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Functional consequences of inhibitory plasticity: homeostasis, the excitation-inhibition balance and beyond

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Computational neuroscience has a long-standing tradition of investigating the consequences of excitatory synaptic plasticity. In contrast, the functions of inhibitory plasticity are still largely nebulous, particularly given the bewildering diversity of interneurons in the brain. Here, we review recent computational advances that provide first suggestions for the functional roles of inhibitory plasticity, such as a maintenance of the excitation-inhibition balance, a stabilization of recurrent network dynamics and a decorrelation of sensory responses. The field is still in its infancy, but given the existing body of theory for excitatory plasticity, it is likely to mature quickly and deliver important insights into the self-organization of inhibitory circuits in the brain.

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Introduction

The notion that synaptic plasticity is the underpinning of learning and memory has become an accepted standard in neuroscience [1]. The overwhelming majority of research on synaptic plasticity has focused on the plasticity of excitatory synapses, a large number of which display long-term potentiation and/or depression [2]. The smaller sibling — plasticity of inhibitory synapses — has attracted less attention, mostly for technical reasons. Inhibitory cells are smaller and less numerous and hence harder to access physiologically. Moreover, they present a confusing variety of cell types [3] that is laborious to control for in classical paired recordings.

Despite their smaller numbers, inhibitory cells play an essential role in shaping the dynamics, response properties and plasticity of neural circuits [4]. In recurrent networks, inhibition is thought to stabilize excitatory feedback loops and support the generation of oscillations [4], as well as mediate neural competition [5], decorrelation [6] and normalization [7]. Inhibition can also act as a gate for neural signal propagation [8], dendritic computation [9,10] and learning [11,12], and sharpen the stimulus selectivity and temporal profile of sensory responses [4].

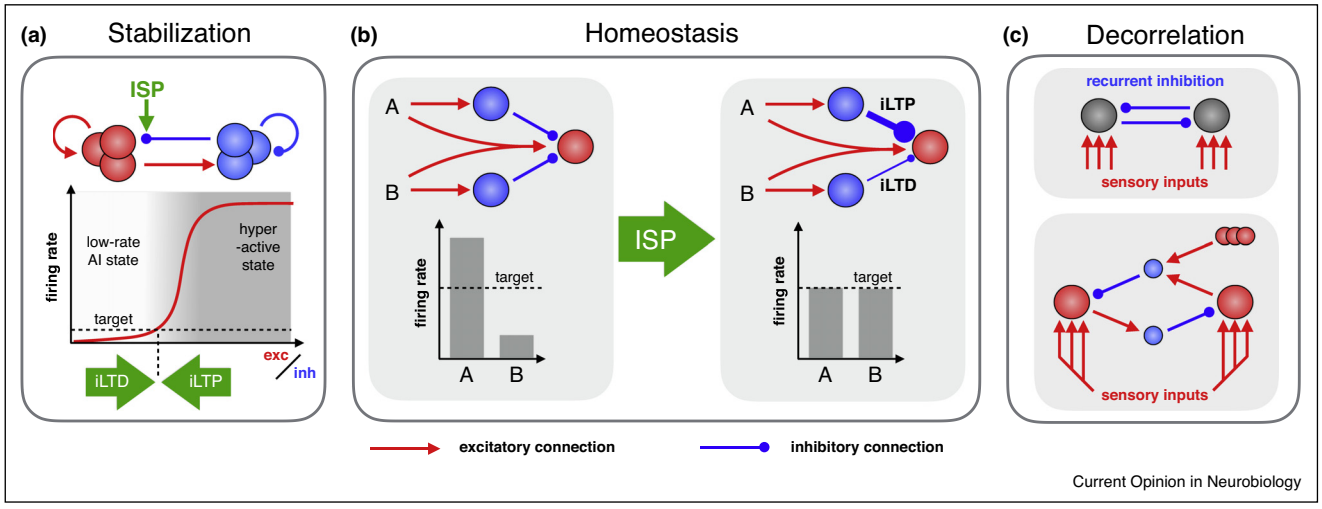
Many of these functions require a suitably titrated amount of inhibition. It is hence likely that the nervous system possesses homeostatic mechanisms that keep the inhibitory tone on a functional level. An obvious candidate for this job is plasticity of inhibitory synapses, or potentially excitatory synapses onto inhibitory neurons. This review is limited to the former, that is, to plasticity in GABAergic synapses, and specifically to recent computational work. Recent advances in the experimental characterization of inhibitory synaptic plasticity (ISP) have been reviewed elsewhere [13–15].

Traditional neural network models mostly ignored Dale's law and contained inhibition in the form of either negative 'neural activations' or negative synaptic weights. Synaptic plasticity could freely turn excitatory into inhibitory synapses and back, so that excitatory and inhibitory plasticity were inextricably intertwined. The transfer of classical neural network concepts to Dalian networks gained momentum in the 1990s, with a series of studies on Dalian attractor networks [16] and the emerging concept of balanced networks [17]. Inhibitory connections in these networks were typically hand-wired, and often required tiresome parameter adjustments, at least in networks with complex structure. The idea that these adjustments could be done in a self-organized way — by reserving an independent role for inhibitory plasticity — has gained popularity only relatively recently.

Inhibitory plasticity for network stabilization and homeostasis

A classical function of recurrent inhibition is to counteract the instability that arises from recurrent excitation [17,18••]. This stabilizing inhibitory feedback loop has led to the notion of a balanced network state, in which excitation and inhibition compensate each other on average and spikes are driven primarily by fluctuations.

Figure 1



Functional roles of inhibitory plasticity. **(a)** When recurrent excitatory connections get stronger than a critical value, spiking recurrent networks undergo a sudden transition from a low-rate, often asynchronous irregular regime (AI state) into a hyperactive, synchronous state [19]. Inhibitory synaptic plasticity (ISP) can stabilize these networks by a suitable potentiation (iLTP) or depression (iLTD) of the inhibitory negative feedback loop [18••,25,28,34], thereby ensuring stability even in the presence of network heterogeneities or changes in recurrent excitation [20••,30••,31–33]. **(b)** Input-specific long-term potentiation or long-term depression allows a pathway-specific, stimulus-specific or context-specific homeostatic control of neural activity, if specialized inhibitory neurons are available. In a given context A, a neuron that has a higher activity than its target can be inhibited by potentiating a context-specific inhibitory input. In a different context B, the activity of the same, but now overly quiet neuron is increased by a depression of inhibitory connections [25], such that the neuron eventually reaches the target rate in both contexts. **(c)** In traditional neural networks, a decorrelation of neural responses can be achieved by Hebbian plasticity in recurrent inhibitory connections. Recurrent inhibition among two neurons is potentiated as long as they are positively correlated, thereby gradually removing the correlation [50]. Hebbian plasticity in feedforward connections from sensory inputs can then permanently imprint the resulting decorrelated representation. If sensory representations reside in excitatory cells, the applicability of this mechanism is not obvious, because inhibition is disynaptic and inhibitory cells receive input from many excitatory cells. Modeling studies suggest that Hebbian inhibitory plasticity tends to decorrelate sensory responses nevertheless [32].

A consequence is an asynchronous and irregular network state [17] that is similar to observed cortical activity. In random networks, this state is quite robust, as long as recurrent inhibition is sufficiently strong [19]. The situation is more complicated in structured networks, for example, in the presence of embedded Hebbian assemblies [20••,21], feedforward chains [22] or other heterogeneities [23]. In inhomogeneous networks, different neurons can receive a drastically different amount of excitatory drive and hence require an individualized level of inhibition to be in a balanced state.

Such a cell-specific balance can be achieved by a synaptic plasticity rule in inhibitory synapses that depends on the postsynaptic firing rate [24–26]. The core idea is that an excess or lack of inhibition manifests itself in the activity of the neuron. High activity indicates a lack of inhibition, which can be counteracted by a potentiation of inhibitory synapses (Figure 1a). Low activity indicates an overshoot of inhibition (or a lack of excitation), which can be reduced by a depression of inhibitory synapses. A side effect of such a plasticity rule is a homeostatic maintenance of the activity level at the point where potentiation and depression compensate each other precisely. If this maintained activity level is much lower than what the cell would show in the absence of inhibition, the homeostasis effectively balances the incoming excitatory drive by inhibition. This balance of excitation and inhibition can be tailored to different input conditions or stimuli, by limiting plasticity to those synapses that deliver inhibition at the respective moment [25] (Figure 1b). Highjacking the terminology of excitatory plasticity, I will call such inhibitory plasticity rules that require coincident presynaptic and postsynaptic activity *Hebbian* in the sense of 'fire together, wire together', although this is at odds with Hebb's original causality condition that the presynaptic cell 'takes part in firing' the postsynaptic cell [27]. The biophysical machinery for the required coincidence detection is not yet fully resolved [15].

Variants of Hebbian inhibitory plasticity have recently been used in many studies to stabilize network dynamics, both in networks where the excitatory connectivity is static [18••,25,28,29], and where excitation is itself plastic [20••,30••,31–33]. In the simplest applications, inhibitory plasticity is merely used to ensure a relatively homogeneous 'background state' in spite of heterogeneities in the form of assemblies [25] or feedforward chains [34]. The resulting inhibition-stabilised networks display interesting transient dynamics [35], which have, for example,

been interpreted as a dynamical 'reservoir' from which complex sequences (e.g. motor commands) can be generated by a simple linear read-out [18••]. Network stabilization by Hebbian inhibitory plasticity is relatively robust in the sense that it can be achieved by a variety of learning rules. Recent studies have shown that excitation and inhibition can be balanced not only by the simple Hebbian rule sketched above [25,28,30••,33,36], but also by rules that depend in an asymmetric way on the precise timing of presynaptic and postsynaptic spikes [26,37,38•], by rules that switch between potentiation and depression depending on global population activity [20••] or by an optimal update rule derived explicitly for the purpose of stabilization [18••].

Interactions of excitatory and inhibitory plasticity

An appealing aspect of GABAergic plasticity is that it could maintain network stability in the presence of excitatory plasticity. Modeling work has shown, for example, that a carefully chosen combination of excitatory and inhibitory plasticity allows to imprint stable Hebbian assemblies online by external stimulation [20••,30••,39], without risking their decay due to background activity [40] or a destabilization of the network. A number of recent modeling studies have also shown that recurrent networks with combined Hebbian excitatory and inhibitory plasticity have a tendency to develop synfire chains [59] or a state of self-organised criticality [28,37,41].

Unfortunately, the interplay of excitatory and inhibitory plasticity is hard to understand in recurrent networks, because the two are coupled through their dependence on the statistics of network activity, which they in turn shape, often in a rather nonlinear way. A solid theoretical foundation for the evolution of such doubly plastic recurrent networks is still missing. In fact, the interaction of even a single form of synaptic plasticity with recurrent network dynamics is not fully understood, although this field is currently advancing rapidly [42,43•]. The crux is a required analytical link between the structure of a network and the statistics of its activity [e.g. 44,45]. Steps towards a theory for the interaction of excitatory and inhibitory plasticity have so far only been taken in feedforward networks [38•,46•,47], which do not suffer from a mutual coupling of the input statistics and plasticity.

Inhibitory plasticity can shape sensory representations

Models of inhibitory plasticity have also been used to reproduce aspects of sensory responses. In particular, it has been suggested that Hebbian plasticity of stimulus-specific inhibitory inputs can account for the correlated stimulus tuning of excitation and inhibition observed in sensory cortices [11,25,48,49], and for the sharpening of neural responses in time [25,38•,48]. Moreover, it has been argued that the development of stimulus selectivity in sensory neurons is supported by a cooperation of excitatory and inhibitory synaptic plasticity [38•,46•,47]. Hebbian plasticity of recurrent inhibition, in combination with plasticity of feedforward sensory inputs, is a standard method to achieve a decorrelation or sparse activation of neurons, and thereby reduce the redundancy in the resulting sensory representation [50] (Figure 1c). Although there is ample evidence for an inhibitory reduction of noise correlations in Dalian networks [6], it is not clear how to generalize this to correlations arising from similarities in sensory tuning, that is, signal correlations. Dale's law requires that inhibition between two excitatory cells is mediated disynaptically via an inhibitory interneuron, and these interneurons will usually receive inputs from more than a single excitatory cell. Hence, there is no single synapse that could measure the correlation between two excitatory cells locally and suitably adjust the inhibition to reduce it. Nevertheless, computational work indicates that inhibitory plasticity can mediate a signal decorrelation even in Dalian networks, when both excitatory and inhibitory recurrent connections are plastic [32,51,52,53•].

An interesting problem of signal decorrelation is the conflict between the apparent existence of assemblies with many neurons that encode similar features, and the idea of a decorrelation of features. How could a decorrelating mechanism know which cells to decorrelate and which to leave correlated? One option is that inhibition decorrelates cells only if their sensory tuning is sufficiently distinct, and leaves them correlated if their correlation exceeds a critical value. In neural terms, this could be mediated by a learning rule that potentiates activated inhibitory synapses when the postsynaptic neurons are depolarized ('the postsynaptic cell has a similar, but not identical stimulus tuning'), but not when it spikes ('the postsynaptic cell seems to belong to the same assembly'). Inhibitory plasticity with these characteristics was observed in visual cortex [54] and later also used in a computational model for the formation of neural assemblies [53•].

Inhibitory gating of signal propagation and plasticity

An emerging theme in recent years is that central functions of the nervous system such as signal transmission or plasticity are by default switched off during a state of balanced excitation and inhibition, and that they can be unleashed by targeted disruptions of this balance [8,12,55]. A gating of signal transmission, in particular, requires a subtle, signal-specific 'detailed balance' of excitation and inhibition [8,55]. Modeling work suggests that if this balance is perpetually maintained by inhibitory plasticity, new associations formed by excitatory plasticity are gradually compensated by an emerging inhibitory counter-association, and that this compensation can be undone by a reduction in inhibitory tone [56••]. In the same article, Barron *et al.* also provided support for this idea, using fMRI recordings to track neuronal activations during the retrieval of previously learned object associations, and perturbing

inhibitory tone by transcranial direct current stimulation [56••].

Inhibition also seems to gate learning and plasticity [12], through mechanisms that are not fully resolved and potentially diverse. One possibility is that inhibitory inputs disrupt dendritic calcium signals that are required for synaptic plasticity [2], for example, by blocking active dendritic processes such as backpropagating action potentials, calcium spikes [10] and/or NMDA spikes. Such a gating would again profit from a well chosen level and timing of inhibition, so that plasticity can be switched on and off by reasonably sized disinhibitory manipulations. Computational modeling suggests that both strength and timing of inhibition could be suitably adjusted by a spike-timing dependent variant of inhibitory plasticity [57].

Discussion and outlook

In recent years, computational neuroscientists have increasingly included inhibitory plasticity in network models that obey Dale's law. The core advantage is that Hebbian inhibitory plasticity provides a convenient tool to stabilize these networks and achieve a balance of excitation and inhibition in a self-organized way. In structured networks, this can save a significant amount of time otherwise spent on parameter tweaking. The resulting networks have interesting behavior, particularly when they also express excitatory plasticity, but it is still early days and we are currently lacking a comprehensive theoretical foundation for these networks.

The probably strongest hypothesis from recent computational work is that inhibitory plasticity can prevent a destabilization of recurrent networks by excitatory plasticity (or other changes). Although it is likely that a balance of excitation and inhibition is re-established by inhibitory plasticity [11], it is not clear if inhibitory plasticity occurs rapidly enough. Network models typically remain stable only if homeostatic mechanisms act faster than their destabilizing counterplayers [58], so that they can adapt swiftly and stop any instability in its tracks. It remains open if the relatively slow time scales of inhibitory adjustments [11] leave inhibitory plasticity up to this task. It cannot be excluded that other mechanisms serve this role, and that inhibitory plasticity (also) serves a variety of other functions, particularly given the diversity of inhibitory cell types.

The phenomenological characterization of inhibitory plasticity is presently considerably less complete than that of excitatory plasticity, and most current models are only weakly constrained by data. Although this situation bears the obvious risk that the models are utterly wrong, it also presents a nice opportunity for modelers. A catalogue of which characteristics of inhibitory plasticity support (or hinder) which network functions will come in handy for the interpretation of future data, particularly because different cell types are likely to express different, maybe even target-dependent forms of long-term plasticity.

Conflict of interest statement

Nothing declared.

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