Inhibitory Plasticity: Balance, Control, and Codependence

Guillaume Hennequin,[1,*] Everton J. Agnes,[2,*] and Tim P. Vogels[2]

[1]Computational and Biological Learning Lab, Department of Engineering, University of Cambridge, Cambridge CB2 3EJ, United Kingdom

[2]Centre for Neural Circuits and Behaviour, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford OX1 3SR, United Kingdom

Annu. Rev. Neurosci. 2017. 40:557–79

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

https://doi.org/10.1146/annurev-neuro-072116-031005

*These authors contributed equally to this review.

Keywords

inhibition, GABA, synaptic plasticity, network dynamics, feedback control, modeling

Abstract

Inhibitory neurons, although relatively few in number, exert powerful control over brain circuits. They stabilize network activity in the face of strong feedback excitation and actively engage in computations. Recent studies reveal the importance of a precise balance of excitation and inhibition in neural circuits, which often requires exquisite fine-tuning of inhibitory connections. We review inhibitory synaptic plasticity and its roles in shaping both feedforward and feedback control. We discuss the necessity of complex, codependent plasticity mechanisms to build nontrivial, functioning networks, and we end by summarizing experimental evidence of such interactions.

Contents

1. INTRODUCTION 558
2. INHIBITORY SYNAPTIC PLASTICITY AND ITS SPIKE-TIMING DEPENDENCE 559
3. GLOBAL NETWORK EFFECTS OF INHIBITORY SYNAPTIC PLASTICITY ON THE BALANCE OF EXCITATION AND INHIBITION .. 560
4. INHIBITORY SYNAPTIC PLASTICITY: A KEY INGREDIENT IN ROBUST COMPUTATIONS 563
5. INHIBITORY MEMORIES 564
5.1. Memory Engrams 565
5.2. Memories That Involve Inhibition 566
5.3. Beyond the Engram 568
6. NEGATIVE FEEDBACK CONTROL 568
6.1. Amplifying Networks 568
6.2. Short-Term Memory Networks 570
6.3. Stabilized Supralinear Networks 571
6.4. Inhibitory Plasticity and Optimal Feedback Control 571
7. CODEPENDENT PLASTICITY 571
8. DISCUSSION 573

1. INTRODUCTION

Learning relies on stereotypical plasticity rules to adjust distinct synaptic connections. Until recently, both memories and signaling pathways were thought to be established predominantly through the modification of excitatory synapses, creating directionally or recurrently wired excitatory cell assemblies that carry out most of the processing work. Such excitatory recurrence has a natural tendency toward catastrophic runaway activity, which calls for additional layers of flexible control via negative feedback. At the circuit level, negative feedback is mediated mainly by GABAergic interneurons and their plastic synapses, and it has emerged as a major mechanism to stabilize and shape the functionality of neuronal dynamics.

In this article, we discuss how such negative feedback control can be learned by inhibitory synaptic plasticity (ISP). We begin with a review of experimental studies of GABAergic spike-timing-dependent rules, which—due to the technical difficulty of probing the activity of the diverse minority of inhibitory neurons—remain less well characterized than their excitatory counterparts. The links between the learning rules, the resulting shape of inhibitory architectures, and their function remain opaque.

In the next sections, we describe how modelers, confronted with such heterogeneous and sometimes perplexing experimental observations, have used tentative, ad hoc, and at times experimentally unsubstantiated learning rules, often to impose a certain function on the network dynamics by, for instance, controlling the balance of excitation and inhibition (E/I balance). Indeed, E/I balance has emerged as a staple of neuronal processing, and ISP is thus an ideal control mechanism to stabilize intricate microprocessing pathways and memories.

We end with the argument that much insight into the mechanics and function of inhibitory plasticity can be gleaned from the rich literature of control theory. We review network models in which inhibitory feedback is critical and relies on known control algorithms. The complexity of

GABA: γ-aminobutyric acid, an inhibitory neurotransmitter

Codependence: an umbrella term that describes helping relationships between synapse types in which activity in one type supports or enables plasticity in the other

these algorithms makes their biological plausibility questionable, at least if their implementation must remain limited to modifications based strictly on simple forms of pre- and postsynaptic events. Interestingly, recent experimental studies suggest that we might have unduly confined models of learning to local environments of single types of synapses: Diverse synaptic plasticity mechanisms often act in concert with one another, and their efficacy is tightly controlled by the activity of other synapses in their proximity. Probing the nature of such codependent interactions necessitates unprecedented experimental intricacy paired with reductionist theory and data-driven modeling, highlighting the reciprocal reliance of theory and experiment.

2. INHIBITORY SYNAPTIC PLASTICITY AND ITS SPIKE-TIMING DEPENDENCE

The plasticity of excitatory synapses has been intensively studied and displays a bewildering collection of vastly different spike-timing-dependent learning rules (Abbott & Nelson 2000, Markram et al. 2011). Similar studies of inhibitory synapses have been relatively scarce (Komatsu & Iwakiri 1993, Kano 1995, Aizenman et al. 1998, Holmgren & Zilberter 2001, Kilman et al. 2002, Woodin et al. 2003, Haas et al. 2006, Maffei et al. 2006, Kurotani et al. 2008, Hartmann et al. 2008, D'amour & Froemke 2015) but even more perplexing. To our best knowledge, only four studies to date have successfully shown spike-timing-dependent plasticity in GABAergic synapses (iSTDP) (Holmgren & Zilberter 2001, Woodin et al. 2003, Haas et al. 2006, D'amour & Froemke 2015; but see Gaiarsa et al. 2002, Maffei et al. 2006, Vogels et al. 2013 for other, non-spike-timing-dependent mechanisms). In each of these four studies, the inhibitory cell type was not known and the target cell was excitatory. The identified learning rules were all different, and their functional consequences often were not intuitive. For example, in somatosensory cortical slices of rat (**Figure 1*a***) (Holmgren

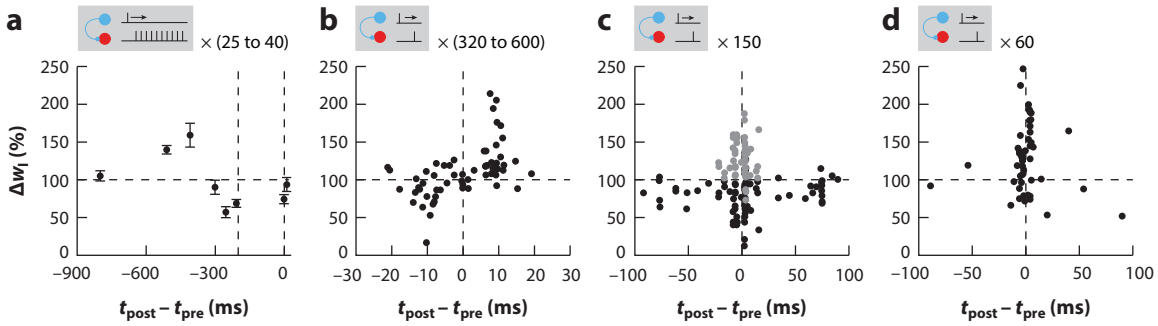


Figure 1

Spike-timing-dependent inhibitory synaptic plasticity in experiments. (*a*) Plasticity of inhibitory synapses from layer 2/3 fast spiking nonaccommodating neurons onto pyramidal neurons in rat cortical slices. Relative changes (percentage) in inhibitory postsynaptic potential (IPSP) size depend on the timing difference, $t_{post} - t_{pre}$, between the first spike in a 200-ms postsynaptic burst (*dashed lines*) and a presynaptic action potential [see inset, showing an inhibitory neuron (*blue*) and its excitatory postsynaptic target (*red*), with their respective spike trains during the induction protocol]. (*b*) Spike-timing-dependent plasticity (STDP) of inhibitory synapses onto stellate cells in rat entorhinal cortex. Repeated pairing of pre- and postsynaptic spikes, separated by $t_{post} - t_{pre}$ (*inset*), changes the relative IPSP slopes (*dots*). (*c*) STDP of inhibitory synapses in rat hippocampus. Repeated pairing (*inset*) similar to that in panel *b* affects both synaptic conductances and inhibitory reversal potentials. Each dot summarizes the two effects by showing the relative change in the magnitude of inhibitory postsynaptic currents (IPSCs). Gray dots represent the original data from Woodin et al. (2003) for near-coincident pre–post spikes; black dots represent recalculated IPSPs. (*d*) STDP of inhibitory synapses onto layer 5 pyramidal cells in mouse auditory cortex. Dots represent relative changes in peak IPSC, under a similar induction protocol as in panels *b* and *c*. Panel *a* modified from Holmgren & Zilberter (2001), panel *b* from Haas et al. (2006), panel *c* from Woodin et al. (2003), and panel *d* from D'amour & Froemke (2015).

& Zilberter 2001), postsynaptic bursts were paired with sole presynaptic spikes to reveal that, as long as there is a single GABAergic spike within the temporal vicinity of a 200-ms-long burst, the GABAergic synapse depresses. Only when inhibitory spiking occurs more than 100 ms after the end of the postsynaptic burst does strengthening of the inhibitory connection occur, with unclear consequences for network dynamics.

Spike-timing-dependent plasticity (STDP): modification of synaptic efficacies that depends on the relative timing of pre- and postsynaptic action potentials

Local learning rule: mathematical description of synaptic changes involving variables that can conceivably be directly accessed at the synapse (e.g., pre- and postsynaptic action potentials)

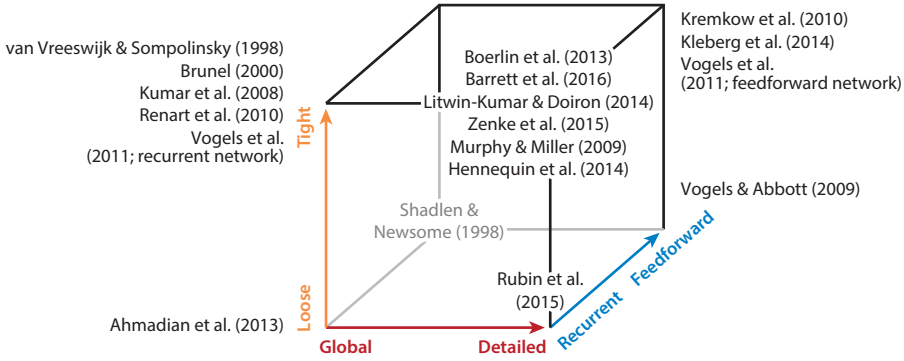
An asymmetric plasticity window on timescales more in line with classical excitatory STDP was observed in slices of rat entorhinal cortex (Haas et al. 2006), where pre- before postsynaptic spikes led to strengthening and the reverse ordering led to weakening (**Figure 1*b***). Surprising in this case were the temporally shifted peaks of maximal efficacy changes, away from strictly coincident pre- and postsynaptic spikes.

Similarly mysterious is a learning rule observed in rat hippocampal cultures and slices (Woodin et al. 2003) in which sole presynaptic events decreased the peak amplitude of the synaptic conductance. Furthermore, temporally proximal spike pairs effected changes in the local chloride reversal potential, and temporally distant spike pairs tended to trigger a mixture of both effects (although not significantly). Notably, the changes in synaptic currents were recorded at −90 mV, so that depolarizations in the reversal potential increased synaptic currents in the original data; thus, it appeared as though the synapses were strengthened. However, the same reversal potential changes would actually lead to an effective weakening of the synapses in the working range of −65 to −50 mV (**Figure 1*c***). Such exclusively weakening responses could conceivably lead to large E/I imbalances and catastrophic runaway activity, and can thus be ruled out as the only determinant of inhibitory efficacy. Indeed, two follow-up studies have shown that the above mechanism may be accompanied by strengthening of inhibitory synapses from other neurons (Ormond & Woodin 2009, 2011). Additionally, it has been observed that the amplitude and direction of inhibitory synaptic changes can be affected by the activity state of the network (Turrigiano 2012), and the membrane potential at the time of induction also plays a role in shaping synaptic change (Maffei et al. 2006). Thus, each of the above experimental observations may be a momentary snapshot of a complicated set of synaptic interactions (see Section 7).

Another symmetric learning rule was discovered in slices of mouse auditory cortex (layer 5 pyramidal neurons) (**Figure 1*d***) (D'amour & Froemke 2015). Unlike in the study by Woodin et al. (2003), the protocol triggered changes in inhibitory synaptic conductance rather than in reversal potential for temporally proximal pre- and postsynaptic pairs regardless of their order. For distal pairs, results were inconsistent, but in contrast to the previous iSTDP windows, the synapses were more often strengthened than weakened, a scenario potentially leading to a silent, inhibition-dominated network. Inhibitory synaptic modifications were often observed concurrently with excitatory changes and required *N*-methyl-D-aspartate (NMDA) receptor activation (Komatsu 1994), again suggesting concerted changes in more than one synapse type (Section 7).

3. GLOBAL NETWORK EFFECTS OF INHIBITORY SYNAPTIC PLASTICITY ON THE BALANCE OF EXCITATION AND INHIBITION

None of these iSTDP windows allow easy intuition regarding how they could affect cortical function, but theorists have begun to explore the role of ISP by trying to distill the essence of the plasticity mechanisms discussed above into simple learning rules amenable to theoretical analysis (Hendin et al. 1997, Haas et al. 2006, Vogels et al. 2011, Luz & Shamir 2012, Wilmes et al. 2016, Kleberg et al. 2014, Weber & Sprekeler 2017, Barrett et al. 2016). A natural place to begin is a minimal model of neuronal network dynamics (**Figure 3*a***), the so-called balanced network (Tsodyks & Sejnowski 1995, van Vreeswijk & Sompolinsky 1998, Brunel 2000), of which the most common form consists of randomly and sparsely connected excitatory and inhibitory



Loose versus tight: The balance is deemed tight if E and I inputs to single neurons balance each other on fast timescales, and loose otherwise. Dynamically, tight balance in a recurrent network manifests itself by the presence of very large negative eigenvalues in the (effective) connectivity matrix, expressing strong inhibitory dominance in the dynamics of the corresponding eigenmodes. In classical balanced spiking networks (van Vreeswijk & Sompolinsky 1998, Renart et al. 2010), very large E and I inputs must cancel tightly to leave a small remainder; in the stabilized supralinear network (Ahmadian et al. 2013, Rubin et al. 2015), moderately large E and I inputs need only cancel loosely.

Global versus detailed: When the spatial patterns of E and I inputs to a given neuron [denoted by vectors $\mathbf{h}_e(t)$ and $\mathbf{h}_i(t)$] balance each other among many dimensions [i.e., one can find many input directions $\mathbf{v}$ for which the projections $\mathbf{v}^T\mathbf{h}_e(t)$ and $\mathbf{v}^T\mathbf{h}_i(t)$ correlate temporally], the balance is said to be detailed, or high dimensional. In recurrent networks, this situation arises when feedback inhibition stabilizes a large number of instabilities in the E → E connectivity (e.g., Hennequin et al. 2014). When detailed balance is also tight (cf. above), it is often referred to as precise balance. In random, unstructured networks, balance usually occurs only globally, i.e., in the summed E and summed I inputs in each neuron [corresponding to a single $\mathbf{v} \approx (1,1,...,1)$], reflecting overall balance of E and I population activities.

Recurrent versus feedforward: Balance can arise either from dynamic feedback inhibition (recurrent) or from feedforward inhibition (even in a recurrent network).

Figure 2

How balanced? Theoretical research has studied many facets of the balance of excitation and inhibition (E/I balance) in neuronal networks. We collected terminology from the literature, with definitions based on both phenomenology and considerations of dynamics.

neurons modeled as leaky integrate-and-fire units. In these models, stability arises from a tight, dynamic balance of excitatory and inhibitory activity (see **Figure 2** for a terminology of E/I balance in neuronal networks). Importantly, the strength of inhibitory connections plays as great a role as that of excitatory connections in controlling most aspects of the dynamics, such as the average firing rate (**Figure 3*b*,*c***); the magnitude of pairwise correlations (Renart et al. 2010, Tetzlaff et al. 2012, Doiron et al. 2016, Stringer et al. 2016, Hennequin et al. 2016); the presence, magnitude, and frequency of network oscillations (Brunel & Hakim 1999, Brunel 2000, Brunel & Wang 2003); the nature and size of spontaneously generated fluctuations (Ostojic 2014, Harish & Hansel 2015); and the way neurons respond collectively to inputs (Ostojic 2014).

The effect of ISP in balanced networks has been explored using a family of simplified, Hebbian forms of iSTDP (Luz & Shamir 2012, Vogels et al. 2011), according to which postsynaptic spikes potentiate inhibitory synapses whereas presynaptic spikes depress them, with net potentiation for near-coincident pre–post pairs. These learning rules automatically and robustly tune the average

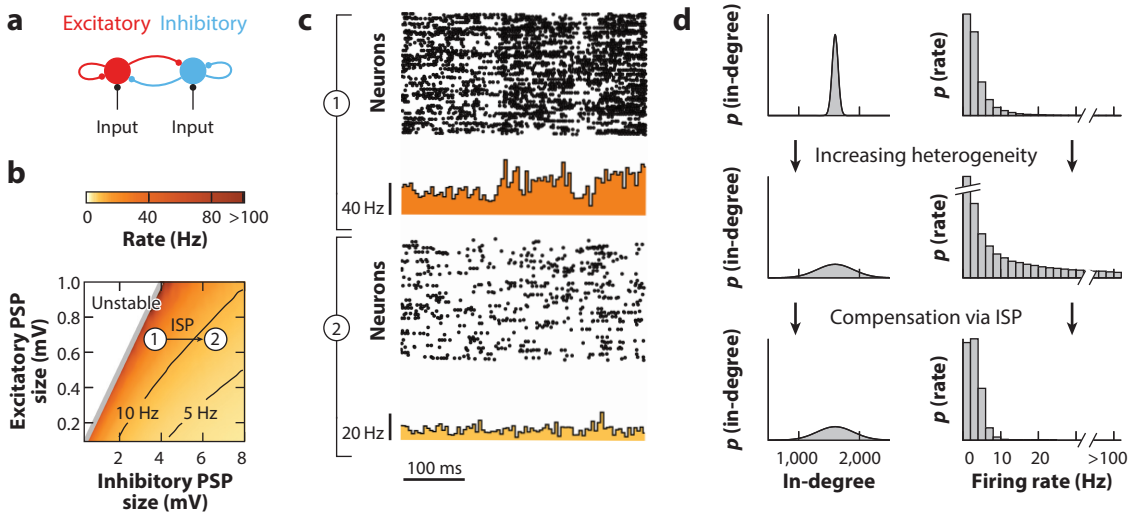


Figure 3

Role of inhibition and inhibitory synaptic plasticity (ISP) in balanced networks. (*a*) Schematic of an excitatory/inhibitory network architecture; two large populations of excitatory (*red*) and inhibitory (*blue*) neurons are randomly and sparsely coupled and receive external input. (*b*) Phase diagram of the classical Brunel (2000) model of excitatory/inhibitory dynamics. The network is unstable if feedback inhibition is too weak (*white area left of the gray line*). In the stable region, the overall network firing rate (*color coded*) varies with the inhibitory and excitatory postsynaptic potential (PSP) sizes (*x* and *y* axes). Regions of oscillatory activity are not shown. (*c*) Representative spike rasters and corresponding fluctuations of the population firing rate in the different regimes labeled ① and ② in panel *b*. (*d*) Randomly connecting any pair of neurons with a fixed probability results in a narrow distribution of in-degrees (*top left*) and a fairly homogeneous distribution of firing rates (*top right*). Greater heterogeneity in in-degrees (*middle left*) causes most cells to become silent and a number to fire at saturation (*middle right*). Homeostatic inhibitory plasticity (based on postsynaptic activity only) rehomogenizes firing rates (*bottom*). Panel *d* modified from Landau et al. (2016).

inhibitory input in single cells, effectively balancing them with the excitatory inputs and stabilizing postsynaptic firing rates near a target value (**Figure 3*b*,*c***). The resulting firing rates depend mainly on the ratio of the potentiation and depression parts of the iSTDP window (Vogels et al. 2011, Luz & Shamir 2012). Any positive (respectively, negative) deviation in postsynaptic firing rate from the target is soon suppressed by strengthening (respectively, weakening) of inhibitory input synapses. Thus, whereas feedback inhibition stabilizes random, recurrent excitation at the millisecond timescale, its plasticity stabilizes firing rates on a slower timescale at which the global E/I balance might be disrupted, for instance, due to slow ongoing modifications of excitatory synapses. ISP thus maintains a tight and global balance.

One can more fully appreciate the benefits of a self-organized E/I balance when contemplating the delicate sensitivity of balanced networks to various deviations from standard uniform wiring statistics (Barrett 2012, Rosenbaum & Doiron 2014). For example, introducing weak clustering among excitatory neurons produces large and slow fluctuations in the activity of the neuron groups (Litwin-Kumar & Doiron 2012). In this regime, the E/I balance is very sensitive to small asymmetries in the wiring diagram, which typically result in winner-take-all behavior. ISP is an effective compensatory mechanism: Its strong tendency toward firing-rate homeostasis does not allow a single cluster of neurons to monopolize the dynamics (Litwin-Kumar & Doiron 2014), resulting in a group-specific, detailed E/I balance. Similarly, implementing a more realistic degree of heterogeneity in the wiring matrix by broadening the distributions of in-degrees causes a dramatic sparsification of the firing rates in the network, with most neurons becoming entirely

silent and a few others firing at very high rates (**Figure 3*d***) (Landau et al. 2016; but see Roxin 2011). ISP can also compensate for this type of heterogeneity by adjusting inhibitory weights so as to equalize the excitatory and inhibitory functional in-degrees (number of input connections, weighted by their strengths).

4. INHIBITORY SYNAPTIC PLASTICITY: A KEY INGREDIENT IN ROBUST COMPUTATIONS

Simple models of neuronal networks have proven remarkably useful in guiding our understanding of the resting-state dynamics of brain circuits, but they usually do not support any specific computation. A first step toward understanding signal processing at the cellular level has been the introduction of feedforward pathways (Diesmann et al. 1999, van Rossum et al. 2002) into large model networks (Vogels et al. 2005; Kumar et al. 2008, 2010) for both synfire (Abeles 1991) and rate-mode signal propagation (Adrian 1926, Shadlen & Newsome 1994). Embedding additional excitatory structures into a network creates perturbations and thus requires relatively robust resting states. In fact, embedded synfire pathways were shown to create so-called synfire explosions (Mehring et al. 2003)—large deviations from baseline activity that fatally perturb the global network dynamics. Carefully hand-wired inhibition alleviates such problems, for instance through the addition of so-called shadow pools (groups of inhibitory neurons) for each layer of the network, connected in a feedforward or recurrent manner (Aviel et al. 2003, 2005; Vogels & Abbott 2009). ISP offers a more elegant solution. In a network model in which one of the experimentally observed iSTDP windows is implemented (**Figure 1*b***) (Haas et al. 2006), inhibitory populations strengthen their synapses such that inhibition outruns and terminates the wave front of a synfire explosion in most directions, enabling stable propagation (**Figure 4*a–c***) (Haas et al. 2006).

Beyond protective stabilization, carefully wired inhibition may enhance stimulus features (Ben-Yishai et al. 1995) or facilitate signal gating by selectively turning off specific nodes of an excitatory feedforward chain (Olshausen et al. 1993). Here, too, the balance of excitatory and inhibitory inputs is thought to play an important role, because balancing excitatory afferents with matching inhibitory signals means that "expected" excitatory synaptic currents are counterbalanced by equal and opposite amounts of inhibitory currents (Boerlin et al. 2013). When the balance is sufficiently precise (**Figure 2**), signal propagation is "off" by default and requires no active maintenance (Vogels & Abbott 2009, Kremkow et al. 2010). Excitatory activity propagates through the network only when the balance is upset by unexpected events, such as fast changes in the inputs, downregulation of inhibitory gains (**Figure 4*e***) (Vogels & Abbott 2009), or changes in the temporal interactions of excitation and inhibition (Kremkow et al. 2010).

Detailed E/I balance can be achieved in models with the simplified iSTDP rule described above (Vogels et al. 2011). Here, coincident presynaptic (inhibitory) and postsynaptic action potentials induce the (Hebbian) strengthening of the inhibitory synapse, whereas sole presynaptic action potentials elicit depression (**Figure 4*f***). In addition to the homeostatic effect on postsynaptic firing rates discussed above, the learning rule picks out correlations between excitatory and inhibitory signals. When inhibitory neurons are driven by the same input as their postsynaptic targets (**Figure 4*e***), both neurons tend to coactivate, leading to an increase in feedforward inhibition by means of Hebbian learning. This process reaches a fixed point of low coactivation, synonymous with a precise E/I balance, which holds true even when multiple feedforward inhibitory pathways converge onto the same postsynaptic neuron (corresponding to different sensory features, such as the frequency content of sound for auditory cortex; Froemke et al. 2007). The spatial profiles of excitatory and inhibitory synaptic weights are initially unmatched, leading to initially unbalanced total excitatory and inhibitory input currents. Through ISP, they become closely aligned—that

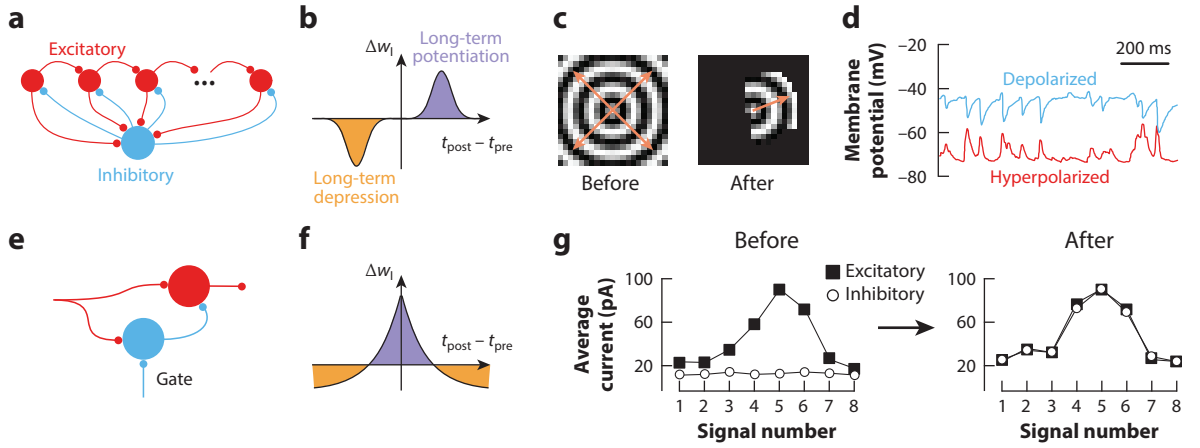


Figure 4

Functional consequences of inhibitory synaptic plasticity (ISP) for signal propagation. (*a*) Feedforward chain of excitatory neurons with feedback inhibition. (*b*) Schematic of the inhibitory spike-timing-dependent plasticity (iSTDP) rule from Haas et al. (2006). (*c*) (*Left*) Synfire explosion (runaway activity propagates radially) in a neuronal network with two-dimensional topology. (*Right*) Following activity-dependent modifications of inhibitory synapses according to panel *b*, feedback inhibition preemptively suppresses activity propagation in all but one direction. (*d*) Experimental evidence of detailed balance in vivo. Neighboring excitatory neurons were depolarized (*blue*) and hyperpolarized (*red*) to extract inhibitory and excitatory currents, respectively, revealing their strong temporal correlation. (*e*) Schematic of a feedforward, gated inhibition motif. (*f*) ISP rule proposed by Vogels et al. (2011). (*g*) Split excitatory and inhibitory currents evoked by inputs going through each of eight feedforward inhibition motifs similar to panel *e*. Initially, strong and pathway-tuned excitation dominates over weak, unspecific inhibition (*left*). After learning with iSTDP as in panel *f*, excitatory and inhibitory tuning curves become precisely matched (*right*). Panel *d* modified from Okun & Lampl (2008) and panel *g* from Vogels et al. (2011).

is, exhibit detailed balance (**Figure 4*g***) (Vogels et al. 2011)—even when perturbed by excitatory plasticity (Clopath et al. 2016), consistent with the maintenance of a stimulus-specific, detailed E/I balance in auditory cortex (Froemke et al. 2007).

In feedforward networks, detailed balance is usually also tight, with excitatory and inhibitory inputs tracking each other with the short delay of disynaptic feedforward inhibition. Such temporal tracking has also been observed in experiments (**Figure 4*d***) (Okun & Lampl 2008, Cafaro & Rieke 2010, Moore & Nelson 1998, Wehr & Zador 2003, Shu et al. 2003), but one should take care in interpreting such close temporal correlations as a signature of detailed balance in a recurrent network. For example, the balanced network model (**Figure 3**) exhibits tight, but not detailed, balance. One possible signature of detailed balance is that the temporal correlation of excitatory and inhibitory inputs recorded in the same cell should be—on average—larger than those of excitatory and inhibitory inputs recorded in different cells (Hennequin et al. 2014). Estimating the former is difficult in practice, as it would require holding a cell's membrane potential at the reversal potentials of excitation and inhibition simultaneously (or in very quick succession; Cafaro & Rieke 2010). How (local) synaptic plasticity rules can establish tight and detailed balance in recurrent networks is still unknown.

5. INHIBITORY MEMORIES

Memories of rich detail, recalled by simple commands or contextual cues, arguably involve elaborate plasticity mechanisms, and they have inspired a long line of scientific inquiry. A common hypothesis is that memories consist of groups of neurons that combine into engrams

(Semon 1921, Josselyn et al. 2015), also known as Hebbian assemblies (Hebb 1949, Harris 2005), which become active when a perceptual construct is made or recalled. Hopfield (1982) mathematically described such memories as patterns of active and silent neurons (**Figure 5*a***) and constructed simplified neuronal networks in which such patterns become fixed points of the collective dynamics. Synapses between neurons of a Hopfield network can be positive or negative (**Figure 5*b***), and as such, inhibitory plasticity was implicitly included, even though Dale's law was not obeyed.

5.1. Memory Engrams

Hebb and Hopfield's idea of assemblies has been widely absorbed by the neuroscience community (Poo et al. 2016, Josselyn et al. 2015). Over the last decades, experimental results such as the discovery of (presumably excitatory) neurons that respond to very specific stimuli in a recognition task (e.g., photographs of Jennifer Aniston; **Figure 5*c***) (Quiroga et al. 2005) seemed congruent with this idea. More supportive results emerged from experiments in which categories of stimuli, such as a sudden drop of the floor or an air blow, evoked simultaneous firing in groups of mouse hippocampal neurons (**Figure 5*d***) (Lin et al. 2005). These patterns of activation were often replayed after the initial stimulus, suggesting that memories of the stimulus categories had been formed and could be spontaneously recalled, similar to place cell replay of rat trajectories recorded earlier (Foster & Wilson 2006); both dynamics were comparable to attractors in the Hopfield network. More recent experimental research has gone beyond finding the engram. Instead, optogenetic manipulations have made it possible to interfere with memories (Liu et al. 2012) or even to imprint fake ones (Ramirez et al. 2013), but most of this work still focuses on purely excitatory engrams.

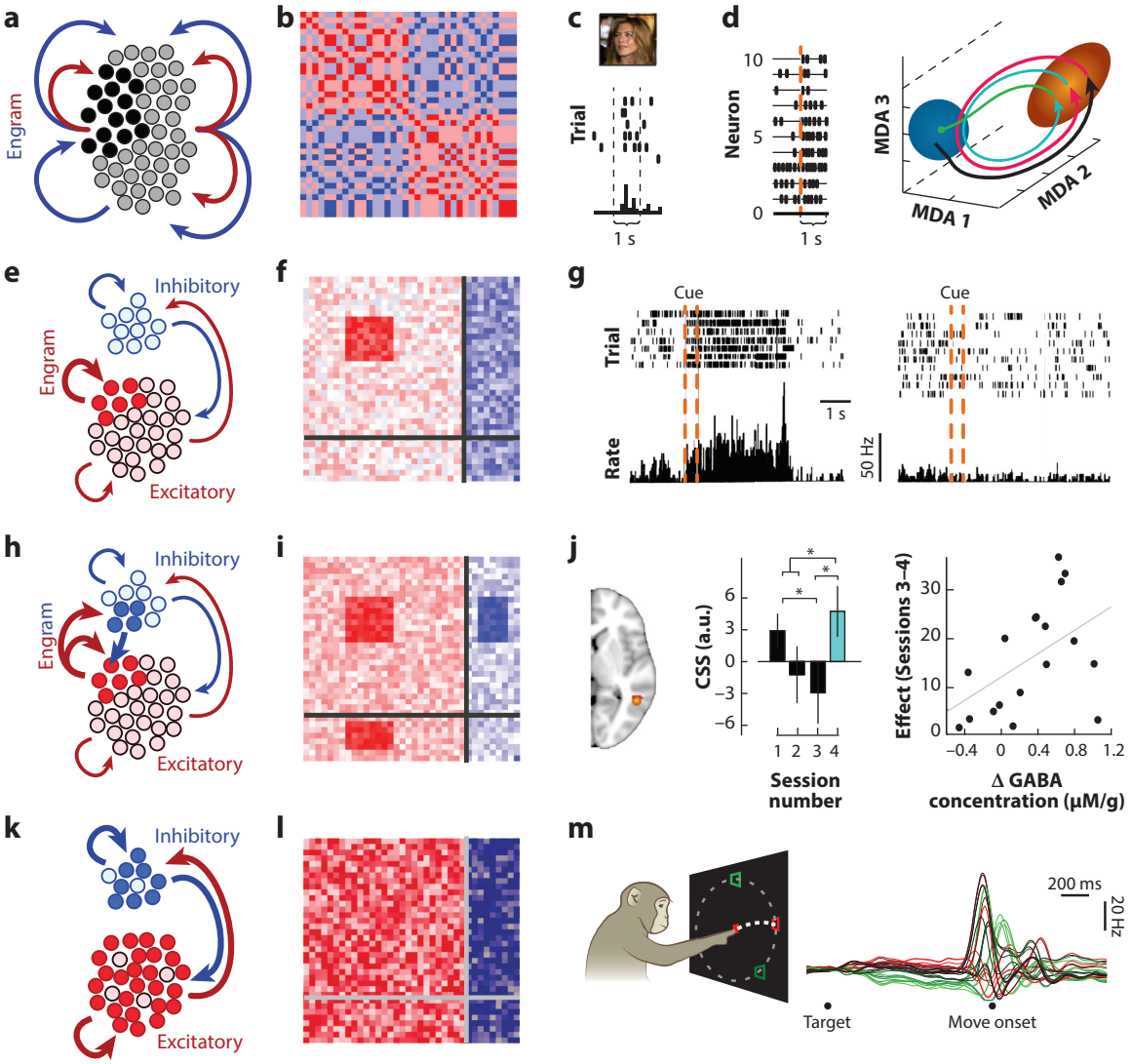
Most modeling research since Hopfield has not explicitly included inhibitory neurons as part of memories. Instead, excitatory neurons are used to create assemblies whose coactivity represents impressions of the outside world (**Figure 5*e*,*g***). Strong recurrent connections between these neurons become the memory, binding cells together as a preferentially coactivated (Hebbian) cell assembly (Gerstner & van Hemmen 1992, Roudi & Latham 2007, Gerstner et al. 2014). Inhibitory neurons, by contrast, serve only to stabilize the network globally by providing a uniform blanket of tight and global inhibition.

Inspired by experimental research (**Figure 5*g***) (Goldman-Rakic 1995, Williams & Goldman-Rakic 1995), modelers included embedded cell assemblies in spiking neural networks that can maintain high firing rates in a self-sustained fashion even after the initial stimulus ends (Brunel & Wang 2001, Amit & Brunel 1997), and multiple assemblies can be stored and individually recalled (Renart et al. 1999, Russo & Treves 2012). However, the number of encodable memories in a spiking network falls short of the theoretical Hopfield network prediction (∼0.138 times the number of available neurons; Hertz et al. 1991, Roudi & Latham 2007) by more than an order of magnitude. The reasons are intuitive. A neuronal assembly must feed back enough excitation on itself to sustain its own activity. At the same time, there must be sufficient inhibition to prevent the excitatory feedback from producing runaway activity. When the number of engrams to be embedded in the connectivity is large and different memory patterns overlap, it becomes difficult for nonspecific inhibition to stabilize a state of high, irregular firing in each assembly (Latham & Nirenberg 2004, Roudi & Latham 2007, Litwin-Kumar & Doiron 2014). Additionally, spiking memory networks tend to produce so-called latching behavior, in which assemblies activate sequentially or in random succession (Russo & Treves 2012, Recanatesi et al. 2015, Miller 2016, Litwin-Kumar & Doiron 2012). Careful parameter adjustment is thus required in order to balance the runaway effects of excitation and the suppressive effects of inhibition in each assembly, while at the same time separating assemblies enough to avoid latching. This cannot be achieved easily

through global inhibition, which often fails to control the specific E/I balance required in each pattern.

5.2. Memories That Involve Inhibition

Precise E/I balance (**Figure 4*d***) (Froemke et al. 2007, Okun & Lampl 2008, Cafaro & Rieke 2010, Xue et al. 2014) can be obtained through a concurrent adjustment of the excitatory and inhibitory weights, but specifically tuned, unique "Mexican hat" or shadow pool connectivity for every neuron is exceedingly difficult to construct by hand. ISP offers an easy way to achieve such cotuning. In a network model with embedded excitatory Hebbian assemblies, a simple form of iSTDP inspired by experiments (**Figure 4*f***) (Vogels et al. 2011, Froemke et al. 2007, Sudhakaran et al. 2012) progressively carves out assembly-specific negative feedback loops through



activity-dependent strengthening of specific inhibitory feedback connections that may stem from many, even all, inhibitory neurons in the network (Vogels et al. 2011). If a specific group of interneurons receives strong excitation from the assembly, it will be those neurons that will, by the nature of their correlated activity, form the strongest inhibitory synapses onto the assembly (**Figure 5*b*,*i***) (Duarte & Morrison 2014, Litwin-Kumar & Doiron 2014, Barron et al. 2016a). Importantly, it is now this pair of amalgamated excitatory and inhibitory neuron groups, as opposed to excitatory neurons only, that defines the memory engram. As expected from the rate-homogenizing effect of the learning rule, the firing rates of the neurons within the engram become indistinguishable from those of the rest of the network. However, the memory can still be reactivated through (even partial, local or network-wide) disruption of the E/I balance.

The inclusion of interneurons in the engram theory of memory gives rise to testable predictions. In humans, the strength of association between two stimuli can be estimated via a functional magnetic resonance imaging measurement termed cross-stimulus suppression (**Figure 5*j***) (Barron et al. 2016b), in which the association of two unrelated stimuli leads to an increase in adaptation when these stimuli are sequentially presented (Barron et al. 2016a). This adaptation effect is thought to be a consequence of newly strengthened excitatory synapses between the cortical representations of the associated stimuli. Over 24 h the effect fades, presumably due to rebalancing of the perturbed representations through inhibitory plasticity. The associative effect resurfaces when the global E/I balance within the brain region of interest is disrupted by means of transcranial direct current stimulation (tDCs). A strong correlation between the measured reduction of GABA (Stagg et al. 2009) and the strength of the resurfacing effect was observed (**Figure 5*j***), further supporting the idea that memory assemblies at least partially comprise inhibitory neurons (Barron et al. 2016a). This notion also underlies recent research in songbirds showing that inhibitory neurons participate in, and protect, memories of newly acquired songs (Vallentin et al. 2016).

In a more bare-bones model of inhibitory memories introduced by Hendin et al. (1997), coactivation of presynaptic inhibition and postsynaptic excitation leads to weakening of the inhibitory synapse, and prominent presynaptic activity leads to its strengthening [i.e., a near inverse of the rule used by Vogels et al. (2011) and very similar in nature to that of Ormond & Woodin (2009, 2011)]. It produces memory engrams in which the activity of excitatory neurons represents the

Figure 5

Inhibitory plasticity and memory formation in recurrent networks. (*a*) Example binary memory pattern as traditionally embedded in the (*b*) (schematized) connectivity matrix of a Hopfield network (*red*, excitatory weights; *blue*, inhibitory weights). (*c*) A single neuron in human hippocampus responds selectively to pictures of a well-known actress (*top*) presented for 1 s (*dashed lines*) in repeated trials; spike raster (*middle*) and trial-averaged histogram (*bottom*). (*d*) (*Left*) Raster plot of multiple neurons in mouse hippocampus responding selectively to an aversive stimulus (floor drop; Stim 1). (*Right*) The population dynamics describe low-dimensional trajectories during (*black*) and after (*red and green loops*) the experience. (*e*) Schematic and (*f*) corresponding connectivity matrix of a network embedding a purely excitatory engram. (*g*) Response of two neurons in monkey prefrontal cortex before, during, and after the presentation of a visual cue. The stimulus triggers persistent, elevated activity in the left neuron but not in the right neuron. (*h*) Schematic and (*i*) corresponding connectivity matrix of a network with an embedded engram comprising both excitatory and inhibitory neurons. (*j*) Experimental evidence for inhibitory memories in humans. The activity footprint of learning simple associations could be localized in functional magnetic resonance imaging (fMRI) (*left*) through cross-stimulus suppression (CSS; *middle*). CSS was measured in the region of interest (ROI; *orange*) over four sessions. The initially strong effect (Session 1) faded away over 24 h (Sessions 2 and 3). After transcranial direct current stimulation (tDCs) over the ROI, CSS resurfaced (Session 4), and the strength of resurgence was correlated with the measured reduction of GABA concentration during tDCs stimulation (*right*). (*k*) Schematic and (*l*) corresponding connectivity matrix of a network with globally distributed memories with recurrently strengthened excitatory and inhibitory connections. (*m*) Trial-averaged activity of a single neuron in monkey primary motor cortex before and during execution of various reaching movements (*color coded*). Panel *c* modified from Quiroga et al. (2005), panel *d* from Lin et al. (2005), panel *g* from Williams & Goldman-Rakic (1995), panel *j* from Barron et al. (2016a), and panel *m* from Churchland et al. (2012).

memory, but the connections that store it are purely inhibitory, because there is no recurrent excitation. Increased activity in excitatory neurons stems merely from feedforward inputs and the fact that inhibitory neurons suppress the activity of all excitatory neurons outside the memory pattern.

5.3. Beyond the Engram

All of the above variations of the engram theory of memory entail a few active neurons that represent a memory in a sea of silence. Hopfield's original formulation was subtly different: Half of all neurons were active for any given memory, many more than in any engram mentioned above. Recent research on dynamical systems has revisited this idea, proposing that neuronal networks represent memories through the dynamic paths traced out by the activity of the whole population (Maass et al. 2002, Sussillo & Abbott 2009, Laje & Buonomano 2013, Hennequin et al. 2014, Song et al. 2016). As such, nearly the entire network is involved (**Figure 5*k***), and consequently one could expect strong, seemingly indiscriminate connections between neurons, balanced tightly by appropriate inhibition (**Figure 5*l***). Indeed, network models built with the help of nonlocal ISP rules to obey such constraints display spatiotemporal activity patterns in response to stimuli (**Figure 5*m***) that can be used to drive stereotypical activation of readout neurons with high reliability (Hennequin et al. 2014).

Finally, a hybrid of purely local engrams and globally distributed memories has emerged from recent research on conceptual memory organization. Constantinescu et al. (2016) showed that the particular hexagonal activity pattern of grid cells, thought to be a unique signature of spatial memory (Rowland et al. 2016), may in fact be a broader principle for the representation of abstract knowledge. The distributed nature of the activity elicited by specific concepts would be in line with globally embedded memories, whereas its spatial periodicity hints at the local organization of individual inhibitory populations. The specificity of the inhibitory feedback that sustains grid cell formation (Couey et al. 2013, Buetfering et al. 2014) may implicate ISP as a necessary component of the formation of grid cell–like populations (Widloski & Fiete 2014, Weber & Sprekeler 2017).

6. NEGATIVE FEEDBACK CONTROL

Sophisticated negative feedback is beginning to emerge as a fundamental component of neural circuit organization. Neuroscientists have begun to incorporate long-matured ideas from control theory (Aström & Murray 2010) to understand how well-balanced combinations of positive and negative feedback enable fast and robust responses with high sensitivity to input signals and low sensitivity to noise.

6.1. Amplifying Networks

High input sensitivity often manifests as amplification of certain input facets and removal of all other "noise." Multiple lines of evidence suggest that sensory cortices perform such recurrent, selective amplification of their inputs (Kenet et al. 2003, Fiser et al. 2004, Luczak et al. 2009, Berkes et al. 2011, Bathellier et al. 2012), and several dynamical mechanisms have been proposed. They are easiest to illustrate in networks with exclusively local connectivity (**Figure 6*a*,*c***). Weak lateral connectivity in such networks will simply relay inputs and any added noise, integrating both on a characteristic single-neuron timescale, $\tau \sim 5$–50 ms (**Figure 6*a***, left). A better signal-to-noise ratio (SNR) can be obtained when the network selectively amplifies the input signal, as is achieved by strengthening local excitatory connections (**Figure 6*a***, middle) (Ben-Yishai et al. 1995, Goldberg et al. 2004, Ganguli et al. 2008a, Ponce-Alvarez et al. 2013, Wimmer et al. 2014).

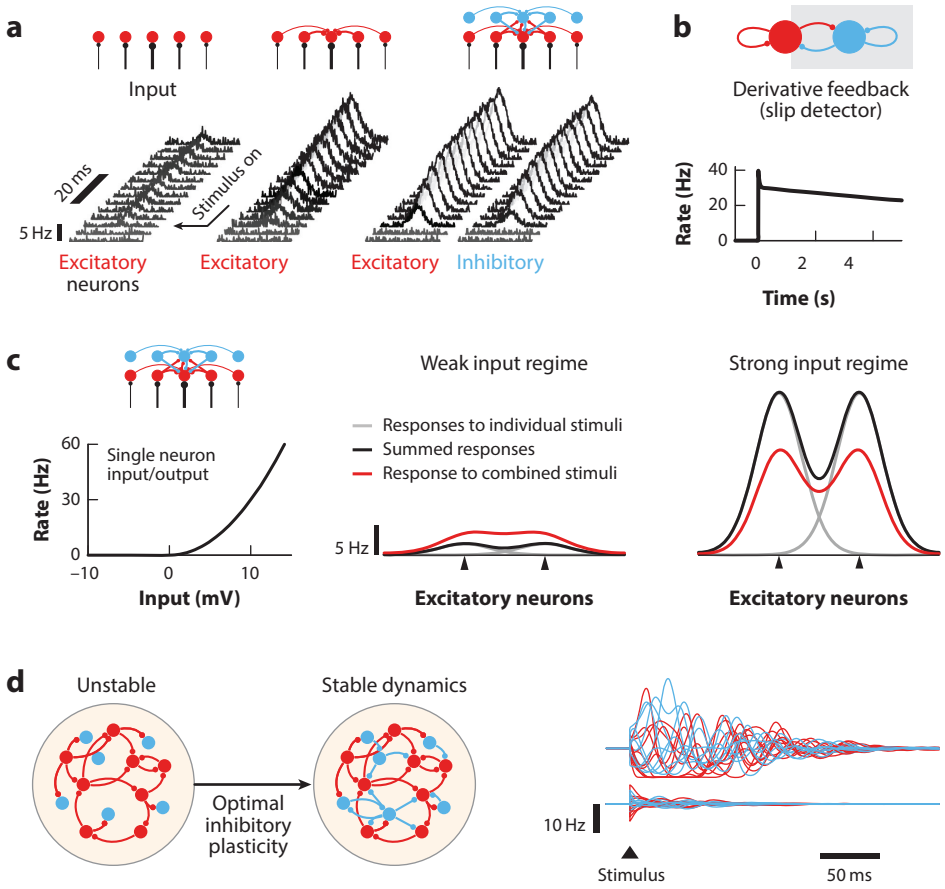


Figure 6

Role of inhibition in functional models of recurrent neuronal networks. (*a*) Response to a step input of a network with weak, negligible connectivity (*left*); distance-dependent excitatory connectivity (*middle*); and distance-dependent, strong excitatory/inhibitory (E/I) connectivity (*right*). The input comprises a smooth bump (signal) and ongoing noise. (*b*) Derivative controller, or slip detector, implemented as an E–I–E feedback loop (*top*), and corresponding success in producing sustained responses for working memory (*bottom*). (*c*) (*Left*) A stabilized supralinear network (SSN) with distance-dependent connectivity and a threshold-quadratic static nonlinearity in each neuron. (*Middle*) Response of the E cells (*red line*) to the superposition of two weak input bumps centered on the two gray arrows. The response is larger than the sum (*black*) of the individual responses (*gray*, *barely visible under black*) to the two stimuli. (*Right*) Same, for the superposition of two strong inputs—the response is now approximately normalized (i.e., less than the sum of the parts). (*d*) Inhibitory stabilization of strong random excitatory connectivity (*left*) through optimal inhibitory wiring yields networks (*middle*) that selectively amplify some inputs (generating rich transient responses; *top right*) while ignoring others (*bottom right*). Panel *a* modified from Murphy & Miller (2009), panel *b* from Lim & Goldman (2013), panel *c* from Rubin et al. (2015), and panel *d* from Hennequin et al. (2014).

This causes the network to feed back onto itself a fraction λ of its own activity, establishing an effective integration time constant, $\sim\tau/(1-\lambda)$, that can be very long if $\lambda \approx 1$. In response to a localized stimulus, the network activity forms a response "bump" whose amplitude ramps up on this new collective timescale, eventually reaching a value $\propto 1/(1-\lambda) \gg 1$, indicating strong amplification (**Figure 6*a***, middle). Crucially, only signal components with low spatial frequency

can reverberate through the lateral connectivity, dwarfing unamplified noise. Thus, the SNR increases steadily during stimulus presentation (**Figure 6*a***, middle).

Short-term memory: active capacity for holding a small amount of information in an active, readily available state

Relying exclusively on positive feedback has two major drawbacks. First, amplification is tied to the slowness of responses. Second, by setting λ near 1, the network exposes itself to instabilities arising from small structural perturbations that could push λ beyond 1, implying positive net feedback—that is, unstable runaway dynamics. In nonlinear continuous-attractor models, which also rely on exclusive (local) positive feedback, this sensitivity manifests as a difficulty in containing the drift of the activity bump—that is, the inability to maintain a true continuum of attractor states (Itskov et al. 2011).

Adding appropriately structured negative feedback (**Figure 6*a***, right) solves both problems at once. The excitatory subnetwork can now feed back onto itself very strongly. This inherently unstable process is dynamically stabilized by inhibition, resulting in fast and robust amplification (Tsodyks et al. 1997, Murphy & Miller 2009, Ozeki et al. 2009, Hennequin et al. 2014; see also Li & Dayan 1999 for a different, nonlinear mechanism also relying on inhibition). Indeed, inhibition-stabilized networks (ISNs) respond to momentary disruptions of the E/I balance through fast growth of both excitatory and inhibitory activity, restoring the E/I balance within a few tens of milliseconds. Collective responses to sustained, select inputs exhibit quick ramp-up to large values (**Figure 6*a***, right), yielding an equally swift increase in SNR. This type of "balanced amplification" (Murphy & Miller 2009) does not require the network to operate near instability, so ISNs can tolerate momentary structural disturbances. This feature may be crucial to give ISP enough time to shape, and reshape, the inhibitory feedback loop in reaction to, for example, excitatory plasticity events. Below, we discuss some of the requirements for ISP to be successful, but it is safe to assume that homeostatic downregulation of excitatory synapses is likely too slow to prevent sudden loss of stability in slow-reverberating, near-unstable networks (Zenke et al. 2013).

6.2. Short-Term Memory Networks

Responses that greatly outlast the single-neuron decay time constant, such as attractor states emerging as part of autoassociative memory recall (**Figure 5*g***) or self-sustained activity used as a working memory trace (Goldman-Rakic 1995), are typically achieved with positive feedback. Recurrent excitation elongates activity decay times, as discussed above (**Figure 6*a***, middle), but also threatens network stability (but see Mongillo et al. 2008 for an alternative, more robust mechanism). Similarly, nonnormal dynamics based on a long chain of functionally feedforward connections can also generate sustained responses (Ganguli et al. 2008b, Goldman 2009) but are exceedingly sensitive to structural perturbations (Trefethen & Embree 2005). Lim & Goldman (2013) solved this robustness problem by using ideas from classical control theory. Prolonged activity decays—that is, activity characterized by small temporal derivatives—can be achieved through so-called derivative feedback control. An estimate of how much the system is momentarily drifting (the derivative) is fed back as a negative contribution to the net input. Although pure derivative control is not physically realizable (it is a noncausal operation), Lim & Goldman (2013, 2014) showed that such a "slip detector" can be robustly and realistically approximated by coupling slow excitation with fast inhibition (**Figure 6*b***).

Although this solution is robust to most common types of perturbations, such as neuronal death (Lim & Goldman 2013, Barrett et al. 2016), it cannot automatically compensate for perturbations that break the E/I balance, namely those that differentially affect the E→E and E→I couplings. ISP is an ideal metacontrol mechanism for preserving functionality in such working memory networks because of its propensity to automatically maintain the E/I balance. Similarly to the rules that construct the ISNs mentioned above, it is unclear what form ISP must take to learn

slip detectors, but the success of the model indicates that future experiments on ISP might benefit from the riches of control theory.

6.3. Stabilized Supralinear Networks

Although the balanced network model explains important aspects of cortical firing, such as high variability and low synchronicity (**Figure 3**), it is unable to account for basic circuit-level nonlinearities, such as the normalization of cortical responses to multiple stimuli (Carandini & Heeger 2012). This is because the tight E/I balance forces the network to respond linearly to changes in external input (van Vreeswijk & Sompolinsky 1996, Rosenbaum & Doiron 2014). Miller and colleagues (Ahmadian et al. 2013, Rubin et al. 2015; see also Persi et al. 2011) showed that loose E/I balance in the so-called stabilized supralinear network (SSN) enables nonlinear collective behavior. Positive feedback arises from the combination of recurrent excitation and supralinear single-neuron nonlinearities (**Figure 6*c***, left) (Priebe & Ferster 2008): The greater the excitatory activity is, the steeper the excitatory neurons' input/output curves at their operating points, and so the stronger the functional excitatory recurrent connectivity. This process would normally result in inconsistent, explosive scaling of responses, but appropriately shaped feedback inhibition prevents it. Consequently, the SSN responds superlinearly to the superposition of two weak inputs (**Figure 6*c***, center) but sublinearly to the superposition of two stronger inputs (**Figure 6*c***, right) (Ahmadian et al. 2013), consistent with contrast-dependent normalization in V1. Several predictions of this simple model, including periodicity of tuning to stimulus size and contrast-dependent resonance, were successfully tested in recent experiments (Rubin et al. 2015).

6.4. Inhibitory Plasticity and Optimal Feedback Control

In all the models discussed above, functionality emerges from dynamic stabilization, requiring feedback inhibition to reflect the spatial structure of the instabilities contained in the recurrent E→E connectivity. When this structure is simple (e.g., when instabilities arise only in a couple of low-spatial-frequency modes), optimal inhibitory feedback is often just as simple, may be constructed by hand in models, and could even be grown from genetic blueprints during development. Yet, cortical circuits evolve constantly at the micro scale (Chklovskii et al. 2004). Is it always possible for inhibition to tame high-dimensional recurrent instabilities? What form should ISP take to succeed? Using methods from control theory and optimization, Hennequin et al. (2014) constructed complex ISNs by progressively adjusting each inhibitory synaptic weight in a strongly connected random network. This method could robustly stabilize a large number of initially unstable activity modes (**Figure 6*d***, left), but the optimal stabilization algorithm could not easily be mapped onto a realistic form of ISP. Much like the simpler ISNs described above, the resulting stability-optimized circuits (SOCs) (**Figure 6*d***, middle) responded vigorously to privileged, balance-breaking input patterns (**Figure 6*d***, top right) while almost completely ignoring others (**Figure 6*d***, bottom right). However, owing to the complexity of recurrent excitatory motifs, amplification occurs by way of rich internal dynamics that elicit multiphasic responses similar to those of neurons in the motor cortex of monkeys executing movements (**Figure 5*m***) (Churchland et al. 2012). Such diverse responses might form useful basis functions to assemble motor primitives, and they suggest that ISP lies at the heart of sequence learning.

7. CODEPENDENT PLASTICITY

The complexity of the control problems in which inhibition participates is perplexing to anyone wishing to understand how feasible learning rules may solve them. Indeed, optimal solutions

derived from control theory (e.g., for the construction of SOCs, described above) often prescribe synaptic modifications based on information not readily available at single synapses. This is difficult to reconcile with the de facto definition of a feasible rule as one that uses only local pre- and postsynaptic spike trains (Morrison et al. 2008), possibly with a global reward signal (Frémaux et al. 2010, Frémaux & Gerstner 2016). One cannot strictly rule out the existence of simple—yet sufficiently effective—approximations of control-theoretic optimal constructs, which the brain could implement using elementary learning rules. Alternatively, complexity might emerge from well-orchestrated combinations of plasticity mechanisms, similar to those hand-tuned to enable formation of stable memories in cortical network models (Litwin-Kumar & Doiron 2014, Duarte & Morrison 2014, Zenke et al. 2015). Intrinsic, self-governed orchestration may result from sophisticated cross talk between different types of synapses, and feasible synaptic plasticity may be more complex than originally anticipated.

Recent experimental evidence from studies that monitored more than one synapse simultaneously demonstrates such coordinated effects. In mouse auditory cortex, inhibitory synapses change according to the E/I balance prior to induction (**Figure 7*a***, left) (D'amour & Froemke 2015), namely the combined state of excitation and inhibition. Moreover, plasticity is completely abolished when NMDA receptors are blocked (**Figure 7*a***, right) (D'amour & Froemke 2015), as also reported in rat cerebellum (**Figure 7*b***) (Mapelli et al. 2016). The fact that synaptic changes occur only when excitatory inputs are coactive and the E/I balance is perturbed suggests that ISP integrates neighboring excitatory and inhibitory inputs (**Figure 7*c***) to maintain a local E/I balance rather than, for instance, to impose an activity set point (as in Vogels et al. 2011). The consequences of such codependent learning rules for network function and architecture have not been explored in network models, but they may be vastly different from those of purely pre–post spike-based ISP (**Figure 7*d***).

Similarly, excitatory synapses depend on activity beyond pre–post spike pairs. For example, long-term potentiation (LTP) requires coactivation of additional excitatory afferents (Debanne et al. 1996, Sjöström & Häusser 2006, Sjöström et al. 2001), reflected in the dependence of LTP on the postsynaptic membrane potential (**Figure 7*e***) (Sjöström & Häusser 2006, Clopath et al. 2010). Additionally, in rat corticostriatal excitatory synapses, an anti-Hebbian STDP window

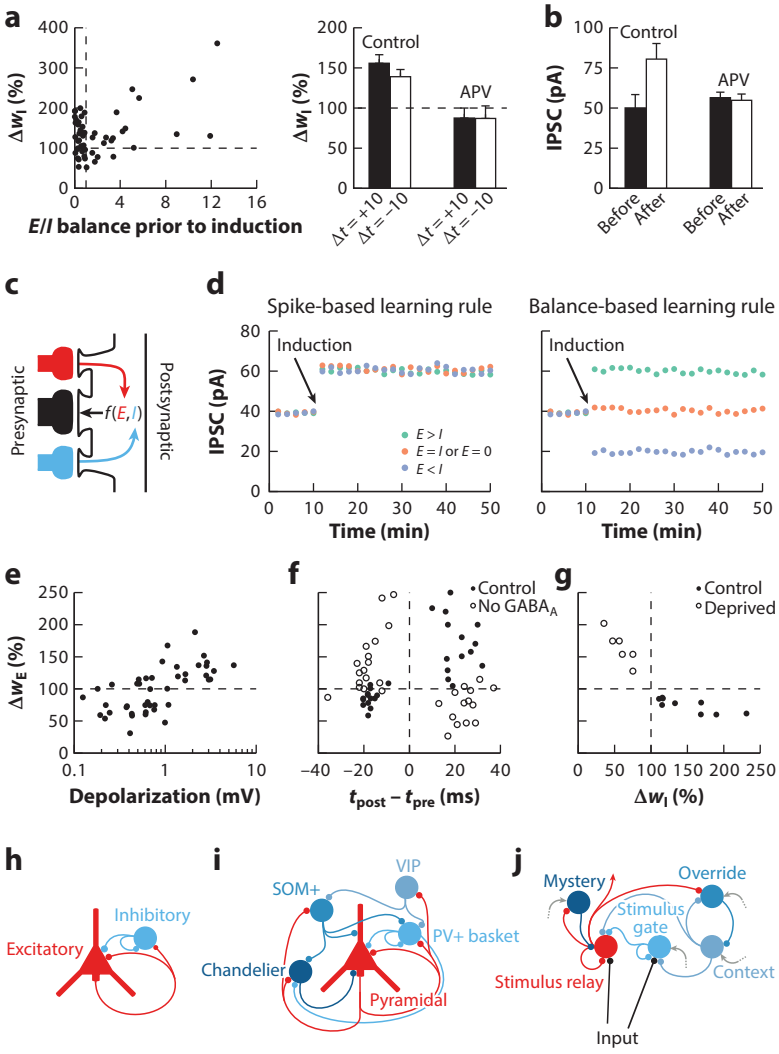
Figure 7

Codependent synaptic plasticity. (*a*) (*Left*) Changes in inhibitory synaptic efficacy as a function of the ratio of excitatory (E) to inhibitory (I) peak currents just before the induction protocol (same data set as in **Figure 1*d***). (*Right*) *N*-Methyl-D-aspartate (NMDA) receptor blockade (APV) prevents plasticity otherwise induced by near-coincident pre- and postsynaptic spikes separated by Δt. (*b*) Inhibitory synaptic plasticity (ISP) in rat cerebellum in a tetanus protocol is also affected by NMDA receptor blockade (APV). (*c*) Illustration of synaptic plasticity codependence. A synapse (*black*, *middle*) is modified according to a function $f(E, I)$ of biochemical signals shared by neighboring E (*red*) and I (*blue*) synapses. (*d*) Illustration of the difference between ISP induced by a purely spike-based (*left*) and a balance-based (*right*) learning rule. When the order of the spikes is the same (for example, pre before post), the spike-based learning rule (Vogels et al. 2011) induces the same change independently of the balance prior to induction. For a codependent learning rule, the amount of excitation and inhibition received by a neuron influences the amount and sign of the synaptic weight change. (*e*) Excitatory synaptic plasticity depends on membrane potential depolarization. (*f*) $GABA_A$ receptor blockade flips the sign of the spike-timing-dependent plasticity (STDP) window in rat corticostriatal synapses, under a protocol similar to that shown in **Figure 1*d***. (*g*) Long-term modifications of E and I synapses are negatively correlated in rat V1, but the magnitude of the effect is modulated by sensory experience (compare monocular deprivation with control). (*h–j*) Most computational studies have focused on a simplistic microcircuit motif with a single E and I cell type (*h*), largely ignoring the wide diversity of interneuron types and connections found in cortex (*i*), potentially serving an equally diverse array of functions (*j*). Abbreviations: IPSC, inhibitory postsynaptic current; PV+, parvalbumin positive; SOM+, somatostatin positive; VIP, vasoactive intestinal polypeptide expressing. Panel *a* modified from D'amour & Froemke (2015), panel *b* from Mapelli et al. (2016), panel *e* from Sjöström & Häusser (2006), panel *f* from Paille et al. (2013), and panel *g* from Wang & Maffei (2014).

becomes Hebbian [LTP becomes LTD (long-term depression), and vice versa] when inhibitory synapses are blocked (**Figure 7*f***) (Paille et al. 2013). Orchestrated modifications of excitatory and inhibitory synapses are also found in rat V1 in response to sensory deprivation (**Figure 7*g***) (Wang & Maffei 2014; see also Maffei et al. 2006) and in the antennal lobe and the mushroom body of *Drosophila* in response to learning (Das et al. 2011, Perisse et al. 2016), where both excitatory and inhibitory synapses undergo concerted changes to restructure local connectivity.

8. DISCUSSION

To fully understand learning and memory in behaving animals, we must uncover the role of every involved synapse type. With current estimates of up to 50 different cell classes that connect in various brain regions, the number of connection type–specific plasticity rules may well be in the thousands. Although neuroscience has focused extensively on excitatory–excitatory plasticity in



experiment and theory, other connection types are moving into the focus of scientific inquiry. Inhibitory plasticity is becoming a major player in the organization of neural circuits. Moreover, the emergence of function seems to be borne out of interactions between different forms of plasticity, which recent experiments have barely begun to explore. Successful identification of these mechanisms and their function will require embracing the complexities of architectures with more than just two cell types and learning rules (**Figure 7*h–j***). Bringing together sophisticated experiments with integrative, reductionist theoretical research will let us distill the essential motifs that organize myriads of synapses, allowing us to eventually articulate a canonical model of synaptic learning.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors thank L.F. Abbott, A. Maffei, G. Miesenböck, W. Podlaski, J. Stroud, and M. Woodin for feedback on figures and manuscript. The writing of this review was supported by a Wellcome Trust Seed Award to G.H. (202111/Z/16/Z), a Sir Henry Dale Wellcome Trust and Royal Society Grant to T.P.V. (WT100000), and a postdoctoral grant from Brazilian CNPq to E.J.A. (235144/2014-2).

LITERATURE CITED

Abbott L, Nelson S. 2000. Synaptic plasticity: taming the beast. *Nat. Neurosci.* 3:1178–83

Abeles M. 1991. *Corticonics: Neural Circuits of the Cerebral Cortex*. Cambridge, UK: Cambridge Univ. Press

Adrian ED. 1926. The impulses produced by sensory nerve endings. *J. Physiol.* 61:49–72

Ahmadian Y, Rubin DB, Miller KD. 2013. Analysis of the stabilized supralinear network. *Neural Comput.* 25:1994–2037

Aizenman CD, Manis PB, Linden DJ. 1998. Polarity of long-term synaptic gain change is related to postsynaptic spike firing at a cerebellar inhibitory synapse. *Neuron* 21:827–35

Amit DJ, Brunel N. 1997. Model of global spontaneous activity and local structured activity during delay periods in the cerebral cortex. *Cereb. Cortex* 7:237–52

Aström KJ, Murray RM. 2010. *Feedback Systems: An Introduction for Scientists and Engineers*. Princeton, NJ: Princeton University Press

Aviel Y, Horn D, Abeles M. 2005. Memory capacity of balanced networks. *Neural Comput.* 17:691–713

Aviel Y, Mehring C, Abeles M, Horn D. 2003. On embedding synfire chains in a balanced network. *Neural Comput.* 15:1321–40

Barrett D. 2012. *Computation in balanced networks*. PhD thesis, Univ. Coll. London

Barrett DT, Denève S, Machens CK. 2016. Optimal compensation for neuron loss. *eLife* 5:e12454

Barron H, Vogels T, Emir U, Makin T, O'Shea J, et al. 2016a. Unmasking latent inhibitory connections in human cortex to reveal dormant cortical memories. *Neuron* 90:191–203

Barron HC, Garvert MM, Behrens TEJ. 2016b. Repetition suppression: a means to index neural representations using BOLD? *Philos. Trans. R. Soc. B* 371:20150355

Bathellier B, Ushakova L, Rumpel S. 2012. Discrete neocortical dynamics predict behavioral categorization of sounds. *Neuron* 76:435–49

Ben-Yishai R, Bar-Or RL, Sompolinsky H. 1995. Theory of orientation tuning in visual cortex. *PNAS* 92:3844

Berkes P, Orbán G, Lengyel M, Fiser J. 2011. Spontaneous cortical activity reveals hallmarks of an optimal internal model of the environment. *Science* 331:83–87

Boerlin M, Machens CK, Denève S. 2013. Predictive coding of dynamical variables in balanced spiking networks. *PLOS Comput. Biol.* 9:e1003258

Brunel N. 2000. Dynamics of sparsely connected networks of excitatory and inhibitory spiking neurons. *J. Comput. Neurosci.* 8:183–208

Brunel N, Hakim V. 1999. Fast global oscillations in networks of integrate-and-fire neurons with low firing rates. *Neural Comput.* 11:1621–71

Brunel N, Wang XJ. 2001. Effects of neuromodulation in a cortical network model of object working memory dominated by recurrent inhibition. *J. Comput. Neurosci.* 11:63–85

Brunel N, Wang XJ. 2003. What determines the frequency of fast network oscillations with irregular neural discharges? I. Synaptic dynamics and excitation–inhibition balance. *J. Neurophysiol.* 90:415–30

Buetfering C, Allen K, Monyer H. 2014. Parvalbumin interneurons provide grid cell–driven recurrent inhibition in the medial entorhinal cortex. *Nat. Neurosci.* 17:710–18

Cafaro J, Rieke F. 2010. Noise correlations improve response fidelity and stimulus encoding. *Nature* 468:964–67

Carandini M, Heeger DJ. 2012. Normalization as a canonical neural computation. *Nat. Rev. Neurosci.* 13:51–62

Chklovskii DB, Mel BW, Svoboda K. 2004. Cortical rewiring and information storage. *Nature* 431:782–88

Churchland MM, Cunningham JP, Kaufman MT, Foster JD, Nuyujukian P, et al. 2012. Neural population dynamics during reaching. *Nature* 487:51–56

Clopath C, Büsing L, Vasilaki E, Gerstner W. 2010. Connectivity reflects coding: a model of voltage-based STDP with homeostasis. *Nat. Neurosci.* 13:344–52

Clopath C, Vogels TP, Froemke RC, Sprekeler H. 2016. Receptive field formation by interacting excitatory and inhibitory synaptic plasticity. bioRxiv 066589. **https://doi.org/10.1101/066589**

Constantinescu AO, O'Reilly JX, Behrens TEJ. 2016. Organizing conceptual knowledge in humans with a gridlike code. *Science* 352:1464–68

Couey JJ, Witoelar A, Zhang SJ, Zheng K, Ye J, et al. 2013. Recurrent inhibitory circuitry as a mechanism for grid formation. *Nat. Neurosci.* 16:318–24

D'amour J, Froemke R. 2015. Inhibitory and excitatory spike-timing-dependent plasticity in the auditory cortex. *Neuron* 86:514–28

Das S, Sadanandappa MK, Dervan A, Larkin A, Lee JA, et al. 2011. Plasticity of local GABAergic interneurons drives olfactory habituation. *PNAS* 108:E646–54

Debanne D, Gähwiler BH, Thompson SM. 1996. Cooperative interactions in the induction of long-term potentiation and depression of synaptic excitation between hippocampal CA3-CA1 cell pairs in vitro. *PNAS* 93:11225–30

Diesmann M, Gewaltig MO, Aertsen A. 1999. Stable propagation of synchronous spiking in cortical neural networks. *Nature* 402:529–33

Doiron B, Litwin-Kumar A, Rosenbaum R, Ocker GK, Josi K. 2016. The mechanics of state-dependent neural correlations. *Nat. Neurosci.* 19:383–93

Duarte RCF, Morrison A. 2014. Dynamic stability of sequential stimulus representations in adapting neuronal networks. *Front. Comput. Neurosci.* 8:124

Fiser J, Chiu C, Weliky M. 2004. Small modulation of ongoing cortical dynamics by sensory input during natural vision. *Nature* 431:573–78

Foster DJ, Wilson MA. 2006. Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* 440:680–83

Frémaux N, Gerstner W. 2016. Neuromodulated spike-timing-dependent plasticity, and theory of three-factor learning rules. *Front. Neural Circuits* 9:85

Frémaux N, Sprekeler H, Gerstner W. 2010. Functional requirements for reward-modulated spike-timing-dependent plasticity. *J. Neurosci.* 30:13326–37

Froemke RC, Merzenich MM, Schreiner CE. 2007. A synaptic memory trace for cortical receptive field plasticity. *Nature* 450:425–29

Gaiarsa JL, Caillard O, Ben-Ari Y. 2002. Long-term plasticity at GABAergic and glycinergic synapses: mechanisms and functional significance. *Trends Neurosci.* 25:564–70

Ganguli S, Bisley JW, Roitman JD, Shadlen MN, Goldberg ME, Miller KD. 2008a. One-dimensional dynamics of attention and decision making in LIP. *Neuron* 58:15–25

Ganguli S, Huh D, Sompolinsky H. 2008b. Memory traces in dynamical systems. *PNAS* 105:18970–75

Gerstner W, Kistler WM, Naud R, Paninski L. 2014. *Neuronal Dynamics: From Single Neurons to Networks and Models of Cognition*. Cambridge, UK: Cambridge Univ. Press

Gerstner W, van Hemmen JL. 1992. Associative memory in a network of 'spiking' neurons. *Netw. Comput. Neural Syst.* 3:139–64

Goldberg JA, Rokni U, Sompolinsky H. 2004. Patterns of ongoing activity and the functional architecture of the primary visual cortex. *Neuron* 42:489–500

Goldman MS. 2009. Memory without feedback in a neural network. *Neuron* 61:621–34

Goldman-Rakic PS. 1995. Cellular basis of working memory. *Neuron* 14:477–85

Haas JS, Nowotny T, Abarbanel HDI. 2006. Spike-timing-dependent plasticity of inhibitory synapses in the entorhinal cortex. *J. Neurophysiol.* 96:3305–13

Harish O, Hansel D. 2015. Asynchronous rate chaos in spiking neuronal circuits. *PLOS Comput. Biol.* 11:e1004266

Harris KD. 2005. Neural signatures of cell assembly organization. *Nat. Rev. Neurosci.* 6:399–407

Hartmann K, Bruehl C, Golovko T, Draguhn A. 2008. Fast homeostatic plasticity of inhibition via activity-dependent vesicular filling. *PLOS ONE* 3:e2979

Hebb DO. 1949. *The Organization of Behavior: A Neuropsychological Approach*. New York: Wiley

Hendin O, Horn D, Tsodyks MV. 1997. The role of inhibition in an associative memory model of the olfactory bulb. *J. Comput. Neurosci.* 4:173–82

Hennequin G, Ahmadian Y, Rubin DB, Lengyel M, Miller KD. 2016. Stabilized supralinear network dynamics account for stimulus-induced changes of noise variability in the cortex. bioRxiv 094334. **https://doi.org/10.1101/094334**

Hennequin G, Vogels TP, Gerstner W. 2014. Optimal control of transient dynamics in balanced networks supports generation of complex movements. *Neuron* 82:1394–406

Hertz J, Krogh A, Palmer R. 1991. *Introduction to the Theory of Neural Computation*. Redwood City, CA: Addison-Wesley

Holmgren CD, Zilberter Y. 2001. Coincident spiking activity induces long-term changes in inhibition of neocortical pyramidal cells. *J. Neurosci.* 21:8270–77

Hopfield JJ. 1982. Neural networks and physical systems with emergent collective computational abilities. *PNAS* 79:2554–58

Itskov V, Hansel D, Tsodyks M. 2011. Short-term facilitation may stabilize parametric working memory trace. *Front. Comput. Neurosci.* 5:40

Josselyn SA, Köhler S, Frankland PW. 2015. Finding the engram. *Nat. Rev. Neurosci.* 16:521–34

Kano M. 1995. Plasticity of inhibitory synapses in the brain: a possible memory mechanism that has been overlooked. *Neurosci. Res.* 21:177–82

Kenet T, Bibitchkov D, Tsodyks M, Grinvald A, Arieli A. 2003. Spontaneously emerging cortical representations of visual attributes. *Nature* 425:954–56

Kilman V, van Rossum MCW, Turrigiano GG. 2002. Activity deprivation reduces miniature IPSC amplitude by decreasing the number of postsynaptic $GABA_A$ receptors clustered at neocortical synapses. *J. Neurosci.* 22:1328–37

Kleberg FI, Fukai T, Gilson M. 2014. Excitatory and inhibitory STDP jointly tune feedforward neural circuits to selectively propagate correlated spiking activity. *Front. Comput. Neurosci.* 8:53

Komatsu Y. 1994. Age-dependent long-term potentiation of inhibitory synaptic transmission in rat visual cortex. *J. Neurosci.* 14:6488–99

Komatsu Y, Iwakiri M. 1993. Long-term modification of inhibitory synaptic transmission in developing visual cortex. *NeuroReport* 4:907–10

Kremkow J, Aertsen A, Kumar A. 2010. Gating of signal propagation in spiking neural networks by balanced and correlated excitation and inhibition. *J. Neurosci.* 30:15760–68

Kumar A, Rotter S, Aertsen A. 2010. Spiking activity propagation in neuronal networks: reconciling different perspectives on neural coding. *Nat. Rev. Neurosci.* 11:615–27

Kumar A, Schrader S, Aertsen A, Rotter S. 2008. The high-conductance state of cortical networks. *Neural Comput.* 20:1–43

Kurotani T, Yamada K, Yoshimura Y, Crair MC, Komatsu Y. 2008. State-dependent bidirectional modification of somatic inhibition in neocortical pyramidal cells. *Neuron* 57:905–16

Laje R, Buonomano DV. 2013. Robust timing and motor patterns by taming chaos in recurrent neural networks. *Nat. Neurosci.* 16:925–33

Landau I, Egger R, Dercksen V, Oberlaender M, Sompolinsky H. 2016. The impact of structural heterogeneity on excitation–inhibition balance in cortical networks. *Neuron* 92:1106–21

Latham PE, Nirenberg S. 2004. Computing and stability in cortical networks. *Neural Comput.* 16:1385–412

Li Z, Dayan P. 1999. Computational differences between asymmetrical and symmetrical networks. *Netw. Comput. Neural Syst.* 10:59–77

Lim S, Goldman MS. 2013. Balanced cortical microcircuitry for maintaining information in working memory. *Nat. Neurosci.* 16:1306–14

Lim S, Goldman MS. 2014. Balanced cortical microcircuitry for spatial working memory based on corrective feedback control. *J. Neurosci.* 34:6790–806

Lin L, Osan R, Shoham S, Jin W, Zuo W, Tsien JZ. 2005. Identification of network-level coding units for real-time representation of episodic experiences in the hippocampus. *PNAS* 102:6125–30

Litwin-Kumar A, Doiron B. 2012. Slow dynamics and high variability in balanced cortical networks with clustered connections. *Nat. Neurosci.* 15:1498–505

Litwin-Kumar A, Doiron B. 2014. Formation and maintenance of neuronal assemblies through synaptic plasticity. *Nat. Commun.* 5:5319

Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, et al. 2012. Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 484:381–85

Luczak A, Barthó P, Harris KD. 2009. Spontaneous events outline the realm of possible sensory responses in neocortical populations. *Neuron* 62:413–25

Luz Y, Shamir M. 2012. Balancing feed-forward excitation and inhibition via Hebbian inhibitory synaptic plasticity. *PLOS Comput. Biol.* 8:e1002334

Maass W, Natschläger T, Markram H. 2002. Real-time computing without stable states: a new framework for neural computation based on perturbations. *Neural Comput.* 14:2531–60

Maffei A, Nataraj K, Nelson SB, Turrigiano GG. 2006. Potentiation of cortical inhibition by visual deprivation. *Nature* 443:81–84

Mapelli J, Gandolfi D, Vilella A, Zoli M, Bigiani A. 2016. Heterosynaptic GABAergic plasticity bidirectionally driven by the activity of pre- and postsynaptic NMDA receptors. *PNAS* 113:9898–903

Markram H, Gerstner W, Sjöström PJ. 2011. A history of spike-timing-dependent plasticity. *Front. Synaptic Neurosci.* 3:1–24

Mehring C, Hehl U, Kubo M, Diesmann M, Aertsen A. 2003. Activity dynamics and propagation of synchronous spiking in locally connected random networks. *Biol. Cybern.* 88:395–408

Miller P. 2016. Itinerancy between attractor states in neural systems. *Curr. Opin. Neurobiol.* 40:14–22

Mongillo G, Barak O, Tsodyks M. 2008. Synaptic theory of working memory. *Science* 319:1543–46

Moore CI, Nelson SB. 1998. Spatio-temporal subthreshold receptive fields in the vibrissa representation of rat primary somatosensory cortex. *J. Neurophysiol.* 80:2882–92

Morrison A, Diesmann M, Gerstner W. 2008. Phenomenological models of synaptic plasticity based on spike timing. *Biol. Cybern.* 98:459–78

Murphy BK, Miller KD. 2009. Balanced amplification: a new mechanism of selective amplification of neural activity patterns. *Neuron* 61:635–48

Okun M, Lampl I. 2008. Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked activities. *Nat. Neurosci.* 11:535–37

Olshausen BA, Anderson CH, Essen DV. 1993. A neurobiological model of visual attention and invariant pattern recognition based on dynamic routing of information. *J. Neurosci.* 13:4700–19

Ormond J, Woodin MA. 2009. Disinhibition mediates a form of hippocampal long-term potentiation in area CA1. *PLOS ONE* 4:e7224

Ormond J, Woodin MA. 2011. Disinhibition-mediated LTP in the hippocampus is synapse specific. *Front. Cell. Neurosci.* 5:17

Ostojic S. 2014. Two types of asynchronous activity in networks of excitatory and inhibitory spiking neurons. *Nat. Neurosci.* 17:594–600

Ozeki H, Finn IM, Schaffer ES, Miller KD, Ferster D. 2009. Inhibitory stabilization of the cortical network underlies visual surround suppression. *Neuron* 62:578–92

Paille V, Fino E, Du K, Morera-Herreras T, Perez S, et al. 2013. GABAergic circuits control spike-timing-dependent plasticity. *J. Neurosci.* 33:9353–63

Perisse E, Owald D, Barnstedt O, Talbot CB, Huetteroth W, Waddell S. 2016. Aversive learning and appetitive motivation toggle feed-forward inhibition in the *Drosophila* mushroom body. *Neuron* 90:1086–99

Persi E, Hansel D, Nowak L, Barone P, van Vreeswijk C. 2011. Power-law input-output transfer functions explain the contrast-response and tuning properties of neurons in visual cortex. *PLOS Comput. Biol.* 7:e1001078

Ponce-Alvarez A, Thiele A, Albright TD, Stoner GR, Deco G. 2013. Stimulus-dependent variability and noise correlations in cortical MT neurons. *PNAS* 110:13162–67

Poo MM, Pignatelli M, Ryan TJ, Tonegawa S, Bonhoeffer T, et al. 2016. What is memory? The present state of the engram. *BMC Biol.* 14:40

Priebe NJ, Ferster D. 2008. Inhibition, spike threshold, and stimulus selectivity in primary visual cortex. *Neuron* 57:482–97

Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I. 2005. Invariant visual representation by single neurons in the human brain. *Nature* 435:1102–7

Ramirez S, Liu X, Lin PA, Suh J, Pignatelli M, et al. 2013. Creating a false memory in the hippocampus. *Science* 341:387–91

Recanatesi S, Katkov M, Romani S, Tsodyks M. 2015. Neural network model of memory retrieval. *Front. Comput. Neurosci.* 9:149

Renart A, de la Rocha J, Barthó P, Hollender L, Parga N, et al. 2010. The asynchronous state in cortical circuits. *Science* 327:587

Renart A, Parga N, Rolls ET. 1999. Associative memory properties of multiple cortical modules. *Netw. Comput. Neural Syst.* 10:237–55

Rosenbaum R, Doiron B. 2014. Balanced networks of spiking neurons with spatially dependent recurrent connections. *Phys. Rev. X* 4:021039

Roudi Y, Latham PE. 2007. A balanced memory network. *PLOS Comput. Biol.* 3:e141

Rowland DC, Roudi Y, Moser MB, Moser EI. 2016. Ten years of grid cells. *Annu. Rev. Neurosci.* 39:19–40

Roxin A. 2011. The role of degree distribution in shaping the dynamics in networks of sparsely connected spiking neurons. *Front. Comput. Neurosci.* 5:8

Rubin D, Van Hooser S, Miller K. 2015. The stabilized supralinear network: a unifying circuit motif underlying multi-input integration in sensory cortex. *Neuron* 85:402–17

Russo E, Treves A. 2012. Cortical free-association dynamics: distinct phases of a latching network. *Phys. Rev. E* 85:051920

Semon RW. 1921. *The Mneme*. London: Allen & Unwin

Shadlen MN, Newsome WT. 1994. Noise, neural codes and cortical organization. *Curr. Opin. Neurobiol.* 4:569–79

Shu Y, Hasenstaub A, McCormick DA. 2003. Turning on and off recurrent balanced cortical activity. *Nature* 423:288–93

Sjöström PJ, Häusser M. 2006. A cooperative switch determines the sign of synaptic plasticity in distal dendrites of neocortical pyramidal neurons. *Neuron* 51:227–38

Sjöström PJ, Turrigiano GG, Nelson SB. 2001. Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. *Neuron* 32:1149–64

Song HF, Yang GR, Wang XJ. 2016. Training excitatory-inhibitory recurrent neural networks for cognitive tasks: a simple and flexible framework. *PLOS Comput. Biol.* 12:e1004792

Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, et al. 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J. Neurosci.* 29:5202–6

Stringer C, Pachitariu M, Steinmetz NA, Okun M, Barthó P, et al. 2016. Inhibitory control of correlated intrinsic variability in cortical networks. *eLife* 5:e19695

Sudhakaran IP, Holohan EE, Osman S, Rodrigues V, Vijayraghavan K, Ramaswami M. 2012. Plasticity of recurrent inhibition in the *Drosophila* antennal lobe. *J. Neurosci.* 32:7225–31

Sussillo D, Abbott L. 2009. Generating coherent patterns of activity from chaotic neural networks. *Neuron* 63:544–57

Tetzlaff T, Helias M, Einevoll GT, Diesmann M. 2012. Decorrelation of neural-network activity by inhibitory feedback. *PLOS Comput. Biol.* 8:e1002596

Trefethen LN, Embree M. 2005. *Spectra and Pseudospectra: The Behavior of Nonnormal Matrices and Operators*. Princeton, NJ: Princeton Univ. Press

Tsodyks MV, Sejnowski T. 1995. Rapid state switching in balanced cortical network models. *Netw. Comput. Neural Syst.* 6:111–24

Tsodyks MV, Skaggs WE, Sejnowski TJ, McNaughton BL. 1997. Paradoxical effects of external modulation of inhibitory interneurons. *J. Neurosci.* 17:4382–88

Turrigiano G. 2012. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb. Perspect. Biol.* 4:a005736

Vallentin D, Kosche G, Lipkind D, Long MA. 2016. Inhibition protects acquired song segments during vocal learning in zebra finches. *Science* 351:267–71

van Rossum MCW, Turrigiano GG, Nelson SB. 2002. Fast propagation of firing rates through layered networks of noisy neurons. *J. Neurosci.* 22:1956–66

van Vreeswijk C, Sompolinsky H. 1996. Chaos in neuronal networks with balanced excitatory and inhibitory activity. *Science* 274:1724

van Vreeswijk C, Sompolinsky H. 1998. Chaotic balanced state in a model of cortical circuits. *Neural Comput.* 10:1321–71

Vogels TP, Abbott LF. 2009. Gating multiple signals through detailed balance of excitation and inhibition in spiking networks. *Nat. Neurosci.* 12:483–91

Vogels TP, Froemke RC, Doyon N, Gilson M, Haas JS, et al. 2013. Inhibitory synaptic plasticity: spike timing-dependence and putative network function. *Front. Neural Circuits* 7:119

Vogels TP, Rajan K, Abbott LF. 2005. Neural network dynamics. *Annu. Rev. Neurosci.* 28:357–76

Vogels TP, Sprekeler H, Zenke F, Clopath C, Gerstner W. 2011. Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. *Science* 334:1569–73

Wang L, Maffei A. 2014. Inhibitory plasticity dictates the sign of plasticity at excitatory synapses. *J. Neurosci.* 34:1083–93

Weber SN, Sprekeler H. 2017. Learning place cells, grid cells and invariances: a unifying model. bioRxiv 102525. **https://doi.org/10.1101/102525**

Wehr M, Zador A. 2003. Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. *Nature* 426:442–46

Widloski J, Fiete I. 2014. A model of grid cell development through spatial exploration and spike time–dependent plasticity. *Neuron* 83:481–95

Williams GV, Goldman-Rakic PS. 1995. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 376:572–75

Wilmes KA, Sprekeler H, Schreiber S. 2016. Inhibition as a binary switch for excitatory plasticity in pyramidal neurons. *PLOS Comput. Biol.* 12:e1004768

Wimmer K, Nykamp DQ, Constantinidis C, Compte A. 2014. Bump attractor dynamics in prefrontal cortex explains behavioral precision in spatial working memory. *Nat. Neurosci.* 17:431–39

Woodin MA, Ganguly K, Poo M. 2003. Coincident pre-and postsynaptic activity modifies GABAergic synapses by postsynaptic changes in Cl-transporter activity. *Neuron* 39:807–20

Xue M, Atallah BV, Scanziani M. 2014. Equalizing excitation–inhibition ratios across visual cortical neurons. *Nature* 511:596–600

Zenke F, Agnes EJ, Gerstner W. 2015. Diverse synaptic plasticity mechanisms orchestrated to form and retrieve memories in spiking neural networks. *Nat. Commun.* 6:6922

Zenke F, Hennequin G, Gerstner W. 2013. Synaptic plasticity in neural networks needs homeostasis with a fast rate detector. *PLOS Comput. Biol.* 9:e1003330