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Neurophysiology and regulation of the balance between excitation and inhibition in neocortical circuits

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Abstract

Brain function relies on the ability of neural networks to maintain stable levels of activity, while experiences sculpt them. In neocortex, the balance between activity and stability relies on the co-regulation of excitatory and inhibitory inputs onto principal neurons. Shifts of excitation or inhibition result in altered excitability impaired processing of incoming information.

In many neurodevelopmental and neuropsychiatric disorders, the excitability of local circuits is altered, suggesting that their pathophysiology may involve shifts in synaptic excitation, inhibition or both. Most studies focused on identifying the cellular and molecular mechanisms controlling network excitability to assess whether may be altered in animal models of disease. The impact of changes in excitation/inhibition (E/I) balance on local circuit and network computations is not clear. Here we report findings on the integration of excitatory and inhibitory inputs in healthy cortical circuits and discuss how shifts in E/I balance may relate to pathological phenotypes.

Keywords

neocortex; excitation; inhibition; synapses; neurodevelopment; disease

Introduction

Neocortical neurons integrate thousands of inputs to produce appropriate outputs. These computations occur while local circuits and networks maintain their stability. The preservation of balanced excitatory and inhibitory synaptic drive onto cortical neurons is thought to be crucial for preserving circuit function (1). How stringent the regulation of the excitation/inhibition balance needs to be to allow flexibility while preserving stability is unknown.

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In this review we will not focus on how the mechanisms controlling the E/I balance, but will discuss published data in the context of possible effects of shifts in E/I balance on network function. We propose that to fully understand the impact of the E/I balance on neural circuits it is not sufficient to identify how it is established. An investigation of the interdependence of changes in excitatory and inhibitory circuits is necessary, as this may offer clues about how they may be coordinated and co-regulated throughout life.

Excitation and inhibition in neocortical circuits

The foundation for balanced excitation and inhibition is the establishment of local and long-range cortical circuits. In neocortex, most neurons are glutamatergic excitatory neurons that synapse locally or project to distant cortical, subcortical, or brainstem targets (2). GABAergic inhibitory neurons, up ~20% of neocortical neurons, project locally, and regulate ongoing activity. Glutamatergic neurons in neocortex are primarily pyramidal neurons, and can be identified by the expression of transcription factors (3) and the source of their inputs and the target region of their projections (4). GABAergic interneurons have been classified by firing type, expression of calcium-binding proteins or neuropeptides, and postsynaptic targets (5). Together, excitatory and inhibitory neurons form local and long-range circuits whose connectivity is specialized for signal processing. Common structural features of neocortex are narrow radial arrays of neurons known as minicolumns that are considered the elemental units of signal processing. Minicolumns are present in prefrontal and sensory cortices, and are important for cognitive functions like working memory and sensory processing (6–8). Vertically aligned pyramidal and excitatory stellate cells constitute the core of a minicolumn. Pyramidal neurons in a minicolumn are connected both within and between layers. Flanking inhibitory neurons provide lateral inhibition, modulating signal propagation across minicolumns (Fig. 1A). The activity of excitatory neurons within a minicolumn is balanced by multiple types of inhibition: parvalbumin-positive (PV^+) neurons are wide-arbor basket or chandelier cells that inhibit nearby minicolumns, while calbindin- or calretinin-positive (CB^+/CR^+) double bouquet cells provide inhibition through translaminar synapses (9, 10). The connection probability and strength of synaptic connections between neurons within and between minicolumns provide the substrate for establishing balanced activity. Thanks to this modular structure, excitatory and inhibitory neurons can be tuned to the same stimulus features and work concurrently to process incoming signals (6, 11). Integration of excitation and inhibition onto cortical neurons within minicolumns regulate network gain, tune responses, and stabilize cortical activity by preventing runaway cortical excitation (12–15). Failure to establish connectivity motifs can lead to imbalanced activity across neocortex and may provide a neurophysiological basis for the cognitive symptoms of several neurological disorders.

Impaired connectivity and its consequences for neocortical circuits

Pathological changes in neuron connectivity impact function within and across neocortical regions. Patients with autism spectrum disorder (ASD) show narrowed minicolumns and reduced proportions of large axons in the white matter underlying certain cortical areas (16–18). In the valproic acid (VPA) rodent model of autism, pyramidal neurons and inhibitory interneurons show increased connection probability (19, 20). These findings suggest that

ASD may be characterized by neurons that are locally hyperconnected, with reduced communication with distant cortical regions (Fig. 1B). This, and evidence for reduced PV^+ interneurons in prefrontal cortex, may provide an anatomical substrate for dysregulated E/I balance and underly the hypersensitivity and hyper-reactivity to stimuli observed in ASD (17). Minicolumn pathology was also observed in schizophrenia, especially in auditory cortex, where structural abnormalities are thought to correlate with the incidence of auditory hallucinations in patients (21, 22). Minicolumns typically thin with age due to plastic changes in the neurons' dendrites and axons. The brains of schizophrenic patients lack this age-dependent thinning (22), especially in regions that rely on plasticity to perform associative functions (22). Inhibitory interneurons are also impacted in schizophrenia (23, 24) and can show a reduced levels of the GABA-synthesizing enzyme GAD-67 (25–27) and of the GABA transported GAT1(28). In animal models of schizophrenia, reduction of inhibition has been associated with reduced cortical oscillations that are thought to mediate important cognitive processes (29–31). Diminished GABAergic inhibition together with minicolumn pathology may underlie a number of circuit alterations associated with ASD and schizophrenia. Specifically, these factors may provide an explanation for how local circuit changes may result in hyperexcitability and hyperplasticity.

Synaptic plasticity and the remodeling of neocortical circuits

Connectivity of long-range and local circuits is refined and remodeled by experience and learning. Hebbian plasticity, a form of long term plasticity based on correlative pre- and postsynaptic activity is one of the plasticity mechanisms involved in circuit reorganization. Plasticity can alter the strength of both excitatory and inhibitory synaptic inputs through multiple presynaptic and postsynaptic mechanisms. Different factors can influence the rules governing Hebbian plasticity in neocortex, including the developmental maturation of GABAergic circuits, patterning of synaptic activity, subtype of pre- or postsynaptic neurons, laminar circuits, cortical areas, and neuromodulatory influences (32–36).

Hebbian-like experience-dependent modifications of synaptic strength or local connectivity can affect the excitability of excitatory and inhibitory neurons (37, 38). Plasticity can also be induced at afferent inputs (39), altering how local excitatory and inhibitory circuits become engaged by an incoming stimulus (40). Feedforward projections such as thalamocortical afferents synapse on both excitatory and inhibitory neurons (41). The feedforward inhibitory circuit activated by afferent inputs in turn provides inhibition onto nearby excitatory neurons (42, 43). The delay between the arrival of a direct thalamocortical input onto an excitatory cell and the feedforward inhibitory signal determines a temporal window for the integration of thalamocortical and intracortical activity (44). Plasticity at cortical synapses can widen or shorten temporal windows for inputs' integration (14), possibly modulating further induction of plasticity (36, 45). Thus, neural plasticity not only influences the state of excitability of a circuit, but can prime neurons so that future patterns of incoming activity will favor one set of changes over another, a process known as metaplasticity (46).

Studies of excitatory synaptic plasticity have revealed some common mechanisms for the activity-dependent strengthening or weakening of connections between neocortical neurons. Postsynaptic NMDA receptor (NMDAR) - dependent plasticity requires presynaptic

glutamate release coupled with postsynaptic depolarization to relieve the magnesium block and allow calcium (Ca^{2+}) influx through NMDARs (47–49). The timing of presynaptic versus postsynaptic activity (50, 51), the amount of postsynaptic depolarization (36), and additional recruitment of postsynaptic voltage-gated Ca^{2+} channels (VDCCs) (35) can affect the magnitude of the Ca^{2+} influx (52), which determines the sign of plasticity (53, 54). Rapid and large increases in postsynaptic Ca^{2+} activate CAMKII, and trigger a cascade of events leading to an increased number of AMPA receptors (AMPARs) in the postsynaptic membrane, inducing long term potentiation of excitatory synaptic responses (LTPe). Slow and small increases of Ca^{2+} influx engage protein phosphatases and promote the removal membrane AMPARs resulting in long term depression (LTDe) (54, 55).

Another postsynaptic form of long-term synaptic plasticity at neocortical excitatory synapses depends on group I metabotropic glutamate receptors (mGluRs), and/or other G-protein coupled receptors. Here, receptor activation triggers G-protein mediated signaling cascades. Receptors coupled to Gs-proteins activate the adenyl cyclase pathway and promote LTPe, whereas Gq11-coupled receptors drive the phospholipase-C pathway and promote LTDe (56). Activity-dependent excitatory neocortical plasticity can also engage changes in presynaptic terminals. Presynaptic NMDARs mediate some forms of cortical LTDe, either alone or in conjunction with the activation of presynaptic cannabinoid receptors type 1 (CB1-R) (57).

A growing body of literature demonstrated that inhibitory synapses in neocortex undergo bidirectional plasticity too, however the mechanisms underlying these changes are less clear. Postsynaptic Ca^{2+} plays a role in some forms of inhibitory plasticity (58–60). At some synapses the relative contribution of different subtypes of VDCCs to Ca^{2+} influx favors the insertion or removal of $GABA_A$ receptors ($GABA_A$Rs), and subsequent LTP or LTD of inhibition (LTPi, LTDi) (61). Postsynaptic activation of $GABA_B$R also contribute to different forms of LTPi, one that engages Ca^{2+} release from intracellular stores (62) and a different type that is Ca^{2+}-independent but depends on Gi/o protein signaling (36). Inhibitory plasticity can also engage presynaptic mechanisms (63), although these often require coincident release of glutamate, and therefore represent heterosynaptic forms of plasticity (64). The activation of mGluRs and coincident activation of presynaptic CB1Rs by retrograde cannabinoid signaling decreases presynaptic protein kinase A (PKA) activity mediated by Gi/o proteins and results in LTDi (65, 66).

The induction of neocortical plasticity can vary greatly across areas and developmental windows. In periods of heightened plasticity for sensory neocortices, critical periods, similar patterns of activity can engage distinct mechanisms depending on the specific developmental window. For instance, in layer (L) 4 of V1 during the pre-critical period, LTDe of unitary connections can be induced by an mGluR mediated spike timing dependent paradigm, or via an NMDAR-mediated presynaptic bursting paradigm. However, during the critical period, LTDe is no longer inducible with spike-timing, while presynaptic bursting leads to NMDAR-dependent LTPe (35). Similar developmental changes in plasticity rules have also been documented for inhibitory synapses (67). This developmental regulation of plasticity correlates with the maturation of glutamatergic synapses (68–70) and GABAergic circuitry (71–73). Developmentally regulated changes in receptor expression or subunit composition

can contribute to switches in the sign of plasticity, and/or changes in the underlying mechanisms recruited by different activity patterns (35, 69, 74). It is therefore important to consider the specific period in development when comparing the capacity for plasticity of different circuits across cortex.

The capacity for plasticity of a neuron can also be affected by its previous activity that can either prime or occlude certain signaling cascades (46). This metaplasticity may not always result in altered neuronal output or significant changes in synaptic strength, but may affect the state of a neuron and its ability to respond to future inputs (75). While conceptually metaplasticity is intuitive, what accounts for metaplastic mechanisms in neurons or circuits is currently unclear. Given the diversity of induction parameters and mechanisms underlying activity-dependent cortical plasticity, future work is needed to elucidate how these factors may subserve plasticity in vivo, in healthy brains and disease states.

Altered plasticity and loss of healthy circuit function disease

During postnatal development and throughout life, Hebbian plasticity plays a fundamental role in how organisms respond to their environment. If unconstrained, Hebbian plasticity can lead to profound circuit instability (76). Based on principles taken from the Bienenstock, Cooper, Munro (BCM) theory (77, 78) (Fig. 2A), the “sliding threshold” hypothesis of plasticity was formulated to propose a framework for how the destabilizing effects of Hebbian plasticity may be prevented (79). The prediction of the “sliding threshold” hypothesis is that previous induction of plasticity shifts the threshold for induction of additional Hebbian changes (75). According to this theory, the magnitude of plasticity in the form of LTP or LTD is constrained between a maximum (ceiling effect) and a minimum (floor effect). If potentiation reached a maximum, future potentiation is prevented and incoming activity would result in a de-potentiation so that the induction threshold can be adjusted (79). Conversely, synapses that have been maximally depressed will not be depressed further, and potentiation will be favored. The framework proposed by the BCM/sliding threshold theory sets the basis for plasticity occlusion experiments according to the principle that if a manipulation or a genetic mutation has changed the strength of a synapse by Hebbian plasticity, the threshold for induction of plasticity has shifted. Thus, further induction of plasticity will either be impaired, or even trigger plasticity with the opposite sign (80). This set of mechanisms can be at play in healthy circuits to maintain circuit stability in the face of changes induced by learning and experience.

If the events regulating circuit development are altered due to mutations in risk genes, or stressors, the capacity for plasticity of a synapse may be impaired. For example, the FMR1KO mouse, a model of Fragile X syndrome, is characterized by hyperexcitability and impaired cortical LTPe (81–83), although LTDe not only is effectively induced but enhanced (84, 85). It is currently unknown whether the altered capacity for plasticity of the FMR1KO mouse is causally related to the change in circuit excitability. In view of the BCM/sliding threshold theory, it was proposed that in the FMR1KO mouse mechanisms for LTPe induction may be impaired or saturated (85), thus this form of plasticity cannot be induced; differently LTDe can be induced as the induction threshold for depression has been shifted.

A similar interpretation could be applied to data obtained from a mouse model of Rett Syndrome. Rett Syndrome is a neurodevelopmental disorder due to a mutation in the X-linked gene, methyl CpG binding protein-2 (MeCP2) (86–88) that is characterized by significant changes in circuit excitability. MeCP2 KO mice show increased GABAergic transmission and reduced glutamatergic transmission in L5 pyramidal neurons of the somatosensory cortex (89). These effects are consistent with an overall shift of the E/I balance toward inhibition. According to the BCM/sliding threshold theory, the MeCP2KO mouse should show impaired LTDe, since excitation is already reduced, and an increased capacity for LTPe. However, experimental data show that the capacity for LTPe at recurrent synapses remains unchanged, (90) suggesting that in the MeCP2KO model of Rett syndrome, the relationship between shifts in excitability and capacity for plasticity is more complex than previously appreciated.

Altered GABAergic inhibition is a common feature of many neuropsychiatric diseases. GABAergic synapses are plastic and can be modified by experience (91–95), however alterations in inhibitory plasticity have not yet been investigated as a possible mechanism for the pathophysiology of psychiatric disorders. Since excitatory and inhibitory forms of plasticity share some common signaling mechanisms (64, 65, 96–98), the possibility arises for crosstalk between signaling pathways that may affect how a neuron responds to incoming inputs. This is particularly relevant for cortical circuits that are recurrently connected, and excitatory and inhibitory synapses can occupy overlapping areas of a postsynaptic neuron (99).

During acute induction of inhibitory (LTPi) and excitatory (LTPe) forms of LTP, signaling mechanisms for excitatory and inhibitory synaptic plasticity can interact (Fig. 2B) (36). In view of results showing cooperative interactions between excitatory and inhibitory forms of plasticity, we propose a number of testable hypotheses regarding how altered inhibition may contribute to the circuit changes observed in psychiatric diseases. For instance, changes in inhibitory drive alter cortical excitability and this may be sufficient to affect further induction of plasticity. Alternatively, changes inhibition may affect the capacity for plasticity due to impaired crosstalk of signaling pathways for excitatory and inhibitory plasticity, changing how signals may be processed.

Circuit perturbations and compensatory mechanisms

Hebbian plasticity could potentially destabilize cortical circuits, as connections between neurons with correlated activity are strengthened and those between neurons with uncorrelated activity are weakened. However, in healthy brains changes in synaptic strength occur without resulting in pathological conditions. To maintain circuit stability, mechanisms are in place for neurons to sense their own excitability (100, 101) or the excitability of the circuit (102) and modulate their intrinsic properties and/or synaptic inputs to maintain functional levels of activity (71, 102–104). These mechanisms, known as homeostatic plasticity, are crucial for healthy brain function (105). Different forms of homeostatic plasticity have been identified, the best studied being synaptic scaling, a form of homeostatic plasticity in which a neuron modulates its input/output curve by globally adjusting the strength of its inputs via insertion or removal of synaptic receptors (101, 106). Thus, a

neuron can maintain relative differences in synaptic strength induced by Hebbian plasticity while preserving functional states of excitability (103). Postsynaptic neurons can also retrogradely control the strength of their inputs through signaling molecules like retinoic acid (RA) (107) or brain-derived neurotrophic factor (BDNF)(108), which modulate neurotransmitter release (109).

Since homeostatic plasticity occurs in multiple neuron populations, it can constrain individual neuron's activity while coordinating the excitability of excitatory and inhibitory neurons within a circuit (102, 110, 111). Perturbations of homeostatic plasticity could leave a circuit vulnerable to destabilizing swings in excitability without means of compensation (105, 109). Although homeostatic plasticity is an understudied area of neural regulation, experimental evidence strongly suggests that these mechanisms are crucial for offsetting shifts in synaptic transmission due to experience (92, 93, 112), and for maintaining healthy E/I balance (113, 114).

Disruption of the E/I balance in models of neurodevelopmental disorders

Even in properly connected circuits, neuronal and local circuit excitability can be altered due to: inappropriate differentiation of neuronal phenotypes (115), improper regulation of neurotransmitter release (116), impaired expression of excitatory (117) or inhibitory postsynaptic receptors (118) and/or their scaffolding proteins (119, 120). As our understanding of the mechanisms for homeostatic plasticity is still limited, most experimental work on disease models focused on identifying changes in synaptic transmission within circuits, but has not yet delved deeply into investigating possible defects in compensatory mechanisms.

Experimental work in animal models has been instrumental to identify some of the mechanisms contributing to the alteration of neocortical excitability. In rodent models of epilepsy altered circuit activity may result from changes in intrinsic properties that in turn affect neurotransmission, or may depend on changes in synaptic transmission only.

In animal models of Dravet's Syndrome, a severe form of myoclonic childhood epilepsy, a loss-of-function mutation in one allele of SCN1A encoding the voltage-gated, type 1, α-subunit NaV1.1 prevents the development of fast spiking behavior in PV^+ neurons of the neocortex (121), a feature that may have significant consequences for how inhibition regulates the circuit in this model. It is currently unknown whether the circuit instability in models of Dravet's syndrome depends on loss or incorrect engagement of compensatory mechanisms. Recently identified additional mutations in the gene for the α-1 subunit of the $GABA_A$ receptor in Dravet's syndrome adds to the complexity of the circuit defects in this disease (122).

An important aspect of many forms of epilepsy is the increase in circuit excitability. In many models decreased amplitude, frequency, or both, of spontaneous and miniature post-synaptic inhibitory currents (sIPSCs and mIPSCs, Fig. 3A) is reported, suggesting dis-inhibition as a mechanism for increased excitability (123, 124). Studies from animal models of intractable epilepsy suggest that the dis-inhibition may result from altered excitatory drive onto

inhibitory neurons (125, 126). Thus, one may speculate that altered excitability in epilepsy may result from alteration or loss of compensatory forms of plasticity, or resulting from perturbations of circuit excitability that exceed the circuits' compensation capabilities.

Circuit disinhibition by reduced excitation onto inhibitory neurons has been reported in a number of neurodevelopmental disorders. In animal models of schizophrenia, the decrease in inhibition is correlated with a reduction in the expression of the GluNR2A subunit of the NMDARs on inhibitory neurons (127–131). Ketamine administration in rodents, a paradigm that in healthy human subjects induces schizophrenic-like symptoms (132–135), decreases the strength of inhibitory inputs onto pyramidal neurons (136) by reducing both frequency and amplitude of mIPSCs (Fig. 3C) (137). Thus ketamine mimics the disinhibition observed in the schizophrenia models and has led investigators to associate dis-inhibition to some aspects of the disease.

The FMR1KO model of Fragile X syndrome, a disease characterized by delayed cognitive development and autistic traits, is also characterized by hyperactive neocortical circuits. The mechanisms underlying increased excitability in this model are only beginning to be unraveled. In the somatosensory cortex of FMR1KO mice, pyramidal neurons display firing rates 3 fold-higher than controls (138). This hyperexcitability may be due to an increase in pyramidal neurons density in the early postnatal neocortex (139) that produces hyperconnected excitatory circuits. In addition, FMR1KO mice show reduced density of PV^+ neurons in the somatosensory cortex (140) and diminished excitatory drive onto fast spiking inhibitory neurons (141). Both these factors likely disrupt the function of inhibitory circuits early in development and may shift in E/I balance of neocortical circuits. The state of hyperexcitability of pyramidal neurons in the FMR1KO mice can alter sensory perception, consistent with results from the auditory cortex where pyramidal neurons are hyper-responsive to sound (142).

Hyperexcitability of pyramidal neurons and impaired cortical inhibition are hallmarks of other models of ASD. As there is a significant degree of comorbidity between ASD and epilepsy (143), it is possible that the defects occurring in these diseases may lead to common functional alterations at the level of cortical circuits. Some of the shared features between epilepsy and ASD are: reduction in the density of interneurons expressing the GABA synthetizing enzyme GAD67 (144–148), reduction in the expression of several $GABA_AR$ subunits (149–152), and reduction in the number of PV^+ neurons (1, 146, 153).

The outcome of altered circuit excitability is quantified as changes in firing rates. However, the underlying mechanisms may be quite different. In fact, even different models of the same disease can produce opposite effects on circuit excitability depending on the specific manipulation of the same gene. Mutations in neuroligin-1 and 3 occur in a subset of ASD patients (1, 154). In animal models, mutations in these genes can produce very different effects. A point mutation of the neuroligin-3 gene is associated with increased inhibition in the somatosensory cortex (155). Double knock-out mice for neuroligin-1 and 3 show decreased spontaneous GABAergic activity in respiratory centers (156). These results suggest that mutations that affect the E/I balance may result in alteration that neurons and

circuits are not capable of compensating, or in activation of compensatory mechanisms that result in loss of circuit function (105).

Another example of complex resulting from mutations of a single gene comes from the MeCP2 mouse models of Rett syndrome. While defects in inhibitory circuits were consistently reported, experimental results differ significantly depending on genetic models. MeCP2KO mice show increased inhibitory and decreased excitatory transmission onto L5 pyramidal neurons of the somatosensory cortex (89) (Fig. 3D), and reduced connection probability between cortical pyramidal neurons (90), shifting the E/I balance toward inhibition and altering plasticity (89, 90). Selective mutations of MeCP2 in specific groups of neurons reported different outcomes. Cre-dependent deletion of MeCP2 from all GABAergic neurons decreases inhibitory quantal size in L2/3 pyramidal neurons of the somatosensory cortex and reduced levels of GABA, GAD65 and 67 (157), without changes in glutamatergic transmission. A similar selective reduction in inhibition has been reported if MeCP2 was deleted selectively in cortical pyramidal neurons (158). Selective deletion of MeCP2 in a subset of L2/3 pyramidal neurons reduced GABAergic transmission only onto MeCP2-deficient neurons (159), suggesting that the defects in synaptic transmission is specific for neurons carrying the mutation. If MeCP2 expression is suppressed selectively in L2/3 neurons using short hairpin (sh) RNA, excitatory synaptic transmission is reduced while inhibition remains unaffected (160), suggesting that the location of genetic defects matters for the dysregulation of local excitability.

A common thread of neurodevelopmental disorders seems to the occurrence of defects in GABAergic synaptic transmission that go uncompensated and result altered circuit excitability. Inappropriate differentiation of inhibitory circuits shifts the E/I balance and may result in loss of tuning, especially if changes in inhibition occur during critical periods early in development (1, 161). Given the different effects of mutations in selected population of neurons it is also possible that coordinated interactions between signaling pathways for excitatory and inhibitory synaptic transmission become impaired resulting in alterations of circuit excitability and capacity for plasticity. This last hypothesis arises from recent studies in healthy brains (36), and has not been tested yet in animal models of psychiatric diseases.

Conclusions

Many neurodevelopmental and neuropsychiatric disorders are characterized by changes in synaptic transmission (Table 1). Most studies focused on investigating mechanisms regulating excitation or inhibition independently. However, there is now sufficient evidence that signaling pathways for GABAergic and glutamatergic transmission may act in a coordinated fashion (36, 162). In view of this evidence, investigating whether factors contributing to the co-regulation of excitatory and inhibitory synaptic transmission are affected in models of neuropsychiatric disorders may lead to the identification of new targets for therapeutic interventions.

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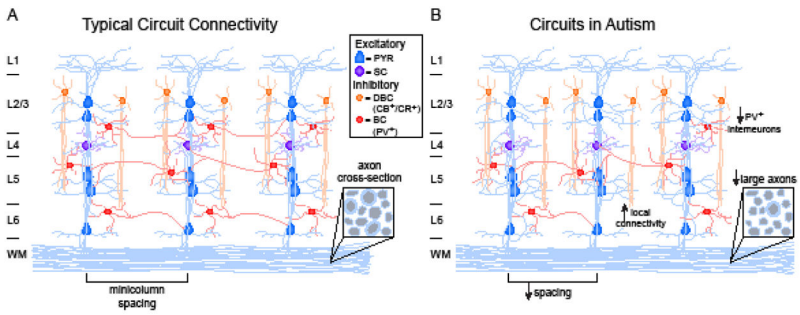

Figure 1. Cortical circuit connectivity and E/I balance

A. Minicolumn structure and long-range connectivity in healthy brains. **B.** Reduced minicolumn spacing, decreased PV^+ interneuron immunoreactivity, local hyperconnectivity, and decreased large axons in white matter characterize circuit structure in ASD.

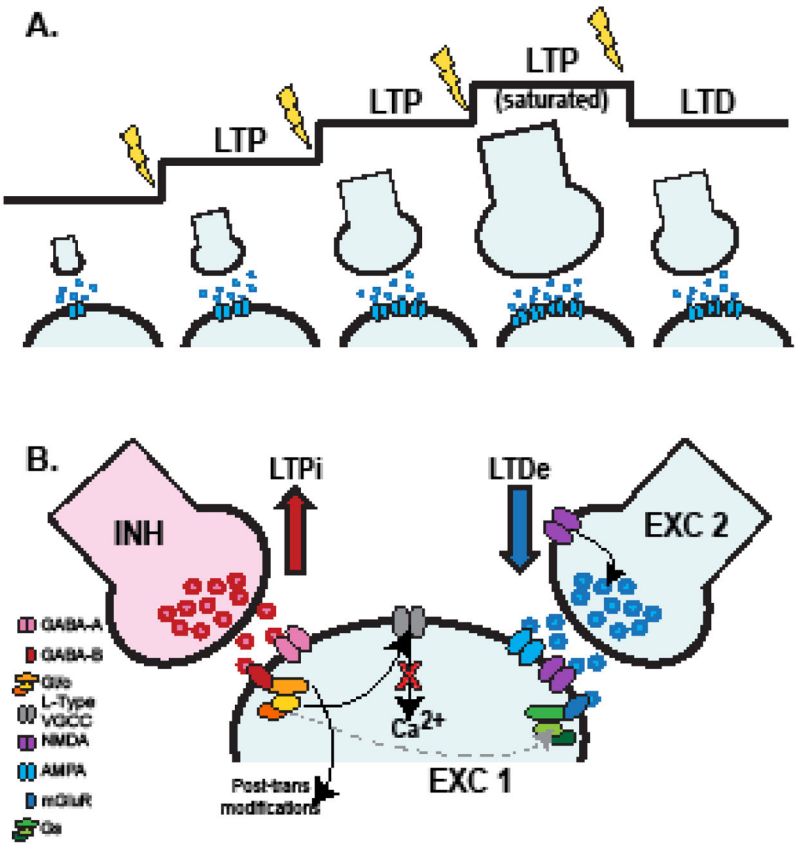

Figure 2. Cortical plasticity models and mechanisms

A. Diagram representation of the sliding threshold for Hebbian plasticity. **B.** Summary diagram of crosstalk between excitatory and inhibitory mechanisms for plasticity (adapted from Wang and Maffei, 2014).

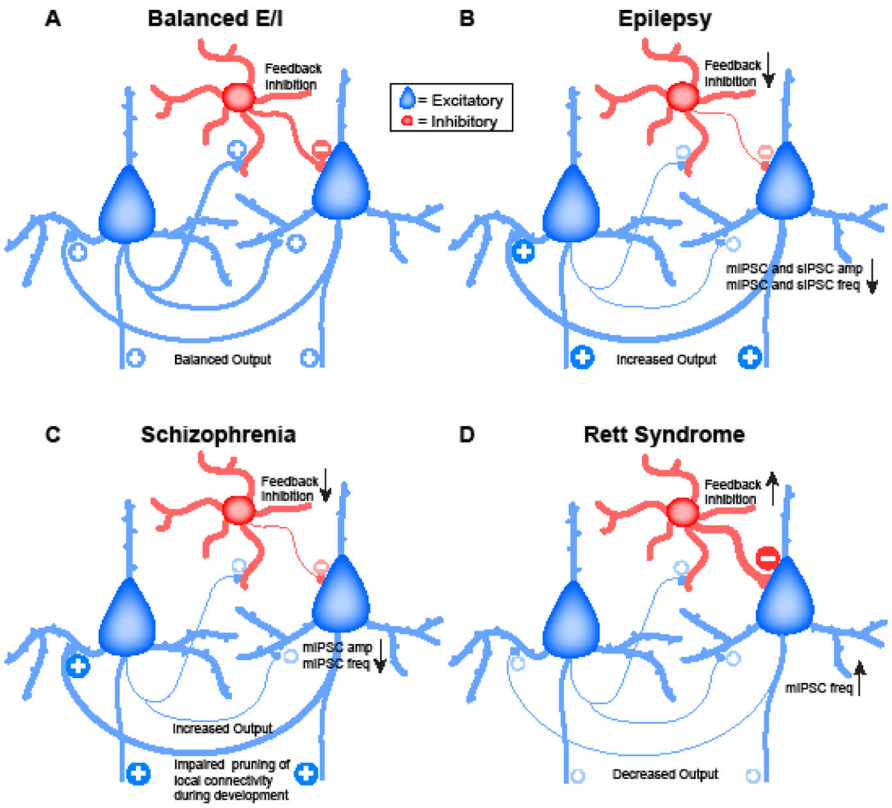

Figure 3. Examples of changes in circuit excitability due to shifts in E/I balance

A. Representative diagram of E/I balance in a healthy circuit. **B.** Representation of E/I balance changes in animal models of epilepsy. **C.** Summary of local circuit changes reported for animal models of schizophrenia. **D.** Diagram of synaptic changes reported in a model of Rett syndrome. Blue neuron: excitatory pyramidal neurons. Red neuron: inhibitory interneuron. Inhibitory neurons types are not specified here, as studies from disease models show primarily spontaneous inhibitory currents, of unidentified presynaptic origin. Line thickness and plus/minus signs indicate the sign of changes in synaptic strength and activity, respectively.

Table 1

Examples of changes in excitation and/or inhibition in mouse models of diseases characterized by altered E/I balance.

Disease	Cell type	Parameters	Animal model	Reference #
Epilepsy	Pyr	↓ mIPSCs and sIPSCs	Pilocarpine treatment and cortical dysplasia	73
		↑ sEPSCs	Cortical dysplasia	75
	FS	↓ sEPSCs and mEPSCs. ↓ sIPSCs and mIPSCs	Cortical dysplasia	74, 75
Schizophrenia	Pyr	↓ mIPSCs and sIPSCs. No change in mEPSCs but increase intrinsic excitability	Ketamine treatment	86
Fragile X syndrome	Pyr	↓ firing rate	FM1 knock-out	87
	FS	↓ uEPSCs	FM1 knock-out	90
	Pyr	Unaltered uIPSCs		
Rett Syndrome	Pyr	↓ spontaneous firing rate ↓ sEPSCs, ↑ sIPSCs ↓ mEPSCs, no change mIPSCs		60
	Pyr	↓ mIPSCs, no change in mEPSCs	Viaat-Mecp2$^{-/y}$ MeCP2 Knock-out	105
	Pyr	↓ mIPSCs, no change in mEPSCs	MeCP2$^{-/y}$; Emx1-Cre	106
	Pyr	↓ EPSCs	Sh-RNA to knock-down MeCP2	107