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Network control through coordinated inhibition

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Coordinated excitatory and inhibitory activity is required for proper brain functioning. Recent computational and experimental studies have demonstrated that activity patterns in recurrent cortical networks are dominated by inhibition. Whereas previous studies have suggested that inhibitory plasticity is important for homeostatic control, this new framework puts inhibition in the driver's seat. Complex neuronal networks in the brain comprise many configurations in parallel, controlled by external and internal 'switches'. Context-dependent modulation and plasticity of inhibitory connections play a key role in memory and learning. It is therefore important to realize that synaptic plasticity is often multisynaptic and that a proper balance between excitation and inhibition is not fixed, but depends on context and activity level.

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Introduction

It has been long recognized that proper functioning of neural networks in the brain requires coordinated actions of excitatory and inhibitory synapses. Early modeling studies have demonstrated that networks are stable when activity is 'balanced' [1]. In these networks, all neurons receive many excitatory and inhibitory inputs, which nearly cancel each other out. The net input to individual neurons is therefore small, but sufficient to allow fast dynamic responses to external (e.g. sensory) stimuli. When network activity levels change, excitation (E) and inhibition (I) stay balanced, which ensures stability of the network. In this framework, the main role of inhibition in the brain is to counteract excitation to prevent instabilities in neural network function.

The concept of E/I balance has proven highly useful, both in experimental and computational neuroscience. In a clinical context, disturbances in E/I balance are thought to underlie several neurodevelopmental and other brain disorders [2,3]. However, the term 'balance' is not always clearly defined. Recent computational studies have demonstrated that the precise E/I balance in a network depends on the (often complex) circuit connectivity, the activity level and the firing properties of the neurons involved. In this review we discuss how computational and experimental studies are redefining the role of inhibition within the brain. We argue that, rather than simply following excitation, inhibition controls the rules for information processing and learning in the brain.

Information processing in the brain is controlled by inhibition

Sensory information arrives in the cortex via the thalamocortical pathway, by direct excitatory and indirect feedforward inhibitory projections. Processing occurs in local cortical networks which include recurrent excitatory connections and external modulation. Recent experimental and theoretical studies indicate that sensory cortex circuits operate in a regime where network activity is dominated by strong inhibitory feedback connections, described as inhibition stabilized networks (ISNs) [4,5•,6,7••]. An ISN is a theoretical network model of excitatory and inhibitory neurons with specific features. In an ISN, the recurrent excitatory connections dominate over external inputs, which renders the excitatory network inherently unstable. However, because the excitatory network is connected to a strong inhibitory network, overall stability of the ISN is secured. The important advantage of a strong recurrent excitatory network is that responses to (behaviorally relevant) stimuli are rapidly amplified [8,9]. This amplification results in a very brief surge in neural activity, as the explosive increase in excitation gets immediately (within tens of milliseconds) stabilized by strong recurrent inhibition [10]. This so-called 'balanced amplification' via strong recurrent connections was recently shown to allow effective signal transmission across several cortical areas in a large-scale model of the macaque cortex [11].

The rapid stabilization after an E/I disturbance also occurs in the opposite direction. Theoretical studies have predicted that external excitatory input to inhibitory cells leads to a counterintuitive lowering of network inhibition. This latter effect is because the initial increase in inhibition is rapidly counteracted by a decrease in overall network activity [12,13]. Rapid E/I rebalancing was also recently observed in an experimental study in which optogenetic silencing of parvalbumin (PV) cells in layer

IV of the auditory cortex led to adjustment of cortical activity level in which E/I ratio was rapidly restored [7••]. This illustrates how networks with recurrent excitatory and inhibitory connections inherently correct E/I disturbances.

Firing properties of neurons are highly nonlinear and this nonlinearity further adds to the instability of the excitatory network. At rest, cortical neurons fire at low rate and their firing is determined by small fluctuations of the membrane potential above the firing threshold. Therefore, cortical responses are nonlinear and highly variable when external (e.g. sensory) inputs are weak. As only a few neurons are active, recurrent connections are mostly silent and network activity is mainly driven by external input. However, when external inputs become stronger, network activity increases and recurrent connections will be recruited. In this activity regime, strong recurrent connections become dominant over external drive. As excitation is now automatically balanced by strong feedback inhibition, the network responses become linear and reliable (Figure 1). This means that graded inputs evoke graded responses over a wide range of activity levels, in which the E/I balance is automatically adjusted to the activity level [4,14].

The transition from highly variable, supralinear network activity to reliable and linear cortical responses with increasing input strength reflects a shift in effective network connectivity depending on the activity level [5•]. This implies that the E/I ratio is not fixed within the network, but that the optimal E/I ratio strongly depends on the network activity level and stimulus properties. Variable E/I ratios have been experimentally observed [6,15,16]. For instance, in the primary visual cortex of awake mice the E/I ratio decreases with increasing stimulus size and contrast [6]. This suggests that the sensory cortex operates as an ISN, in which feedback inhibitory connections are only employed when external inputs are strong enough to recruit the recurrent connections.

Even though the computational framework was originally developed to explain sensory processing, supralinear neuronal networks which are stabilized by inhibition can display a large diversity of activity patterns, including bimodal, persistent and oscillatory activity [17]. This matches with experimental observations of the remarkable versatility of cortical function and illustrates the potential as a general principle of cortical organization.

Inhibition is context-dependent and essential for memory

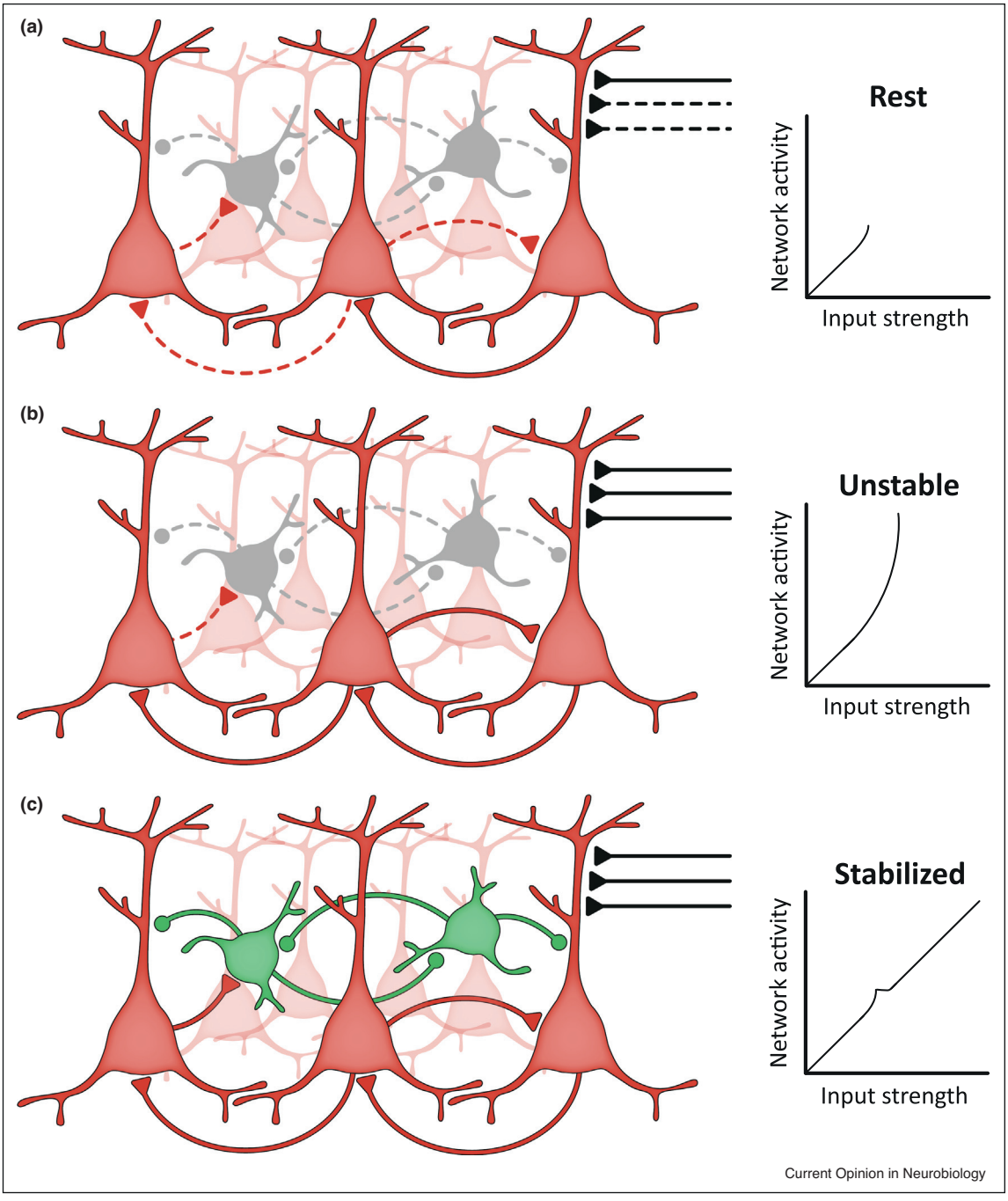
The above studies emphasize that inhibition is an integral part of neuronal circuits and information processing. More importantly, it highlights the central role of inhibition in governing cortical activity, function and effective architecture. Previous excellent reviews have discussed the role of inhibition in controlling activity levels, sharpening tuning and modulating oscillations [18–20]. Here we will focus on recent new insights in the role of inhibition in learning and memory.

Context-dependent information processing

Cortical responses to external (e.g. sensory) stimuli are profoundly influenced by context and by the behavioral state of the animal. For instance, active and passive responses are different already in the primary sensory cortex [21,22] and responses are modulated by expectations [23,24]. Interestingly, context-dependent differences are often reflected in differences in inhibitory currents [25•,26]. For instance, active versus passive hearing modulates inhibitory rather than excitatory inputs in the auditory cortex [25•]. Inhibition may change the overall activity level of the network, which can fundamentally alter information processing and behavioral outcome [27]. Experimental studies showed that context-dependent modulation occurs via activation of specific subsets of GABAergic cells through long-range connections from other brain areas [22,24,28]. Long-range context signals often converge onto inhibitory neurons in layer I and vasoactive intestinal protein (VIP) cells [29–31] and act to 'switch' network inhibition. Multiple network configurations are implemented in parallel within the same cortical circuitry, controlled by external 'switches' to specific subset of inhibitory neurons (Figure 2) [32,33]. This demonstrates the power of inhibition to fine-tune the E/I balance in the network and to control the responses of the network via a highly specific gain control mechanism.

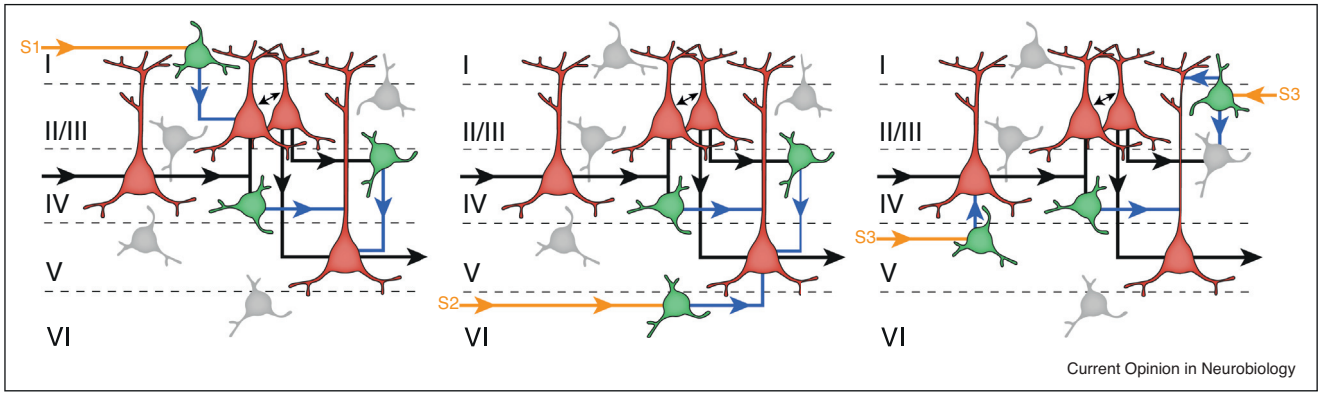
Recent experimental findings demonstrate that neuronal networks can switch between learning-competent and learning-resistant configurations. Activity-dependent reorganization of excitatory connection is gated by a transient decrease in inhibition [34,35]. In one study, rats were trained to run on a treadmill. Learning of this coordinated movement involves establishing reliable sequential activation of pyramidal cells in layer II/III of the motor cortex. This learning process was found to be under control of somatostatin (SST) and VIP interneurons. Learning only occurred when SST cells were inhibited, either directly using optogenetics or indirectly via activation of local VIP cells [36]. In another study, low-threshold spiking interneurons in the striatum were shown to play a similar role in mice that learned to press a lever to obtain a reward. Learning was facilitated by suppression of these interneurons, and hindered when they were activated [37]. A similar VIP-controlled mechanism involved in fear conditioning was found in the striatum [38]. In all cases, learning involved specific reconfigurations of the network by dedicated changes in the inhibitory circuitry.

Figure 1



Recurrent excitatory networks are stabilized by inhibition.
(a) When external input is weak, only a few excitatory neurons are activated and recurrent connections are mostly silent (dashed lines). Network responses are mainly driven by noise.
(b) With stronger external input, recurrent excitatory connections are recruited and the network response becomes supralinear and unstable.
(c) As excitation is quickly balanced by strong feedback inhibitory connections, the network stabilizes and network responses become linear. The E/I ratio in the network is decreased with stronger input.

Figure 2



Context-dependent inhibition in cortical circuits.
Cortical circuit with several inhibitory neurons controlled by 'switches'. Depending on context-signals from other brain areas (orange), or activity level, different sets of inhibitory neurons are involved, which leads to context-dependent information processing in the cortical circuit. Three hypothetical configurations controlled by external switches S1, S2 and S3 are illustrated. Excitatory connections are indicated by black lines, inhibitory connections are blue.

Memory

Memory is generally considered to be represented by long-lasting changes in synaptic connections. Learning is well associated with experience-dependent changes in spines, where excitatory synapses are located. New spines are rapidly formed while some pre-existing spines are removed, such that long-term changes in connectivity are implemented without changing total spine density [39,40]. The newly formed spines assure that the network will respond in a different way to the same external stimulus at subsequent occurrences — it has learned from the previous experience.

Multiple activity patterns ('memories') are stored in parallel in the same circuit. As explained above, activity patterns in neuronal circuits are dominated by the inhibitory, rather than the excitatory, synapses. Computational models have shown that balanced E/I networks allow storage of multiple memory activity patterns, which can be evoked by external inputs via controlled transient unbalancing [41,42]. In line with this, an increasing number of experimental studies are showing that inhibitory plasticity is important in memory processes, including fear memory [43], grid cell formation for spatial memory [44], and in the human brain [45].

A recent computational study showed that the storage capacity of memories (e.g. specific activity patterns) in a recurrent network is surprisingly larger when memory-related changes are implemented in inhibitory, rather than in excitatory, synapses [46••]. Changes in activity patterns in the network (e.g. memories) can be stored in relatively few changes of the inhibitory circuit, while ongoing excitatory changes serve to rebalance network activity. This also explains how memories are kept stable over time, despite ongoing and extensive changes in spine number and size [46••].

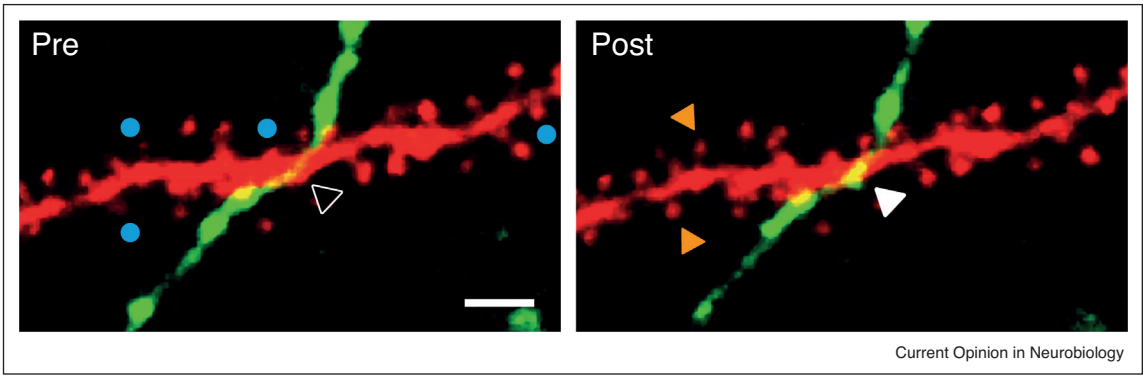
In another computational study, changes in inhibitory synapses are used to 'teach' a network about rewarded stimuli. Here, a reward signal (modeled via VIP interneuron activation) alters the network configuration via inhibitory synaptic changes. This initial inhibitory change is then corroborated by further excitatory plasticity such that the pyramidal cells in the network develop a preference for the rewarded stimulus [47•]. Interestingly, it is not necessary to maintain the reward signal. A transient 'training period' is enough to sculpt the inhibitory network to store the reward information. Subsequent network activity further entrains the network [47•].

Although the number of computational studies in which coordinated inhibitory and excitatory plasticity are implemented are still limited, these few examples demonstrate their great promise.

Codependent plasticity of excitatory and inhibitory synapses

To fully appreciate the impact of coordinated changes in excitatory and inhibitory synapses, it is necessary to understand the underlying mechanisms of E/I coordination. To facilitate unraveling of molecular mechanisms in experiments, synaptic plasticity is mostly studied in isolation. However, *in vivo* synaptic plasticity integrates neighboring excitatory and inhibitory inputs, and often induces concerted changes in multiple inputs. For instance, learning a motor task causes coordinated changes in excitatory and inhibitory synapses onto the same dendrites in the mouse motor cortex [48]. Multi-synaptic changes at excitatory and inhibitory synapses are needed to maintain overall network performance [35,49].

Figure 3



Excitatory and inhibitory plasticity co-occur within dendrites.
Two-photon microscopy images of a dendrite (red) of an excitatory CA1 pyramidal cell and an inhibitory axon (green). After local glutamate uncaging at excitatory synapses (blue circles), several spines undergo plasticity (orange arrowheads), and a new inhibitory presynaptic bouton (white arrowhead) occurs at the crossing. This indicates local crosstalk between inhibitory and excitatory synapses. Scale bar is 2 μm.

This coordination may be especially important in dendrites, where the first stage of neuronal computation takes place [50,51]. Within dendrites, excitatory and inhibitory synapses are close together (within a few micrometers; Figure 3) and dendritic plasticity signaling pathways at nearby synapses will inevitably interfere [52,53], rendering plasticity inherently heterosynaptic.

A number of recent studies are highlighting coordinated changes in excitatory and inhibitory synapses and emphasize the importance of considering the heterosynaptic nature of plasticity. In the developing auditory cortex, plasticity at one synaptic input induces subsequent changes to a broad range of excitatory and inhibitory inputs to the same neuron [54•]. These heterosynaptic changes were shown to maintain overall E/I ratio, presumably allowing dynamic experience-dependent updates of synapses, while preserving overall network function [54•,55]. In adult neurons, there is also clear evidence for heterosynaptic plasticity [48,56–58]. Two recent papers demonstrated that strong excitatory activity induces plasticity at nearby inhibitory synapses within dendrites [59•,60•]. In some cases, inhibitory plasticity precedes and gates excitatory plasticity [48,58], while in other cases inhibitory plasticity seems to follow from changes in excitatory activity patterns [46••,61,62]. Heterosynaptic plasticity, in which dendritic inhibition affects local excitatory plasticity, may be specifically important for clustering and matching of synaptic inputs within dendrites [55]. However, the computational consequences of excitatory activity inducing local inhibitory plasticity are much less understood [63].

Molecular mechanisms

Inhibitory synapses display various forms of synaptic plasticity, which are extensively described elsewhere [19,53,64,65]. The induction of GABAergic plasticity often requires a non-GABAergic triggering signal, such as glutamate or a retrograde messenger from nearby cells, but external signals from other brain areas may also be involved. This property underscores the heterosynaptic nature of inhibitory plasticity.

The same molecular pathways (via CaMKII and calcineurin) that govern glutamate receptor levels at excitatory synapses can also regulate insertion and endocytosis of postsynaptic $GABA_A$ receptors at inhibitory synapses [53,57,59•,66], making a direct molecular coupling between excitatory and inhibitory synapses. For instance, dendritic SST synapses are strengthened upon NMDA receptor activation, while somatic PV synapses are not affected [59•]. Specificity between different inhibitory synapses can be achieved via molecular specializations, such as the presence of specific $GABA_A$ receptor subunits and calcium channels [59•,67].

Presynaptic forms of plasticity occur more prominent at inhibitory synapses compared to excitatory synapses [53,68]. This may be explained by the more active role played by the presynaptic inhibitory axon during synapse formation and plasticity [69,70]. Axons contain receptors and signaling pathways that can regulate presynaptic function via local factors (e.g. BDNF, nitric oxide or endocannabinoids from the postsynaptic cell), but neuromodulatory signals from other brain areas may also be involved (e.g. dopamine or acetylcholine). For instance, perisomatic PV synapses are precisely matched with local network activity via a nitric oxide feedback mechanism [71,72]. This matching shapes network oscillations and decreases network correlations [73]. Dendrites which receive strong excitatory input produce endocannabinoids, which can trigger the growth of a new inhibitory

bouton on the same dendrite [60•]. These mechanisms maintain local E/I balance in an activity-dependent manner. Dopamine signaling can also regulate the number of inhibitory synapses [43,48]. Interestingly, many presynaptic mechanisms converge onto axonal cAMP and cGMP signaling pathways, which seem conserved between mice and humans [74]. Axonal receptors may provide local and long-range control of inhibitory synapses. Future research will need to further unravel axonal signaling pathways and plasticity mechanisms [68], especially in inhibitory axons.

Conclusion and outlook

Inhibitory neurons and their synapses have traditionally been understudied. The emerging concept that neuronal networks in the brain are dominated by inhibition puts inhibitory neurons in the spotlight. Recurrent excitatory cortical networks are chaotic and cannot function by themselves, so they need to be stabilized by inhibitory connections. This provides GABAergic inhibition with previously unrecognized power to determine when and where excitatory activity can occur, even though inhibitory synapses are noticeably in the minority. Rather than simply dividing the inhibitory labor in cortical circuits, different interneuron types may form multiple entry points for differential control over network function, activity patterns and effective connectivity. The broad spectrum of different interneurons and external controls may provide cortical circuits with their remarkable versatility.

In future studies it will be important to understand how simple ISN network models fit to the complex circuit architecture and many cell types that are found in the brain. In complex networks, it is not always possible to precisely define the role of specific interneurons [7••,75,76]. Cortical circuits may accommodate several modes of network function in parallel, and local imbalances may be well tolerated, or even exploited [77]. Future efforts, combining experimental and computational approaches, should be aimed at further understanding the molecular mechanisms and functional consequences of codependent excitatory and inhibitory plasticity.

The ISN concept will also help to understand the role of inhibition in brain development and disease. Developmental inhibitory plasticity is important for determining adult brain function and learning capacity [78]. Here, inhibitory plasticity may play an instructive role, setting the boundary conditions for further excitatory plasticity later in life. In line with this, a number of recent studies show that restoring inhibitory plasticity at the proper developmental time has a major and long-lasting impact on brain function and behavior in a wide variety of brain disorders [79–81]. Many brain diseases, including neurodevelopmental disorders, are associated with E/I imbalances, causing instabilities in neuronal function. In complex networks, an E/I imbalance does not simply translate into defective inhibitory synapses or an excess of dendritic spines, but requires more careful analysis [82,83]. It will be important to fully understand the different modes of cortical operation and their (external and internal) control mechanisms to examine how subtle defects can cause context-dependent problems.

Conflict of interest statement

Nothing declared.

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