connection strength between inhibitory and excitatory cells are not well understood. Third, while inhibitory deficits have been well-documented in diseases with learning and memory impairments, the diverse circuit mechanisms

by which interneurons influence learning and memory have not been elucidated. Finally, multiple brain regions may have unifying inhibitory mechanisms for learning and disease susceptibility, which opens avenues for future research. Studies that bridge multiple scales, from single neurons to networks to behavior, will shine light on the inhibitory mechanisms of learning and memory in health and disease.

Conflict of interest statement

Nothing declared.

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