Published in final edited form as:

Hippocampus. 2018 September ; 28(9): 659–671. doi:10.1002/hipo.22803.

Inhibition shapes the organization of hippocampal representations

Sam McKenzie¹

¹NYU Langone Medical Center, 450 E29th St., 9th Floor New York, NY 10016

Abstract

Hippocampal neurons become tuned to stimuli that predict behaviorally salient outcomes. This plasticity suggests that memory formation depends upon shifts in how different anatomical inputs can drive hippocampal activity. Here, I present evidence that inhibitory neurons can provide such a mechanism for learning-related changes in the tuning of pyramidal cells. Inhibitory currents arriving on the dendrites of pyramidal cells determine whether an excitatory input can drive action potential output. Specificity and plasticity of this dendritic modulation allows for precise, modifiable changes in how afferent inputs are integrated, a process that defines a neuron's receptive field. In addition, feedback inhibition plays a fundamental role in biasing which excitatory neurons may be co-active. By defining the rules of synchrony and the rules of input integration, interneurons likely play a fundamental role in the organization of memory representation within the hippocampus.

Keywords

Feedforward inhibition; feedback inhibition; shunting inhibition; remapping; memory schema

Introduction

The demands of lifelong learning require constant comparison and relation of events separated in time. In cognitive terms, this problem boils down to recalling and updating the right memory at the right moment. One way in which the brain could perform this function is by modulating which networks are activated and changed during learning.

Memories are thought to be encoded by how groups of neurons fire together. Hippocampal neurons respond differently before and after learning to the same constellation of stimuli (Komorowski et al., 2009; McKenzie et al., 2014). When distinct circumstances come to predict equivalent behavioral outcomes, hippocampal firing patterns generally become more similar to one another. In contrast, when different stimuli must be disambiguated to meet behavioral demands, firing patterns become anti-correlated (McKenzie and Eichenbaum, 2011; McKenzie et al., 2013, 2014). New evidence supports the theory that when the same neurons participate in the encoding of distinct experiences, the memories for those

Corresponding author: Sam McKenzie mckens04@nyumc.org.

I declare no conflicts of interest.

experiences become linked as well, as demonstrated by generalized behavioral responding to the non-conditioned stimuli that are represented by neurons that also respond to the conditioned stimulus (Tanaka et al., 2014; Cai et al., 2016; Yokose et al., 2017). Therefore, the web of such mnemonic associations, the mental schema, likely depends upon how neuronal receptive fields span various dimensions of the subjects' experience.

The hippocampus has access to inputs of all sensory modalities through the entorhinal cortex and other subcortical afferents (Wyss et al., 1979; Witter et al., 2000). Therefore, in principle, hippocampal neurons can discriminate any two stimuli by distributing their receptive fields along the appropriate dimension. How does the correct anatomical input drive hippocampal firing at the correct time to create behaviorally relevant receptive fields?

In this review, I propose that inhibitory interneurons influence the hippocampal code to drive excitatory network changes that are relevant to learning. Interneurons shape the tuning properties of excitatory cells by (1) gating afferent inputs, (2) defining the rules of competition amongst active ensembles, (3) setting the time constant for integrating inputs and (4) coordinating brain regions for communication through synchrony. Each of these control mechanisms has the potential to be modulated through plasticity between excitatory to inhibitory cells (Lamsa et al., 2005, 2007) and vice versa (Rozov et al., 2017).

Inhibition sculpts neuronal input/output functions

Before turning to the evidence that inhibition influences the hippocampal code, it is useful to first review the basic properties of inhibitory control of single cell excitability.

Though principle cells far outnumber inhibitory neurons (Woodson et al., 1989; Bezaire and Soltesz, 2013), the inhibitory spiking rate is higher, resulting in near parity in the number of excitatory and inhibitory spikes (Buzsáki et al., 2007). Furthermore, interneurons tend to show high convergence of inputs (Gulyás et al., 1999; Bezaire and Soltesz, 2013) and divergence of outputs (Sik et al., 1995; Bezaire and Soltesz, 2013), placing them as hubs for controlling many aspects of network activity (Roux and Buzsáki, 2015). The diffuse pattern of interneuron connectivity and the lack of well-defined receptive fields suggest that interneurons play a global role in establishing overall network excitability by normalizing the amount of input arriving into a region (Pouille et al., 2009) and the total number of output spikes (Kohonen, 1993). However, recent studies revealing highly structured connectivity patterns between excitatory and inhibitory cells (Lee et al., 2014; Bloss et al., 2016).

Inhibition in the hippocampus is achieved by the binding of γ -Aminobutyric acid (GABA) to one of two broad classes of receptors: the ionotropic GABA_A receptor and the metabotropic GABA_B receptor (Hill and Bowery, 1981). Binding of GABA to the GABA_AR directly opens a chloride-permeable ion pore that drives the cell towards the reversal potential of Cl⁻ which is approximately -70 mV (Alger and Nicoll, 1982). Since the resting membrane potential of pyramidal cells approaches the chloride reversal potential (Barmashenko et al., 2011), one effect of GABA_AR-mediated inhibition in excitatory cells is to shunt excitatory drive. Hyperpolarization also activates a set of voltage-gated channels

that depolarize the neuron and can cause rebound spiking following inhibition (Robinson and Siegelbaum, 2003). Therefore, in pyramidal cells that receive common inhibitory input, GABA_AR activation causes an initial period of co-silence followed by co-activity due to similarly timed rebound spiking (Cobb et al., 1995).

GABA_B receptors indirectly modulate neuronal activity through G-protein coupled heterodimers (Marshall et al., 1998; Robbins et al., 2001). Different splice variants dramatically change the binding efficacy of GABA and downstream signaling pathways (Dutar and Nicoll, 1988; Bettler et al., 1998) as well as localization on the pre- versus the post-synaptic membrane (Gassmann and Bettler, 2012). GABA_BR indirectly modulates ion channel conductance primarily by blocking voltage gated calcium channels (Chalifoux and Carter, 2011) and opening inward rectifying potassium channels (Fajardo-Serrano et al., 2013); GABA_BRs also modulate important second messenger signaling pathways (Chalifoux and Carter, 2010). By decreasing dendritic calcium levels, GABA_BR activation can have a sustained and profound effect on excitatory post-synaptic potential (EPSP) integration and dendritic spiking hundreds of milliseconds after receptor activation (Palmer et al., 2012). High-affinity GABA_BRs located outside of the synapse can also modulate overall excitability by binding “spill over” GABA (Scanziani, 2000) thereby setting tonic levels of excitability.

Synapses perform an input-output operation in which changes in ion channel conductance drive changes in voltage potential to alter the likelihood of generating an action potential. Inhibitory currents affect this operation by changing the slope of the input-output curve (divisive inhibition/gain control), adjusting the threshold for activation (subtractive inhibition), or both (Holt and Koch, 1997; Mitchell and Silver, 2003; Ferrante et al., 2009; Ferrante and Ascoli, 2015). In passive dendrites that lack voltage-gated ion channels, theoretical studies have shown that shunting inhibition will always be subtractive (Holt and Koch, 1997; Abbott and Chance, 2005). However, active dendrites show non-linear input summation (Magee, 2000) due to voltage-gated channel permeability, which causes multiplicative changes in input/output gain (Mehaffey et al., 2005). Therefore, dendritic inhibition acting on dendrites with active channels can theoretically cause both subtractive and divisive modulation (Mehaffey et al., 2005; Ferrante et al., 2009; Ferrante and Ascoli, 2015).

In support of these computational predictions, photo-uncaging of GABA at the dendrites causes a massive decrease in the gain of the input output curve, causing much lower firing in response to the same degree of synaptic excitation (Lovett-Barron et al., 2012), whereas this effect is less prominent at after somatic inhibition. On the other hand, pharmacogenetic silencing of dendrite-targeting interneurons (Lovett-Barron et al., 2012) causes large increases in gain, while silencing soma-targeting interneurons does not produce this effect. Optogenetic interneuron activation causes the reverse effects, shunting the excitatory drive from CA3 and the entorhinal cortex (Milstein et al., 2015). Therefore, synapse- or branch-specific changes in inhibition can change the gain or the threshold of particular synapses, as a function of the degree to which that excitatory input contributes to dendritic non-linearity (Larkum et al., 1999; Mehaffey et al., 2005; Müller et al., 2012; Chiu et al., 2013; Milstein et al., 2015).

Excitability patterns are regulated through feedback and feedforward inhibition

Pyramidal cells receive inhibition from three primary sources: local recurrent connections (feedback inhibition), excitatory afferents that impinge upon local inhibitory interneurons (feedforward inhibition), and long range inhibitory projection cells. One well-accepted role of inhibition from these sources is to control the total number of active excitatory cells (Kaski and Kohonen, 1994). In fact, near complete silencing of the hippocampus is achieved during infusions of the GABA_A receptor agonist muscimol (Martin and Ghez, 1999), while pathological hyper-excitability is observed after GABA_AR antagonism (Stark et al., 2014).

Recurrent, feedback inhibition promotes competition amongst pyramidal cells, ensuring that the neurons that receive strong excitatory inputs fire at the expense of those that receive weaker drive. *In vivo*, reliable spiking of local interneurons is observed after spontaneous pyramidal firing (Csicsvari et al., 1999), or after experimentally driven activation of one to several pyramidal cells (Marshall et al., 2002; Stark et al., 2015; Wu et al., 2015).

Theoretically, mutual feedback inhibition of neighboring excitatory cells causes ensembles of pyramidal cells that code for distinct locations to fire at distinct moments during theta (Harris et al., 2003) and during ripples (Pfeiffer and Foster, 2015). Though full demonstration of this fast-timescale lateral inhibition is lacking, the indirect effects of silencing a sub-population of pyramidal cells has been studied. By using the immediate early gene *c-fos* to drive expression of a silencing opsin, it is possible to optogenetically modulate the firing patterns of groups of neurons that are co-active for a period of hours (Liu et al., 2012). Optogenetically silencing such a sub-population disinhibits other neurons, which is reflected as an increase in the amount of *c-fos* in neurons that do not express the silencing opsin (Tayler et al., 2013; Stefanelli et al., 2016)) and through the emergence of novel place fields in the untagged population of pyramidal cells (Touche et al., 2016). Another such silencing study in the dentate gyrus showed that interneurons that target cell dendrites play a large role in modulating the total number of active neurons (Stefanelli et al., 2016). Since information is thought to be carried by the precise pattern of co-active neurons, these competitive interactions have the potential to play a central role in defining which coincident signals are generated by the hippocampus.

While feedback inhibition allows a region to regulate its own output, feedforward inhibition regulates the integration of incoming information. Anatomical tracing and electrophysiological recordings have shown evidence for feedforward inhibition from cortical and sub-cortical regions into the hippocampus as well as between the hippocampal subfields (Buzsáki and Eidelberg, 1981; Ashwood et al., 1984; Seress and Ribak, 1984; Pouille and Scanziani, 2001; Kajiwara et al., 2008; Takács et al., 2012; Bezaire and Soltesz, 2013). For example, electrical or optogenetic stimulation of the Schaffer collaterals (SC) causes fast monosynaptic excitation of CA1 pyramidal cells followed by delayed, disinaptic inhibition. This is referred to as the “canonical EPSP-IPSP sequence” and is emblematic of feedforward inhibition (Schwartzkroin, 1975; Alger and Nicoll, 1982; Miles, 1990; Buhl et al., 1996; Pouille and Scanziani, 2001; Lovett-Barron et al., 2012). Antagonizing GABA_AR eliminates the feedforward peri-somatic IPSPs, which widens the EPSP integration window

and increases spike-timing jitter (Pouille and Scanziani, 2001). Therefore, one crucial role for feedforward inhibition is to enforce pyramidal spiking preferentially to highly synchronous afferent EPSPs.

It has been proposed that the integration time window can be tightened or relaxed according to computational demands by changing the dynamics of feedforward inhibition (Assisi et al., 2007). This can be accomplished through plastic changes in excitatory to inhibitory connections or by recruiting different populations of interneurons (Hu et al., 2014). In one assessment of feed-forward inhibition, two populations of interneurons were found, one with fast, reliable EPSPs, and another with slow onset, slow offset, variable EPSPs. The two classes differed mostly by their expression of NMDA receptors, as NMDAR antagonism converted the slow-type to a fast responder (Maccaferri and Dingledine, 2002). Therefore, dynamic changes to the integration window could be accomplished through differential connectivity to these interneuron populations, or even by modulating NMDA receptor density within single interneurons. Others have suggested that the mismatch in the time constants between excitatory and inhibitory short term plasticity at feedforward synapses could further allow for more complex filtering of particular input frequencies (Klyachko and Stevens, 2006).

Another important function of feedforward inhibition is to maintain a constant number of output neurons despite large fluctuations in the number of inputs. This normalization requires rapid adjustment of the EPSC amplitude required to reach spike threshold. A natural solution to this problem is to scale feedforward inhibition with feedforward excitation, as larger excitatory inputs will be needed to counteract a larger GABA conductance. *In vitro*, variable-intensity input pulses result in a significant correlation in the size of experimentally evoked feedforward EPSPs and IPSPs (Pouille et al., 2009). *In vivo*, cortical EPSPs and IPSPs are well correlated on a moment-to-moment basis (D'amour and Froemke, 2015) suggesting a global utility for this type of input normalization, though such recordings have not yet been conducted in the hippocampus *in vivo*.

The precise pattern of neural output given some input pattern can depend upon the heterogeneity of the excitation, inhibition or both. Homogenous decreases in feedforward inhibition, relative to feedforward excitation, may reveal previously subthreshold firing fields while increases may sparsen the representation. Heterogeneity in feedforward inhibition or excitation will lead to the selective activation of some output neurons over others. To experimentally test whether spiking of one group of neurons over another is due to heterogeneity in feedforward excitation versus inhibition, Pouille et al (2009) minimally stimulated the Schaffer collaterals *in vitro* until one of a pair of simultaneously recorded cells fired. An assessment of feedforward excitation and inhibition revealed that differences in evoked EPSPs, more so than the evoked IPSPs, explained the propensity for one neuron to fire over another (Pouille et al., 2009). These results show that, despite the importance of inhibition, imbalances in excitatory drive may play a larger role in defining which cells become active.

Several studies have emphasized that inhibition is “homogeneous” across neurons (Pouille et al., 2009) and “spatially uniform” as animals move about their environment (Grienberger et

al., 2017). This characterization may be overly simplistic, as recent evidence shows heterogeneity in the connectivity between principal cells and interneurons according to their anatomical location and long-distance projection targets (Krook-Magnuson et al., 2012; Lee et al., 2014; Valero et al., 2015; McGarry and Carter, 2016). For example, by using multi-color retrograde fluorescent labelling, it was discovered that CA1 pyramidal cells that project to the amygdala receive larger amplitude IPSCs from parvalbumin positive (PV+) basket cells as compared to pyramidal cells that project to the medial prefrontal cortex. However, the mPFC-projecting pyramidal cells are more likely to innervate PV+ basket cells (Lee et al., 2014) showing that circuit specialization occurs according to efferent connectivity.

Across the neocortex, the tuning curves for IPSPs tend to match those of EPSPs (Clopath et al., 2016) suggesting that inhibitory input is highly stimulus-dependent. Spatial tuning of hippocampal interneurons has been described in multiple studies (Nitz and McNaughton, 2004; Maurer et al., 2006; Wilent and Nitz, 2007; Hangya et al., 2010; Grienberger et al., 2017). The spatial information carried by interneuron spike count has been shown to exceed that of “place cells”, according to a common information-theoretic analysis (Wilent and Nitz, 2007) showing reliable, highly non-uniform inhibitory signaling across space. Therefore, inhibitory signals carrying behavioral meaningful information are available to particular excitatory neurons at particular times.

Inhibitory neurons gate hippocampal afferents

By targeting different regions of pyramidal dendrites, inhibitory cells are able to affect the driving force of inputs arriving from different presynaptic regions. The anatomical specificity of inhibitory modulation of excitatory afferents is due to the alignment of the inhibitory axonal arborization with the laminar distribution of excitatory inputs arriving to the dendritic shaft of pyramidal cells. For example, in CA1, bistratified cells innervate the stratum radiatum and basal dendrites, the regions that also receive inputs from area CA3. In this way interneuron classes that differ according to the pattern of axonal targetting can gate signals arriving from different parts of the brain (Miles et al., 1996; Bloss et al., 2016) (Figure 1A).

In vitro perturbation experiments support a role for inhibitory control over access to the soma. For example, Oriens-lacunosum moleculare (OLM) cells synapse on the distal dendrites of pyramidal cells (Freund and Buzsáki, 1996) to suppress inputs arriving from layer III of the entorhinal cortex via the temporoammonic pathway (Leão et al., 2012; Amilhon et al., 2015). OLM interneurons also disinhibit Schaffer collateral (SC) inputs arriving from CA3 (Leão et al., 2012; Lovett-Barron et al., 2012), presumably by inhibiting interneurons that synapse on the same dendritic compartments that receive SC inputs (Miles et al., 1996; Cobb et al., 1997; Sik et al., 1997; Katona et al., 1999; Banks et al., 2000; Lovett-Barron et al., 2012; Tyan et al., 2014; Amilhon et al., 2015). Therefore, excitatory input to OLM cells, which mostly comes from local pyramidal cells (Blasco-Ibáñez and Freund, 1995; Takács et al., 2012) boosts CA3 inputs while suppressing drive from the entorhinal cortex.

Unlike OLM cells, the axonal arborization of Cholecystokinin-immunopositive (CCK+) basket cells and CCK+ Schaffer collateral-associated interneurons are well aligned to affect CA3 input. CCK+ basket cells target the soma and the proximal dendrites in stratum radiatum and oriens, while the axons of the Schaffer collateral-associated interneurons show highly overlapping ramifications as that of the Schaffer collaterals from CA3 (Cope et al., 2002). During electrical stimulation of the Schaffer collateral, pharmacogenetic silencing of CCK+ interneurons decreases feedforward IPSCs impinging on pyramidal cells and disinhibits somatic depolarization. This reveals an important role of CCK+ interneurons in gating CA3 inputs, though feedforward inhibition from ECIII was also affected (Basu et al., 2013). Experiments using voltage-sensitive dyes have found that temporoammonic EPSPs are strongly compartmentalized to the apical dendritic tuft by feedforward inhibition (Ang et al., 2005). However, when SC stimulation precedes stimulation of stratum lacunosum moleculare (SLM), the dendritic gate is disinhibited and temporoammonic EPSPs can potentiate the soma (Ang et al., 2005), revealing a timing-dependent mechanism by which feedforward inhibition influences when neurons fire and how inputs are integrated.

In vivo, correlational evidence that interneurons gate input can be found in the analysis of how afferent and local signals coordinate with the 8–12 Hz theta rhythm that synchronizes the extended hippocampal system. Normal hippocampal theta depends upon inhibitory inputs from the septum to hippocampal inhibitory neurons (Freund and Antal, 1988) and on glutamatergic signaling to NMDAR of PV+ interneurons (Korotkova et al., 2010). Different interneuron classes lock to theta at different phases (Klausberger et al., 2003, 2004, 2005, Fuentealba et al., 2008, 2010; Klausberger and Somogyi, 2008; Varga et al., 2012; Bezaire et al., 2016). Across interneuron types the range of theta phase preferences gives rise to sequential inhibitory inputs across principal neurons during each theta period (Milstein et al., 2015)(Figure 1A). Estimating the spatiotemporal extent of IPSPs caused by these waves of GABAergic inputs is more challenging, since different dendritic regions will have different cable properties, thereby altering the magnitude and spread of the IPSPs even for equivalent input (Bloss et al., 2016). Furthermore, GABAergic receptor types possess a range of binding affinities and kinetics and are expressed non-uniformly, both across the dendritic arbor (Banks et al., 2000; Klausberger et al., 2002; Capogna, 2011; Hu et al., 2014) and within the pre-synaptic GABAergic terminals (Mott and Lewis, 1991; Price et al., 2008). Finally, intracellular recordings have revealed theta-paced waves of inhibition in the dendrites and soma that is 180 degrees out of phase during theta (Kamondi et al., 1998) (Figure 1B). This temporally offset pattern of inhibition may bias the efficacy of afferent input according to the location of the synapse on the dendritic arbor and the timing of signal input during theta.

During theta, the strong phase modulation of interneuron firing correlates with the phasic modulation of activity of CA3 and entorhinal cells (Hasselmo et al., 2002; Colgin et al., 2009; Mizuseki et al., 2009; Schomburg et al., 2014; Fernández-Ruiz et al., 2017). Current source density analysis (CSD) shows that on the descending phase of pyramidal theta there are strong sinks in the stratum radiatum, where the SC terminates, reflecting the strong CA3 drive (Buzsáki et al., 1986) (Figure 1C). On the rising phase of theta, entorhinal input dominates. Though the source of this phase offset is unknown, the pattern of inhibition and disinhibition on the descending phase of theta presents a favorable electrotonic environment

for post-synaptic drive from CA3 inputs (Wyble et al., 2000; Fernández-Ruiz et al., 2012). At the descending phase, somatic inhibition is decreasing (Kamondi et al., 1998), as does the firing rate of CCK+ basket cells (Klausberger et al., 2005), Ivy cells (Fuentelba et al., 2008), and bistratified cells (Klausberger et al., 2004), which target the soma and the dendritic compartments that receive CA3 input. The descending phase of theta is associated with a low (30–50Hz) frequency gamma rhythm. This CA1 rhythm is coherent with CA3 gamma (Colgin et al., 2009; Schomburg et al., 2014) and is phase locked to somatic-targeting CA1 PV+ interneurons (Zemankovics et al., 2013; Lasztóczy and Klausberger, 2014), which in turn are thought to induce gamma modulation of pyramidal cells (Lasztóczy and Klausberger, 2014; Fernández-Ruiz et al., 2017)(Figure 1E). Finally, *in vivo* optogenetic silencing of PV+ interneurons causes maximal disinhibition of pyramidal cell firing during the first moments upon place field entry, when spikes normally fall on the ascending phase of theta and ECIII input dominates (Royer et al., 2012). Therefore, silencing PV+ interneurons likely disinhibited CA3 inputs to increase early field firing on the theta trough (Figure 1D); presumably during place field exit CA3 inputs are already disinhibited thus occluding the optogenetic manipulation. Together these results show that interneurons that target the soma and proximal dendrites can powerfully gate CA3 inputs.

On the ascending phase of CA1 theta, entorhinal inputs dominate pyramidal cell input. Current source density analysis reveals strong sinks in the SLM during the peak of theta (Buzsáki et al., 1986) reflecting maximal entorhinal drive during peak activity of entorhinal layer III principal cells (Mizuseki et al., 2009)(Figure 1C). During the same phase, OLM interneuron firing rate decreases (Klausberger et al., 2004) and pyramidal dendrites are depolarized (Kamondi et al., 1998). The ascending phases are also associated with a local high frequency (60 – 100Hz) gamma that is coherent with high frequency entorhinal gamma (Colgin et al., 2009). This late phase, high frequency gamma paces distal dendritic-targeting interneurons which likely causes gamma phase locking of pyramidal cell activity (Fernández-Ruiz et al., 2017)(Figure 1E). Importantly, optogenetic activation of OLM cells suppresses dendritic depolarization due to electrical stimulation of the temporoammonic pathway (Leão et al., 2012). Finally, silencing dendritic-targeting, somatostatin positive (SOM+) interneurons increases firing upon place field exit, when spikes normally fall on the descending phase of theta and CA3 input dominates (Royer et al., 2012). Silencing SOM+ interneurons likely gated EC3 inputs to increase late field firing (Figure 1D); presumably during place field entry ECIII inputs are already disinhibited thus occluding the optogenetic manipulation.

Several studies have begun to reveal how feedforward and feedback signals regulate these inhibitory gates. For example, in CA1, 100 Hz electrical stimulation of recurrent pyramidal feedback fibers in the stratum alveus causes feedback inhibition at the soma early in the pulse train, followed by dendritic inhibition (Pouille and Scanziani, 2004). The authors hypothesized that in soma-targeting interneurons, the excitatory feedback inhibition underwent short-term depression which decreased feedback inhibition late in the spike train. On the other hand, in dendritic targeting interneurons, the excitatory drive was thought to have facilitated thus driving more spiking at the end of the spike train (Pouille and Scanziani, 2004; but see Elfant et al., 2008) (Figure 1F). Remarkably, these dynamics can be seen in the strong coupling strength of pyramidal cells to soma-targeting, PV+ interneurons

early in a place field, when entorhinal input to the distal dendrites dominates spiking. Upon exiting the place field, coupling of pyramidal cells to dendrite-targeting, somatostatin positive interneurons increases and CA3 inputs begin to drive spiking (Fernández-Ruiz et al., 2017). Therefore, local feedback onto different types of interneurons may be able to time which input region can drive a neuron and when (Fernández-Ruiz et al., 2017).

The inhibitory modulation of pyramidal cell excitability can also affect the plasticity of the excitatory inputs. For example, it is well known that pharmacological GABAR antagonism facilitates the induction of long-term potentiation (LTP) of SC to CA1 (Wigström and Gustafsson, 1983; Davies et al., 1991; Mott and Lewis, 1991). The GABAergic modulation of excitatory connectivity is highly dependent upon the precise protocol used to generate plasticity and the way in which inhibition is modulated (Mott and Lewis, 1991; Chapman et al., 1998; Chevaleyre and Castillo, 2003; Slanina et al., 2005; Karson et al., 2009; McQuiston, 2010; Nishiyama et al., 2010; Kondo et al., 2013; Basu et al., 2016). Despite these complexities, a relatively simple rule has emerged in neocortical circuits, where transient mismatches in the rate and amplitude of EPSPs and IPSPs define time windows in which receptive fields can be re-turned to novel stimuli (Froemke et al., 2007; Froemke, 2015). According to some models, the plasticity window is open because of the presence of active dendritic events (Kampa et al., 2006; Bittner et al., 2017) that, in CA1, are known to be strongly modulated by dendritic inhibition (Lovett-Barron et al., 2012). In the hippocampus, active dendritic events (e.g. plateau potentials) are known to gate plasticity at excitatory synapses (Takahashi and Magee, 2009) and can precede the formation of novel place fields (Bittner et al., 2015, 2017). Future experiments should test whether the disinhibitory modulation of these active dendritic causes large increases in synaptic gain which in turn gate synaptic plasticity mechanisms.

Neuromodulators strongly affect how inhibition influences network processing. For example, acetylcholine is known to bias afferent drive from the entorhinal cortex to CA1 and weaken that coming from CA3 (Hasselmo et al., 1996). In part, this redirecting of inputs is due to the differential effects of cholinergic inputs to different classes of interneuron (Lovett-Barron et al., 2014; McQuiston, 2014). In addition to acetylcholine, the inhibitory modulation of excitatory networks is affected by serotonergic centers (Varga et al., 2009) and dopamine binding (Ito and Schuman, 2007) and through retrograde endocannabinoid signaling (Chevaleyre and Castillo, 2003). The combined effects of these neuromodulators provide a plausible mechanism by which inputs are gated and receptive fields are changed only during behaviorally relevant moments.

Inhibition affects the hippocampal neural code

Given the various ways in which interneurons modulate pyramidal cell excitability, what is the evidence that inhibitory cells influence hippocampal coding? Indirect support comes from experiments in which stimuli (e.g. tones, electrical tooth pulps) were presented transiently while monitoring the hippocampal response. In these studies, if stimuli were presented during natural theta (e.g. during grooming) or during artificially driven theta (e.g. physostigmine infusion) the evoked field response and principal cell firing was greatly diminished (Branká k and Buzsáki, 1986; Vinogradova et al., 1993). On the other hand,

disrupting theta with lesions to the medial septum or through pharmacology (e.g. with systemic scopolamine) increases hippocampal responsiveness to various stimuli (Vinogradova et al., 1993; Khanna, 1997; Zheng and Khanna, 2001; Kitchigina, 2010). Salient stimuli can trigger a global phase reset of hippocampal theta that relies upon long range GABAergic signaling from the medial septum specifically to hippocampal interneurons (Freund and Antal, 1988; Tóth et al., 1997; Vinogradova et al., 1998). The inferential conclusion from this body of work is that when a stimulus can reset theta, the afferent inputs that continue to carry relevant information arrive at theta phases where inhibition is minimal thus allowing maximal excitatory drive (Bilkey and Goddard, 1985). On the other hand, inputs carrying unrelated information arrive asynchronously from the ongoing hippocampal activity and are effectively “locked out” due to the inhibitory mechanisms described above (Vinogradova et al., 1993; but see Shan et al., 2016). Correlational studies that have tracked neural activity across learning have shown changes in theta phase synchronization between the hippocampus and afferent brain regions (Hyman et al., 2005; Jones and Wilson, 2005; Siapas et al., 2005; Paz et al., 2008; Sirota et al., 2008; Tort et al., 2008; Young and McNaughton, 2009; Benchenane et al., 2010; Lesting et al., 2011; van der Meer and Redish, 2011; Backus et al., 2016) suggesting that in principle phasic coordination may be important for information transfer between regions.

More direct evidence comes from analysis of hippocampal tuning properties after artificial manipulation of different classes of interneurons. Two-photon calcium imaging can reveal somatic calcium spikes as well as the pre-synaptic calcium transients that trigger transmitter release (Lovett-Barron et al., 2014). Using focal viral injections into the rhinal cortices or CA1, Lovett-Barron et al. showed that an aversive puff of air (US) caused strong activation of the terminals from the medial and lateral rhinal cortices but only a minimal activation of CA1 pyramidal cells. On the other hand, the US strongly activated SOM+ axons in the SLM, and not those in the radiatum suggesting that feedforward inhibition from these interneurons suppressed pyramidal firing. In support of that conclusion, pharmacogenetic silencing of dendrite-targeting SOM+ interneurons significantly increased responsiveness of CA1 cells to the air puff (Lovett-Barron et al., 2014), demonstrating for the first time how a particular class of interneuron could shape the non-spatial tuning properties of hippocampal cells.

Artificial neuronal depolarization can reveal tuning properties that would otherwise fall under the spiking-threshold defined by the balance of excitation and inhibition. Intracellular recordings in awake, behaving mice have shown that direct current injection to a single neuron uncovers novel, spatially tuned firing fields in locations where the cell had earlier been silent (Lee et al., 2012). Since no sub-threshold somatic EPSPs were observed in the future place field location, it is possible that spatially tuned EPSPs were dendritically compartmentalized or too small to trigger dendritic spiking (Lee et al., 2012).

On the other hand, optogenetic interneuron modulation has a surprisingly subtle effect on place field activity. Silencing PV+ interneurons or SOM+ interneurons, or both, modulates intra-place field firing rate, burstiness, and firing phase, but never reveals novel place fields (Royer et al., 2012; Grienberger et al., 2017). These results suggest that the spatial tuning in the hippocampus is due to increased excitation as opposed to transient, spatially tuned disinhibition (Grienberger et al., 2017).

However, most studies of hippocampal cells have demonstrated that non-spatial coding emerges via refinement of existing place fields (Kobayashi et al., 1997; Alvernhe et al., 2008; Komorowski et al., 2009; Singer et al., 2010; Navratilova et al., 2012). As pyramidal cells become tuned to different sensory inputs (presumably coming from different afferents), hippocampal neurons increase their coupling to different high frequency oscillations. For example, as rats learn to associate an odor with a future food location, CA1 place cells begin to develop odor-tuning that correlates with an increase in beta frequency (20–40 Hz) coupling between CA1 and LEC (Igarashi et al., 2014). Since the generation of beta oscillations, at least in the neocortex, is thought to depend upon excitatory-inhibitory coupling (Kopell et al., 2011), the concomitant increase in beta and odor tuning suggest novel coupling between excitatory and inhibitory cells. Similar recordings have shown that odor tuning in the dentate gyrus correlates with an increase in phase coupling in both principal cells and interneurons to beta (Rangel et al., 2016). Other studies have shown that increases in theta-gamma coupling and the degree to which pyramidal cells are paced at gamma frequencies correlates with spatial working memory (Montgomery et al., 2009; Schomburg et al., 2014; Yamamoto et al., 2014) and object coding (Tort et al., 2009; Zheng et al., 2016). These findings are consistent with a model in which both learning and the development of complex receptive fields are due to novel excitatory to inhibitory connections (Kalweit et al., 2017) which manifest as novel oscillatory dynamics.

The most direct evidence that changes in excitatory to inhibitory coupling support learning was measured in a study on spatial memory. As rats learned to find food rewards in novel locations, place fields changed locations, or remapped. Importantly, this remapping was associated with novel, putatively synaptic coupling between excitatory and inhibitory cells such that different maps were associated with different interneurons. The change in synaptic coupling strength was well predicted by how many times the excitatory and inhibitory cells fired together during learning, but only for hippocampal cells that fired at the goal locations, suggesting a co-requirement for neuromodulatory inputs during co-activation (Dupret et al., 2013). During such ripple events, when the subject is stationary, hippocampal cells show sequential activity, replaying the order in which they fired during movement. Silencing ripples disrupts hippocampal spatial representations (van de Ven et al., 2016), as well as long-term (Girardeau et al., 2009) and working memory (Jadhav et al., 2012). Since ripples emerge from excitatory-inhibitory reciprocal connectivity (Stark et al., 2014) and since spike transmission from excitatory to inhibitory cells is largest during sharp-wave ripples (personal observations), it is possible that changes in coupling of excitatory to inhibitory cells during ripples may be an important component of memory consolidation.

Conclusion

Most memory models focus on plasticity amongst excitatory neurons. The anatomical complexity of the interneuron network and the role inhibitory neurons play in modulating activity-dependent plasticity suggest that inhibition does more than “simply” normalize the excitatory drive. There is accumulating evidence that inhibitory connections influence the shape of the landscape that defines which neuronal patterns are stable and which are not. Through inhibitory gating, hippocampal cells can be tuned to any constellation of inputs. Learning-related changes in these inhibitory-excitatory connections allow for long-term

shifts in the balance of which afferent inputs can drive output spike. These shifts, in turn may alter the coding of hippocampal neurons. As the similarity in such coding patterns across different episodes is thought to define the similarity of those episodes in memory space (McKenzie et al., 2014), inhibition, and plasticity in inhibitory signaling, may be a vital component in creating mental shemas. Future studies are required to show that inhibitory connections indeed serve these complex functions in defining the organization of the hippocampal memory space.

Acknowledgments

I would like to thank Howard Eichenbaum and György Buzsáki for many interesting conversations that inspired this manuscript. I would like to acknowledge Daniel English, Viktor Varga, Antonio Fernández-Ruiz, Horacio Rotstein and Jonathan Platkiewicz for discussing an earlier version of this review. This work was supported by NIMH grant F32 MH107159.

References

- Abbott LF, Chance FS. Drivers and modulators from push-pull and balanced synaptic input. *Prog Brain Res.* 2005;147–155. [PubMed: 16226582]
- Alger BE, Nicoll RA. Pharmacological evidence for two kinds of GABA receptors on rat hippocampal pyramidal cells studied *in vitro*. *J Physiol.* 1982; 328:125–141. [PubMed: 7131310]
- Alvernhe A, Van Cauter T, Save E, Poucet B. Different CA1 and CA3 representations of novel routes in a shortcut situation. *J Neurosci.* 2008; 28:7324–33. [PubMed: 18632936]
- Amilhon B, Huh CYL, Manseau F, Ducharme G, Nichol H, Adamantidis A, Williams S. Parvalbumin Interneurons of Hippocampus Tune Population Activity at Theta Frequency. *Neuron.* 2015; 86:1277–1289. [PubMed: 26050044]
- Ang CW, Carlson GC, Coulter DA. Hippocampal CA1 circuitry dynamically gates direct cortical inputs preferentially at theta frequencies. *J Neurosci.* 2005; 25:9567–80. [PubMed: 16237162]
- Ashwood TJ, Lancaster B, Wheal HV. In vivo and in vitro studies on putative interneurons in the rat hippocampus: Possible mediators of feed-forward inhibition. *Brain Res.* 1984; 293:279–291. [PubMed: 6320970]
- Assisi C, Stopfer M, Laurent G, Bazhenov M. Adaptive regulation of sparseness by feedforward inhibition. *Nat Neurosci.* 2007; 10:1176–1184. [PubMed: 17660812]
- Backus AR, Schoffelen J-M, Szebényi S, Hanslmayr S, Doeller CF. Hippocampal-Prefrontal Theta Oscillations Support Memory Integration. *Curr Biol.* 2016; 26:450–7. [PubMed: 26832442]
- Banks MI, White JA, Pearce RA. Interactions between distinct GABA(A) circuits in hippocampus. *Neuron.* 2000; 25:449–57. [PubMed: 10719898]
- Barmashenko G, Hefft S, Aertsen A, Kirschstein T, Köhling R. Positive shifts of the GABAA receptor reversal potential due to altered chloride homeostasis is widespread after status epilepticus. *Epilepsia.* 2011; 52:1570–1578. [PubMed: 21899534]
- Basu J, Srinivas KV, Cheung SK, Taniguchi H, Huang ZJ, Siegelbaum SA. A cortico-hippocampal learning rule shapes inhibitory microcircuit activity to enhance hippocampal information flow. *Neuron.* 2013; 79:1208–21. [PubMed: 24050406]
- Basu J, Zaremba JD, Cheung SK, Hitti FL, Zemelman BV, Losonczy A, Siegelbaum SA. Gating of hippocampal activity, plasticity, and memory by entorhinal cortex long-range inhibition. *Science* (80-). 2016; 351:aaa5694–aaa5694.
- Benchenane K, Peyrache A, Khamassi M, Tierney PL, Gioanni Y, Battaglia FP, Wiener SI. Coherent theta oscillations and reorganization of spike timing in the hippocampal-prefrontal network upon learning. *Neuron.* 2010; 66:921–36. [PubMed: 20620877]
- Bettler B, Kaupmann K, Malitschek B, Schuler V, Heid J, Froestl W, Beck P, Mosbacher J, Bischoff S, Kulik A, Shigemoto R, Karschin A. GABA(B)-receptor subtypes assemble into functional heteromeric complexes. *Nature.* 1998; 396:683–687. [PubMed: 9872317]

- Bezaire MJ, Raikov I, Burk K, Vyas D, Soltesz I. Interneuronal mechanisms of hippocampal theta oscillations in a full-scale model of the rodent CA1 circuit. *Elife*. 2016; 5:e18566. [PubMed: 28009257]
- Bezaire MJ, Soltesz I. Quantitative assessment of CA1 local circuits: Knowledge base for interneuron-pyramidal cell connectivity. *Hippocampus*. 2013; 23:751–785. [PubMed: 23674373]
- Bilkey DK, Goddard GV. Medial septal facilitation of hippocampal granule cell activity is mediated by inhibition of inhibitory interneurons. *Brain Res*. 1985; 361:99–106. [PubMed: 4084813]
- Bittner KC, Grienberger C, Vaidya SP, Milstein AD, Macklin JJ, Suh J, Tonegawa S, Magee JC. Conjunctive input processing drives feature selectivity in hippocampal CA1 neurons. *Nat Neurosci*. 2015; 18:1133–1142. [PubMed: 26167906]
- Bittner KC, Milstein AD, Grienberger C, Romani S, Magee JC. Behavioral time scale synaptic plasticity underlies CA1 place fields. *Science* (80-). 2017:357.
- Blasco-Ibáñez JM, Freund TF. Synaptic input of horizontal interneurons in stratum oriens of the hippocampal CA1 subfield: structural basis of feed-back activation. *Eur J Neurosci*. 1995; 7:2170–80. [PubMed: 8542073]
- Bloss EB, Cembrowski MS, Karsh B, Colonell J, Fetter RD, Spruston N. Structured Dendritic Inhibition Supports Branch-Selective Integration in CA1 Pyramidal Cells. *Neuron*. 2016; 89:1016–1030. [PubMed: 26898780]
- Branka k J, Buzsáki G. Hippocampal responses evoked by tooth pulp and acoustic stimulation: Depth profiles and effect of behavior. *Brain Res*. 1986; 378:303–314. [PubMed: 3730880]
- Buhl EH, Szilágyi T, Halasy K, Somogyi P. Physiological properties of anatomically identified basket and bistratified cells in the CA1 area of the rat hippocampus in vitro. *Hippocampus*. 1996; 6:294–305. [PubMed: 8841828]
- Buzsáki G, Czopf J, Kondákor I, Kellényi L. Laminar distribution of hippocampal rhythmic slow activity (RSA) in the behaving rat: current-source density analysis, effects of urethane and atropine. *Brain Res*. 1986; 365:125–37. [PubMed: 3947979]
- Buzsáki G, Eidelberg E. Commissural projection to the dentate gyrus of the rat: evidence for feed-forward inhibition. *Brain Res*. 1981; 230:346–350. [PubMed: 7317783]
- Buzsáki G, Kaila K, Raichle M. Inhibition and Brain Work. *Neuron*. 2007; 56:771–783. [PubMed: 18054855]
- Cai DJ, Aharoni D, Shuman T, Shobe J, Biane J, Song W, Wei B, Veshkini M, La-Vu M, Lou J, Flores SE, Kim I, Sano Y, Zhou M, Baumgaertel K, Lavi A, Kamata M, Tuszyński M, Mayford M, Golshani P, Silva AJ. A shared neural ensemble links distinct contextual memories encoded close in time. *Nature*. 2016; 534:115–118. [PubMed: 27251287]
- Capogna M. Neurogliaform cells and other interneurons of stratum lacunosum-moleculare gate entorhinal-hippocampal dialogue. *J Physiol*. 2011; 589:1875–83. [PubMed: 21135049]
- Chalifoux JR, Carter AG. GABAB Receptors Modulate NMDA Receptor Calcium Signals in Dendritic Spines. *Neuron*. 2010; 66:101–113. [PubMed: 20399732]
- Chalifoux JR, Carter AG. GABAB receptor modulation of synaptic function. *Curr Opin Neurobiol*. 2011; 21:339–344. [PubMed: 21376567]
- Chapman CA, Perez Y, Lacaille JC. Effects of GABA(A) inhibition on the expression of long-term potentiation in CA1 pyramidal cells are dependent on tetanization parameters. *Hippocampus*. 1998; 8:289–98. [PubMed: 9662142]
- Chevalleyre V, Castillo PE. Heterosynaptic LTD of hippocampal GABAergic synapses: a novel role of endocannabinoids in regulating excitability. *Neuron*. 2003; 38:461–72. [PubMed: 12741992]
- Chiu CQ, Lur G, Morse TM, Carnevale NT, Ellis-Davies GCR, Higley MJ. Compartmentalization of GABAergic Inhibition by Dendritic Spines. *Science* (80-). 2013; 340:759–762.
- Clopath C, Vogels TP, Froemke RC, Sprekeler H. Receptive field formation by interacting excitatory and inhibitory synaptic plasticity. *bioRxiv*. 2016
- Cobb SR, Buhl EH, Halasy K, Paulsen O, Somogyi P. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature*. 1995; 378:75–8. [PubMed: 7477292]

- Cobb SR, Halasy K, Vida I, Nyiri G, Tamás G, Buhl EH, Somogyi P. Synaptic effects of identified interneurons innervating both interneurons and pyramidal cells in the rat hippocampus. *Neuroscience*. 1997; 79:629–48. [PubMed: 9219929]
- Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser M-B, Moser EI. Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature*. 2009; 462:353–7. [PubMed: 19924214]
- Cope DW, Maccaferri G, Márton LF, Roberts JDB, Cobden PM, Somogyi P. Cholecystokinin-immunopositive basket and Schaffer collateral-associated interneurons target different domains of pyramidal cells in the CA1 area of the rat hippocampus. *Neuroscience*. 2002; 109:63–80. [PubMed: 11784700]
- Csicsvari J, Hirase H, Czurkó A, Mamiya A, Buzsáki G. Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving Rat. *J Neurosci*. 1999; 19:274–87. [PubMed: 9870957]
- D'amour JA, Froemke RC. Inhibitory and excitatory spike-timing-dependent plasticity in the auditory cortex. *Neuron*. 2015; 86:514–28. [PubMed: 25843405]
- Davies CH, Starkey SJ, Pozza MF, Collingridge GL. GABA autoreceptors regulate the induction of LTP. *Nature*. 1991; 349:609–11. [PubMed: 1847993]
- Dupret D, O'Neill J, Csicsvari J. Dynamic reconfiguration of hippocampal interneuron circuits during spatial learning. *Neuron*. 2013; 78:166–80. [PubMed: 23523593]
- Dutar P, Nicoll RA. Pre- and postsynaptic GABAB receptors in the hippocampus have different pharmacological properties. *Neuron*. 1988; 1:585–91. [PubMed: 2856099]
- Elfant D, Pál BZ, Emptage N, Capogna M. Specific inhibitory synapses shift the balance from feedforward to feedback inhibition of hippocampal CA1 pyramidal cells. *Eur J Neurosci*. 2008; 27:104–13. [PubMed: 18184315]
- Fajardo-Serrano A, Wydeven N, Young D, Watanabe M, Shigemoto R, Martemyanov KA, Wickman K, Luján R. Association of Rgs7/Gβ5 complexes with girk channels and GABA_B receptors in hippocampal CA1 pyramidal neurons. *Hippocampus*. 2013; 23:1231–1245. [PubMed: 23804514]
- Fernández-Ruiz A, Makarov VA, Benito N, Herreras O. Schaffer-specific local field potentials reflect discrete excitatory events at gamma frequency that may fire postsynaptic hippocampal CA1 units. *J Neurosci*. 2012; 32:5165–76. [PubMed: 22496562]
- Fernández-Ruiz A, Oliva A, Nagy GA, Maurer AP, Berényi A, Buzsáki G. Entorhinal-CA3 Dual-Input Control of Spike Timing in the Hippocampus by Theta-Gamma Coupling. *Neuron*. 2017; 93:1213–1226. e5. [PubMed: 28279355]
- Ferrante M, Ascoli GA. Distinct and synergistic feedforward inhibition of pyramidal cells by basket and bistratified interneurons. *Front Cell Neurosci*. 2015; 9:439. [PubMed: 26594151]
- Ferrante M, Migliore M, Ascoli GA. Feed-forward inhibition as a buffer of the neuronal input-output relation. *Proc Natl Acad Sci U S A*. 2009; 106:18004–9. [PubMed: 19815518]
- Freund TF, Antal M. GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus. *Nature*. 1988; 336:170–173. [PubMed: 3185735]
- Freund TF, Buzsáki G. Interneurons of the hippocampus. *Hippocampus*. 1996; 6:347–470. [PubMed: 8915675]
- Froemke RC. Plasticity of Cortical Excitatory-Inhibitory Balance. *Annu Rev Neurosci*. 2015; 38:195–219. [PubMed: 25897875]
- Froemke RC, Merzenich MM, Schreiner CE. A synaptic memory trace for cortical receptive field plasticity. *Nature*. 2007; 450:425–429. [PubMed: 18004384]
- Fuentealba P, Begum R, Capogna M, Jinno S, Márton LF, Csicsvari J, Thomson A, Somogyi P, Klausberger T. Ivy Cells: A Population of Nitric-Oxide-Producing, Slow-Spiking GABAergic Neurons and Their Involvement in Hippocampal Network Activity. *Neuron*. 2008; 57:917–929. [PubMed: 18367092]
- Fuentealba P, Klausberger T, Karayannis T, Suen WY, Huck J, Tomioka R, Rockland K, Capogna M, Studer M, Morales M, Somogyi P. Expression of COUP-TFII Nuclear Receptor in Restricted GABAergic Neuronal Populations in the Adult Rat Hippocampus. *J Neurosci*. 2010; 30:1595–1609. [PubMed: 20130170]

- Gassmann M, Bettler B. Regulation of neuronal GABAB receptor functions by subunit composition. *Nat Rev Neurosci.* 2012; 13:380–394. [PubMed: 22595784]
- Girardeau G, Benchenane K, Wiener SI, Buzsáki G, Zugaro MB. Selective suppression of hippocampal ripples impairs spatial memory. *Nat Neurosci.* 2009; 12:1222–3. [PubMed: 19749750]
- Grienberger C, Milstein AD, Bittner KC, Romani S, Magee JC. Inhibitory suppression of heterogeneously tuned excitation enhances spatial coding in CA1 place cells. *Nat Neurosci.* 2017; 20:417–426. [PubMed: 28114296]
- Gulyás AI, Megias M, Emri Z, Freund TF. Total number and ratio of excitatory and inhibitory synapses converging onto single interneurons of different types in the CA1 area of the rat hippocampus. *J Neurosci.* 1999; 19:10082–97. [PubMed: 10559416]
- Hangya B, Li Y, Muller RU, Czurkó A. Complementary spatial firing in place cell-interneuron pairs. *J Physiol.* 2010; 588:4165–4175. [PubMed: 20819942]
- Harris KD, Csicsvari J, Hirase H, Dragoi G. Organization of cell assemblies in the hippocampus. *Nature.* 2003; 424:552–556. [PubMed: 12891358]
- Hasselmo ME, Bodelón C, Wyble BP. A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Comput.* 2002; 14:793–817. [PubMed: 11936962]
- Hasselmo ME, Wyble BP, Wallenstein GV. Encoding and retrieval of episodic memories: role of cholinergic and GABAergic modulation in the hippocampus. *Hippocampus.* 1996; 6:693–708. [PubMed: 9034856]
- Hill DR, Bowery NG. 3H-baclofen and 3H-GABA bind to bicuculline-insensitive GABAB sites in rat brain. *Nature.* 1981; 290:149–152. [PubMed: 6259535]
- Holt GR, Koch C. Shunting inhibition does not have a divisive effect on firing rates. *Neural Comput.* 1997; 9:1001–13. [PubMed: 9188191]
- Hu H, Gan J, Jonas P. Fast-spiking, parvalbumin+ GABAergic interneurons: From cellular design to microcircuit function. *Science (80-).* 2014; 345:1255263–1255263.
- Hyman JM, Zilli EA, Paley AM, Hasselmo ME. Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior. *Hippocampus.* 2005; 15:739–49. [PubMed: 16015622]
- Igarashi KM, Lu L, Colgin LL, Moser M-B, Moser EI. Coordination of entorhinal-hippocampal ensemble activity during associative learning. *Nature.* 2014; 510:143–7. [PubMed: 24739966]
- Ito HT, Schuman EM. Frequency-dependent gating of synaptic transmission and plasticity by dopamine. *Front Neural Circuits.* 2007; 1:1. [PubMed: 18946543]
- Jadhav SP, Kemere C, German PW, Frank LM. Awake Hippocampal Sharp-Wave Ripples Support Spatial Memory. *Science (80-).* 2012; 336:1454–1458.
- Jones MW, Wilson MA. Phase precession of medial prefrontal cortical activity relative to the hippocampal theta rhythm. *Hippocampus.* 2005; 15:867–873. [PubMed: 16149084]
- Kajiwara R, Wouterlood FG, Sah A, Boekel AJ, Baks-te Bulte LTG, Witter MP. Convergence of entorhinal and CA3 inputs onto pyramidal neurons and interneurons in hippocampal area CA1—An anatomical study in the rat. *Hippocampus.* 2008; 18:266–280. [PubMed: 18000818]
- Kalweit AN, Amanpour-Gharaei B, Colitti-Klausnitzer J, Manahan-Vaughan D. Changes in Neuronal Oscillations Accompany the Loss of Hippocampal LTP that Occurs in an Animal Model of Psychosis. *Front Behav Neurosci.* 2017; 11:36. [PubMed: 28337131]
- Kamondi A, Acsády L, Wang XJ, Buzsáki G. Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: activity-dependent phase-precession of action potentials. *Hippocampus.* 1998; 8:244–61. [PubMed: 9662139]
- Kampa BM, Letzkus JJ, Stuart GJ. Requirement of dendritic calcium spikes for induction of spike-timing-dependent synaptic plasticity. *J Physiol.* 2006; 574:283–290. [PubMed: 16675489]
- Karson MA, Tang A-H, Milner TA, Alger BE. Synaptic cross talk between perisomatic-targeting interneuron classes expressing cholecystokinin and parvalbumin in hippocampus. *J Neurosci.* 2009; 29:4140–54. [PubMed: 19339609]
- Kaski S, Kohonen T. Winner-take-all networks for physiological models of competitive learning. *Neural Networks.* 1994; 7:973–984.

- Katona I, Acsády L, Freund TF. Postsynaptic targets of somatostatin-immunoreactive interneurons in the rat hippocampus. *Neuroscience*. 1999; 88:37–55. [PubMed: 10051188]
- Khanna S. Dorsal hippocampus field CA1 pyramidal cell responses to a persistent versus an acute nociceptive stimulus and their septal modulation. *Neuroscience*. 1997; 77:713–21. [PubMed: 9070747]
- Kitchigina VF. Theta oscillations and reactivity of hippocampal stratum oriens neurons. *ScientificWorldJournal*. 2010; 10:930–43. [PubMed: 20495772]
- Klausberger T, Magill PJ, Márton LF, Roberts JDB, Cobden PM, Buzsáki G, Somogyi P. Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. *Nature*. 2003; 421:844–848. [PubMed: 12594513]
- Klausberger T, Márton LF, Baude A, Roberts JDB, Magill PJ, Somogyi P. Spike timing of dendrite-targeting bistratified cells during hippocampal network oscillations in vivo. *Nat Neurosci*. 2004; 7:41–47. [PubMed: 14634650]
- Klausberger T, Marton LF, O'Neill J, Huck JHJ, Dalezios Y, Fuentealba P, Suen WY, Papp E, Kaneko T, Watanabe M, Csicsvari J, Somogyi P. Complementary Roles of Cholecystokinin- and Parvalbumin-Expressing GABAergic Neurons in Hippocampal Network Oscillations. *J Neurosci*. 2005; 25:9782–9793. [PubMed: 16237182]
- Klausberger T, Roberts JDB, Somogyi P. Cell type- and input-specific differences in the number and subtypes of synaptic GABA(A) receptors in the hippocampus. *J Neurosci*. 2002; 22:2513–21. [PubMed: 11923416]
- Klausberger T, Somogyi P. Neuronal Diversity and Temporal Dynamics: The Unity of Hippocampal Circuit Operations. *Science* (80-). 2008; 321:53–57.
- Klyachko VA, Stevens CF. Excitatory and Feed-Forward Inhibitory Hippocampal Synapses Work Synergistically as an Adaptive Filter of Natural Spike Trains. *PLoS Biol*. 2006; 4:e207. [PubMed: 16774451]
- Kobayashi T, Nishijo H, Fukuda M, Bures J, Ono T. Task-dependent representations in rat hippocampal place neurons. *J Neurophysiol*. 1997; 78:597–613. [PubMed: 9307098]
- Kohonen T. Physiological interpretation of the self-organizing map algorithm. *Neural Networks*. 1993; 6:895–905.
- Komorowski RW, Manns JR, Eichenbaum H. Robust conjunctive item-place coding by hippocampal neurons parallels learning what happens where. *J Neurosci*. 2009; 29:9918–29. [PubMed: 19657042]
- Kondo M, Kitajima T, Fujii S, Tsukada M, Aihara T. Modulation of synaptic plasticity by the coactivation of spatially distinct synaptic inputs in rat hippocampal CA1 apical dendrites. *Brain Res*. 2013; 1526:1–14. [PubMed: 23711890]
- Kopell N, Whittington MA, Kramer MA. Neuronal assembly dynamics in the beta1 frequency range permits short-term memory. *Proc Natl Acad Sci U S A*. 2011; 108:3779–84. [PubMed: 21321198]
- Korotkova T, Fuchs EC, Ponomarenko A, von Engelhardt J, Monyer H. NMDA Receptor Ablation on Parvalbumin-Positive Interneurons Impairs Hippocampal Synchrony, Spatial Representations, and Working Memory. *Neuron*. 2010; 68:557–569. [PubMed: 21040854]
- Krook-Magnuson E, Varga C, Lee S-H, Soltesz I. New dimensions of interneuronal specialization unmasked by principal cell heterogeneity. *Trends Neurosci*. 2012; 35:175–184. [PubMed: 22119146]
- Lamsa K, Heeroma JH, Kullmann DM. Hebbian LTP in feed-forward inhibitory interneurons and the temporal fidelity of input discrimination. *Nat Neurosci*. 2005; 8:916–924. [PubMed: 15937481]
- Lamsa KP, Heeroma JH, Somogyi P, Rusakov DA, Kullmann DM. Anti-Hebbian Long-Term Potentiation in the Hippocampal Feedback Inhibitory Circuit. *Science* (80-). 2007; 315:1262–1266.
- Larkum ME, Zhu JJ, Sakmann B. A new cellular mechanism for coupling inputs arriving at different cortical layers. *Nature*. 1999; 398:338–341. [PubMed: 10192334]
- Lasztóczy B, Klausberger T. Layer-specific GABAergic control of distinct gamma oscillations in the CA1 hippocampus. *Neuron*. 2014; 81:1126–39. [PubMed: 24607232]

- Leão RN, Mikulovic S, Leão KE, Munguba H, Gezelius H, Enjin A, Patra K, Eriksson A, Loew LM, Tort ABL, Kullander K. OLM interneurons differentially modulate CA3 and entorhinal inputs to hippocampal CA1 neurons. *Nat Neurosci.* 2012; 15:1524–30. [PubMed: 23042082]
- Lee D, Lin B-J, Lee AK. Hippocampal Place Fields Emerge upon Single-Cell Manipulation of Excitability During Behavior. *Science* (80-). 2012; 337:849–853.
- Lee S-H, Marchionni I, Bezaire M, Varga C, Danielson N, Lovett-Barron M, Losonczy A, Soltesz I. Parvalbumin-Positive Basket Cells Differentiate among Hippocampal Pyramidal Cells. *Neuron.* 2014; 82:1129–1144. [PubMed: 24836505]
- Lesting J, Narayanan RT, Kluge C, Sangha S, Seidenbecher T, Pape H-C. Patterns of Coupled Theta Activity in Amygdala-Hippocampal-Prefrontal Cortical Circuits during Fear Extinction. *PLoS One.* 2011; 6:e21714. [PubMed: 21738775]
- Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K, Tonegawa S. Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature.* 2012; 484:381–5. [PubMed: 22441246]
- Lovett-Barron M, Kaifosh P, Kheirbek MA, Danielson N, Zaremba JD, Reardon TR, Turi GF, Hen R, Zemelman BV, Losonczy A. Dendritic inhibition in the hippocampus supports fear learning. *Science.* 2014; 343:857–63. [PubMed: 24558155]
- Lovett-Barron M, Turi GF, Kaifosh P, Lee PH, Bolze F, Sun X-H, Nicoud J-F, Zemelman BV, Sternson SM, Losonczy A. Regulation of neuronal input transformations by tunable dendritic inhibition. *Nat Neurosci.* 2012; 15:423–430. [PubMed: 22246433]
- Maccaferri G, Dingledine R. Control of feedforward dendritic inhibition by NMDA receptor-dependent spike timing in hippocampal interneurons. *J Neurosci.* 2002; 22:5462–72. [PubMed: 12097498]
- Magee JC. Dendritic integration of excitatory synaptic input. *Nat Rev Neurosci.* 2000; 1:181–190. [PubMed: 11257906]
- Marshall FH, White JH, Wise A, Main MJ, Green A, Fraser NJ, Disney GH, Barnes AA, Emson P, Foord SM. Heterodimerization is required for the formation of a functional GABAB receptor. *Nature.* 1998; 396:679–682. [PubMed: 9872316]
- Marshall L, Henze DA, Hirase H, Leinekugel X, Dragoi G, Buzsáki G. Hippocampal pyramidal cell-interneuron spike transmission is frequency dependent and responsible for place modulation of interneuron discharge. *J Neurosci.* 2002; 22:RC197. [PubMed: 11784809]
- Martin JH, Ghez C. Pharmacological inactivation in the analysis of the central control of movement. *J Neurosci Methods.* 1999; 86:145–59. [PubMed: 10065983]
- Maurer AP, Cowen SL, Burke SN, Barnes CA, McNaughton BL. Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *J Neurosci.* 2006; 26:13485–92. [PubMed: 17192431]
- McGarry LM, Carter AG. Inhibitory Gating of Basolateral Amygdala Inputs to the Prefrontal Cortex. *J Neurosci.* 2016; 36:9391–406. [PubMed: 27605614]
- McKenzie S, Eichenbaum H. Consolidation and reconsolidation: two lives of memories? *Neuron.* 2011; 71:224–33. [PubMed: 21791282]
- McKenzie S, Frank AJ, Kinsky NR, Porter B, Rivière PD, Eichenbaum H. Hippocampal Representation of Related and Opposing Memories Develop within Distinct, Hierarchically Organized Neural Schemas. *Neuron.* 2014; 83:202–215. [PubMed: 24910078]
- McKenzie S, Robinson NTM, Herrera L, Churchill JC, Eichenbaum H. Learning Causes Reorganization of Neuronal Firing Patterns to Represent Related Experiences within a Hippocampal Schema. *J Neurosci.* 2013; 33:10243–56. [PubMed: 23785140]
- McQuiston AR. Cholinergic modulation of excitatory synaptic input integration in hippocampal CA1. *J Physiol.* 2010; 588:3727–3742. [PubMed: 20693290]
- McQuiston AR. Acetylcholine release and inhibitory interneuron activity in hippocampal CA1. *Front Synaptic Neurosci.* 2014; 6:20. [PubMed: 25278874]
- van der Meer MAA, Redish AD. Theta phase precession in rat ventral striatum links place and reward information. *J Neurosci.* 2011; 31:2843–54. [PubMed: 21414906]
- Mehaffey WH, Doiron B, Maler L, Turner RW. Deterministic Multiplicative Gain Control with Active Dendrites. *J Neurosci.* 2005; 25:9968–9977. [PubMed: 16251445]

- Miles R. Synaptic excitation of inhibitory cells by single CA3 hippocampal pyramidal cells of the guinea-pig in vitro. *J Physiol.* 1990; 428:61–77. [PubMed: 2231426]
- Miles R, Tóth K, Gulyás AI, Hájos N, Freund TF. Differences between somatic and dendritic inhibition in the hippocampus. *Neuron.* 1996; 16:815–23. [PubMed: 8607999]
- Milstein AD, Bloss EB, Apostolides PF, Vaidya SP, Dilly GA, Zemelman BV, Magee JC. Inhibitory Gating of Input Comparison in the CA1 Microcircuit. *Neuron.* 2015; 87:1274–1289. [PubMed: 26402609]
- Mitchell SJ, Silver RA. Shunting inhibition modulates neuronal gain during synaptic excitation. *Neuron.* 2003; 38:433–45. [PubMed: 12741990]
- Mizuseki K, Sirota A, Pastalkova E, Buzsáki G. Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop. *Neuron.* 2009; 64:267–80. [PubMed: 19874793]
- Montgomery SM, Betancur MI, Buzsáki G. Behavior-Dependent Coordination of Multiple Theta Dipoles in the Hippocampus. *J Neurosci.* 2009; 29:1381–1394. [PubMed: 19193885]
- Mott DD, Lewis DV. Facilitation of the induction of long-term potentiation by GABAB receptors. *Science.* 1991; 252:1718–20. [PubMed: 1675489]
- Müller C, Beck H, Coulter D, Remy S. Inhibitory Control of Linear and Supralinear Dendritic Excitation in CA1 Pyramidal Neurons. *Neuron.* 2012; 75:851–864. [PubMed: 22958825]
- Navratilova Z, Hoang LT, Schwindel CD, Tatsuno M, McNaughton BL. Experience-dependent firing rate remapping generates directional selectivity in hippocampal place cells. *Front Neural Circuits.* 2012;6. [PubMed: 22363267]
- Nishiyama M, Togashi K, Aihara T, Hong K. GABAergic activities control spike timing- and frequency-dependent long-term depression at hippocampal excitatory synapses. *Front Synaptic Neurosci.* 2010; 2:22. [PubMed: 21423508]
- Nitz D, McNaughton B. Differential modulation of CA1 and dentate gyrus interneurons during exploration of novel environments. *J Neurophysiol.* 2004; 91:863–72. [PubMed: 14523073]
- Palmer L, Murayama M, Larkum M. Inhibitory Regulation of Dendritic Activity in vivo. *Front Neural Circuits.* 2012; 6:26. [PubMed: 22654734]
- Paz R, Bauer EP, Pare D. Theta synchronizes the activity of medial prefrontal neurons during learning. *Learn Mem.* 2008; 15:524–531. [PubMed: 18612069]
- Pfeiffer BE, Foster DJ. Autoassociative dynamics in the generation of sequences of hippocampal place cells. *Science.* 2015; 349:180–3. [PubMed: 26160946]
- Pouille F, Marin-Burgin A, Adesnik H, Atallah BV, Scanziani M. Input normalization by global feedforward inhibition expands cortical dynamic range. *Nat Neurosci.* 2009; 12:1577–1585. [PubMed: 19881502]
- Pouille F, Scanziani M. Enforcement of Temporal Fidelity in Pyramidal Cells by Somatic Feed-Forward Inhibition. *Science (80-).* 2001; 293:1159–1163.
- Pouille F, Scanziani M. Routing of spike series by dynamic circuits in the hippocampus. *Nature.* 2004; 429:717–23. [PubMed: 15170216]
- Price CJ, Scott R, Rusakov DA, Capogna M. GABAB Receptor Modulation of Feedforward Inhibition through Hippocampal Neurogliaform Cells. *J Neurosci.* 2008; 28:6974–6982. [PubMed: 18596171]
- Rangel LM, Rueckemann JW, Riviere PD, Keefe KR, Porter BS, Heimbuch IS, Budlong CH, Eichenbaum H. Rhythmic coordination of hippocampal neurons during associative memory processing. *Elife.* 2016; 5:e09849. [PubMed: 26751780]
- Robbins MJ, Calver AR, Filippov AK, Hirst WD, Russell RB, Wood MD, Nasir S, Couve A, Brown DA, Moss SJ, Pangalos MN. GABAB2 Is Essential for G-Protein Coupling of the GABAB Receptor Heterodimer. *J Neurosci.* 2001;21.
- Robinson RB, Siegelbaum SA. Hyperpolarization-Activated Cation Currents: From Molecules to Physiological Function. *Annu Rev Physiol.* 2003; 65:453–480. [PubMed: 12471170]
- Roux L, Buzsáki G. Tasks for inhibitory interneurons in intact brain circuits. *Neuropharmacology.* 2015; 88:10–23. [PubMed: 25239808]

- Royer S, Zemelman BV, Losonczy A, Kim J, Chance F, Magee JC, Buzsáki G. Control of timing, rate and bursts of hippocampal place cells by dendritic and somatic inhibition. *Nat Neurosci.* 2012; 15:769–75. [PubMed: 22446878]
- Rozov AV, Valiullina FF, Bolshakov AP. Mechanisms of long-term plasticity of hippocampal GABAergic synapses. *Biochem.* 2017; 82:257–263. [PubMed: 28320266]
- Scaziani M. GABA spillover activates postsynaptic GABA(B) receptors to control rhythmic hippocampal activity. *Neuron.* 2000; 25:673–81. [PubMed: 10774734]
- Schomburg EW, Fernández-Ruiz A, Mizuseki K, Berényi A, Anastassiou CA, Koch C, Buzsáki G. Theta Phase Segregation of Input-Specific Gamma Patterns in Entorhinal-Hippocampal Networks. *Neuron.* 2014; 84:470–85. [PubMed: 25263753]
- Schwartzkroin PA. Characteristics of CA1 neurons recorded intracellularly in the hippocampal in vitro slice preparation. *Brain Res.* 1975; 85:423–436. [PubMed: 1111846]
- Seress L, Ribak CE. Direct commissural connections to the basket cells of the hippocampal dentate gyrus: anatomical evidence for feed-forward inhibition. *J Neurocytol.* 1984; 13:215–225. [PubMed: 6726288]
- Shan KQ, Lubenov EV, Papadopolou M, Siapas AG. Spatial tuning and brain state account for dorsal hippocampal CA1 activity in a non-spatial learning task. *Elife.* 2016:5.
- Siapas AG, Lubenov EV, Wilson MA. Prefrontal phase locking to hippocampal theta oscillations. *Neuron.* 2005; 46:141–51. [PubMed: 15820700]
- Sik A, Penttonen M, Buzsáki G. Interneurons in the hippocampal dentate gyrus: an in vivo intracellular study. *Eur J Neurosci.* 1997; 9:573–88. [PubMed: 9104599]
- Sik A, Penttonen M, Ylinen A, Buzsáki G. Hippocampal CA1 interneurons: an in vivo intracellular labeling study. *J Neurosci.* 1995; 15:6651–65. [PubMed: 7472426]
- Singer AC, Karlsson MP, Nathe AR, Carr MF, Frank LM. Experience-dependent development of coordinated hippocampal spatial activity representing the similarity of related locations. *J Neurosci.* 2010; 30:11586–604. [PubMed: 20810880]
- Sirota A, Montgomery S, Fujisawa S, Isomura Y, Zugaro M, Buzsáki G. Entrainment of Neocortical Neurons and Gamma Oscillations by the Hippocampal Theta Rhythm. *Neuron.* 2008; 60:683–697. [PubMed: 19038224]
- Skaggs WE, McNaughton BL, Wilson MA, Barnes CA. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus.* 1996; 6:149–72. [PubMed: 8797016]
- Slanina KA, Roberto M, Schweitzer P. Endocannabinoids restrict hippocampal long-term potentiation via CB1. *Neuropharmacology.* 2005; 49:660–668. [PubMed: 15950248]
- Stark E, Roux L, Eichler R, Buzsáki G. Local generation of multineuronal spike sequences in the hippocampal CA1 region. *Proc Natl Acad Sci U S A.* 2015; 112:10521–6. [PubMed: 26240336]
- Stark E, Roux L, Eichler R, Senzai Y, Royer S, Buzsáki G. Pyramidal Cell-Interneuron Interactions Underlie Hippocampal Ripple Oscillations. *Neuron.* 2014; 83:467–480. [PubMed: 25033186]
- Stefanelli T, Bertolini C, Lüscher C, Muller D, Mendez P. Hippocampal Somatostatin Interneurons Control the Size of Neuronal Memory Ensembles. *Neuron.* 2016; 89:1074–1085. [PubMed: 26875623]
- Takács VT, Klausberger T, Somogyi P, Freund TF, Gulyás AI. Extrinsic and local glutamatergic inputs of the rat hippocampal CA1 area differentially innervate pyramidal cells and interneurons. *Hippocampus.* 2012; 22:1379–1391. [PubMed: 21956752]
- Takahashi H, Magee JC. Pathway Interactions and Synaptic Plasticity in the Dendritic Tuft Regions of CA1 Pyramidal Neurons. *Neuron.* 2009; 62:102–111. [PubMed: 19376070]
- Tanaka KZ, Pevzner A, Hamidi AB, Nakazawa Y, Graham J, Wiltgen BJ. Cortical Representations Are Reinstated by the Hippocampus during Memory Retrieval. *Neuron.* 2014; 84:347–54. [PubMed: 25308331]
- Taylor KK, Tanaka KZ, Reijmers LG, Wiltgen BJ. Reactivation of neural ensembles during the retrieval of recent and remote memory. *Curr Biol.* 2013; 23:99–106. [PubMed: 23246402]
- Tort ABL, Komorowski RW, Manns JR, Kopell NJ, Eichenbaum H. Theta-gamma coupling increases during the learning of item-context associations. *Proc Natl Acad Sci.* 2009; 106:20942–20947. [PubMed: 19934062]

- Tort ABL, Kramer MA, Thorn C, Gibson DJ, Kubota Y, Graybiel AM, Kopell NJ. Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. *Proc Natl Acad Sci*. 2008; 105:20517–20522. [PubMed: 19074268]
- Tóth K, Freund TF, Miles R. Disinhibition of rat hippocampal pyramidal cells by GABAergic afferents from the septum. *J Physiol*. 1997;463–74.
- Trouche S, Perestenko PV, van de Ven GM, Bratley CT, McNamara CG, Campo-Urriza N, Black SL, Reijmers LG, Dupret D. Recoding a cocaine-place memory engram to a neutral engram in the hippocampus. *Nat Neurosci*. 2016; 19:564–567. [PubMed: 26900924]
- Tyan L, Chamberland S, Magnin E, Camire O, Francavilla R, David LS, Deisseroth K, Topolnik L. Dendritic Inhibition Provided by Interneuron-Specific Cells Controls the Firing Rate and Timing of the Hippocampal Feedback Inhibitory Circuitry. *J Neurosci*. 2014; 34:4534–4547. [PubMed: 24671999]
- Valero M, Cid E, Averkin RG, Aguilar J, Sanchez-Aguilera A, Viney TJ, Gomez-Dominguez D, Bellistri E, de la Prida LM. Determinants of different deep and superficial CA1 pyramidal cell dynamics during sharp-wave ripples. *Nat Neurosci*. 2015; 18:1281–1290. [PubMed: 26214372]
- Varga C, Golshani P, Soltesz I. Frequency-invariant temporal ordering of interneuronal discharges during hippocampal oscillations in awake mice. *Proc Natl Acad Sci*. 2012; 109:E2726–E2734. [PubMed: 23010933]
- Varga V, Losonczy A, Zemelman BV, Borhegyi Z, Nyiri G, Domonkos A, Hangya B, Holderith N, Magee JC, Freund TF. Fast Synaptic Subcortical Control of Hippocampal Circuits. *Science* (80-). 2009; 326:449–453.
- van de Ven GM, Trouche S, McNamara CG, Allen K, Dupret D. Hippocampal Offline Reactivation Consolidates Recently Formed Cell Assembly Patterns during Sharp Wave-Ripples. 2016
- Vinogradova OS, Brazhnik ES, Kitchigina VF, Stafekhina VS. Acetylcholine, theta-rhythm and activity of hippocampal neurons in the rabbit--IV. Sensory stimulation. *Neuroscience*. 1993; 53:993–1007. [PubMed: 8506032]
- Vinogradova OS, Kitchigina VF, Zenchenko CI. Pacemaker neurons of the forebrain medial septal area and theta rhythm of the hippocampus. *Membr Cell Biol*. 1998; 11:715–25. [PubMed: 9718568]
- Wigström H, Gustafsson B. Heterosynaptic modulation of homosynaptic long-lasting potentiation in the hippocampal slice. *Acta Physiol Scand*. 1983; 119:455–458. [PubMed: 6666625]
- Wilent WB, Nitz DA. Discrete Place Fields of Hippocampal Formation Interneurons. *J Neurophysiol*. 2007:97.
- Witter MP, Naber PA, van Haeften T, Machielsen WC, Rombouts SA, Barkhof F, Scheltens P, Lopes da Silva FH. Cortico-hippocampal communication by way of parallel parahippocampal-subicular pathways. *Hippocampus*. 2000; 10:398–410. [PubMed: 10985279]
- Woodson W, Nitecka L, Ben-Ari Y. Organization of the GABAergic system in the rat hippocampal formation: A quantitative immunocytochemical study. *J Comp Neurol*. 1989; 280:254–271. [PubMed: 2925894]
- Wu F, Stark E, Ku P-C, Wise KD, Buzsáki G, Yoon E. Monolithically Integrated μ LEDs on Silicon Neural Probes for High-Resolution Optogenetic Studies in Behaving Animals. *Neuron*. 2015; 88:1136–1148. [PubMed: 26627311]
- Wyble BP, Linster C, Hasselmo ME. Size of CA1-evoked synaptic potentials is related to theta rhythm phase in rat hippocampus. *J Neurophysiol*. 2000; 83:2138–44. [PubMed: 10758123]
- Wyss JM, Swanson LW, Cowan WM. A study of subcortical afferents to the hippocampal formation in the rat. *Neuroscience*. 1979; 4:463–76. [PubMed: 107474]
- Yamamoto J, Suh J, Takeuchi D, Tonegawa S. Successful Execution of Working Memory Linked to Synchronized High-Frequency Gamma Oscillations. *Cell*. 2014; 157:845–857. [PubMed: 24768692]
- Yokose J, Okubo-Suzuki R, Nomoto M, Ohkawa N, Nishizono H, Suzuki A, Matsuo M, Tsujimura S, Takahashi Y, Nagase M, Watabe AM, Sasahara M, Kato F, Inokuchi K. Overlapping memory trace indispensable for linking, but not recalling, individual memories. *Science*. 2017; 355:398–403. [PubMed: 28126819]

- Young CK, McNaughton N. Coupling of Theta Oscillations between Anterior and Posterior Midline Cortex and with the Hippocampus in Freely Behaving Rats. *Cereb Cortex*. 2009; 19:24–40. [PubMed: 18453538]
- Zemankovics R, Veres JM, Oren I, Hájos N. Feedforward inhibition underlies the propagation of cholinergically induced gamma oscillations from hippocampal CA3 to CA1. *J Neurosci*. 2013; 33:12337–51. [PubMed: 23884940]
- Zheng C, Wood Bieri K, Hwaun E, Lee Colgin L. Fast Gamma Rhythms in the Hippocampus Promote Encoding of Novel Object-Place Pairings. *eNeuro*. 2016:3.
- Zheng F, Khanna S. Selective destruction of medial septal cholinergic neurons attenuates pyramidal cell suppression, but not excitation in dorsal hippocampus field CA1 induced by subcutaneous injection of formalin. *Neuroscience*. 2001; 103:985–98. [PubMed: 11301206]

Figure 1.

(A) Different CA1 interneuron classes fire at different phases of theta and target different pyramidal dendritic compartments. The red histograms show the probability density functions of action potentials across phases of theta ordered from left to right by preferred firing phase for each interneuron class (axo-axonic cells → CCK+ basket cells). For each class, the range of axonal arborization is depicted in red above the post-synaptic pyramidal dendritic compartment. The afferent inputs arriving to CA1 show laminar connectivity that co-registers with the pattern of inhibitory modulation by different interneuron types. (B) *i* The probability density of pyramidal spikes referenced to local theta; most spikes occur at the trough. *ii* Extracellularly recorded theta *iii* Simultaneously recorded intracellular theta in a rat under urethane-anesthesia. Note somatic depolarization at the trough of local theta, when most spikes are emitted. *iv* Intracellularly recorded dendritic theta is in phase with extracellular theta. Note that dendritic and somatic recordings were performed separately and the dendritic recordings were aligned here for illustration (C) *Top* Probability density of spiking phase-locked to the same reference theta rhythm. For the entorhinal cortex layer III (ECIII), CA1, and CA3 each distribution was made for spikes observed at different instantaneous firing rates with higher rates shown in “hotter” colors. *Bottom* Current source density analysis from local field potentials recorded from across CA1 lamina. Blue colors reveal current sinks reflecting extracellular cations flowing into the pyramidal dendrites causing dendritic depolarization. Note the out of phase current sinks in the stratum radiatum (blue arrow) and stratum lacunosum moleculare (red arrow) coincident to phasic increases in

afferent neurons in CA3 and ECIII, respectively. (D) *i* As rats move through space (left to right), the firing rate of pyramidal cells increases in a limited region known as a place field. *ii* When rats enter a place field the first spikes are emitted on the ascending phase of theta and precess to the descending phase upon place field exit. *iii* Silencing somatic targeting PV + interneurons changes firing mostly upon place field entry, when neurons spike late in the theta period, suggesting inhibition by PV+ neurons at this phase. Silencing dendritic-targeting SOM+ interneurons changes firing mostly at the end of a place field, when spiking occurs on the ascending phases, suggesting SOM+ inhibition at these phases. (E) *Top* For spikes observed at the beginning of a place field, gamma phase modulation is most apparent for a slow frequency gamma in the stratum radiatum, where CA3 inputs terminate. *Bottom* For spikes observed at the end of a place field, gamma phase modulation is most evident for a high frequency gamma in the stratum lacunosum moleculare where ECIII inputs terminate. (F) *Top* Stimulation of feedback axons of the alveus *in vitro* shows strong somatic inhibition and moderate dendritic inhibition after a single electrical stimulation. After three stimulations, the pattern of inhibition shifts such that dendritic inhibition dominates. *Bottom* During such stimulation some interneurons fired immediately (onset transient) while others fired later in the stimulation train (late persistent). These interneurons were found to synapse on different regions of the dendritic arbor known to modulate inputs coming from either CA3 (onset-transient) or ECIII (late-persistent). Adapted from Skaggs et al., 1996; Kamondi et al., 1998; Pouille and Scanziani, 2004; Mizuseki et al., 2009; Royer et al., 2012; Schomburg et al., 2014; Bezaire et al., 2016; Fernández-Ruiz et al., 2017.