Molecular Neurobiology
https://doi.org/10.1007/s12035-025-05020-2

REVIEW

# Hippocampal Interneurons Shape Spatial Coding Alterations in Neurological Disorders

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Received: 19 September 2024 / Accepted: 29 April 2025


## Abstract

Hippocampal interneurons (INs) play a fundamental role in regulating neural oscillations, modulating excitatory circuits, and shaping spatial representation. While historically overshadowed by excitatory pyramidal cells in spatial coding research, recent advances have demonstrated that inhibitory INs not only coordinate network dynamics but also contribute directly to spatial information processing. This review aims to provide a novel integrative perspective on how distinct IN subtypes participate in spatial coding and how their dysfunction contributes to cognitive deficits in neurological disorders such as epilepsy, Alzheimer's disease (AD), traumatic brain injury (TBI), and cerebral hypoxia–ischemia. We synthesize recent findings demonstrating that different IN classes—including parvalbumin (PV)-, somatostatin (SST)-, cholecystokinin (CCK)-, and calretinin (CR)-expressing neurons—exhibit spatially selective activity, challenging traditional views of spatial representation, and influence memory consolidation through network-level interactions. By leveraging cutting-edge techniques such as in vivo calcium imaging and optogenetics, new evidence suggests that INs encode spatial information with a level of specificity previously attributed only to pyramidal cells. Furthermore, we investigate the impact of inhibitory circuit dysfunction in neurological disorders, examining how disruptions in interneuronal activity lead to impaired theta-gamma coupling, altered sharp wave ripples, and destabilized place cell representations, ultimately resulting in spatial memory deficits. This review advances the field by shifting the focus from pyramidal-centered models to a more nuanced understanding of the hippocampal network, emphasizing the active role of INs in spatial coding. By highlighting the translational potential of targeting inhibitory circuits for therapeutic interventions, we propose novel strategies for restoring hippocampal network function in neurological conditions. Readers will gain a comprehensive understanding of the emerging role of INs in spatial representation and the critical implications of their dysfunction, paving the way for future research on interneuron-targeted treatments for cognitive disorders.

**Keywords** Hippocampal interneurons · Spatial coding · Inhibitory circuit dysfunction · Theta-gamma coupling · Alzheimer's disease · Temporal lobe epilepsy

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Published online: 20 May 2025

## Introduction

Over the past decades, numerous studies have investigated the brain's intricate mechanisms underlying memory acquisition, retention, and spatial navigation. The investigation of the role of the hippocampus significantly advanced our comprehension of these processes. Anatomically, the hippocampus comprises the hippocampal formation, encompassing the hippocampus proper, the dentate gyrus (DG), the entorhinal cortex, and the subiculum. These components are interconnected by excitatory projections, facilitating the transmission of information through multiple parallel pathways. Proper distinct subregions within the hippocampus house two primary types of neurons: glutamatergic pyramidal cells and γ-aminobutyric acid (GABA)ergic inhibitory neurons, the interneurons (INs).

The intricate interplay between pyramidal cells and INs generates rhythmic oscillations, which are crucial for memory acquisition and spatial information processing. Within the hippocampus, these rhythms encompass theta (4–12 Hz), slow (25–55 Hz) and fast (60–100 Hz) gamma, and sharp wave ripples (SWRs; 110–200 Hz). Theta rhythms, predominant during exploration, play a key role in memory encoding and consolidation [1–3], while SWRs are associated with memory consolidation [4, 5]. Additionally, theta rhythms are coupled with gamma oscillations, a phenomenon known as theta-gamma coupling, which has been suggested to enhance memory encoding and retrieval [6–9]. These oscillatory patterns are tightly regulated by the activity of distinct INs subtypes and the dynamic interaction between excitatory and inhibitory inputs [10–14]. Disruptions in INs activity can impair these oscillations, as observed in conditions such as traumatic brain injury (TBI) and Alzheimer's disease (AD) [15–17].

Beyond their role in rhythmic oscillations, hippocampal pyramidal cells also contribute to spatial representation. A specific subset of these neurons, known as place cells, exhibit selective firing patterns corresponding to specific spatial locations, effectively constructing a neural representation of the explored environment, referred to as a 'place field' [3, 18–20]. For a long time, research on spatial processing has primarily focused primarily on pyramidal cells. However, recent studies have highlighted the significant role of INs in spatial coding [21–23]. These findings emphasize the importance of the intricate interneuronal network in modulating dynamic neural activity and their crucial role in cognition.

Building on this perspective, recent breakthroughs have advanced our understanding of the dynamic organization of hippocampal inhibitory circuits and their critical role in encoding spatial information. While pyramidal neurons in spatial coding have been extensively studied, the contribution of inhibitory INs remains poorly explored. Given that numerous neurological disorders affect the hippocampus and, consequently, cognitive functions, this review provides an integrative perspective on how inhibitory circuits shape spatial memory. We will focus on temporal lobe epilepsy (TLE), Alzheimer's disease (AD), traumatic brain injury (TBI), and cerebral hypoxia–ischemia (HI) as the focal neurological disorders. This selection is based on their profound impact on hippocampal function, particularly in spatial memory encoding. While hippocampal dysfunction is widely recognized in AD, growing evidence indicates that similar impairments occur in TLE, TBI, and HI, albeit through distinct mechanisms. A key unifying feature of these conditions is the disruption of inhibitory interneuron networks, which play a crucial role in orchestrating hippocampal rhythmic activity and ensuring the precise encoding of spatial information.

Despite extensive research on the cognitive deficits associated with each of these disorders individually, there remains a significant gap in understanding the shared and distinct mechanisms through which interneuron dysfunction contributes to spatial memory impairments across conditions. By comparing these disorders, we aim to identify common patterns of inhibitory circuit disruption, such as interneuron loss, hyperexcitability, and oscillatory desynchronization, and examine how these alterations manifest differently in each pathology. The inclusion of these four disorders allows for a comprehensive examination of both acute and chronic disruptions in hippocampal interneuron function, ranging from the progressive neurodegeneration of AD to the sudden yet enduring effects of TLE, TBI, and HI on inhibitory networks.

## Hippocampal Interneurons

The hippocampus is composed of three main regions, the CA1, CA3, and DG. The CA1 and CA3 have five layers, the stratum alveus (SA), stratum oriens (SO), stratum pyramidales (SPY), stratum radiatum (SR) and stratum lacunosum-moleculare (SLM), and DG have three layers, the molecular, granular cell and polymorphic layers. Hippocampal microcircuits comprise three major components: principal cells (PCs), a diverse group of INs which are responsible to control PCs activity and modulate the activity of other INs. Despite representing only about 10% of the hippocampal neuronal population, INs play a crucial role in network dynamics by releasing GABA as their primary neurotransmitter [18, 24–26]. Each IN subtype is distributed across one or more hippocampal layers. Their integration occurs during the late prenatal and early postnatal development, resulting in highly ordered and complex functional networks

[27–30]. Although INs constitute a small fraction of hippocampal neurons, they display remarkable anatomical and functional diversity. They provide a critical source of inhibition, regulating neuronal signaling and neural oscillations, and maintaining the balance between excitation and inhibition (E/I), which is critical for optimizing neuronal information processing [31–33]. INs are classified into distinct populations based on their neurochemical markers, such as calcium-binding proteins or neuropeptides expression.

The advances in genetic manipulation of transgenic animals or viral vectors, coupled with techniques such as optogenetics or pharmacological interventions (i.e., Designer Receptors Exclusively Activated by Designer Drugs, DREADDs), made it possible to elucidate the functional role of these INs. Here, we discuss the main types of INs, according to their cell-specific expression of a molecular marker, that modulate the PCs in the hippocampus, such as the parvalbumin (PV), cholecystokinin (CCK), somatostatin (SST), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), calretinin (CR) interneurons, and calbindin (CB) interneurons.

Among the diverse population of inhibitory INs, PV is expressed in various neuron morphological types, including basket cells, axo-axonic cells, bistratified cells, and oriens-lacunosum-moleculare (O-LM) cells, with their predominantly perisomatic projections onto pyramidal neurons [34]. PV cells have received significant attention due to their remarkably fast-spiking electrophysiological profile, a high-frequency firing rate, and their influence on cognitive processes [35, 36]. The PV neurons can generate high-frequency trains of action potential due to the expression and subcellular distribution of specific ion channels, including voltage-gated sodium channel (Nav1.1) and voltage-gated potassium channel 1 (Kv1) and 3 (Kv3) [35]. These voltage-gated ion channels contribute to a rapid dynamic of high activation threshold, fast repolarization, short action potential duration, and rapid action potential propagation in the axon, resulting in the fast-spiking profile [35, 37, 38]. The high-frequency firing of action potentials is followed by extremely fast GABA release within a few milliseconds [39]. PV cells also express high levels of P/Q-type calcium channels that contribute to quick and precise GABA release from PV axon terminals [40]. This rapid GABA release makes PV INs critical for proper microcircuit temporal control [39]. Indeed, hippocampal INs expressing PV regulate the output of pyramidal neuron ensembles by forming synapses on their soma and axon initial segments [41]. Their firing is closely phase-locked to theta and gamma rhythms, suggesting a causal relationship between their activity and the establishment of these oscillations [10].

Given the importance of PV-INs in the precise temporal control of microcircuits, they have a tremendous functional impact on memory, learning, and spatial coding processes. For example, PV-INs in CA1 alter their firing patterns during memory consolidation through enhancements in delta and theta oscillations [42]. Such GABAergic activity is essential for memory consolidation and instructive, as it promotes synaptic changes in specific neuronal subpopulations. The rhythmic firing of PV INs drives and stabilizes coherent firing in neighboring CA1 pyramidal neurons, generating the appropriate pattern of synchronous neural activity capable of inducing Hebbian synaptic plasticity in the CA1 network. PV cells also participate in the occurrence of high-frequency electrophysiological patterns like sharp-wave ripples (SWRs) [43], a specific hippocampal pattern activity associated with memory consolidation [5, 42, 44]. They are involved in coupling theta and gamma oscillations in CA1 [9] and may enhance phase-locking uniformity during theta oscillations [13, 34]. Perturbation of PV cells leads to a decreased SWR power and disruption of phase-locking between multiunit activity from SPY and SWR [34, 45–47] and decoupling of theta-gamma oscillations, culminating in spatial memory deficits [9, 44, 46, 48–52]. PV neurons are also thought to regulate the spatial tuning of place cells and the maintenance of place fields [53, 54]. These functions highlight the multifaceted roles of PV-INs in contextual memory consolidation, underscoring their importance in several cognitive processes.

In addition to the PV cells, other types of GABAergic INs also densely innervate the cell soma and proximal dendrites of pyramidal cells, such as the CCK-INs, which are primarily basket cells [55–64]. CCK-INs exhibit distinct electrophysiological properties compared to PV-INs, displaying regular-spiking (RS) activity [63, 65]. This characteristic enables them to provide prolonged and robust rapid feedforward inhibition onto pyramidal cells through asynchronous GABA release [66–68]. CCK-INs are distinguished from other classes for their highly plastic synaptic connections that can be modulated by various neurotransmitters from ascending projection systems [69]. Some CCK-INs also express vasoactive intestinal peptide (VIP), high levels of cannabinoid receptor type 1 (CB1), and vesicular glutamate transporter type 3 (VGLUT3), all of which are linked to synaptic plasticity mechanisms underlying learning and memory [70–72] (for review, see [57]). The expression of several neuromodulatory receptors on CCK-INs indicates their involvement in behavioral state-dependent processing and spatial learning by facilitating hippocampal neuroplasticity [73–75]. For instance, theta oscillations in the CA1 region, induced by cholinergic activity, involve an inhibitory circuit primarily composed of CCK-INs [34].

CCK-INs co-release CCK and GABA, with CCK playing a regulatory role in the activity of diverse INs [76]. In pyramidal cells, CCK activates CCK2 receptors, triggering endocannabinoid release that activates type 1 cannabinoid receptors (CB1Rs) on the presynaptic terminals of CCK-INs

[77]. The CBR1 receptor is selectively expressed in these GABAergic cells, defining a specific mechanism for regulating neuronal excitation solely through the CCK-INs population [76]. The reduction in GABA release in CCK cells facilitates long-term synaptic potentiation (LTP) at connections between CA3 and CA1, thereby promoting the establishment of spatial memory traces [75]. Optogenetic inhibition of CCK-INs enhances pyramidal cell burst firing, disrupts theta phase precession, and alters the temporal coding of place cells in CA1, emphasizing their role in spatial representation and organization of place cells activation [78]. Indeed, abnormal integration of CCK cells into the network during development leads to alterations in theta power oscillations, disruption of spatial coding, and deficits in spatial learning in adult mice [79].

SST-INs are defined by their expression of the neuropeptide somatostatin and the somatostatin receptor. While PV cells primarily project onto the soma of pyramidal neurons, SST cells are characterized by dendritic projections. Additionally, to the SST features, SST cells exhibit high levels of spontaneous activity due to their intrinsic membrane conductance [80]. This inherent activity persists in the absence of synaptic input and is fine-tuned by synaptic activity and neuromodulatory factors. Morphologically, the SST includes bistratified cells that specifically innervate the dendritic zones of PCs that receive input from CA3 [81] and O-LM cells that modulate input from the entorhinal cortex [82]. In the hilar region of the DG, a separate population of SST cells has been proposed to participate in the feedback inhibition of granule cells [83].

SST-INs primarily receive input from pyramidal cells, providing feedback inhibition. This mechanism is crucial in locally regulating hippocampal neural networks [84, 85]. Additionally, these GABAergic neurons exert long-range inhibition, facilitating synchronization between hippocampal activity and other brain structures [86]. These dual functions have been observed to dynamically regulate the input–output transformation and firing patterns of pyramidal cells during exploratory activities [13]. The differences between SST cells in the hippocampus may have discrete effects on network function. A recent study demonstrated that SST-INs in DG are necessary for natural contextual fear memory recall, while inhibiting CA1 SST cells during foot shocks prevents contextual fear memory recall [87, 88]. Indeed, the inhibition of CA1 SST cells during fear conditioning showed an essential role of SST in memory recall since the re-inhibition, with no other stimuli in a neutral context, recalled the fear memory. The differences between SST cells in the hippocampus may have discrete effects on network function. A recent study demonstrated that SST-INs in DG are necessary for natural contextual fear memory recall, while inhibiting CA1 SST cells during foot shocks prevents contextual fear memory recall [87, 88]. Indeed, the inhibition of CA1 SST cells during fear conditioning showed an essential role of SST in memory recall since the re-inhibition, with no other stimuli in a neutral context, recalled the fear memory.

Most VIP cells in the hippocampus play an essential role in disinhibitory mechanisms, once they are IN-specific (IS), i.e. target other GABAergic INs instead of PCs. A small subpopulation of VIP, known as basket cells, which co-express CCK and VIP, targets PCs. VIP ISs have different locations in CA1 layers. While VIP IS-2 cells have soma in SLM, VIP IS-3 cells have soma located in SP and SR. There are also some VIP-expressing long-range projecting (VIP-LRP) cells in the hippocampus that synapse onto both PCs and INs in CA1 oriens-lacunosum-moleculare (OLM), and subicular area [3, 20]. VIP IS-3 cells increased their activity during animal locomotion, including during specific theta-run phases. On the other hand, VIP-LRP cells decreased their activity under the same circumstances. However, both IS-3 and VIP-LRP cells remain silent during SWRs [3, 20, 89]. VIP-INs, which become highly active during spatial exploration in novel environments, support novelty encoding and recognition memory [90].

NPY is coexpressed with neuronal nitric oxide synthase (nNOS) in GABAergic INs known as Ivy cells. Their somata are located within the pyramidal cell layer, with highly arborized axons extending into both the SO and SR, primarily forming connections with CA1 pyramidal cells [3, 20]. A recent study found that Ivy cells are more numerous in the CA1 pyramidal layer compared to any subtype of PV-INs. Unlike PV cells, Ivy cells exhibit a slow-spiking firing pattern, which may play a role in regulating network states [91]. LRP cells that project extra-hippocampally to retrohippocampal areas and the medial septum may also express NPY and other molecules, such as CB and SOM [3].

The two primary types of CR-INs in the hippocampus are 1) spine-free CR neurons, which establish dendro-dendritic and axo-dendritic connections with each other, forming interconnected clusters, and 2) CR neurons with axons featuring spaced boutons. While CR-IN boutons have a preference for other INs, a considerable proportion also target pyramidal cells [92]. Gulyás et al. demonstrated that CR cells exhibit high target selectivity, predominantly innervating other GABAergic neurons through multiple synapses. These GABAergic targets include CB-INs, VIP-INs, CCK-INs, and CR-INs, which project to the SO layer [93]. Once CR-INs can effectively synchronize dendritic inhibitory interneurons, they have a key function in the hippocampal network [94].

CB-INs usually contact pyramidal cell dendrites and could be distinguished two different types of them: 1) type I, multipolar or bitufted cells, which are most numerous in SR,SPY and SO of the CA3 and CA1 regions; and 2) type II cells, with large cell bodies and long dendrites, which are exclusively found in the SO of the CA1 and CA3

regions [95]. Interestingly, transgenic mice deficient in calbindin D28 K, a calcium-binding protein abundant in these interneurons and pyramidal cells, exhibited selective impairments in spatial learning tasks and failed to maintain long-term potentiation [96].

As discussed, a diversity of INs directly modulates the pyramidal cell activity and the activity of other INs in the hippocampus. The specific manipulation of each type of interneuron impacts cognitive processes such as memory, acquisition, consolidation, recall, or spatial navigation. After elucidating the role of each type of INs specifically in memory formation and spatial coding, in the next session, we will bring studies that have highlighted the dynamics of INs activity in spatial information coding [52, 97–99].

## Interneurons in Spatial Coding

Pyramidal cells constitute the majority of excitatory neurons in the hippocampus. As mentioned before, some of these neurons, the place cells, exhibit increased firing rates when the animal is at a specific location within the environment. Based on this landmark finding, extensive experimental research has investigated excitatory neurons and spatially specific activity patterns [100–106]. Indeed, several studies have examined how environmental changes, such as lengthening or shortening a rectangular enclosure, rotating proximal and distal cues, exploring three-dimensional spaces, and aversive experiences affect place cell pattern activity [107–111]. The place fields of pyramidal cells arise from a complex interaction between the spatial arrangement of environmental cues and self-motion information.

The activity of place cells is regulated by networks of INs, which orchestrate the timing and coordination of neural ensembles for processing the spatiotemporal information conveyed by the pyramidal cells [13]. Also, several studies demonstrated a dynamic interaction between pyramidal cells and INs, the spatially discrete output of place cells, and even the participation of INs in spatial coding [23, 112–114]. However, for a long time, much of the research has focused primarily on the pyramidal neurons and their activation patterns in memory formation and spatial orientation while the INs had a secondary role in this cognitive process. Recent works have shifted this focus to the importance of inhibitory neurons, significantly enriching our understanding, showing through in vivo calcium imaging recordings by miniscope, and transgenic mice, track with more precision, the INs activity during the spatial coding across days [21–23].

Hangya et al. [113] elucidated the dynamic interaction between INs and place cells using in vivo electrophysiological recordings [113]. The authors showed complementary spatial firing, i.e., a negative spatial correlation between pairs of interneurons-pyramidal cells. In the region where a place cell is firing, the paired interneuron does not, and vice-versa, in both monosynaptic and non-monosynaptic connections. This interaction is much more likely for interneuron-pyramidal cells that are prospective neighbors than distant neurons coupling based on the short-latency peaks in cross-correlogram plots [115]. Indeed, a single interneuron can have at least two negatively correlated place cells [113]. Recent studies have supported these prior findings that evaluated the pyramidal-interneuron connection. Geiller et al. [116] used a method to label and record the activity of a single pyramidal cell and its presynaptic INs connected by direct synapses in the hippocampus of mice [116]. For these experiments, animals were allowed to run on a belt decorated with different tactile cues. This investigation demonstrated the formation and maintenance of the place field of this unique early pyramidal cell and the dynamic interaction of INs.

During the spontaneous formation of a place field of labeled pyramidal cells, the presynaptic INs demonstrated no alteration in their activity, suggesting a lack of significant contribution of INs in this process. However, when the pyramidal cell presented an established place field, the presynaptic INs exhibited inverse spatial selectivity [116] (Fig. 1A). These findings counter the idea that spatial modulation of interneuron firing was merely a reflection of input received by pyramidal cells.

Following the hypothesis that INs have a minimal role in spatial modulation, Grienberger et al. [117] showed that the spatial modulation of place cells requires a uniform inhibitory firing pattern across the environmental exploration, suppressing out-of-field heterogeneously tuned excitation [117]. This uniform inhibition would enhance the temporal coding in place cells. This work suggests that little spatially specific inhibitory input is required, while the central role in the spatial modulation of place cells arises from specific excitatory inputs [117–119]. Nevertheless, recent findings have demonstrated a more complex role of interneurons-place cell interaction in the hippocampal spatial network [112–114].

The hippocampal interneuron electrophysiological firing pattern can be characterized by a well-defined region where these cells fire, with areas of high firing rate ("ON" fields) and specific locations with decreased firing rate ("OFF" fields) [98–100]. Interestingly, the 'ON' and "OFF" fields carry similar spatial information as place cells, such as spatial selectivity and theta-phase precession, suggesting that INs can also code spatial information [112–114]. While the "OFF" fields could reflect decrease in inhibitory input into a PC that can facilitate suprathreshold excitation, contributing to the discharge rate of the PC at any position; the "ON" fields of INs could reflect excitatory input from one or more PCs, decreasing the probability of spiking in their principal neuron targets [114, 120]. Curiously, some pairs of

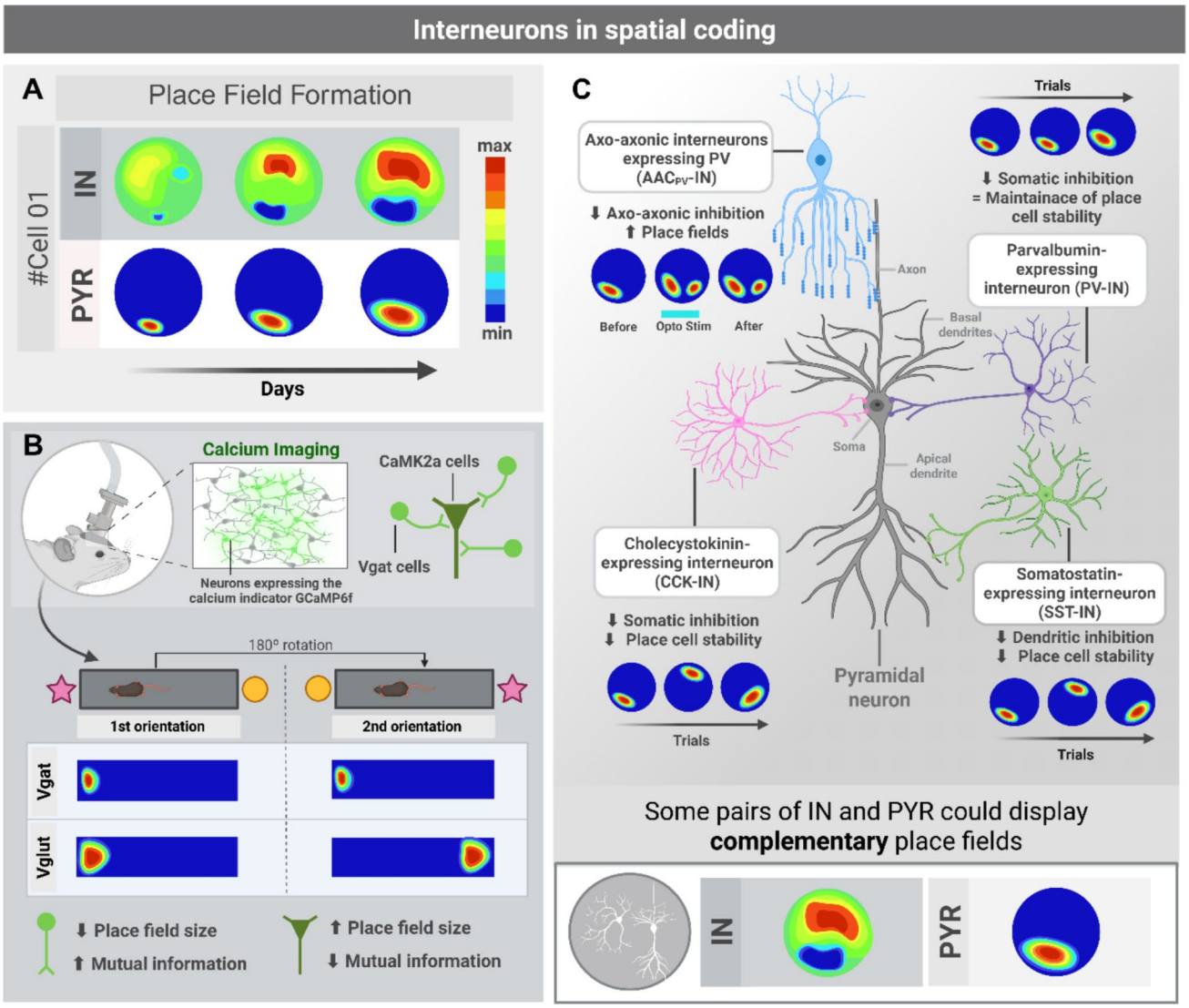


**Fig. 1** Interneurons in spatial coding. **A)** Scheme showing that during spontaneous place field formation, pyramidal cells (PYR) display an established place field, while the presynaptic INs exhibit inverse spatial selectivity. **B)** In *vivo* calcium-imaging experiments considering contextual changes in the environment (180º linear track rotation), showed that INs (Vgat cells) exhibited a smaller place field size and higher mutual information in comparison to place cells (CaMK2a cells). **C)** Top: scheme showing a pyramidal neuron receiving different inputs from INs: dendritic inputs from SST-INs, somatic inputs from CCK-INs and basket PV-INs, axonic inputs from axo-axonic-INs (AACs). The Optogenetic suppression of AAC cells disinhibits pyramidal cells and induces the formation of new place fields that are maintained (blue cell). Reduced dendritic inhibition of SST-INs into place cells decreases their stability across sessions (green cell), while reduced somatic inhibition of PV-INs into place cells maintains the stability (lilac cell). Reduced somatic inhibition of CCK-INs in place cells decreases their stability across sessions (pink cell). Bottom: scheme showing that some connected pairs of place cells (PYR) have a complementary spatial firing to INs, i.e., in the region where a place cell is firing, the interneuron does not

INs-PCs that present negative spatial correlation were often accompanied by complementary place maps, suggesting a bidirectional interplay between these cells (Fig. 1C, bottom) [113]. Nevertheless, even if many hippocampal interneurons are capable of encoding space, it is necessary to consider and characterize the contribution of different interneuron subtypes to this property [114].

A recent study by Schuette et al. [23] investigated the role of GABAergic neurons in different contextual changes in spatial information coding by using in vivo calcium imaging and miniaturized microscopes. The experimental design consisted of expressing a genetically encoded $Ca^{2+}$ indicator in CA1 hippocampal INs using a Vgat-cre mouse line. The mice were exposed to various spatial contexts during multiple days, allowing the recording and characterization of the interneurons'activity across sessions. The identified Vgat place cells in the dorsal hippocampus exhibited less remapping induced by contextual changes

in the same session but paradoxically presented increased remapping and cell turnover across days. On average, INs had smaller place fields and higher mutual information between neural activity and mouse location than pyramidal cells. Contrary to electrophysiological data, "OFF" fields were not observed, likely because a spatially localized decrease in neural activity is challenging to detect using calcium imaging, which has a lower temporal resolution than electrophysiology (Fig. 1B). The INs also exhibited less remapping induced by contextual changes in the same session divided into two halves but paradoxically presented increased remapping and cell turnover across days [23].

We discussed the participation of pre- and post- synaptic INs in the place field formation and INs per se as a type of neuron that can code spatial information. However, the role of INs in spatial coding can be much more complex since there are various interneuron types. In this way, some studies have investigated the contribution of specific INs. A study has investigated the CA1 interneuron dynamics in behaving mice through two-photon calcium imaging in three dimensions [22]. In this work, the researchers identified and characterized six types of INs: the PV basket cells, SST cells, bistratified cells, axo-axonic chandelier (AAC) cells, CCK cells and ivy/neurogliaform cells.

Geiller et al. [22] found that, although all interneuron subtypes present spatial selectivity, the bistratified cells had a higher probability of staying spatially modulated on different sessions (Fig. 1C). Additionally, the PV basket cells that present spatial selectivity were more stable across sessions than SST cells [22]. While reduced PV perisomatic inhibition onto pyramidal neurons maintains the stability of place cell representations over time, reduced dendritic SST inhibition onto pyramidal neurons disrupts the stability [121] (Fig. 1C, top). In another study, Dudok et al. [21] created a genetic mouse line to target and manipulate specifically axo-axonic chandelier cells [21]. The AAC cells are fast-spiking INs that express PV, which innervate the axon initial segment exclusively of pyramidal cells [122–124]. The location of the AAC cells'synapses allows them to regulate action potential output and synchronize pyramidal cell assemblies [41, 125]. Dudok et al. found that AAC cells, which inhibit the firing activity of pyramidal cells in awake mice, were synchronously activated during specific behaviors, such as locomotion or whisking during rest periods. However, during the SWRs generation in immobility, the ACC cells are not recruited. Additionally, suppressing AAC cells leads to disinhibiting pyramidal cells and, consequently, the induction of new place fields [21] (Fig. 1C, top), showing the role of AAC interneurons in suppressing PC activity outside their place fields (OFF fields) during exploration, and the importance of this type of interneurons during the remapping of place fields. These results highlight the findings that different interneurons fire more "ON fields" or "OFF fields," which can be related to the features of those cells.

## Mesial Temporal Lobe Epilepsy

Epilepsy is one of the most prevalent neurological disorders that affect approximately 50 million individuals globally [126]. This condition is primarily marked by recurrent epileptic seizures stemming from abnormal, excessive, or synchronous neuronal activity [127]. This spectrum of disorders arises from diverse etiologies, leading to aberrant electrical brain activity. Epileptic seizures often initiate in specific brain circuits, particularly within cortical, hippocampal and parahippocampal regions [128], such as the mesial temporal lobe epilepsy (MTLE), which involves the hippocampal formation and is the most frequent form of chronic focal epilepsy [129].

Epileptic activity, including seizures, emerges from abnormal neuronal activity leading to a hyperactivity and hyper synchronization state [130–133]. These conditions result from substantial alterations in the neuronal network, potentially causing excitatory/inhibitory imbalances [134] and changing information-encoding mechanisms [135]. In the MTLE, these modifications arise from myriad processes, including high-interconnected glutamatergic cells [130, 136] and changes in GABAergic neuronal mechanisms (Fig. 2A). Additionally, in the hippocampus, alterations have been identified in the expression of $GABA_A$ receptors subunits [137], a loss of GABAergic INs [83], and increased intracellular chloride $[Cl^-]i$ concentration due to changes in expression of the $Na^+$-dependent $K^+$-$Cl^-$ cotransporter (NKCC1) and $K^+$-$Cl^-$ cotransporter (KCC2), which may affect the neuronal excitability [138].

Recordings from hippocampal slices have helped elucidate the role of chloride cotransporters in neuronal function. KCC2 and NKCC1 are essential for maintaining proper neuronal inhibition by controlling $Cl^-$ homeostasis, mediating potassium and sodium concentration, respectively, and, together with Cl- influx through Cl- leak and GABAA receptors, are related to $Cl^-$ accumulation [139, 140]. Its dysfunction can lead to pathological neuronal excitability, contributing to various neurological disorders. Impairment of KCC2 expression leads to high $[Cl^-]i$ levels. Under these conditions, $GABA_A$ receptor activation can lead to $Cl^-$ efflux instead of influx, causing depolarization (excitation) rather than inhibition, as observed in epilepsy [139, 141]. As a result, the GABAergic transmission is affected during ictal epileptiform activity in rat hippocampus [142].

A biophysical computational model replicates the pattern of focal seizures and reveals the mechanism of seizure initiation driven by intense interneuronal spiking. Sustained IN firing gradually increases $[Cl^-]i$ and extracellular potassium

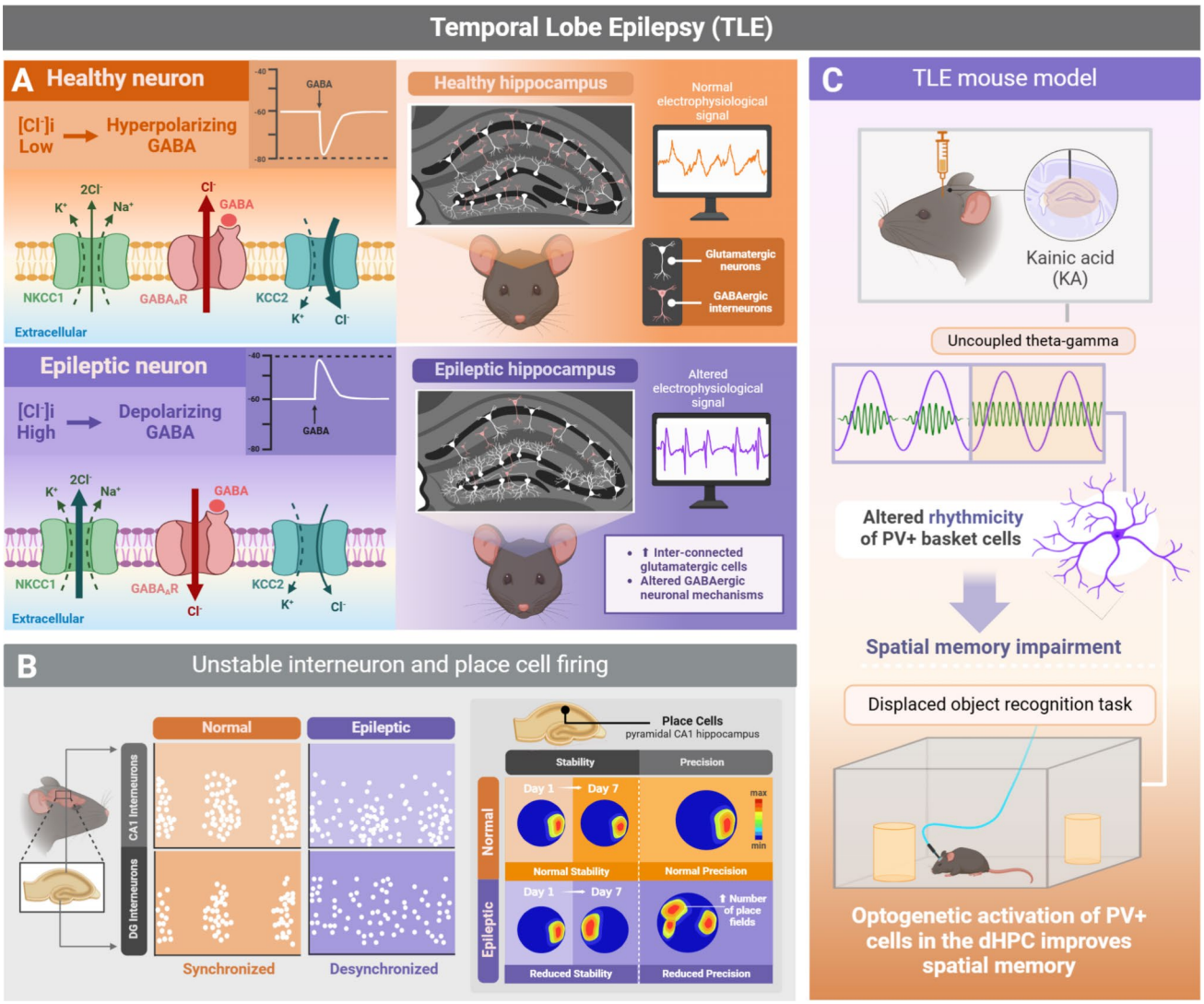


**Fig. 2** The role of inhibitory neurons in Mesial Temporal Lobe Epilepsy (MTLE). **A)** In MTLE, changes in information-decoding emerge from excitatory/inhibitory imbalance, which is linked to highly interconnected glutamatergic cells and altered GABAergic neuronal mechanisms. During epileptogenesis, a high chloride ion concentration is associated with increased NKCC1 activity and decreased KCC2 activity, resulting in depolarization of the GABAergic postsynaptic potential. **B)** In pilocarpine-treated epileptic mice, desynchronized interneuron firing in CA1 and DG (on the left) is related to unstable place cell firing and remapping in the pyramidal layer of the hippocampus, reducing both place cell stability and precision, represented by a heatmap of the place field across days (on the right). C) Top: schematic representation of a TLE Kainic Acid (KA) mouse model, showing theta-gamma rhythmopathy in epileptic rats, linked to altered PV-IN excitability. Bottom: optogenetic activation of PV-INs in the dHPC improved spatial memory performance in a KA model

([$K^+$]o) in PYR cells, shifting in K + reversal potential and leading to increased depolarization. The accumulation of [$Cl^-$]i weakens inhibitory currents, further promoting sustained firing in PYR as observed in epileptic seizures. The model highlights [K +]o, [Na +]i, and [$Cl^-$]i as critical factors in seizure dynamics [143]. Experimental studies in hippocampal slices have shown depolarizing inhibitory postsynaptic potentials (IPSPs) and altered expression of chloride transporters, particularly NKCC1 and KCC2 [144–146]. During epileptogenesis, the upregulation of NKCC1 and the downregulation of KCC2 lead to increased [$Cl^-$]i, which not only reduces GABAergic inhibition but can even revert it, promoting excitation [147]. In general, chloride dysregulation alters the ionic gradient, resulting in decreased GABAergic postsynaptic potentials. Both static and dynamic Cl- imbalances can elevate intracellular Cl- levels, ultimately promoting epileptiform activity [148]. Given the central role of Cl- regulation in seizure dynamics, drugs targeting KCC2 and NKCC1 have shown seizure attenuation [149], offering a potential strategy to enhance epilepsy treatment by

restoring chloride homeostasis and strengthening inhibitory neurotransmission [150, 151] (Fig. 2B).

Beyond its role in seizure dynamics, inhibitory transmission dysfunction in MTLE also impacts spatial navigation and memory. Notably, status epilepticus (SE) induced during early life of rat development is sufficient to alter place cell activity in adulthood. Rats subjected to SE in their developmental stages exhibit place fields that are less precise and stable, which correlates with poor performance in the spatial memory tasks [147]. The dynamic encoding of spatial information relies on the interplay between CA1 pyramidal neurons and INs, particularly the fast-spiking interneuron, which enables the codification of spatial and temporal information during exploratory behavior [152]. Precise intrahippocampal communication is essential for spatial processing, yet interneuron loss and circuit reorganization during epileptogenesis may disrupt this synchrony. To test the hypothesis, Shuman et al. conducted in vivo electrophysiological recordings from the CA1 and DG regions of pilocarpine-treated epileptic mice during a virtual navigation task. Their findings revealed desynchronized interneuron firing between CA1 and DG during spatial tasks. Additionally, miniscope recordings from the CA1 showed that the place cells were highly unstable and exhibited remapping over a week before the onset of seizures. A computational model further confirmed that desynchronized inhibitory inputs from DG had a more significant impact on place cell instability than the loss of CA1 interneurons [153].

Another key mechanism underlying spatial memory deficits in MTLE involves impairments in theta-gamma coupling, particularly in the CA1 region. These oscillatory disruptions have been well-documented in temporal lobe epilepsy (TLE). To investigate the role of theta-gamma coupling in the absence of epileptiform activity, Lopez-Pigozzi et al. studied epilepsy in rats and found attenuated theta and gamma oscillations, along with a rhythmopathy involving theta-gamma coupling at lower frequency bands in the SLM of CA1. Interestingly, altered rhythmicity of PV-IN basket cells, likely due to changes in their excitability, is thought to contribute to these deficits [154]. Similar alterations are also observed in AD models [155]. Accordingly, optogenetic intervention was proposed to address the spatial memory deficits observed in the kainic acid mouse model of chronic TLE. By expressing channelrhodopsin in PV-INs, researchers implemented a closed-loop optogenetic activation targeting these specific INs. Mice that received this intervention performed significantly better in a subsequent object location memory task compared to their initial performance [156].

OLM SST-INs innervate approximately 92% of pyramidal cell dendrites and play a crucial role in feedback inhibition—a mechanism in which an inhibitory interneuron receives input from excitatory neurons and subsequently inhibits those same neurons. Drexel et al. investigated the role of these cells in the development of recurrent seizures by selectively silencing GABA release from subicular and ventral hippocampal SST-INs [157]. The silencing of SST-INs led to the emergence of pre- or interictal spikes and recurrent spontaneous seizures. Previously, the same group observed that the selective silencing of PV-INs in the subiculum, the major output region of the hippocampus, was also associated with the development of recurrent spontaneous limbic seizures in mice [158]. These findings suggest that both perisomatic inhibition by PV-INs and dendritic inhibition by SST-INs play a potential role in the development of TLE.

Since perisomatic inhibition from basket cells is a key mechanism for regulating pyramidal cell firing, another study focused on investigating potential alterations in the major subclasses of CA1 basket cells, which express either CCK or PV, in the pilocarpine model of TLE [159]. Despite the preservation of GABAergic boutons in the pyramidal cell layer of CA1 in this model, PV-expressing basket cells exhibited resilience to the insults, whereas CCK-expressing basket cells showed a significant reduction, especially hours after status epilepticus. This finding suggests that subtype-specific loss is sufficient to disrupt the circuit. According to the authors, this phenomenon may be explained by a compensatory mechanism in which the unavailability of the lost CCK cells enhances inhibition from PV cells [159].

The vulnerability of calretinin-positive (CR) hippocampal INs in TLE has also been highlighted, given their role in synchronizing specific interneuronal populations. Tóth and Maglóczky reported a decreased density of CR-INs in the sclerotic hippocampus, as well as an asynchronous and less effective dendritic inhibition in pyramidal cells [94]. Confirming this vulnerability, in the human epileptic hippocampus, further alterations in CR-IN distribution, density, and synaptic target selectivity have also been observed, with reductions in CR-INs correlating with massive PC loss [160].

Despite ongoing efforts to understand the role of INs in spatial memory encoding within epileptic hippocampal networks, this remains an evolving field of research. Nevertheless, the upcoming methodological tools enable the investigation of different aspects of the hippocampal INs in epilepsy. The development of novel transgenic animal models now allows the real-time tracking of specific IN populations across various experimental conditions. This advancement enables a more precise characterization of dysfunctions associated with epilepsy, linking specific cellular alterations to distinct disease states. Ultimately, these insights may drive the development of targeted therapeutic interventions (for a review see [161]).

## Alzheimer's Disease

AD is a progressive neurodegenerative disorder and a leading cause of cognitive impairment and dementia worldwide, currently affecting approximately 50 million individuals. Projections suggest that global dementia prevalence will triple by 2050 [162]. The neuropathological hallmarks of AD include extracellular amyloid-β (Aβ) deposition within plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (p-Tau), which culminate in synaptic loss, dendritic atrophy, and widespread neuronal degeneration [163–165] (Fig. 3A).

Approximately 5% of AD cases manifest early-onset familial AD, whereas the vast majority are classified as late-onset sporadic AD. Despite extensive research, the precise cascade of pathophysiological events leading to late-onset AD remains incompletely understood [166–168]. Consequently, the failure of clinical trials targeting AD pathology has become commonplace, highlighting significant challenges in therapeutic development.

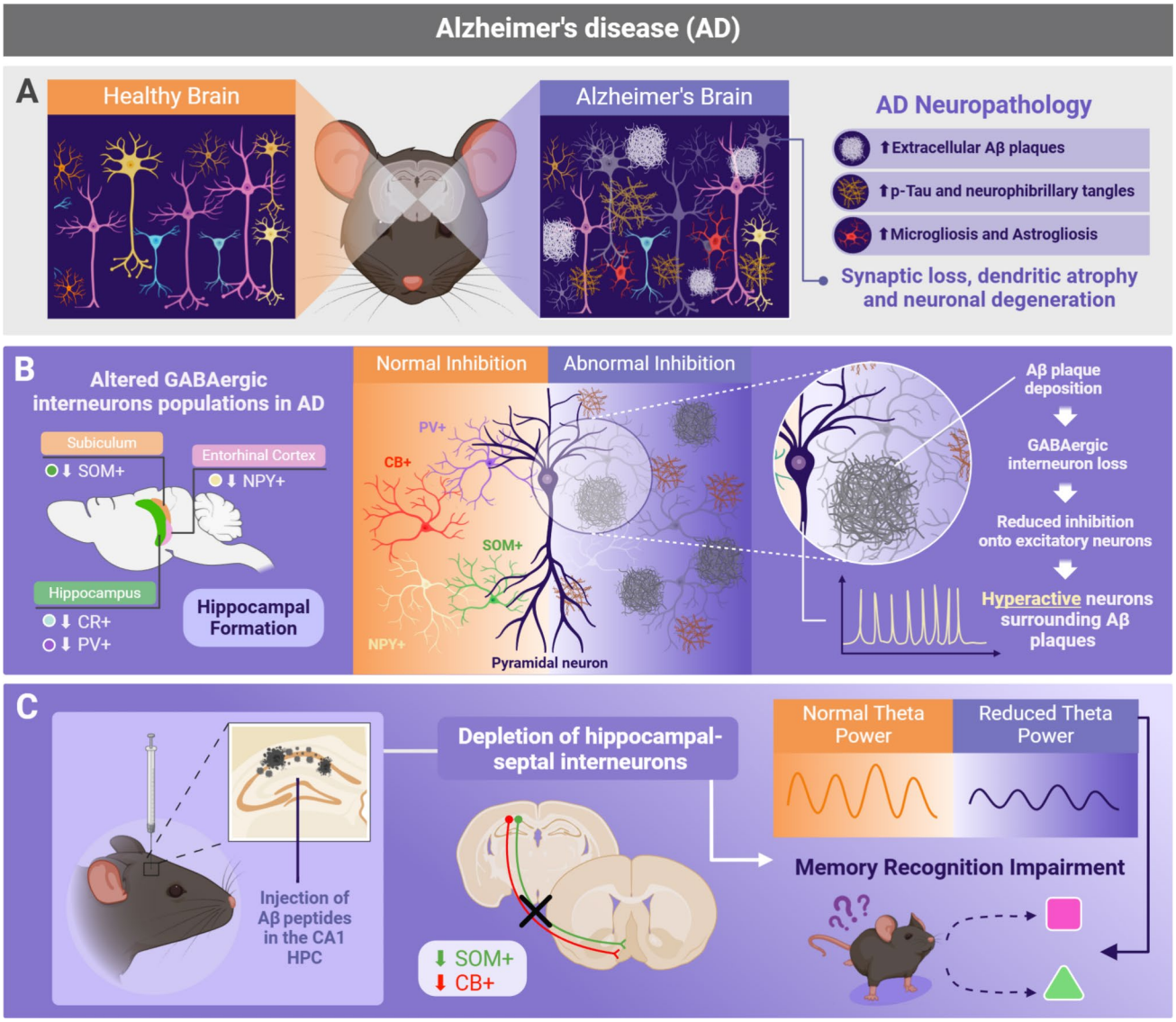


**Fig. 3** The role of inhibitory interneurons in Alzheimer's disease (AD). **A)** AD pathogenesis is characterized by dysfunctional amyloid-β (Aβ) and tau protein deposition in different brain regions, besides microgliosis and astrogliosis processes. The consequences to the nervous system comprise mainly synaptic loss, dendritic atrophy, and neuronal degeneration. **B)** Left: significant reduction in different GABAergic interneuron populations is observed in the hippocampal formation. Right: excitatory neurons surrounding Aβ plaques are hyperactive due to an impaired synaptic inhibition promoted by an extensive interneuron loss. **C)** The depletion of hippocampal-septal SOM-INs and CB-INs in a rat amyloid model impaired memory recognition, coinciding with a reduced theta power

The aggregation of Aβ into various forms, including monomers, oligomers, fibrils, and plaques, has been a central focus of AD research [169, 170]. The Aβ hypothesis posits that Aβ accumulation triggers a pathological sequence by impairing synapses, leading to the formation of NFTs, and ultimately resulting in neuron loss [171]. However, substantial evidence challenges this hypothesis, including the presence of significant amyloid plaques in the brains of asymptomatic individuals and cognitively normal individuals, which has fueled critical debate and raised concerns even among supporters [172, 173]. Further challenges to the amyloid hypothesis arise from observations of tau positivity independent of amyloid deposition [174], discrepancies in the spatial distribution of tau and amyloid pathologies [175], and the limited clinical efficacy of amyloid-targeting therapeutics in improving cognitive outcomes [176, 177]. Moreover, the safety profiles of anti-amyloid therapies have raised concerns, with a notable proportion of treated individuals experiencing adverse events such as inflammation and/or cerebral microhemorrhages [178, 179]. Nonetheless, there remains substantial evidence supporting the hypothesis, including the neuropathological similarities between the autosomal dominant form of AD—driven by mutations in genes involved in β-amyloid accumulation—and the sporadic form [180], as well as the temporal progression of the disease, suggests that widespread neocortical tau pathology emerges only after significant β-amyloid deposition [181]. Furthermore, the advent of novel anti-amyloid therapies, combined with the growing emphasis on testing these interventions in earlier stages of AD, holds the potential to reignite hope in the pursuit of effective disease-modifying treatments.

Dysfunctions in cholinergic and glutamatergic neurotransmission have been extensively documented in AD, contributing to widespread network alterations [182, 183]. Notably, GABAergic terminals appear more resilient to Aβ pathology than glutamatergic and cholinergic terminals, suggesting their involvement only in the later stages of the disease progression [184–186]. Considering these findings, scientific investigations have predominantly focused on elucidating the impact of Aβ on excitatory neurons or excitatory synaptic transmission. Pharmacotherapeutic strategies for cognitive improvement in AD patients, such as acetylcholinesterase inhibitors and NMDA receptor antagonists (e.g., memantine), provide only transient symptomatic relief and do not halt disease progression, emphasizing the need for alternative approaches (reviewed by [187, 188]).

One of the hallmark cognitive deficits in AD is impaired spatial memory. Studies in AD mouse models, which recapitulate some pathogenesis features of the disease, such as dysfunctional amyloid-β and tau protein deposition, aspects of disease pathology such as Aβ and tau deposition, have consistently demonstrated disruptions in hippocampal place cell firing and entorhinal grid cell dysfunction, correlating with severe impairments in spatial navigation [189–195]. Using APP mice overexpressing amyloid precursor protein, Jun et al. [193] observed that place and grid cell remapping in response to environmental changes was significantly impaired in APP mice, alongside disrupted fast-gamma coupling between the medial entorhinal cortex and CA1 hippocampus. Similarly, Broussard et al. [190] reported reduced spatial information content and stability of place cells across days in aged TgF3344-AD rats that exhibited hippocampal amyloid-β deposition [190]. Accordingly, unstable place cell representation was observed in 3xTg mice, such as a small proportion of place cells phase-locked to theta and gamma rhythms [194]. Additionally, Ridler et al. [195] demonstrated that tau pathology severely disrupted grid cell firing and local field potential oscillations, resulting in impairments in path integration in a mouse model of tauopathy. In aged EC mice, the development of mature tangles was also associated with unstable grid fields and reduced firing rates [195].

On the other hand, different interneuron populations are also being studied for their roles in AD dysfunctions and spatial memory impairments. A recent study identified a specific type of interneuron, known as I-S3 (type-3 interneuron-specific cells), which co-expresses VIP and CR, has been associated with early dysfunctions in CA1 hippocampal circuits. Rather than directly regulating the activity of PCs, these INs are specialized in modulating the activity of SOM-INs and PV-INs in the CA1 region, thereby influencing incoming signals, learning, and memory formation. In 3xTg-AD mice, modulate SOM-INs and PV-INs [196].

The GABAergic system plays a pivotal role in orchestrating precise temporal control over neuronal activity, operating at both the cellular and population levels within the brain. Given the critical importance of timing in receptor activation, meticulous regulation of extracellular GABA levels is crucial [197]. Neurons acting as "rhythm generators" are essential for generating intrinsic oscillations in the brain, with rhythmically discharging inhibitory neurons particularly adept at imposing periodicity on their target cells [198, 199]. These GABAergic "waves" enforce alternating periods of heightened and diminished excitability on neuronal ensembles oscillating at congruent frequencies [200, 201]. Conversely, dysrhythmias are associated with cognitive impairments [201, 202]. Disruptions in glutamatergic and cholinergic excitatory signaling, resulting in inadequate inhibitory control, may contribute to the excitatory-inhibitory imbalance observed in patients with AD, potentially exacerbating the disease pathology or even acting as one of the causes of the disease [189, 203].

Given that disruptions in sharp-wave ripples (SWRs), a hippocampal oscillation event associated with memory consolidation, which is commonly observed in mouse models of AD, Caccavano et al. conducted a study using the

5xFAD familial AD mouse model. They crossed this model with various mouse lines that label excitatory pyramidal cells and inhibitory PV-INs to investigate how a selective reduction in PV IN activity contributes to hyperactivity and SWR disruptions in the CA1 region. Notably, they observed a reduced spike rate in PV basket cells during SWR events, with no significant changes in other PV subtypes, such as bistratified and axo-axonic cells. Consistent with this, PCs exhibited an increased excitatory/inhibitory (E/I) ratio and participated in larger ensembles during sharp-wave ripples (SPWs), suggesting a disinhibitory mechanism affecting these cells. Therefore, specifically PV basket cells may be involved in memory consolidation impairments associated with AD [155].

Biochemical analyses of brains obtained from elderly individuals or AD patients consistently suggest that the GABAergic system indeed exhibits a relatively low vulnerability [155, 204, 205]. However, abnormalities in GABA levels and loss of function of the GABAA receptor have been detected in AD-affected brains [206, 207], suggesting a potential disruption in the delicate balance between excitation and inhibition within local neuronal circuits [208, 209]. Dysfunction in AD extends to long-range inhibitory microcircuits linking the hippocampus with various brain structures, including the amygdaloid complex, entorhinal cortex, and medial septum [87, 210, 211]. In the APP/PS1 model, both firing patterns and spike morphology exhibit abnormalities in the sensory cortex [212]. Moreover, clusters of hyperactive neurons have been discovered near amyloid plaques, suggesting a potential decrease in synaptic inhibition [213]. Notably, in the cortex of 8-month-old mice of the APP23xPS45 model, Aβ plaques are surrounded by clusters of hyperactive neurons exhibiting impaired synaptic inhibition [213] (Fig. 3B). Consequently, there is growing interest in understanding the role of GABA-secreting inhibitory neurons and their dysfunction in AD pathology—and possibly, its pathogenesis (e.g., [189, 203]).

In the brains of AD patients, there is a substantial loss of PV-INs, which represent the largest class of GABAergic inhibitory neurons in the central nervous system, from both the CA1 (58%) and the DG (60%) regions [214]. Correspondingly, investigations utilizing animal models of AD consistently reveal impaired survival and function of GABAergic INs in brain regions primarily affected by Aβ and tau pathology, including the hippocampus and entorhinal cortex (Fig. 3B). This impairment coincides with increased Aβ levels and abnormal tau phosphorylation [215–218]. Interestingly, the population of GABA inhibitory INs significantly diminishes as cognitive deficits progress due to Aβ and hyperphosphorylated tau accumulation, accompanied by decreased neural activity, ultimately leading to a cascade of downstream symptoms associated with AD [219, 220]. In AD models, the loss of specific interneuron subtypes occurs sequentially, with CR-INs being the first to decline in the hippocampus, followed by a decrease in the SST-IN population in the subiculum [221, 222](Fig. 3B). Subsequently, SST/NPY-INs are lost within the entorhinal cortex of 6-month-old animals [218, 223]. In APPSL/PS1 ho knock-in mice, approximately 43% of PV-positive cells in CA1 and nearly 50% of CR-INs in the DG are lost by ten months of age [224] (Fig. 3B). Furthermore, a significant loss of CB/SST-INs has been observed following Aβ injection in a nontransgenic AD model [225]; somatostatin-positive interneurons are exceptionally vulnerable to excitatory/inhibitory imbalance in AD, which could be implicated in place cell instability and disrupted spatial coding (for reviews, [189]).

The depletion of a significant population of hippocampal-septal neurons appears to induce a state wherein the sustenance of theta oscillations is compromised, consequently impacting cognitive performance [225, 226]. In a rat amyloid model, decreases in theta power coincided with declines in recognition memory [226] (Fig. 3C). Theta oscillations, ranging from 6 to 10 Hz, have been intricately associated with exploratory behaviors such as spatial–temporal mental navigation, various forms of attention, and episodic memory [227]. Dysfunction in GABAergic INs may contribute to these network alterations by impairing adult neurogenesis in the DG, as evidenced in apolipoprotein E4 knock-in mice [216]. Moreover, when Aβ oligomers are applied to hippocampal cell cultures, they disrupt the spontaneous activity of neurons by depressing vesicular release at GABAergic and glutamatergic synapses, thereby reducing the likelihood of vesicle exocytosis from presynaptic terminals [228].

Alterations in GABA transporter expression have been detected in the brain of patients with AD, revealing notable reductions in GAT1 density within regions including the entorhinal cortex and superior temporal gyrus, alongside astrocytes located in these brain regions. These findings underscore the complex interplay of GABAergic neurotransmission in AD pathophysiology, potentially impacting neurotransmitter dynamics crucial for brain function [229]. Evidence suggests a relationship between the formation of neurofibrillary tangles (NFTs) and GABAergic dysfunction in AD, with NFT proliferation linked to alterations in the distribution of GABAAR subunits within the hippocampus of AD patients [230, 231]. Moreover, both human amyloid precursor protein (hAPP) mice, characterized by high amyloid-beta (Aβ) burden, and individuals with AD patients exhibit reduced expression of Nav1.1, an essential sodium channel primarily found on PV-INs, thereby affecting the synaptic activity of these cells [232].

These findings have sparked the consideration that augmenting the population of GABA inhibitory INs could represent a potential therapeutic avenue in AD. Indeed, studies have shown promising results, wherein transplanting

precursor neurons specializing in GABA into the hippocampus improved the learning and memory capabilities of mice overexpressing Aβ [233]. Verret et al. [232] demonstrated that restoring Nav1.1 levels in hAPP transgenic mice via Nav1.1-BAC expression enhanced inhibitory synaptic activity, gamma oscillations, and mitigated hypersynchrony, memory deficits, and premature mortality. It was concluded that decreased Nav1.1 levels and PV-positive cell dysfunction significantly disrupt oscillatory rhythms, memory, and network coordination in hAPP mice, potentially reflecting mechanisms in AD pathogenesis. Another emerging strategy involves cell therapy utilizing grafts derived from ganglionic eminence, the embryonic origin of GABAergic neurons. Tong and colleagues transplanted progenitors of GABAergic neurons into the hilus of the DG, where they successfully matured and integrated into INs, including SST, NPY, and PV subpopulations [233]. Seventy days post-grafting into 17-month-old apoE4-KI mice and 12-month-old apoE4-KI/hAPPFAD mice, spatial navigation and memory impairments were significantly alleviated. These findings underscore the critical role of inhibitory interneuron impairments in age-related cognitive impairment detected in mouse models of AD.

Moreover, GABA signaling appears crucial for the Aβ uptake by microglia. Artificial induction of gamma oscillations within the hippocampus led to a notable decrease in Aβ peptide levels [234]. This reduction in amyloid levels likely occurred through diminished amyloidogenesis and enhanced amyloid endocytosis by microglia. The treatment also upregulated microglial genes associated with morphological alterations, as confirmed by histological analysis demonstrating increased co-localization of microglia with Aβ and enhanced Aβ peptide uptake by microglia. Importantly, these effects were contingent on GABAergic neurotransmission, as pretreatment of 5× FAD mice with a GABA-A antagonist, picrotoxin, completely abolished the advantageous impact of neuronal gamma rhythms. Furthermore, induction of gamma oscillations via visual stimulation reduced pTau levels, thereby preserving neuronal and synaptic density and ultimately ameliorating cognition in the AD model Tau P301S [235].

To investigate the distinct roles of three subtypes of CA1 hippocampal INs in the AppNL-F/NL-F knock-in mouse model of AD, a model characterized by amyloid-beta (Aβ) deposition and increased neuroinflammation, Shi and colleagues observed that CCK-INs and SST-INs were hyperactive. At the same time, CR-INs remained resilient in the early stages, before the hallmark features of AD were fully established. However, the resilience of CR-INs was tested when purinoceptors, which were upregulated and strongly expressed in CR cells and astrocytes at later stages of AD, were blocked. Purinoreceptors, which are activated by purines such as ATP and adenosine, play a key role in neuroinflammation and neuronal signaling. Therefore, their upregulation may contribute to the exacerbation of neuroinflammatory responses, as indicated by studies on their involvement in neurodegenerative diseases [236].

While there are some debates in the scientific community, a substantial body of evidence supports the view that GABAergic remodeling is a prominent feature of neurodegenerative diseases, particularly AD. This remodeling emerges as a pivotal factor influencing both the initial and advanced stages of AD progression, rather than merely a secondary response to pathology. The findings presented in this context underscore the critical role of GABAergic mechanisms as a regulatory factor. Therapeutic interventions targeting GABAergic pathways hold promise for restoring the excitatory/inhibitory steadiness in the brain of individuals with AD, thereby mitigating the neurotoxic effects of Aβ and p-Tau. Understanding the changes occurring in the GABAergic system associated with AD is crucial to harnessing the potential of GABA-targeted therapies for slowing or halting disease progression and preserving or restoring cognitive function in affected individuals.

## Traumatic Brain Injury

Traumatic brain injury (TBI) is a severe neurological condition that occurs when an external mechanical force, such as a bump, blow, or jolt to the head, damages the brain. This disorder leads to a wide range of health issues, including physical, cognitive, emotional, social, and psychiatric problems [237, 238] (Fig. 4A). One of the most concerning consequences of TBI is its role as a common cause of medically intractable epilepsy in humans and may facilitate the development of AD [239–241] and commonly patients with mild TBI frequently experience cognitive impairments, particularly in memory and learning (Fig. 4A). Following TBI, the brain undergoes substantial reorganization, characterized by progressive neuron loss, synaptic circuit remodeling, particularly affecting inhibitory neurotransmission and excitatory-inhibitory balance, contributing to the observed cognitive deficits and changes in the cellular environment [242]. These changes are part of two distinct phases: the primary injury and a secondary phase characterized by ongoing damage and neuron loss in the days following the injury [243]. The secondary injury is driven by inflammatory, excitotoxic, and oxidative stresses, partly due to excessive calcium influx through ionotropic glutamate receptors. This phase can extend considerably, with initial hippocampal pyramidal cell loss in CA1 and CA3 regions within a week of TBI, and continued cell death in CA1 up to six months post-injury [244].

Animal models of TBI reveal that inhibitory circuits are also compromised. The model consists of using a controlled

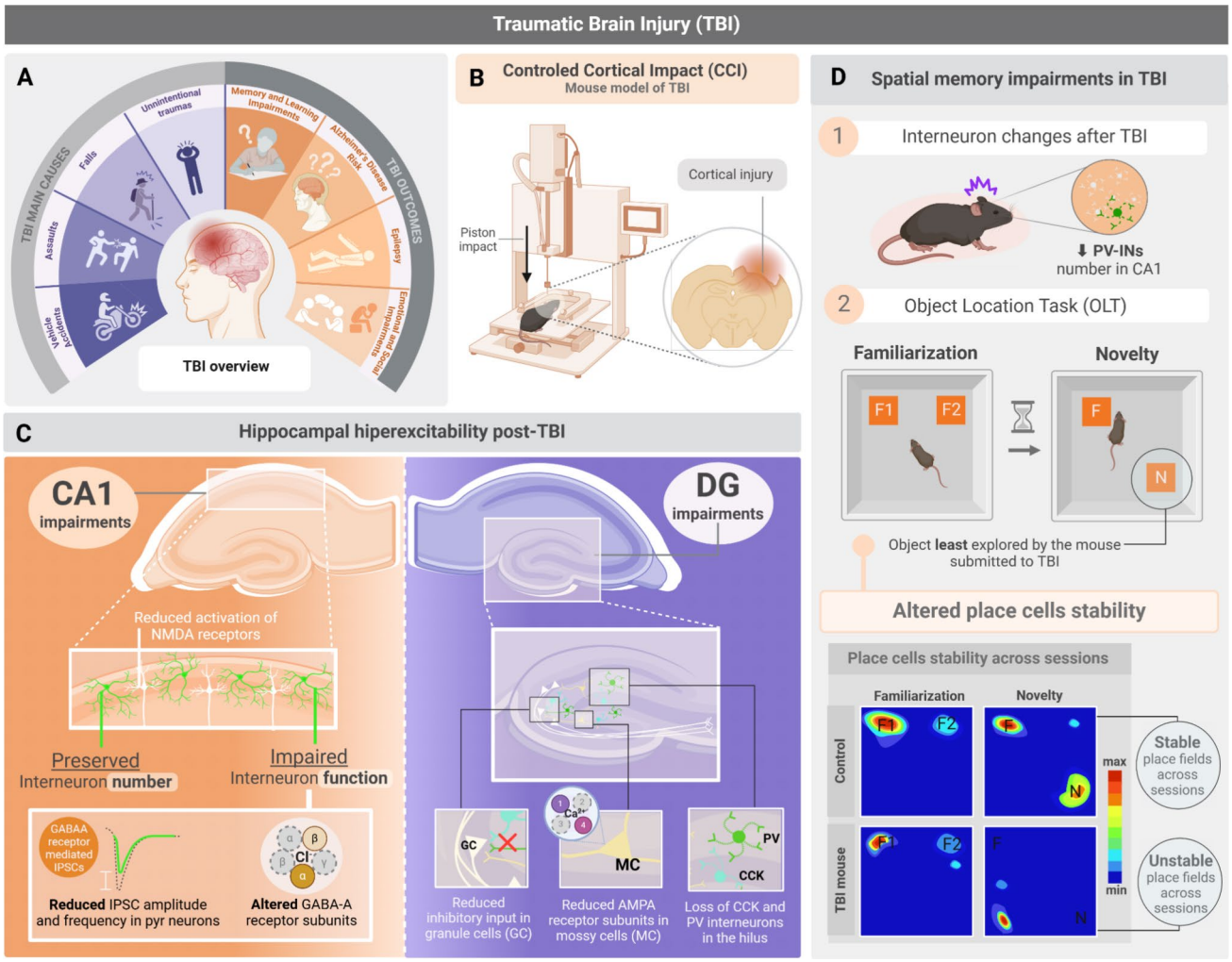


**Fig. 4** The role of inhibitory interneurons in traumatic brain injury (TBI). **A)** Representative scheme showing the main causes and outcomes of TBI. **B)** Representation of the main mouse model of TBI, the controlled cortical impact, where a pneumatic device delivers a precise impact to the exposed cortex. **C)** Interneuron loss and impairments in hippocampus post-TBI injury, especially in CA1 area and DG, leading to a hyperexcitable network. **D)** Spatial memory impairments and altered place cell stability, resulting from the loss of PV-INs in CA1 region after TBI

cortical impact (CCI) controlled by a pneumatical or electromagnetic piston to induce reproducible and well-controlled injury, usually in the cortex [245, 246] (Fig. 4B). This cortical injury leads to increased excitatory neurotransmission and decreased spontaneous inhibitory neurotransmission in the cortex, linked to a selective loss of PV-INs and SST-INs [245, 246]. Interestingly, TBI to the neocortex results in the loss of CCK and PV-INs in the DG, specifically in the hilus, but not in the granular layer, and a decrease in AMPA-type glutamate receptor subunit 2/3 mossy cells. Then, reduced inhibitory input is observed in granule cells, even though excitatory input to hilar INs increases, suggesting a compensatory mechanism in inhibitory circuits following injury [247] (Fig. 4C, left). In CA1 there is no evident alteration in interneuron numbers [247, 248], but some changes are observed such as deficits in LTP of synaptic transmission, related to reduced activation of NMDA receptors, but not AMPA receptors; decreased frequency and amplitude of the spontaneous and miniature inhibitory postsynaptic current (IPSCs) mediated by GABAA-receptors; and reduced surface expression of α1, ß2/3, and γ2 subunits of the GABAA receptor, contributing to changes in miniature IPSC. These results suggest that TBI significantly diminishes GABAergic inhibitory transmission and NMDA receptor-mediated currents in the CA1, leading to altered hippocampal excitability and subsequent cognitive impairments [248] (Fig. 4C, right).

Cognitive deficits observed in TBI include spatial navigation during object location tasks. This test comprises two parts: 1) familiarization with two identical objects placed in an arena, and 2) training when one object is displaced

[249]. TBI impairs object location recognition memory in animals and leads to a broad place field that was not stable across training and testing sessions, indicating that place cells poorly codify spatial information [250]. Although previous studies have observed no alterations in the CA1 interneuron population [247, 248], Broussard et al. reported delayed maturation of PV-INs, both in the hippocampus and in the medial prefrontal cortex, with a decreased numbers of PV-INs in the CA1 subfield, which is correlated to poor performance of TBI animals in the object location task and altered place field [250] (Fig. 4D).

## Cerebral Hypoxia–Ischemia

Perinatal oxygen deprivation is one of the most common causes of morbidity and death in newborns [6, 126, 251, 252] (Fig. 5A). The sequels include cerebral palsy, motor and cognitive deficits, and epilepsy [253] (Fig. 5A). It can occur at any stage of life to varying degrees; total deprivation is termed anoxia, while partial deprivation is referred to as hypoxia. Also, depending on the time that the event occurs, it may affect different stages of neurodevelopment, when different processes are happening, such as neurogenesis, migration, myelinization, synaptic formation or synaptic pruning (Fig. 5B). The lack of oxygen in cells triggers various biochemical cascades, which can lead to cell death through different biological processes, such as calcium influx, excitotoxicity, neuroinflammation, and the release of free radicals (Fig. 5B) Several studies have shown that oxygen deprivation is not a single acute event resulting in cell death only in a specific timeframe, but an event involving various processes, such as cytokine release, decreased release of trophic factors, and increased inflammation that may persist for days or even weeks after the insult.

Since the key stages of neurodevelopment in fetal stages of brain formation are remarkably conserved between mammalian species [254–256], studies have used rodents to neonatal anoxia or hypoxia models [99, 257, 258]. These studies have shown that oxygen deprivation leads to cell death in the hippocampal region and delays the maturation of INs [99, 257–259]. Additionally, it was also observed in the neonatal anoxia model that animals exhibited a delay in learning spatial memory tasks. In contrast, in tests of fear conditioning to context, it was observed that animals subjected to anoxia had a deficit in the extinction of aversive memory [257, 260–263]. This effect of perinatal oxygen deprivation on the INs was also observed by Komitova et al. A possible explanation for the increase in PV neurons is the integration of these INs after oxygen deprivation. Typically, neurons that do not integrate into the neuronal network end up dying due to lack of stimulation and maintenance. Interestingly, a study using an animal model of schizophrenia showed an increase in PV cells in the hippocampus and deficits in spatial memory tests. Furthermore, it was observed that the memory deficit was likely due to a generalization of place cell activity, reducing the precision of spatial information in the hippocampus despite the increased PV cells [264].

Although oxygen deprivation causes cell death, an exacerbation of neuronal activity can alter neuron connectivity. For this reason, oxygen deprivation is one of the factors that can lead to the development of epileptic seizures [265, 266]. A study conducted by Duan and collaborators showed that reducing GABA release and synaptic inputs on pyramidal cells leads to increased network synchrony. This aberrant activity blocks the natural apoptosis of INs, causing an increase in the survival of PV and SST-INs [267].

Another study also aimed to evaluate two populations of INs, which express NPY and SST, during human hippocampal development following hypoxic-ischemic encephalopathy (HIE) conditions, which lead to a decrease in oxygen and/or blood supply to the brain. This evaluation was conducted on human tissues from individuals who underwent HI. The results showed a decrease in the density of both interneuron populations throughout the hippocampus and DG—one of the most sensitive regions to HI insult—which may result from decreased expression of these peptides or cell death. On the other hand, in a more comparative analysis, the density of neurons expressing SST was higher than that of interneuron cell bodies expressing NPY in all hippocampal regions—especially in CA1—except for CA2, which showed the opposite. In summary, these findings suggest that the evaluated neuronal populations, particularly SST-INs, show lower density in the DG and other hippocampal layers, a neuronal loss that may be related to the excitatory/inhibitory imbalance in hippocampal circuitry [268].

Studies using animal models of hypoxic-ischemic encephalopathy (HIE) have shown that it causes lasting impairments in hippocampal circuitry. In P10 HI-injured mice treated with normothermia or therapeutic hypothermia (TH), persistent deficits in PV-INs and working memory were observed at P40. These deficits were linked to an excitatory-inhibitory (E/I) imbalance, disrupted long-term depression (LTD), heightened long-term potentiation (LTP), and altered synaptic protein ratios. While neonatal HIE increased hippocampal neuroregulin-1 (Nrg1) levels early, ErbB4 activation was reduced both shortly after injury and at later stages, suggesting impaired PV-IN survival and maintenance. ErbB4 is crucial for the development and maintenance of PV-IN and is dysregulated in this condition (PMID: 36613949). Unlike pyramidal cell death, which occurs acutely after HIE, IN injury is delayed and independent of injury severity. Another study on P10 HIE mice found reduced synaptic protein levels (VGlut1, GAD65/67, PSD95) and PV-IN numbers by P18. Compared to control mice, HIE mice exhibited impaired PV-IN development,

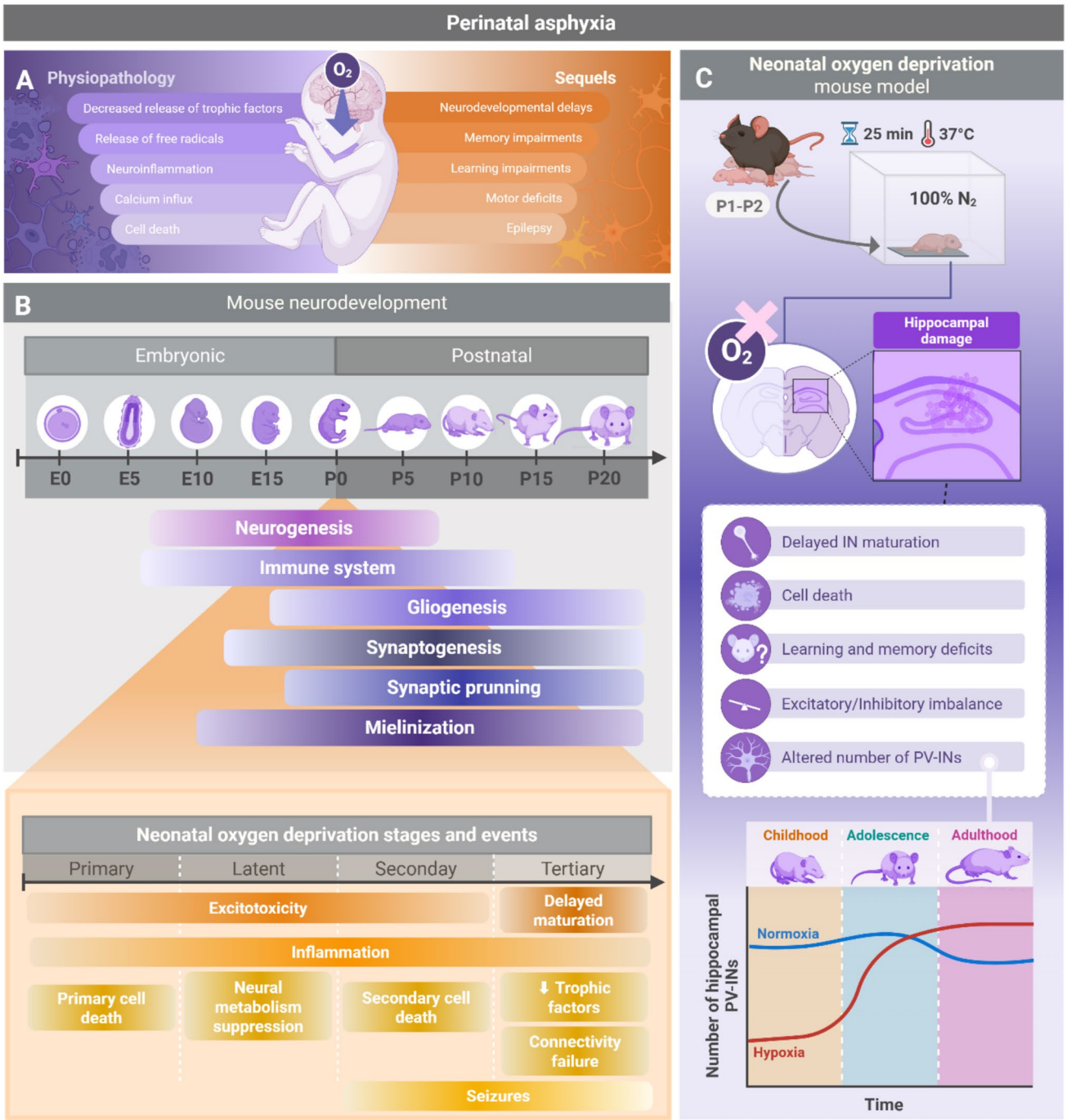


**Fig. 5** Perinatal asphyxia. **A)** Representative scheme showing the physiopathology and the main sequels of oxygen deprivation during birth. **B)** Representative timeline of mouse neurodevelopment in lilac, and stages and events associated with neonatal oxygen deprivation during birth in orange. E corresponds to the abbreviation of "embryonic" and P to "postnatal." **C)** Top: illustration of a neonatal oxygen deprivation mouse model and its impact on the hippocampus. Bottom: graph showing changes in the number of interneurons (INs) across different developmental stages. Under normoxic conditions, IN numbers remain stable from childhood to adulthood and are consistently higher than in hypoxic conditions until adolescence. During adolescence, the number of parvalbumin-positive interneurons (PV-INs) increases, surpassing normoxic levels in adulthood

somatodendritic attrition, and decreased calbindin-1 (CB1) protein and mRNA [269].

HIE also impairs key processes in the hippocampal postnatal critical period of synaptic plasticity, such as BDNF-TrkB signaling, interneuron maturation, and the development of perineuronal nets and myelination. These disruptions result in significant deficits in hippocampal network development and working memory [270]. There is a common understanding among studies that the limited efficacy of TH in protecting PV-INs or hippocampal function suggests that TH does not address the mechanisms driving these deficits [269, 271].

## Concluding Remarks

The understanding of hippocampal function has long been centered on excitatory pyramidal neurons, while interneurons (INs) were primarily considered as modulators of network inhibition. However, recent findings challenge this perspective, revealing that inhibitory circuits play an integral role in shaping spatial representations, stabilizing memory traces, and orchestrating neural oscillations essential for cognition. This review synthesizes emerging evidence demonstrating that different IN subtypes—rather than being passive regulators—actively contribute to spatial coding by exerting precise control over pyramidal cell activity and encoding location-specific information.

By consolidating findings from recent experimental and computational studies, we highlight the growing recognition that INs participate directly in the formation, maintenance, and refinement of spatial maps. Their ability to synchronize neural ensembles via theta-gamma coupling, regulate the stability of place cells, and influence sharp wave ripple dynamics underscores their fundamental contribution to hippocampal computations. Moreover, we bring attention to the underexplored role of interneuron dysfunction in neurological disorders, showing how disruptions in inhibitory circuits are linked to spatial memory deficits in epilepsy, Alzheimer's disease, traumatic brain injury, and cerebral hypoxia–ischemia.

A particularly novel aspect of this review is its shift away from traditional, pyramidal-centric models of hippocampal function. Instead, we propose a more integrated framework that recognizes interneurons as key elements in spatial representation and cognitive processes. This shift has significant implications for both fundamental neuroscience and clinical research. Understanding how interneurons encode spatial information and how their dysfunction contributes to cognitive deficits opens new avenues for therapeutic intervention. Future research should focus on selectively targeting IN subpopulations using approaches such as optogenetics, interneuron transplantation, and pharmacological modulation to restore balance in the hippocampal network.

By reframing the role of hippocampal interneurons in spatial coding and cognitive function, this review provides a new conceptual foundation for studying inhibitory networks in both health and disease. Moving forward, a deeper mechanistic understanding of how specific IN subtypes contribute to spatial representation—and how their activity can be harnessed for therapeutic purposes—will be crucial for developing innovative treatments for neurodegenerative diseases and cognitive disorders.

**Author Contribution** AHK proposed the reviewed topic. JMI, RSJ, LSRM, GSVH, FMCVR, FSB wrote the first draft. JMI and RSJ prepared the figures. JMI, RSJ, AA, HU, SHT, RDP, AHK revised the manuscript. All authors reviewed the manuscript.

**Funding** S.H.T., G.S.V.H., R.D.P., H.U., and A.H.K. acknowledge grant support by the São Paulo Research Foundation [Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) Project No. 2020/16268-6, 2022/09277-4, 2022/00850-3, 2018/07366-4, 2020/11667-0] and by the National Council of Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq Project No. 406396/2021 and 308012/2021-6).

Brain & Behavior Research Foundation (Grants # 27654, # 31093 to F.M.C.V.R.). Judy Genshaft and Steven Greenbaum for funding the 2022 Young Investigator Award (Grant # 31093, F.M.C.V.R.) and The Nancy and Jon Glaser Family Friends of Semel Scholar Award (F.M.C.V.R.). This work was supported by NIDDK grant U24DK132746-01, UCLA LIFT-UP (Leveraging Institutional support for Talented, Underrepresented Physicians and/or Scientists) and National Institutes of Health Office of Disease Prevention, (ODP) (F.M.C.V.R.).

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Office of Disease Prevention (ODP), the Office of Nutrition Research (ONR), the Chief Officer for Scientific Workforce Diversity (COSWD), and the Office of Behavioral and Social Sciences Research (OBSSR) of the National Institutes of Health under award number U24DK132746-01, UCLA LIFT-UP (Leveraging Institutional support for Talented, Underrepresented Physicians and/or Scientists). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**Data Availability** No datasets were generated or analyzed during the current study.

## Declarations

**Competing interests** The authors declare no competing interests.

## References

1. Buzsáki G et al (1994) Oscillatory and intermittent synchrony in the hippocampus: relevance to memory trace formation. Springer Berlin Heidelberg, Berlin, Heidelberg
2. Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304(5679):1926–1929

3. Tzilivaki A et al (2023) Hippocampal GABAergic interneurons and memory. Neuron 111(20):3154–3175
4. Fernandez-Ruiz A et al (2019) Long-duration hippocampal sharp wave ripples improve memory. Science 364(6445):1082–1086
5. Girardeau G et al (2009) Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 12(10):1222–1223
6. Abdo RA et al (2019) Prevalence and contributing factors of birth asphyxia among the neonates delivered at Nigist Eleni Mohammed memorial teaching hospital, Southern Ethiopia: a cross-sectional study. BMC Pregnancy Childbirth 19(1):536
7. Scheffer-Teixeira R, Tort AB (2016) On cross-frequency phase-phase coupling between theta and gamma oscillations in the hippocampus. elife 5:e20515
8. Tamura M et al (2017) Hippocampal-prefrontal theta-gamma coupling during performance of a spatial working memory task. Nat Commun 8(1):2182
9. Wulff P et al (2009) Hippocampal theta rhythm and its coupling with gamma oscillations require fast inhibition onto parvalbumin-positive interneurons. Proc Natl Acad Sci U S A 106(9):3561–3566
10. Amilhon B et al (2015) Parvalbumin interneurons of hippocampus tune population activity at theta frequency. Neuron 86(5):1277–1289
11. Fuchs EC et al (2007) Recruitment of parvalbumin-positive interneurons determines hippocampal function and associated behavior. Neuron 53(4):591–604
12. Korotkova T et al (2010) NMDA receptor ablation on parvalbumin-positive interneurons impairs hippocampal synchrony, spatial representations, and working memory. Neuron 68(3):557–569
13. Royer S et al (2012) Control of timing, rate and bursts of hippocampal place cells by dendritic and somatic inhibition. Nat Neurosci 15(5):769–775
14. Stark E et al (2014) Pyramidal cell-interneuron interactions underlie hippocampal ripple oscillations. Neuron 83(2):467–480
15. Adam CD et al (2024) Disrupted hippocampal theta-gamma coupling and spike-field coherence following experimental traumatic brain injury. Preprint at https://www.biorxiv.org/content/https://doi.org/10.1101/2024.05.30.596704v1
16. Wang B et al (2014) The amyloid precursor protein controls adult hippocampal neurogenesis through GABAergic interneurons. J Neurosci 34(40):13314–13325
17. Zhang X et al (2016) Impaired theta-gamma coupling in APP-deficient mice. Sci Rep 6:21948
18. Markram H et al (2004) Interneurons of the neocortical inhibitory system. Nat Rev Neurosci 5(10):793–807
19. O'Keefe J, Dostrovsky J (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34(1):171–5
20. Topolnik L, Tamboli S (2022) The role of inhibitory circuits in hippocampal memory processing. Nat Rev Neurosci 23(8):476–492
21. Dudok B et al (2021) Recruitment and inhibitory action of hippocampal axo-axonic cells during behavior. Neuron 109(23):3838-3850 e8
22. Geiller T et al (2020) Large-scale 3D two-photon imaging of molecularly identified CA1 interneuron dynamics in behaving mice. Neuron 108(5):968-983 e9
23. Schuette PJ et al (2022) GABAergic CA1 neurons are more stable following context changes than glutamatergic cells. Sci Rep 12(1):10310
24. Douglas RJ, Martin KA (2004) Neuronal circuits of the neocortex. Annu Rev Neurosci 27:419–451
25. Douglas RJ, Martin KA (2009) Inhibition in cortical circuits. Curr Biol 19(10):R398-402
26. Olbrich HG, Braak H (1985) Ratio of pyramidal cells versus non-pyramidal cells in sector CA1 of the human Ammon's horn. Anat Embryol (Berl) 173(1):105–110
27. Gelman DM, Marin O (2010) Generation of interneuron diversity in the mouse cerebral cortex. Eur J Neurosci 31(12):2136–2141
28. Rudy B et al (2011) Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons. Dev Neurobiol 71(1):45–61
29. Tau GZ, Peterson BS (2010) Normal development of brain circuits. Neuropsychopharmacology 35(1):147–168
30. Wonders CP, Anderson SA (2006) The origin and specification of cortical interneurons. Nat Rev Neurosci 7(9):687–696
31. Farrant M, Kaila K (2007) The cellular, molecular and ionic basis of GABA(A) receptor signalling. Prog Brain Res 160:59–87
32. Le Magueresse C, Monyer H (2013) GABAergic interneurons shape the functional maturation of the cortex. Neuron 77(3):388–405
33. Zhou S, Yu Y (2018) Synaptic E-I balance underlies efficient neural coding. Front Neurosci 12:46
34. Klausberger T et al (2005) Complementary roles of cholecystokinin- and parvalbumin-expressing GABAergic neurons in hippocampal network oscillations. J Neurosci 25(42):9782–9793
35. Hu H, Gan J, Jonas P (2014) Fast-spiking, parvalbumin+ GABAergic interneurons: from cellular design to microcircuit function. Science 345(6196):1255263
36. Lapray D et al (2012) Behavior-dependent specialization of identified hippocampal interneurons. Nat Neurosci 15(9):1265–1271
37. Hu H, Martina M, Jonas P (2010) Dendritic mechanisms underlying rapid synaptic activation of fast-spiking hippocampal interneurons. Science 327(5961):52–58
38. Rudy B, McBain CJ (2001) Kv3 channels: voltage-gated K+ channels designed for high-frequency repetitive firing. Trends Neurosci 24(9):517–526
39. Bucurenciu I et al (2008) Nanodomain coupling between Ca2+ channels and Ca2+ sensors promotes fast and efficient transmitter release at a cortical GABAergic synapse. Neuron 57(4):536–545
40. Zaitsev AV et al (2007) P/Q-type, but not N-type, calcium channels mediate GABA release from fast-spiking interneurons to pyramidal cells in rat prefrontal cortex. J Neurophysiol 97(5):3567–3573
41. Cobb SR et al (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. Nature 378(6552):75–78
42. Ognjanovski N et al (2017) Erratum: Parvalbumin-expressing interneurons coordinate hippocampal network dynamics required for memory consolidation. Nat Commun 8:16120
43. Bazelot M, Telenczuk MT, Miles R (2016) Single CA3 pyramidal cells trigger sharp waves in vitro by exciting interneurones. J Physiol 594(10):2565–2577
44. Xia F et al (2017) Parvalbumin-positive interneurons mediate neocortical-hippocampal interactions that are necessary for memory consolidation. Elife 6:e27868
45. Hajos N et al (2013) Input-output features of anatomically identified CA3 neurons during hippocampal sharp wave/ripple oscillation in vitro. J Neurosci 33(28):11677–11691
46. Klausberger T et al (2003) Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. Nature 421(6925):844–848
47. Schlingloff D et al (2014) Mechanisms of sharp wave initiation and ripple generation. J Neurosci 34(34):11385–11398
48. Gan J et al (2017) Phase-locked inhibition, but not excitation, underlies hippocampal ripple oscillations in awake mice in vivo. Neuron 93(2):308–314
49. Leppa E et al (2011) Removal of GABA(A) receptor gamma2 subunits from parvalbumin neurons causes wide-ranging behavioral alterations. PLoS ONE 6(9):e24159

50. Murray AJ et al (2011) Parvalbumin-positive CA1 interneurons are required for spatial working but not for reference memory. Nat Neurosci 14(3):297–299
51. Ognjanovski N et al (2018) Hippocampal network oscillations rescue memory consolidation deficits caused by sleep loss. Cereb Cortex 28(10):3711–3723
52. Palop JJ, Mucke L (2016) Network abnormalities and interneuron dysfunction in Alzheimer disease. Nat Rev Neurosci 17(12):777–792
53. Jeong N, Singer AC (2022) Learning from inhibition: functional roles of hippocampal CA1 inhibition in spatial learning and memory. Curr Opin Neurobiol 76:102604
54. Miao C et al (2017) Parvalbumin and somatostatin interneurons control different space-coding networks in the medial entorhinal cortex. Cell 171(3):507-521 e17
55. Bezaire MJ, Soltesz I (2013) Quantitative assessment of CA1 local circuits: knowledge base for interneuron-pyramidal cell connectivity. Hippocampus 23(9):751–785
56. Cope DW et al (2002) Cholecystokinin-immunopositive basket and Schaffer collateral-associated interneurones target different domains of pyramidal cells in the CA1 area of the rat hippocampus. Neuroscience 109(1):63–80
57. Freund TF (2003) Interneuron diversity series: rhythm and mood in perisomatic inhibition. Trends Neurosci 26(9):489–495
58. Halasy K et al (1996) Synaptic target selectivity and input of GABAergic basket and bistratified interneurons in the CA1 area of the rat hippocampus. Hippocampus 6(3):306–329
59. Harris KM, Marshall PE, Landis DM (1985) Ultrastructural study of cholecystokinin-immunoreactive cells and processes in area CA1 of the rat hippocampus. J Comp Neurol 233(2):147–158
60. Kawaguchi Y, Kondo S (2002) Parvalbumin, somatostatin and cholecystokinin as chemical markers for specific GABAergic interneuron types in the rat frontal cortex. J Neurocytol 31(3–5):277–287
61. Megias M et al (2001) Total number and distribution of inhibitory and excitatory synapses on hippocampal CA1 pyramidal cells. Neuroscience 102(3):527–540
62. Nunzi MG et al (1985) Cholecystokinin-immunoreactive cells form symmetrical synaptic contacts with pyramidal and nonpyramidal neurons in the hippocampus. J Comp Neurol 237(4):485–505
63. Pawelzik H, Hughes DI, Thomson AM (2002) Physiological and morphological diversity of immunocytochemically defined parvalbumin- and cholecystokinin-positive interneurones in CA1 of the adult rat hippocampus. J Comp Neurol 443(4):346–367
64. Somogyi P et al (1984) Different populations of GABAergic neurons in the visual cortex and hippocampus of cat contain somatostatin- or cholecystokinin-immunoreactive material. J Neurosci 4(10):2590–2603
65. Kawaguchi Y, Kubota Y (1998) Neurochemical features and synaptic connections of large physiologically-identified GABAergic cells in the rat frontal cortex. Neuroscience 85(3):677–701
66. Basu J et al (2013) A cortico-hippocampal learning rule shapes inhibitory microcircuit activity to enhance hippocampal information flow. Neuron 79(6):1208–1221
67. Daw MI et al (2009) Asynchronous transmitter release from cholecystokinin-containing inhibitory interneurons is widespread and target-cell independent. J Neurosci 29(36):11112–11122
68. Hefft S, Jonas P (2005) Asynchronous GABA release generates long-lasting inhibition at a hippocampal interneuron-principal neuron synapse. Nat Neurosci 8(10):1319–1328
69. Chevaleyre V, Piskorowski R (2014) Modulating excitation through plasticity at inhibitory synapses. Front Cell Neurosci 8:93
70. Bodor AL et al (2005) Endocannabinoid signaling in rat somatosensory cortex: laminar differences and involvement of specific interneuron types. J Neurosci 25(29):6845–6856
71. Dudok B et al (2015) Cell-specific STORM super-resolution imaging reveals nanoscale organization of cannabinoid signaling. Nat Neurosci 18(1):75–86
72. Katona I et al (1999) Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J Neurosci 19(11):4544–4558
73. Cea-del Rio CA, McBain CJ, Pelkey KA (2012) An update on cholinergic regulation of cholecystokinin-expressing basket cells. J Physiol 590(4):695–702
74. Keimpema E et al (2012) Sticking out of the crowd: the molecular identity and development of cholecystokinin-containing basket cells. J Physiol 590(4):703–714
75. Su J et al (2023) Entorhinohippocampal cholecystokinin modulates spatial learning by facilitating neuroplasticity of hippocampal CA3-CA1 synapses. Cell Rep 42(12):113467
76. Foldy C et al (2007) Cell type-specific gating of perisomatic inhibition by cholecystokinin. Nat Neurosci 10(9):1128–1130
77. Karson MA, Whittington KC, Alger BE (2008) Cholecystokinin inhibits endocannabinoid-sensitive hippocampal IPSPs and stimulates others. Neuropharmacology 54(1):117–128
78. Rangel Guerrero DK et al (2024) Hippocampal cholecystokinin-expressing interneurons regulate temporal coding and contextual learning. Neuron 112(12):2045-2061 e10
79. Del Pino I et al (2017) Abnormal wiring of CCK(+) basket cells disrupts spatial information coding. Nat Neurosci 20(6):784–792
80. Urban-Ciecko J, Fanselow EE, Barth AL (2015) Neocortical somatostatin neurons reversibly silence excitatory transmission via GABAb receptors. Curr Biol 25(6):722–731
81. Buhl EH et al (1994) Physiological properties of anatomically identified axo-axonic cells in the rat hippocampus. J Neurophysiol 71(4):1289–1307
82. McBain CJ, DiChiara TJ, Kauer JA (1994) Activation of metabotropic glutamate receptors differentially affects two classes of hippocampal interneurons and potentiates excitatory synaptic transmission. J Neurosci 14(7):4433–4445
83. Freund TF, Buzsáki G (1996) Interneurons of the hippocampus. Hippocampus 6(4):347–470
84. Blasco-Ibanez JM, Freund TF (1995) Synaptic input of horizontal interneurons in stratum oriens of the hippocampal CA1 subfield: structural basis of feed-back activation. Eur J Neurosci 7(10):2170–2180
85. Lacaille JC, Williams S (1990) Membrane properties of interneurons in stratum oriens-alveus of the CA1 region of rat hippocampus in vitro. Neuroscience 36(2):349–359
86. Honore E et al (2021) Hippocampal somatostatin interneurons, long-term synaptic plasticity and memory. Front Neural Circuits 15:687558
87. Lovett-Barron M et al (2014) Dendritic inhibition in the hippocampus supports fear learning. Science 343(6173):857–863
88. Zicho K et al (2023) Fear memory recall involves hippocampal somatostatin interneurons. PLoS Biol 21(6):e3002154
89. Francavilla R et al (2018) Connectivity and network state-dependent recruitment of long-range VIP-GABAergic neurons in the mouse hippocampus. Nat Commun 9(1):5043
90. Tamboli S et al (2024) Mouse hippocampal CA1 VIP interneurons detect novelty in the environment and support recognition memory. Cell Rep 43(4):114115
91. Fuentealba P et al (2008) Ivy cells: a population of nitric-oxide-producing, slow-spiking GABAergic neurons and their involvement in hippocampal network activity. Neuron 57(6):917–929
92. Urban Z, Magloczky Z, Freund TF (2002) Calretinin-containing interneurons innervate both principal cells and interneurons in

the CA1 region of the human hippocampus. Acta Biol Hung 53(1–2):205–220
93. Gulyas AI, Hajos N, Freund TF (1996) Interneurons containing calretinin are specialized to control other interneurons in the rat hippocampus. J Neurosci 16(10):3397–3411
94. Toth K, Magloczky Z (2014) The vulnerability of calretinin-containing hippocampal interneurons to temporal lobe epilepsy. Front Neuroanat 8:100
95. Gulyas AI, Freund TF (1996) Pyramidal cell dendrites are the primary targets of calbindin D28k-immunoreactive interneurons in the hippocampus. Hippocampus 6(5):525–534
96. Molinari S et al (1996) Deficits in memory and hippocampal long-term potentiation in mice with reduced calbindin D28K expression. Proc Natl Acad Sci U S A 93(15):8028–8033
97. Frankowski JC, Kim YJ, Hunt RF (2019) Selective vulnerability of hippocampal interneurons to graded traumatic brain injury. Neurobiol Dis 129:208–216
98. Knopp A et al (2008) Loss of GABAergic neurons in the subiculum and its functional implications in temporal lobe epilepsy. Brain 131(Pt 6):1516–1527
99. Komitova M et al (2013) Hypoxia-induced developmental delays of inhibitory interneurons are reversed by environmental enrichment in the postnatal mouse forebrain. J Neurosci 33(33):13375–13387
100. Eichenbaum H, Stewart C, Morris RG (1990) Hippocampal representation in place learning. J Neurosci 10(11):3531–3542
101. Ferbinteanu J, Shapiro ML (2003) Prospective and retrospective memory coding in the hippocampus. Neuron 40(6):1227–1239
102. Knierim JJ, Kudrimoti HS, McNaughton BL (1995) Place cells, head direction cells, and the learning of landmark stability. J Neurosci 15(3 Pt 1):1648–1659
103. McNaughton BL, Barnes CA, O'Keefe J (1983) The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. Exp Brain Res 52(1):41–49
104. O'Keefe J, Conway DH (1978) Hippocampal place units in the freely moving rat: why they fire where they fire. Exp Brain Res 31(4):573–590
105. Wilson MA, McNaughton BL (1993) Dynamics of the hippocampal ensemble code for space. Science 261(5124):1055–1058
106. Wood ER, Dudchenko PA (2003) Aging, spatial behavior and the cognitive map. Nat Neurosci 6(6):546–548
107. Diba K, Buzsaki G (2008) Hippocampal network dynamics constrain the time lag between pyramidal cells across modified environments. J Neurosci 28(50):13448–13456
108. Gothard KM, Skaggs WE, McNaughton BL (1996) Dynamics of mismatch correction in the hippocampal ensemble code for space: interaction between path integration and environmental cues. J Neurosci 16(24):8027–8040
109. Grieves RM et al (2020) The place-cell representation of volumetric space in rats. Nat Commun 11(1):789
110. O'Keefe J, Burgess N (1996) Geometric determinants of the place fields of hippocampal neurons. Nature 381(6581):425–428
111. Schuette PJ et al (2020) Long-term characterization of hippocampal remapping during contextual fear acquisition and extinction. J Neurosci 40(43):8329–8342
112. Ego-Stengel V, Wilson MA (2007) Spatial selectivity and theta phase precession in CA1 interneurons. Hippocampus 17(2):161–174
113. Hangya B et al (2010) Complementary spatial firing in place cell-interneuron pairs. J Physiol 588(Pt 21):4165–4175
114. Wilent WB, Nitz DA (2007) Discrete place fields of hippocampal formation interneurons. J Neurophysiol 97(6):4152–4161
115. Csicsvari J et al (1998) Reliability and state dependence of pyramidal cell-interneuron synapses in the hippocampus: an ensemble approach in the behaving rat. Neuron 21(1):179–189
116. Geiller T et al (2022) Local circuit amplification of spatial selectivity in the hippocampus. Nature 601(7891):105–109
117. Grienberger C et al (2017) Inhibitory suppression of heterogeneously tuned excitation enhances spatial coding in CA1 place cells. Nat Neurosci 20(3):417–426
118. Bittner KC et al (2015) Conjunctive input processing drives feature selectivity in hippocampal CA1 neurons. Nat Neurosci 18(8):1133–1142
119. Bittner KC et al (2017) Behavioral time scale synaptic plasticity underlies CA1 place fields. Science 357(6355):1033–1036
120. Valero M et al (2022) Inhibitory conductance controls place field dynamics in the hippocampus. Cell Rep 40(8):111232
121. Udakis M et al (2020) Interneuron-specific plasticity at parvalbumin and somatostatin inhibitory synapses onto CA1 pyramidal neurons shapes hippocampal output. Nat Commun 11(1):4395
122. Kisvarday ZF, Adams CB, Smith AD (1986) Synaptic connections of axo-axonic (chandelier) cells in human epileptic temporal cortex. Neuroscience 19(4):1179–1186
123. Somogyi P (1977) A specific "axo-axonal" interneuron in the visual cortex of the rat. Brain Res 136(2):345–350
124. Somogyi P, Freund TF, Cowey A (1982) The axo-axonic interneuron in the cerebral cortex of the rat, cat and monkey. Neuroscience 7(11):2577–2607
125. Li XG et al (1992) Axonal and dendritic arborization of an intracellularly labeled chandelier cell in the CA1 region of rat hippocampus. Exp Brain Res 90(3):519–525
126. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, Pringsheim T, Lorenzetti DL, Jette N (2017) Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 88(3):296–303. https://doi.org/10.1212/WNL.0000000000003509
127. Fisher RS et al (2014) ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55(4):475–482
128. Chauhan PPS, Chauhan G, Mehra S (2022) The anatomical basis of seizures. In Epilepsy, e. Czuczwar SJ, Editor. Brisbane (AU), Exon Publications
129. Wu D et al (2020) The morphological characteristics of hippocampus and thalamus in mesial temporal lobe epilepsy. BMC Neurol 20(1):235
130. Borges FS et al (2023) Intermittency properties in a temporal lobe epilepsy model. Epilepsy Behav 139:109072
131. Kinjo ER et al (2016) Pilocarpine-induced seizures trigger differential regulation of microRNA-stability related genes in rat hippocampal neurons. Sci Rep 6:20969
132. Li X et al (2007) Synchronization measurement of multiple neuronal populations. J Neurophysiol 98(6):3341–3348
133. Protachevicz PR et al (2019) Bistable firing pattern in a neural network model. Front Comput Neurosci 13:19
134. Toth K et al (2018) Hyperexcitability of the network contributes to synchronization processes in the human epileptic neocortex. J Physiol 596(2):317–342
135. Lenck-Santini PP, Scott RC (2015) Mechanisms responsible for cognitive impairment in epilepsy. Cold Spring Harb Perspect Med 5(10):a022772
136. Kinjo ER et al (2018) New insights on temporal lobe epilepsy based on plasticity-related network changes and high-order statistics. Mol Neurobiol 55(5):3990–3998
137. Fritschy JM et al (1999) GABAergic neurons and GABA(A)-receptors in temporal lobe epilepsy. Neurochem Int 34(5):435–445
138. Munoz A et al (2007) Cation-chloride cotransporters and GABA-ergic innervation in the human epileptic hippocampus. Epilepsia 48(4):663–673
139. Kaila K et al (2014) Cation-chloride cotransporters in neuronal development, plasticity and disease. Nat Rev Neurosci 15(10):637–654

140. Yang X, Wang Q, Cao E (2020) Structure of the human cation-chloride cotransporter NKCC1 determined by single-particle electron cryo-microscopy. Nat Commun 11(1):1016
141. Blaesse P et al (2009) Cation-chloride cotransporters and neuronal function. Neuron 61(6):820–838
142. Viitanen T et al (2010) The K+-Cl cotransporter KCC2 promotes GABAergic excitation in the mature rat hippocampus. J Physiol 588(Pt 9):1527–1540
143. Gentiletti D et al (2022) Focal seizures are organized by feedback between neural activity and ion concentration changes. elife 11:e68541
144. Barmashenko G et al (2011) Positive shifts of the GABAA receptor reversal potential due to altered chloride homeostasis is widespread after status epilepticus. Epilepsia 52(9):1570–1578
145. Benini R et al (2011) Perirhinal cortex hyperexcitability in pilocarpine-treated epileptic rats. Hippocampus 21(7):702–713
146. Bragin DE et al (2009) Development of epileptiform excitability in the deep entorhinal cortex after status epilepticus. Eur J Neurosci 30(4):611–624
147. Liu X et al (2003) Seizure-induced changes in place cell physiology: relationship to spatial memory. J Neurosci 23(37):11505–11515
148. Weiss SA (2023) Chloride ion dysregulation in epileptogenic neuronal networks. Neurobiol Dis 177:106000
149. Galandra C et al (2018) The alcoholic brain: neural bases of impaired reward-based decision-making in alcohol use disorders. Neurol Sci 39(3):423–435
150. Belperio G et al (2022) Molecular Mechanisms of Epilepsy: the Role of the Chloride Transporter KCC2. J Mol Neurosci 72(7):1500–1515
151. McMoneagle E et al (2024) Neuronal K(+)-Cl(-) cotransporter KCC2 as a promising drug target for epilepsy treatment. Acta Pharmacol Sin 45(1):1–22
152. Gloveli T (2010) Hippocampal spatial navigation: interneurons take responsibility. J Physiol 588(Pt 23):4609–4610
153. Shuman T et al (2020) Breakdown of spatial coding and interneuron synchronization in epileptic mice. Nat Neurosci 23(2):229–238
154. Lopez-Pigozzi D et al (2016) Altered oscillatory dynamics of CA1 parvalbumin basket cells during theta-gamma rhythmopathies of temporal lobe epilepsy. eNeuro 3(6)
155. Caccavano A et al (2020) Inhibitory parvalbumin basket cell activity is selectively reduced during hippocampal sharp wave ripples in a mouse model of familial Alzheimer's disease. J Neurosci 40(26):5116–5136
156. Kim HK et al (2020) Optogenetic intervention of seizures improves spatial memory in a mouse model of chronic temporal lobe epilepsy. Epilepsia 61(3):561–571
157. Drexel M, Rahimi S, Sperk G (2022) Silencing of hippocampal somatostatin interneurons induces recurrent spontaneous limbic seizures in mice. Neuroscience 487:155–165
158. Drexel M et al (2017) Selective silencing of hippocampal parvalbumin interneurons induces development of recurrent spontaneous limbic seizures in mice. J Neurosci 37(34):8166–8179
159. Wyeth MS et al (2010) Selective reduction of cholecystokinin-positive basket cell innervation in a model of temporal lobe epilepsy. J Neurosci 30(26):8993–9006
160. Toth K et al (2010) Loss and reorganization of calretinin-containing interneurons in the epileptic human hippocampus. Brain 133(9):2763–2777
161. Dudok B, Klein PM, Soltesz I (2022) Toward understanding the diverse roles of perisomatic interneurons in epilepsy. Epilepsy Curr 22(1):54–60
162. Scheltens P et al (2021) Alzheimer's disease. Lancet 397(10284):1577–1590
163. Ashe KH (2020) The biogenesis and biology of amyloid beta oligomers in the brain. Alzheimers Dement 16(11):1561–1567
164. Hanseeuw BJ et al (2019) Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. JAMA Neurol 76(8):915–924
165. Hayden EY, Teplow DB (2013) Amyloid beta-protein oligomers and Alzheimer's disease. Alzheimers Res Ther 5(6):60
166. Breijyeh Z, Karaman R (2020) Comprehensive review on Alzheimer's disease: causes and treatment. Molecules 25(24):5789
167. Saez-Atienzar S, Masliah E (2020) Cellular senescence and Alzheimer disease: the egg and the chicken scenario. Nat Rev Neurosci 21(8):433–444
168. Tabanez M et al (2023) The impact of hydroxytyrosol on the metallomic-profile in an animal model of Alzheimer's disease. Int J Mol Sci 24(19):14950
169. Greenberg SM et al (2020) Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. Nat Rev Neurol 16(1):30–42
170. Riek R, Eisenberg DS (2016) The activities of amyloids from a structural perspective. Nature 539(7628):227–235
171. Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. Science 256(5054):184–185
172. Frisoni GB et al (2022) The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. Nat Rev Neurosci 23(1):53–66
173. Hoilund-Carlsen PF et al (2024) Alzheimer's amyloid hypothesis and antibody therapy: melting glaciers? Int J Mol Sci 25(7):3892
174. Hsiao K et al (1996) Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science 274(5284):99–102
175. Thal DR et al (2002) Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 58(12):1791–1800
176. Farlow MR et al (2015) Long-term treatment with active Abeta immunotherapy with CAD106 in mild Alzheimer's disease. Alzheimers Res Ther 7(1):23
177. Holmes C et al (2008) Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. Lancet 372(9634):216–223
178. Espay AJ, Kepp KP, Herrup K (2024) Lecanemab and Donanemab as Therapies for Alzheimer's disease: an illustrated perspective on the data. eNeuro 11(7). https://doi.org/10.1523/ENEURO.0319-23.2024
179. Villain N, Planche V, Levy R (2022) High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 1: meta-analysis and review of efficacy and safety data, and medico-economical aspects. Rev Neurol (Paris) 178(10):1011–1030
180. Ringman JM et al (2016) Neuropathology of autosomal dominant Alzheimer disease in the national Alzheimer coordinating center database. J Neuropathol Exp Neurol 75(3):284–290
181. Jack CR Jr et al (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 9(1):119–128
182. Ferreira-Vieira TH et al (2016) Alzheimer's disease: targeting the cholinergic system. Curr Neuropharmacol 14(1):101–115
183. Hampel H et al (2018) The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain 141(7):1917–1933
184. Bell KF et al (2003) Structural involvement of the glutamatergic presynaptic boutons in a transgenic mouse model expressing early onset amyloid pathology. Neurosci Lett 353(2):143–147
185. Bell KF et al (2006) The amyloid pathology progresses in a neurotransmitter-specific manner. Neurobiol Aging 27(11):1644–1657
186. Rossor MN et al (1982) A post-mortem study of the cholinergic and GABA systems in senile dementia. Brain 105(Pt 2):313–330

187. Kaushik V et al (2018) Acetylcholinesterase inhibitors: beneficial effects on comorbidities in patients with Alzheimer's disease. Am J Alzheimers Dis Other Demen 33(2):73–85
188. Sharma K (2019) Cholinesterase inhibitors as Alzheimer's therapeutics (Review). Mol Med Rep 20(2):1479–1487
189. Almeida VN (2024) Somatostatin and the pathophysiology of Alzheimer's disease. Ageing Res Rev 96:102270
190. Broussard JI et al (2022) Impaired experience-dependent refinement of place cells in a rat model of Alzheimer's disease. J Alzheimers Dis 86(4):1907–1916
191. Cacucci F et al (2008) Place cell firing correlates with memory deficits and amyloid plaque burden in Tg2576 Alzheimer mouse model. Proc Natl Acad Sci U S A 105(22):7863–7868
192. Fu H et al (2017) Tau pathology induces excitatory neuron loss, grid cell dysfunction, and spatial memory deficits reminiscent of early Alzheimer's disease. Neuron 93(3):533-541 e5
193. Jun H et al (2020) Disrupted place cell remapping and impaired grid cells in a knockin model of Alzheimer's disease. Neuron 107(6):1095-1112 e6
194. Mably AJ et al (2017) Impairments in spatial representations and rhythmic coordination of place cells in the 3xTg mouse model of Alzheimer's disease. Hippocampus 27(4):378–392
195. Ridler T et al (2020) Impaired speed encoding and grid cell periodicity in a mouse model of tauopathy. eLife 9:e59045
196. Michaud F et al (2024) Altered firing output of VIP interneurons and early dysfunctions in CA1 hippocampal circuits in the 3xTg mouse model of Alzheimer's disease. Elife 13:RP95412
197. Scimemi A (2014) Structure, function, and plasticity of GABA transporters. Front Cell Neurosci 8:161
198. Gong N et al (2009) GABA transporter-1 activity modulates hippocampal theta oscillation and theta burst stimulation-induced long-term potentiation. J Neurosci 29(50):15836–15845
199. Somogyi P, Klausberger T (2005) Defined types of cortical interneurone structure space and spike timing in the hippocampus. J Physiol 562(Pt 1):9–26
200. Perez-Zabalza M et al (2020) Modulation of cortical slow oscillatory rhythm by GABA(B) receptors: an in vitro experimental and computational study. J Physiol 598(16):3439–3457
201. Salib M et al (2019) GABAergic medial septal neurons with low-rhythmic firing innervating the dentate gyrus and hippocampal area CA3. J Neurosci 39(23):4527–4549
202. Babiloni C et al (2013) Cortical sources of resting state EEG rhythms are sensitive to the progression of early stage Alzheimer's disease. J Alzheimers Dis 34(4):1015–1035
203. Almeida VN, Higa GS (2025) Somatostatin interneurons and the pathogenesis of Alzheimer's disease. Neural Regen Res 10–4103. https://doi.org/10.4103/NRR.NRR-D-24-01277
204. Marczynski TJ (1998) GABAergic deafferentation hypothesis of brain aging and Alzheimer's disease revisited. Brain Res Bull 45(4):341–379
205. Rissman RA, Mobley WC (2011) Implications for treatment: GABA. J Neurochemistry 117(4):613. https://doi.org/10.1111/j.1471-4159.2011.07237.x
206. Limon A, Reyes-Ruiz JM, Miledi R (2012) Loss of functional GABA(A) receptors in the Alzheimer diseased brain. Proc Natl Acad Sci U S A 109(25):10071–10076
207. Seidl R et al (2001) Differences between GABA levels in Alzheimer's disease and down syndrome with Alzheimer-like neuropathology. Naunyn Schmiedebergs Arch Pharmacol 363(2):139–145
208. Palop JJ, Mucke L (2010) Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nat Neurosci 13(7):812–818
209. Siskova Z et al (2014) Dendritic structural degeneration is functionally linked to cellular hyperexcitability in a mouse model of Alzheimer's disease. Neuron 84(5):1023–1033
210. Harris JA et al (2010) Transsynaptic progression of amyloid-beta-induced neuronal dysfunction within the entorhinal-hippocampal network. Neuron 68(3):428–441
211. Nava-Mesa MO et al (2014) GABAergic neurotransmission and new strategies of neuromodulation to compensate synaptic dysfunction in early stages of Alzheimer's disease. Front Cell Neurosci 8:167
212. Beker S et al (2016) Amyloid-beta disrupts ongoing spontaneous activity in sensory cortex. Brain Struct Funct 221(2):1173–1188
213. Busche MA et al (2008) Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. Science 321(5896):1686–1689
214. Brady DR, Mufson EJ (1997) Parvalbumin-immunoreactive neurons in the hippocampal formation of Alzheimer's diseased brain. Neuroscience 80(4):1113–1125
215. Levenga J et al (2013) Tau pathology induces loss of GABAergic interneurons leading to altered synaptic plasticity and behavioral impairments. Acta Neuropathol Commun 1:34
216. Li G et al (2009) GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knockin mice. Cell Stem Cell 5(6):634–645
217. Mahar I et al (2016) Phenotypic alterations in hippocampal NPY- and PV-expressing interneurons in a presymptomatic transgenic mouse model of Alzheimer's disease. Front Aging Neurosci 8:327
218. Ramos B et al (2006) Early neuropathology of somatostatin/NPY GABAergic cells in the hippocampus of a PS1xAPP transgenic model of Alzheimer's disease. Neurobiol Aging 27(11):1658–1672
219. Andrews-Zwilling Y et al (2010) Apolipoprotein E4 causes age- and Tau-dependent impairment of GABAergic interneurons, leading to learning and memory deficits in mice. J Neurosci 30(41):13707–13717
220. Umeda T et al (2017) Mutation-induced loss of APP function causes GABAergic depletion in recessive familial Alzheimer's disease: analysis of Osaka mutation-knockin mice. Acta Neuropathol Commun 5(1):59
221. Baglietto-Vargas D et al (2010) Calretinin interneurons are early targets of extracellular amyloid-beta pathology in PS1/AbetaPP Alzheimer mice hippocampus. J Alzheimers Dis 21(1):119–132
222. Trujillo-Estrada L et al (2014) Early neuronal loss and axonal/presynaptic damage is associated with accelerated amyloid-beta accumulation in AbetaPP/PS1 Alzheimer's disease mice subiculum. J Alzheimers Dis 42(2):521–541
223. Moreno-Gonzalez I et al (2009) Extracellular amyloid-beta and cytotoxic glial activation induce significant entorhinal neuron loss in young PS1(M146L)/APP(751SL) mice. J Alzheimers Dis 18(4):755–776
224. Takahashi H et al (2010) Hippocampal interneuron loss in an APP/PS1 double mutant mouse and in Alzheimer's disease. Brain Struct Funct 214(2–3):145–160
225. Villette V et al (2012) A new neuronal target for beta-amyloid peptide in the rat hippocampus. Neurobiol Aging 33(6):1126 e1–14
226. Villette V et al (2010) Decreased rhythmic GABAergic septal activity and memory-associated theta oscillations after hippocampal amyloid-beta pathology in the rat. J Neurosci 30(33):10991–11003
227. Karakas S (2020) A review of theta oscillation and its functional correlates. Int J Psychophysiol 157:82–99
228. Nimmrich V et al (2008) Amyloid beta oligomers (A beta(1–42) globulomer) suppress spontaneous synaptic activity by inhibition of P/Q-type calcium currents. J Neurosci 28(4):788–797
229. Fuhrer TE et al (2017) Impaired expression of GABA transporters in the human Alzheimer's disease hippocampus,

subiculum, entorhinal cortex and superior temporal gyrus. Neuroscience 351:108–118
230. Iwakiri M et al (2009) An immunohistochemical study of GABA A receptor gamma subunits in Alzheimer's disease hippocampus: relationship to neurofibrillary tangle progression. Neuropathology 29(3):263–269
231. Mizukami K et al (1998) Immunohistochemical study of GABAA receptor alpha1 subunit in the hippocampal formation of aged brains with Alzheimer-related neuropathologic changes. Brain Res 799(1):148–155
232. Verret L et al (2012) Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. Cell 149(3):708–721
233. Tong LM et al (2014) Inhibitory interneuron progenitor transplantation restores normal learning and memory in ApoE4 knock-in mice without or with Abeta accumulation. J Neurosci 34(29):9506–9515
234. Iaccarino HF et al (2016) Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 540(7632):230–235
235. Adaikkan C et al (2019) Gamma entrainment binds higher-order brain regions and offers neuroprotection. Neuron 102(5):929-943 e8
236. Shi A et al (2020) Preserved calretinin interneurons in an app model of Alzheimer's disease disrupt hippocampal inhibition via upregulated P2Y1 purinoreceptors. Cereb Cortex 30(3):1272–1290
237. Gasquoine PG (1997) Postconcussion symptoms. Neuropsychol Rev 7(2):77–85
238. Miotto EC et al (2010) Cognitive deficits in patients with mild to moderate traumatic brain injury. Arq Neuropsiquiatr 68(6):862–868
239. Blennow K et al (2016) Traumatic brain injuries. Nat Rev Dis Primers 2:16084
240. Fleminger S et al (2003) Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry 74(7):857–862
241. Pavlov I et al (2011) Progressive loss of phasic, but not tonic, GABAA receptor-mediated inhibition in dentate granule cells in a model of post-traumatic epilepsy in rats. Neuroscience 194:208–219
242. Maas AI, Stocchetti N, Bullock R (2008) Moderate and severe traumatic brain injury in adults. Lancet Neurol 7(8):728–741
243. Shah SS, Shetty AJ, Johnston DT, Hanan CL, O'Reilly BT, Skibber MA, Massoud AT, Zhu B, Sevick-Muraca EM, Juranek J, Cox CS, Jr., Shah MN (2025) Implications and pathophysiology of neuroinflammation in pediatric patients with traumatic brain injury: an updated review. Front Neurosci 19:1587222. https://doi.org/10.3389/fnins.2025.1587222
244. Maxwell WL et al (2003) There is differential loss of pyramidal cells from the human hippocampus with survival after blunt head injury. J Neuropathol Exp Neurol 62(3):272–279
245. Cantu D et al (2015) Traumatic brain injury increases cortical glutamate network activity by compromising GABAergic control. Cereb Cortex 25(8):2306–2320
246. Lighthall JW, Dixon CE, Anderson TE (1989) Experimental models of brain injury. J Neurotrauma 6(2):83–97
247. Toth Z et al (1997) Instantaneous perturbation of dentate interneuronal networks by a pressure wave-transient delivered to the neocortex. J Neurosci 17(21):8106–8117
248. Almeida-Suhett CP et al (2015) GABAergic interneuronal loss and reduced inhibitory synaptic transmission in the hippocampal CA1 region after mild traumatic brain injury. Exp Neurol 273:11–23
249. Vogel-Ciernia A, Wood MA (2014) Examining object location and object recognition memory in mice. Curr Protoc Neurosci 69:8311–17
250. Broussard JI et al (2020) Mild traumatic brain injury decreases spatial information content and reduces place field stability of hippocampal CA1 neurons. J Neurotrauma 37(2):227–235
251. Lawn J, Shibuya K, Stein C (2005) No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. Bull World Health Organ 83(6):409–417
252. Liu L et al (2019) National, regional, and state-level all-cause and cause-specific under-5 mortality in India in 2000–15: a systematic analysis with implications for the sustainable development goals. Lancet Glob Health 7(6):e721–e734
253. Wainwright MS et al (2004) Increased susceptibility of S100B transgenic mice to perinatal hypoxia-ischemia. Ann Neurol 56(1):61–67
254. Clancy B et al (2007) Extrapolating brain development from experimental species to humans. Neurotoxicology 28(5):931–937
255. Finlay BL, Darlington RB (1995) Linked regularities in the development and evolution of mammalian brains. Science 268(5217):1578–1584
256. Semple BD et al (2013) Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol 106–107:1–16
257. Takada SH et al (2015) Neonatal anoxia in rats: hippocampal cellular and subcellular changes related to cell death and spatial memory. Neuroscience 284:247–259
258. Takada SH et al (2011) A modified rat model of neonatal anoxia: Development and evaluation by pulseoximetry, arterial gasometry and Fos immunoreactivity. J Neurosci Methods 198(1):62–69
259. Ikebara JM et al (2017) Functional role of intracellular calcium receptor inositol 1,4,5-trisphosphate type 1 in rat hippocampus after neonatal anoxia. PLoS ONE 12(1):e0169861
260. Matsuda VDV et al (2021) Impact of neonatal anoxia and hypothermic treatment on development and memory of rats. Exp Neurol 340:113691
261. Motta-Teixeira LC et al (2016) Spatial learning and neurogenesis: effects of cessation of wheel running and survival of novel neurons by engagement in cognitive tasks. Hippocampus 26(6):794–803
262. Myers KM, Davis M (2007) Mechanisms of fear extinction. Mol Psychiatry 12(2):120–150
263. Myers KM, Ressler KJ, Davis M (2006) Different mechanisms of fear extinction dependent on length of time since fear acquisition. Learn Mem 13(2):216–223
264. Mesbah-Oskui L, Georgiou J, Roder JC (2015) Hippocampal place cell and inhibitory neuron activity in disrupted-in-schizophrenia-1 mutant mice: implications for working memory deficits. NPJ Schizophr 1:15011
265. Shetty J (2015) Neonatal seizures in hypoxic-ischaemic encephalopathy–risks and benefits of anticonvulsant therapy. Dev Med Child Neurol 57(Suppl 3):40–43
266. Sun H, Juul HM, Jensen FE (2016) Models of hypoxia and ischemia-induced seizures. J Neurosci Methods 260:252–260
267. Duan ZRS et al (2020) GABAergic restriction of network dynamics regulates interneuron survival in the developing cortex. Neuron 105(1):75-92 e5
268. Gonzalez Fuentes J et al (2021) Neuropeptides in the developing human hippocampus under hypoxic-ischemic conditions. J Anat 239(4):856–868
269. Chavez-Valdez R et al (2018) Delayed injury of hippocampal interneurons after neonatal hypoxia-ischemia and therapeutic hypothermia in a murine model. Hippocampus 28(8):617–630

270. Parmar P et al (2024) Neonatal hypoxia-ischemia alters the events governing the hippocampal critical period of postnatal synaptic plasticity leading to deficits in working memory in mice. Neurobiol Dis 202:106722
271. Spahic H et al (2022) Dysregulation of ErbB4 signaling pathway in the dorsal hippocampus after neonatal hypoxia-ischemia and late deficits in PV(+) interneurons, synaptic plasticity and working memory. Int J Mol Sci 24(1):508