HOMEOSTATIC PLASTICITY IN THE DEVELOPING NERVOUS SYSTEM

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Activity has an important role in refining synaptic connectivity during development, in part through 'Hebbian' mechanisms such as long-term potentiation and long-term depression. However, Hebbian plasticity is probably insufficient to explain activity-dependent development because it tends to destabilize the activity of neural circuits. How can complex circuits maintain stable activity states in the face of such destabilizing forces? An idea that is emerging from recent work is that average neuronal activity levels are maintained by a set of homeostatic plasticity mechanisms that dynamically adjust synaptic strengths in the correct direction to promote stability. Here we discuss evidence from a number of systems that homeostatic synaptic plasticity is crucial for processes ranging from memory storage to activity-dependent development.

Homeostasis has been a central concept in physiology since the term was coined by Cannon more than seventy years ago to describe the complex set of mechanisms that maintain what the French physician Bernard called 'la fixité du milieu intérieur' or the constancy of the internal environment[1]. Cannon realized that the normal activity of neurons and other excitable cells depends crucially on constancy of pH, temperature and electrolyte concentrations. Indeed, Cannon and Bernard speculated that a primary function of these homeostatic mechanisms was to maintain an environment in which the brain could function normally, independently of fluctuations in the external environment.

More recently, it has become apparent that neural activity is itself subject to homeostatic regulation to prevent neural circuits from becoming hyper- or hypoactive. Without stabilizing mechanisms operating at the level of neural circuits, activity-dependent forms of plasticity such as long-term potentiation (LTP) and long-term depression (LTD) could drive neural activity towards runaway excitation or quiescence[2]. Similarly, without these mechanisms operating at the level of single cells, the complex interplay of inward and outward conductances that subserve each neuron's unique pattern of electrical activity would be difficult to maintain in the face of morphological change and protein turnover[3].

One way to illustrate the importance of regulating overall activity, or what is often loosely called the 'excitability' of a neural circuit, is to consider the problem of propagating patterned activity from the sensory periphery to higher-order neurons deep within the brain. This process can be schematized as a series of networks or layers, linked by feedforward connections (FIG. 1). Activity in each layer (for example, photoreceptors, bipolar cells, ganglion cells, lateral geniculate neurons, primary visual cortical neurons, and so on) is driven by activity in the preceding layer. This topology is grossly oversimplified, but even in such simple networks it is apparent that the gain of transmission from one layer to the next must be close to unity for propagation to occur. If the gain is lower than one, activity will die out and will fail to reach higher centres, whereas if it is greater than one, specificity will be lost because more neurons will be recruited at successive stages, and at the highest levels all neurons will fire regardless of the pattern of firing at the input layer.

The problem of propagation of activity in a feedforward circuit is formally analogous to the problem of stable ongoing activity in a recurrent circuit. In the recurrent case, activity is fed back to the circuit from which it originates, rather than being fed forward to subsequent layers, and the 'propagation' occurs in time, but not in space. In models of recurrent excitatory

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doi:10.1038/nrn1327

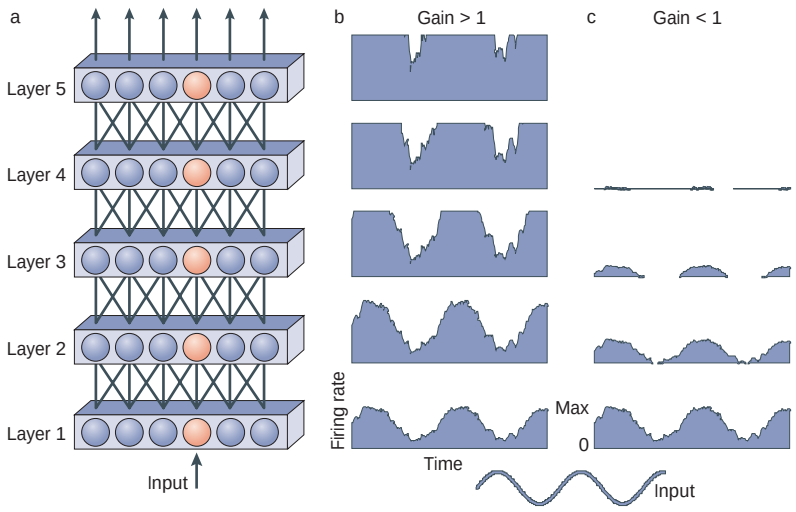

Figure 1 | **The problem of stability in feedforward networks. a** | Schematic feedforward network consisting of five layers of neurons. **b**,**c** | Expected firing rates of the red neuron in each layer in response to a sinusoidal input. If each action potential in a preceding layer causes more than one action potential in neurons at the next layer (**b**), the firing rates saturate and eventually all information about the stimulus is lost. If each action potential causes less than one action potential in neurons at the next layer (**c**), the signals eventually fail to propagate.

circuits in the visual[4] or prefrontal cortices[5], or of recurrent inhibitory circuits in the crustacean stomatogastric ganglion[6], synaptic and intrinsic properties must be carefully adjusted (or 'tuned') to achieve stable activity patterns. Without this tuning, activity explodes or crashes.

This stability problem is compounded by the fact that synaptic connections are highly plastic, and the number and strength of synapses can change markedly during development or in response to experience. As a consequence, setting connections up at the correct initial strength will not prevent instability from developing over time. Hebbian (or associative) forms of plasticity have a particularly strong destabilizing effect on network activity, because they are essentially positive feedback rules that tend to drive synaptic strengths towards their maximum or minimum values. Imagine a situation in which some of the inputs onto a postsynaptic neuron become potentiated through an LTP-like process. This will increase the excitatory drive to the neuron and the probability that any given input will make the neuron fire. This will in turn make it easier for those inputs to undergo LTP, and the cycle will begin again. From virtually the first time computational modellers explored the properties of Hebbian learning rules, it became apparent that selective changes in synaptic weights are difficult to achieve without building in some homeostatic or 'normalizing' mechanism to regulate total synaptic strength or excitability[7–10].

A number of mechanisms have been proposed that could provide stability to neurons and networks in the face of ongoing plasticity. These include sliding plasticity thresholds that adjust the ease with which LTP and LTD can be induced in an activity-dependent manner[8,11], rapid heterosynaptic plasticity that balances homosynaptic changes[12,13], and spike-timing-dependent plasticity rules coupled to hard synaptic weight boundaries[14]. In this review, we will consider evidence for a simple and robust way to 'tune' synaptic connections to the right values initially, and to keep them within the correct dynamic range in the face of ongoing plasticity — the ability of neurons to adjust synaptic or intrinsic excitability in a homeostatic manner to keep firing rates relatively constant[2,15]. If each neuron can sense how active it is and adjust its properties to keep this activity close to a set-point value (FIG. 2), then network activity will automatically settle towards some desired average level, and will remain stable in the face of correlation-based learning rules or changing connectivity. Experimental evidence is rapidly accumulating that such homeostatic mechanisms exist and are important in circuit function. Homeostatic changes in intrinsic excitability have recently been reviewed in this journal[16]. Here we will focus on homeostatic forms of synaptic plasticity in central neurons and their potential roles in activity-dependent development.

The neuromuscular junction

One of the first examples in the literature of homeostatic plasticity was the discovery of 'denervation supersensitivity'. Some of the changes induced by denervation of skeletal muscle can be viewed as a homeostatic response to loss of synaptic drive — in particular, the increase in excitability and spontaneous muscle contractions that is induced when innervation to skeletal muscles is lost. This increased excitability is produced by a number of changes to the muscle fibre, including increased input resistance and a huge increase in the number of extrajunctional acetylcholine receptors[17–20].

More recently, sophisticated genetic manipulations of synaptic properties have revealed a complex set of compensatory mechanisms that act to keep neuromuscular transmission relatively constant[21]. An elegant set of studies has shown that when one synaptic property of the *Drosophila* neuromuscular junction is altered genetically, other aspects of synaptic transmission are regulated homeostatically to compensate[22–26]. For example, decreasing the number of synapses generates a compensatory increase in QUANTAL AMPLITUDE, and reducing quantal amplitude postsynaptically leads to increased presynaptic transmitter release. Hyperpolarization of muscle fibres by selective expression of an inwardly rectifying (K_{ir}) potassium channel also induces a compensatory increase in presynaptic release, indicating that postsynaptic depolarization might be an important signal that triggers homeostatic plasticity[26]. A similar phenomenon has been shown at the mouse neuromuscular junction, where a reduction in postsynaptic clustering of acetylcholine receptors (resulting from a knockdown of neuregulin) generates a compensatory presynaptic increase in transmitter release[27]. These studies indicate that homeostatic mechanisms adjust neuromuscular transmission during development to compensate for changes in muscle fibre growth, or for altered synaptic drive as SYNAPTIC COMPETITION reduces the number of inputs.

QUANTAL AMPLITUDE
The amplitude of the postsynaptic response to a single vesicle of neurotransmitter.

SYNAPTIC COMPETITION
When increasing the strength of a subset of inputs generates a decrease in strength of other inputs.

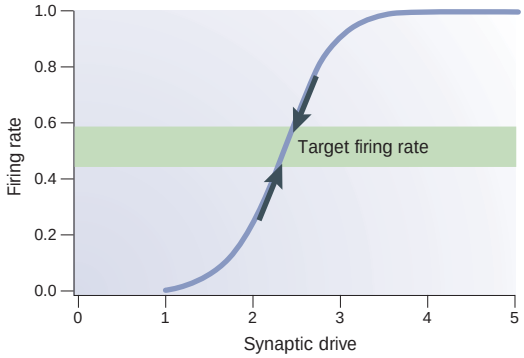

Figure 2 | **Stabilization of firing rates though global, homeostatic regulation of synaptic strengths.** Illustration of the relationship between synaptic drive and firing rate for an individual neuron. As synaptic drive increases (through addition or increased strength of excitatory synapses, for example) and firing rate rises above the target level, homeostatic mechanisms (arrows) are engaged that reduce the strength of all inputs, thereby moving the neuron down the curve and back into the target zone. Conversely, if synaptic drive falls too low and firing rate falls below the target rate, the homeostatic regulatory process will increase the strength of all inputs and bring the neuron back within the target firing zone.

Homeostasis in central neurons

The stability problem faced by the neuromuscular junction is relatively simple: as the muscle fibre grows, the motor neuron must remain consistently able to bring the fibre over threshold for the generation of action potentials. For central neurons, the problem is much more complex. These neurons integrate inputs from hundreds or even thousands of synaptic partners, and synapses arising from different sources can target different regions of the neuron and involve clusters of distinct receptor subtypes. Firing of each of these inputs fluctuates as a function of changes in sensory drive or internal state. Over short timescales, the activity of a central neuron must fluctuate considerably, as these fluctuations carry information. Over longer timescales, however, the same constraints apply as at the neuromuscular junction: forces that generate net increases or decreases in excitation over time will disrupt the function of central circuits if they are unopposed by homeostatic forms of synaptic plasticity.

There is now compelling evidence from a number of systems for homeostatic control of firing rates in central neurons. In invertebrate networks and the vertebrate spinal cord, blocking some inputs initially abolishes spontaneous activity, but over time activity recovers[28–30]. Initial observations using cortical cultures indicated that cortical pyramidal neurons maintain a set-point firing rate in the face of changing synaptic input. Cortical and other central neurons in culture form excitatory and inhibitory networks that develop spontaneous activity, and early studies found that blocking this activity for prolonged periods resulted in hyperactivity in these networks when activity was allowed to resume[31–34] (FIG. 3). The reciprocal manipulation — elevating network activity by reducing a fraction of inhibition — initially raises firing rates, but over many hours firing rates fall again until they approach control levels[35] (FIG. 3). A similar regulation of firing rates was observed when a K_{ir} potassium channel was expressed in individual cultured hippocampal neurons; this channel generates a hyperpolarizing current that initially lowers firing rates, but over time firing rates recover despite the continued expression of the channel[36]. This shows that homeostatic regulation of firing rates can occur at the level of individual neurons in response to postsynaptic changes in activity. These results indicate that when cortical networks are deprived of activity, some property (or properties) of the networks is altered to promote excitability.

One powerful mechanism for adjusting firing rates is the global regulation of excitatory synaptic strengths. In cortical, hippocampal and spinal cultures, principal neurons can adjust the strength of all of their excitatory synapses in the correct direction to compensate for changes in activity[35,37–39]. Decreased activity (due to blockade of synaptic transmission or spiking) causes an increase in the strength of all excitatory synapses onto excitatory neurons, whereas increased activity (generally induced by partially blocking inhibitory synapses) reduces the strength of all excitatory synapses. These changes occur relatively slowly and cumulatively, requiring many hours of altered activity to produce measurable changes in synaptic strength[35], which indicates that activity alters the kinetics of a process that regulates synaptic strength. This slowness is probably important: if this homeostatic plasticity occurred rapidly, it would dampen the moment-to-moment fluctuations in activity that are used by the nervous system to transmit information. On the other hand, homeostatic plasticity must be fast enough to keep up with the changes in drive produced by other plasticity mechanisms. The rate at which destabilizing forms of plasticity accumulate *in vivo* is unknown for any central neuron.

Synaptic scaling of quantal currents

To determine whether there are plasticity mechanisms that adjust all of a neuron's synaptic weights up or down in response to altered activity, it is necessary to measure the strength of a large number of a neuron's synapses. This can be done by measuring MINIATURE EXCITATORY POSTSYNAPTIC CURRENTS (mEPSCs) arising from random spontaneous release of presynaptic vesicles at many different synaptic sites. Measurement of mEPSCs has shown that their average amplitude is increased or decreased in response to altered activity[35,37,39] (FIG. 4).

Interestingly, the entire distribution of mEPSC amplitudes is scaled up or down in a proportional manner by chronic changes in activity — hence this form of plasticity has been termed 'SYNAPTIC SCALING' (FIG. 4). Computational studies have shown that both proportional (or 'multiplicative') adjustments, where each synaptic strength is multiplied or divided by the same factor, and 'additive' adjustments, which add or subtract the same amount from each synaptic weight, can stabilize HEBBIAN PLASTICITY[9]. So, why is multiplicative scaling important? One attractive computational feature of multiplicative scaling is that the relative differences between synapses (such as those produced by LTP or

MINIATURE EXCITATORY POSTSYNAPTIC CURRENT
The postsynaptic current evoked by release of a single vesicle of neurotransmitter – the quantal amplitude.

SYNAPTIC SCALING
Scaling up or down of the quantal amplitude of all synapses onto a postsynaptic neuron in response to long-lasting changes in neuronal activity.

HEBBIAN PLASTICITY
Changes in the connection strength between two neurons as a result of correlated firing.

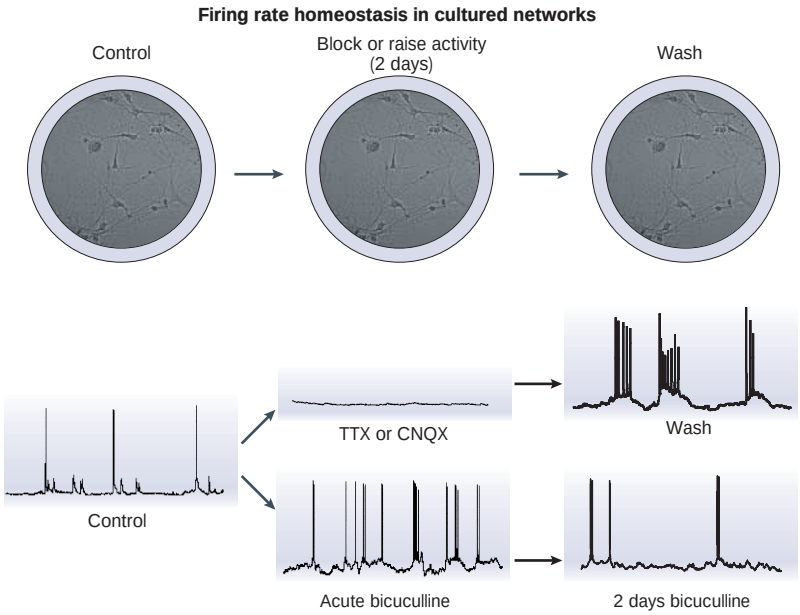

Figure 3 | **Evidence for firing rate homeostasis in cultured networks.** Cultured cortical networks are composed of interconnected excitatory pyramidal and inhibitory interneurons, and develop spontaneous activity after a few days *in vitro* (control). This activity can be pharmacologically manipulated for long periods. Blockade for two days of spiking activity with tetrodotoxin (TTX), or of excitatory glutamagergic synapses with CNQX, generates a rebound phenomenon whereby the excitability of the network is increased when the drugs are removed (wash). A more direct test of the idea of firing rate homeostasis is to raise activity acutely with bicuculline (acute bicuculline), and then to follow activity over time. After two days in bicuculline, activity has returned almost to control levels (2 days bicuculline). These experiments, and others like them, indicate that homeostatic mechanisms adjust the cellular and synaptic properties of cortical networks to compensate for changes in synaptic drive.

LTD) are preserved, because each synapse is strengthened or weakened in proportion to its initial strength. This allows total excitatory synaptic strength to be adjusted up or down to compensate for altered activity while keeping the relative efficacy of different synapses intact. By contrast, additive and subtractive adjustments in synaptic weights will alter relative efficacy by disproportionately affecting small synapses.

Simple Hebbian learning rules do not automatically generate competition between inputs[2], something that is a hallmark of many forms of developmental plasticity[40,41]. An interesting feature of many types of homeostatic plasticity is that by coupling changes in strength of a subset of inputs to compensatory changes in overall strength, they automatically introduce competition between synapses[2,14,42]. However, the strength of this competition can vary depending on the form of homeostatic plasticity. For example, additive homeostatic rules will punish weak synapses more than multiplicative rules, because the efficacy of small synapses can be reduced to zero after potentiation of other synapses.

Regulation of synaptic receptor number

In principle, total synaptic strength could be regulated through changes in postsynaptic receptor clustering, presynaptic transmitter release or reuptake, or the number of functional synapses. There is evidence that each of these mechanisms is engaged by some neurons at some developmental times, indicating that a palette of homeostatic mechanisms can probably be called into play by particular manipulations. Here, and in the next section, we summarize evidence for (or against) each of these mechanisms for cortical and hippocampal pyramidal neurons.

Early studies of denervation supersensitivity at the neuromuscular junction and in the central nervous system indicated that loss of synaptic drive has a profound effect on the localization and accumulation of receptors[17–20]. Similarly, the first reports of homeostatic regulation of excitatory synapses in cortical, hippocampal and spinal cultures indicated that these changes were mediated through postsynaptic changes in accumulation of AMPARS (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors)[35,38,39]. One piece of evidence for postsynaptic changes is the change in mEPSC amplitude. An mEPSC is the postsynaptic response to the release of an individual vesicle, so a change in mEPSC amplitude is generally interpreted as a change in receptor number or conductance. However, it is possible that changes in the amount of transmitter that is packaged into individual vesicles contribute to the change in mEPSC amplitude, as, at central synapses, postsynaptic receptors are not saturated by the glutamate released by single vesicles[37,43–45]. Although there is no direct evidence against changes in glutamate concentration in vesicles, there is direct evidence for changes in postsynaptic sensitivity. First, application of glutamate to the postsynaptic neuron elicits larger responses in cortical neurons that have been grown without synaptic activity than in control neurons[35,39]. Second, in hippocampal and spinal neurons, antibodies directed against AMPARs have been used to visualize decreases or increases in synaptic receptor accumulation at synapses after chronic raising or lowering of activity, respectively[38,39].

Synaptic receptors turn over in the membrane through endo- and exocytosis of receptor-containing vesicles. Once in the membrane, receptors are tethered to synaptic sites through association with multi-protein scaffolding complexes that ultimately link receptors to the cytoskeleton[46]. To generate a steady-state increase in synaptic receptor accumulation, not only must more receptors end up in the synaptic membrane, but enough tethering sites must be available for these additional receptors. The changes in receptor accumulation produced by synaptic scaling are accompanied by changes in the turnover and synaptic localization of many postsynaptic proteins that are involved in clustering receptors at synapses, indicating that altered activity produces a coordinated set of changes in receptors and their scaffolding proteins that together result in an increase in the number of AMPARs at synapses[47] (FIG. 5).

Rapid insertion of AMPARs contributes to the increase in synaptic transmission induced by some LTP protocols[48]. The prevailing model is that LTP inserts a bolus of AMPARs containing GluR1/2 subunits into the synaptic membrane through a regulated process. These receptors are then replaced with receptors composed of GluR2/3 subunits through constitutive receptor turnover[48,49]. It is not clear whether this model can

AMPARS
A subtype of ligand-gated glutamate receptor; these receptors generate the majority of excitatory current at central synapses.

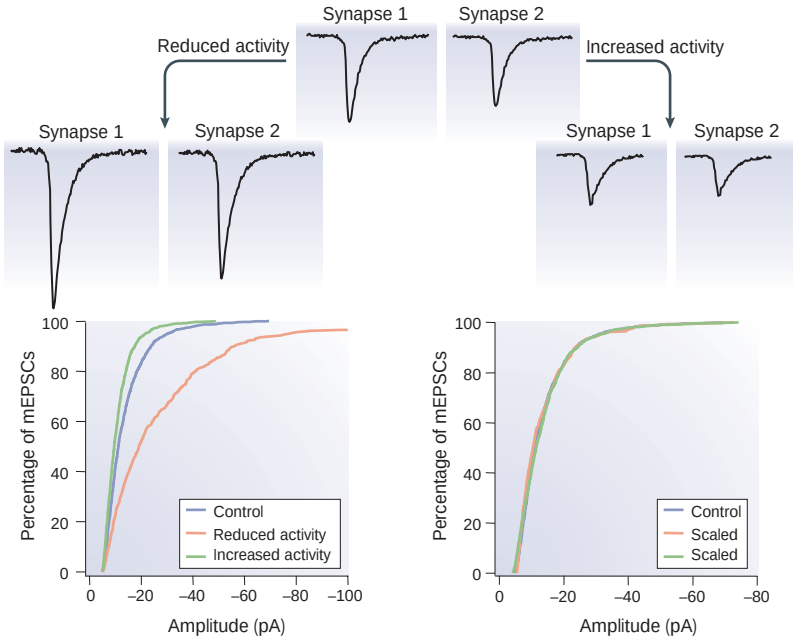

Figure 4 | **Synaptic scaling induces a multiplicative change in the distribution of synaptic weights.** Increased activity reduces the amplitudes of miniature excitatory postsynaptic currents (mEPSCs) onto cortical pyramidal neurons, whereas decreased activity has the opposite effect, indicating that quantal amplitude is regulated in a homeostatic manner by prolonged changes in activity. Plotting mEPSC amplitudes as a cumulative histrogram (lower panels) shows that the entire distribution of amplitudes is increased (reduced activity) or decreased (increased activity). If these distributions are scaled up or down by multiplying each value in the experimental distribution by the same factor, they overlay the control distribution almost perfectly, indicating that all excitatory synapses onto pyramidal neurons are scaled up or down multiplicatively by prolonged changes in activity. Lower panels modified, with permission, from REF. 77 © (1999) Elsevier Science.

NMDARS
A subtype of ligand- and voltage-gated glutamate receptors that are calcium permeable.

COEFFICIENT OF VARIATION
(CV). A measure of variability — the mean response divided by the standard deviation of the response. The CV of evoked synaptic transmission (determined by repeatedly evoking release and calculating the mean and the standard deviation of the postsynaptic response) depends strongly on neurotransmitter release probability.

PROBABILITY OF TRANSMITTER RELEASE
Release of vesicles at presynaptic release sites is a stochastic process. Generally, when a spike invades the presynaptic terminal the probability that a vesicle will be released is significantly less than one. Increasing this probability would result in more vesicles released/spike (on average) and would therefore increase synaptic strength.

explain the slow accumulation (or loss) of synaptic AMPARs that characterizes synaptic scaling. On the face of it, synaptic scaling and LTP seem to be fundamentally different processes, as they have opposite relationships between activity and receptor accumulation. Reduced activity increases receptor accumulation over long timescales (synaptic scaling), whereas increased activity leads to rapid receptor insertion over short timescales (LTP). However, it is possible that the intracellular signal transduction cascades activated by these two activity regimes eventually converge on the same molecular machinery for AMPAR insertion and removal.

An important feature of receptor accumulation during synaptic scaling is that all synapses gain in strength proportionally — so that, for example, all synapses in a particular neuron double in amplitude, regardless of initial strength. If synaptic scaling occurs by many iterations of the 'regulated' insertion that contributes to LTP, one might expect that each synapse would gain the same number of receptors, so that synaptic strength would change additively (through addition of a similar number of receptors at each synapse). On the other hand, a process that speeds up (or slows down) the constitutive rate of receptor insertion will scale up (or down) the steady-state number of receptors across all synapses proportionally, as is observed after prolonged inactivity[39,47,50,51] (FIG. 5). So, it is possible that 'constitutive' receptor turnover is actually regulated over long timescales by ongoing activity. This idea is supported by the observation that the rate of receptor turnover is reduced by activity deprivation[39].

Scaling of AMPA and NMDA currents

Most cortical synapses cluster both AMPARs and NMDARS (*N*-methyl-D-aspartatate receptors)[52], and the ratio of current through these two receptor types remains nearly constant after early postnatal development[53]. During synaptic scaling of excitatory neocortical synapses, AMPAR- and NMDAR-mediated currents are scaled up and down proportionally[37]. Furthermore, careful measurement of the NMDA and AMPA components of individual quantal currents has revealed a strong correlation across synapses, indicating that the ratio of current through the two receptor types is remarkably constant from synapse to synapse[37,54,55]. In primary sensory cortex, both AMPARs and NMDARs are a significant source of excitatory current, and both receptor types carry sensory information[56]. Functionally, maintaining a relatively constant ratio of AMPA to NMDA current might ensure that plasticity mechanisms such as synaptic scaling can normalize activity without fundamentally altering the information content of synaptic transmission. There is evidence that activity regulates NMDAR accumulation through alternative splicing of the NR1 subunit of the receptor, which regulates export from the endoplasmic reticulum and accumulation at the surface[57]. An unresolved question is how such a constant ratio of AMPA to NMDA current can be maintained across synapses as receptor accumulation is altered by activity, and why this ratio does not degrade in the face of independent regulation of AMPARs and NMDARs during Hebbian plasticity[48].

Presynaptic expression of homeostasis

Presynaptic changes in transmission clearly contribute to some forms of homeostatic plasticity at the neuromuscular junction[21], but for central neurons the issue is less clear. In cortical and spinal cultures, the effects of altered activity can be largely accounted for by postsynaptic changes in receptor accumulation. However, there is evidence in some hippocampal culture systems for both postsynaptic and presynaptic effects after pharmacological blockade of excitatory synaptic transmission. Lowering activity before the formation of synapses has complex effects on synaptic maturation and competition that depend on whether activity is blocked everywhere or only in individual neurons[36,58]. Here we focus on the effects of altered activity after synaptic connections have been established and network activity has developed.

Blocking activity or AMPAR signalling in postnatal cortical and spinal cultures for one or two days after synapses have been established increases the amplitude of AMPA mEPSCs, but does not affect mEPSC frequency or the density of excitatory synapses[35,37,39,59]. The increase in mEPSC amplitude is accompanied by an increase in spike-mediated transmission between pairs of pyramidal neurons[35,37] and there is no change in the COEFFICIENT OF VARIATION of EPSC amplitude, as predicted if the PROBABILITY OF TRANSMITTER RELEASE is unaltered

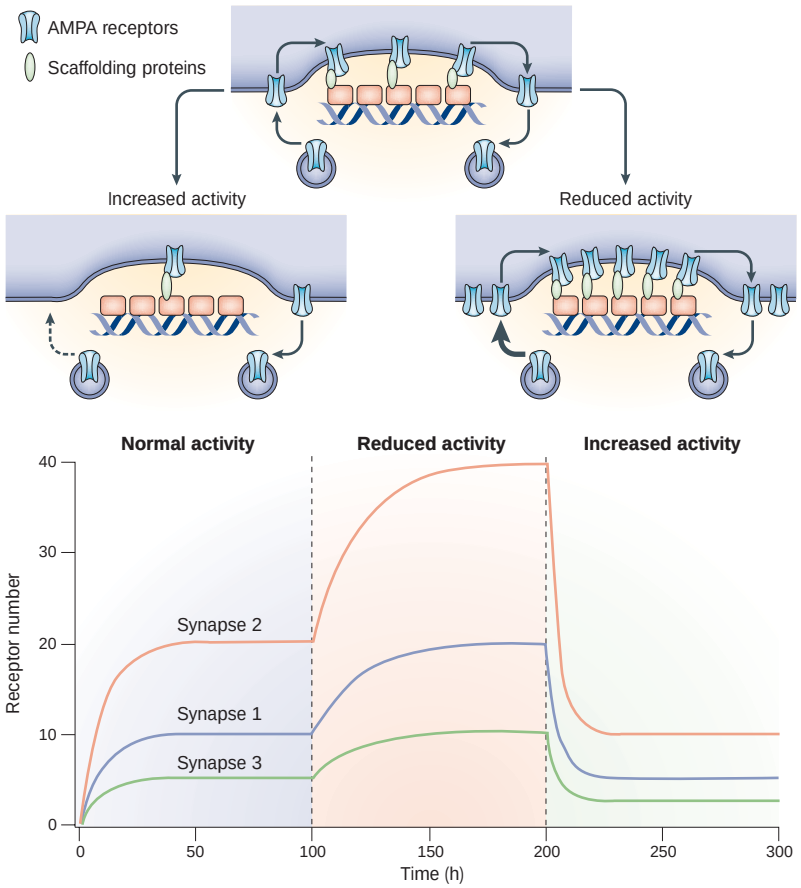

Figure 5 | **Changes in AMPA receptor accumulation.** Synaptic scaling is accompanied by changes in the accumulation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors at synaptic sites (turquoise), as well as turnover of scaffolding proteins that tether AMPA receptors to the cytoskeleton (green). One possible mechanism for such changes is if activity targets the rate of constitutive receptor insertion, so that increased activity reduces this rate (dashed arrow) whereas reduced activity increases this rate (wide arrow). A simple simulation shows that such a mechanism can account for multiplicative scaling of synaptic strengths (plot). In this simulation, the number of receptors at the synapse is the result of dynamic equilibrium between insertion and removal rates. If the insertion rate is 1 receptor per hour, and the probability that any given receptor will be removed is 10% in an hour, then receptors will build up until the removal rate matches the insertion rate, which will occur when there are 10 receptors (synapse 1). If a second synapse has the same insertion rate but a removal rate of 5% each hour, then 20 receptors will accumulate (synapse 3), and if the removal rate is 20% each hour, then 5 receptors will accumulate (synapse 2). So, in the simulation, variability in synaptic strength from synapse to synapse is due to synapse-specific differences in removal rates. By contrast, synaptic scaling is modelled as the result of a global change in insertion rate at all synapses. If the insertion rate doubles (reduced activity), each synapse will reach a new steady-state level of receptor accumulation that is double the initial value at that synapse. Conversely, if the insertion rate is cut in half (increased activity), each synapse will end up with half the initial number of receptors. Bottom panel reproduced, with permission, from REF. 50 © (1998) Elsevier Science.

(C. Wierenga and G.G.T., unpublished data). These data are all consistent with an increase in postsynaptic receptor clustering that occurs without changes in presynaptic release probability. By contrast, AMPAR blockade in hippocampal cultures during a similar developmental stage increases both the frequency and amplitude of mEPSCs[60]. To further complicate matters, lowering activity in individual hippocampal neurons by expression of a K_{ir} potassium channel produced a small increase in mEPSC frequency but no change in amplitude[36]. One explanation for the difference between these two hippocampal studies is that the compensatory mechanisms activated by lowering activity in individual neurons are distinct from those engaged by lowering network activity. Unfortunately, the effects of blocking global activity and blocking activity in individual neurons were not compared in the same preparation at the same developmental stage, so these differences might be attributable to other factors.

Changes in mEPSC frequency are often interpreted as arising from a change in the probability of transmitter release[61], but mEPSC frequency can change without affecting evoked release, and vice versa[62–64]. An increase in the number of docked vesicles can also increase mEPSC frequency — for example, if the number of synaptic boutons, or the number of functional release sites per bouton, goes up. In general, the total number of synaptic boutons is not greatly affected by a few days of activity blockade[36,59], but there is an increase in synapse size and in the number of docked vesicles[65]. Finally, mEPSC frequency could increase because the number of functional release sites that are apposed to AMPAR clusters increases — in other words, through conversion of postsynaptically 'silent' synapses into functional ones. The proportion of morphologically defined silent synapses is quite low in cortical cultures (<10%)[66,67]. In hippocampal cultures, however, up to 40–50% of excitatory synapses have no detectable AMPARs[68,69]. If changes in mEPSC frequency result from insertion of AMPARs at such sites, the difference in the proportion of silent synapses between cortical and hippocampal cultures could explain why mEPSC frequency changes in the latter but not the former preparation.

The most direct evidence that a change in release probability contributes to homeostatic synaptic plasticity in central neurons comes from measurements of vesicle recycling and synaptic morphology in hippocampal cultures. The sizes of active zones and the number of docked vesicles per active zone are increased after 2–5 days of activity blockade, and the size of the recycling vesicle pool increases. Although an expansion in the recycling vesicle pool was taken to indicate an increase in release probability, the available data cannot rule out an increase in the number of boutons that release more than one vesicle simultaneously during spike-mediated transmission. There is now mounting evidence for such multivesicular release at some synapses[70–72].

Given that synapse size increases during activity blockade, a potential explanation for the postsynaptic increase in receptor number is that receptor density at synapses is relatively constant, so that expansion of the postsynaptic density automatically increases the number of synaptic receptors. This explanation cannot fully account for the available data, because there is a large discrepancy in the time course and magnitude of change in mEPSC amplitude and of synapse growth. After 1 day of activity blockade, mEPSC amplitude increases by about 50%, and by 2 days it about doubles[35]. The increased synapse size is not as great and is much slower to develop — 2 days of activity deprivation increases the postsynaptic area and number of

docked vesicles by only about 30% (REF. 65). An increase in synapse area is therefore unlikely to account fully for the increased accumulation of receptors and increase in mEPSC amplitude seen in cortical, spinal and hippocampal cultures after 1–2 days of lowered activity. An interesting possibility is that on shorter timescales (hours to a few days), receptor density is adjusted up or down through changes in insertion rates and tethering sites. Presumably receptor density will saturate at some point, so that an expanded synapse area will be necessary to recruit more receptors. Perhaps increases in synapse size (and accompanying presynaptic changes in the number of docked vesicles) are recruited as an additional homeostatic mechanism by longer periods of activity deprivation.

Induction mechanisms

The induction mechanisms of homeostatic plasticity are poorly understood. In part, this is due to the difficulty of interfering with a process that operates over hours to days without producing non-specific effects on neuronal viability or other vital cellular processes. At the moment, there are more questions about the induction mechanism than answers. Pressing questions include: whether homeostatic plasticity requires changes in pre- and postsynaptic activity together, or is CELL-AUTONOMOUS; how changes in activity are integrated over time and 'read out' by the intracellular machinery; and what intracellular signal transduction cascades generate global changes in synaptic strength.

It is clear that a number of protocols can induce homeostatic plasticity. Blocking AMPAR signalling or blocking spiking with tetrodotoxin (TTX), both of which lower firing rates, can induce a scaling up of excitatory synaptic weights. Blocking NMDAR signalling alone, on the other hand, neither induces nor prevents synaptic scaling [35,37,73] (but see REF. 38). This indicates that synaptic scaling differs from many forms of LTP and LTD in that it is independent of NMDAR signalling. Blocking or raising network activity could act by changing the firing rate, or average level of depolarization, of pyramidal neurons. However, it might also act by directly changing the degree of activation of AMPARs, as these manipulations will also increase or decrease presynaptic release of glutamate. Two recent studies have addressed this issue. Leslie *et al.*[73] blocked synaptic transmission and directly depolarized neurons by parametrically raising extracellular potassium, which produced a parametric reduction in mEPSC amplitude. Burrone *et al.*[36] used expression of a K_{ir} channel to hyperpolarize individual neurons. Although this initially lowered firing rates, over time firing rates increased again despite the continued expression of the K_{ir} channel. Taken together, these studies indicate that, as in the neuromuscular junction[26], an important signal for triggering homeostatic plasticity in central neurons is the average level of depolarization of the postsynaptic neuron. A fascinating and unsolved question is how the intracellular machinery of a neuron can monitor and integrate the average level of depolarization, and translate this into compensatory changes in synaptic and/or intrinsic properties. An obvious possibility is that the read-out of average depolarization is some measure of average intracellular calcium, but although there is evidence that calcium is instrumental in inducing homeostatic changes in intrinsic excitability[15,29,74], its role in homeostatic synaptic plasticity has not been directly established. In hippocampal neurons, an inhibitor of the calcium/calmodulin-dependent family of kinases (KN93) prevents the changes in mEPSC amplitude and frequency that are produced by activity blockade, raising the possibility that calcium participates in this form of plasticity through activation of a calcium-dependent kinase[60].

The Burrone study[36] indicates that some forms of homeostatic plasticity are cell-autonomous, and do not require changes in activity of presynaptic inputs. However, it is not clear that all homeostatic plasticity mechanisms are entirely cell-autonomous. For example, excitatory synapses onto GABA (γ-aminobutyric acid) interneurons are also adjusted homeostatically, but this process seems to depend on the activity-dependent release of the neurotrophin BDNF (BRAIN-DERIVED NEUROTROPHIC FACTOR) from pyramidal neurons[75]. This indicates that excitatory synapses onto interneurons are regulated not by their own activity, but by the activity of nearby pyramidal neurons. Release of BDNF can also regulate the strength of synapses between pairs of pyramidal neurons and between interneurons and pyramidal neurons, indicating that activity-dependent release of BDNF translates pyramidal neuron activity into a network-wide signal for homeostatic synaptic adjustments[75–77]. The (presumably cell-autonomous) scaling that is induced by depolarization is independent of BDNF release[73], so there are at least two independent pathways for generating homeostatic changes in synaptic strengths. This indicates that different homeostatic responses might be elicited by disruptions in network activity (such as those induced by sensory deprivation, see below) and by mismatches between input firing and the activity of an individual neuron (as when an individual neuron is chronically hyperpolarized).

Balancing excitation and inhibition

For highly recurrent cortical networks, tuning of excitatory synaptic strengths is probably not sufficient to maintain network stability. There are extensive positive feedback connections between excitatory pyramidal neurons both within and between cortical layers, which are kept in check by feedback and feedforward inhibition mediated by complex networks of inhibitory interneurons (FIG. 6). Even small changes in the balance between excitation and inhibition in such networks can result in runaway excitability[78,79], disrupt sensory responses in primary visual cortex[80], and profoundly alter experience-dependent plasticity[81–84], indicating that excitation and inhibition must be delicately balanced to keep cortical networks functional. An important component of firing rate homeostasis in recurrent networks occurs through dynamic adjustments in the relative strengths of excitatory and inhibitory feedback onto pyramidal neurons[59,75].

CELL-AUTONOMOUS PLASTICITY
Plasticity in the properties of an individual neuron resulting from changes in its own activity, independent of the activity of other neurons in the network.

BRAIN-DERIVED NEUROTROPHIC FACTOR
A neurotrophin that is expressed at high levels in the central nervous system, and implicated in many forms of synaptic plasticity and maturation, as well as dendritic and axonal growth.

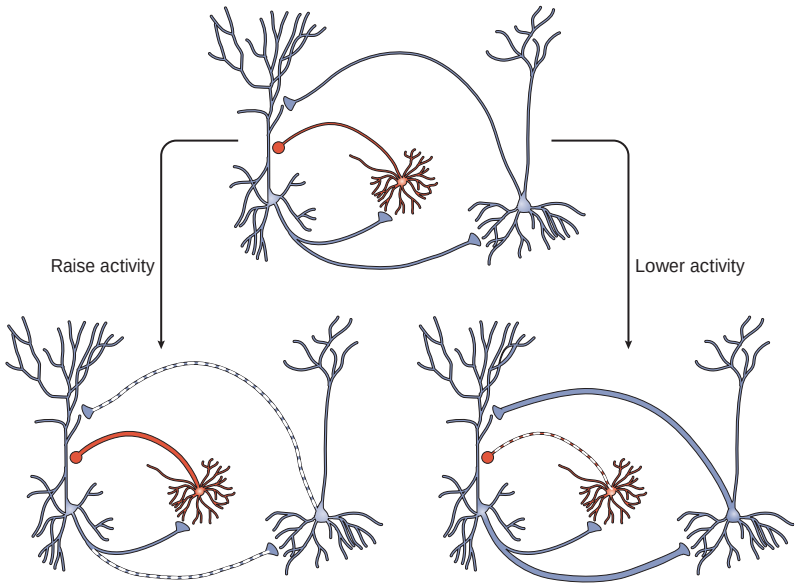

Figure 6 | **Homeostatic regulation of the excitation–inhibition balance in cortical networks.** Activity in recurrent cortical networks is strongly affected by feedback excitation and inhibition. Pyramidal neurons (blue) make excitatory outputs (triangles) onto other pyramidal neurons, and also onto inhibitory interneurons (red). These inhibitory neurons in turn feed inhibition (red circles) back onto the pyramidal neurons. In cortical cultures, raising activity for two days produces a coordinated set of changes in synaptic strength that result in reduced feedback excitation and increased feedback inhibition onto pyramidal neurons (lower left). Conversely, blocking activity for two days increases the gain of excitatory feedback and decreases inhibitory feedback. Similar changes in the cortical excitation–inhibition balance are induced by sensory deprivation.

Chronic changes in visual experience have long been known to regulate inhibition in the primary visual cortex of rodents and primates[82–87]. A similar phenomenon has been found in dissociated cortical and hippocampal networks, where activity blockade reversibly decreases GABA immunoreactivity[76,85,86] and reduces the amount of functional inhibition received by pyramidal neurons[76]. The mechanisms by which chronic changes in activity regulate inhibition differ in an important respect from those that regulate excitation. Although inhibition, like excitation, is modified through changes in quantal amplitude and receptor clustering, there is also a marked reduction in the number of functional inhibitory synapses[59]. Inhibition and excitation onto pyramidal neurons are therefore regulated in opposite directions, and in fundamentally different ways, by activity blockade. An important open question is whether different classes of interneurons, which have distinct roles in the cortical microcircuit, are regulated differently by long-lasting changes in activity.

The data from *in vitro* cortical networks indicate that homeostatic synaptic plasticity rules independently adjust excitatory and inhibitory feedback loops within recurrent cortical networks so that activity is preserved despite changes in drive. When activity falls too low (because, for example, sensory drive is reduced), excitation between pyramidal neurons is boosted and feedback inhibition is reduced (FIG. 6). This should raise the firing rates of pyramidal neurons. Conversely, when activity is too high, excitation between pyramidal neurons is reduced, and excitation onto interneurons and inhibitory inputs back onto pyramidal neurons are increased, thereby boosting feedback inhibition. This should lower the activity of pyramidal neurons. So, homeostatic regulation of network activity in recurrent cortical circuits is accomplished through a coordinated set of changes that selectively adjust different classes of synapse to drive network activity towards some set point.

MONOCULAR PRIMARY VISUAL CORTEX
The region of visual cortex in some species (notably rodents) that receives visual input from only one eye.

MONOCULAR DEPRIVATION
Depriving one eye of visual experience, while leaving the other eye unaffected.

Scaling in the developing visual system

The work on synaptic scaling in culture raises the legitimate question of whether this form of plasticity also operates in intact cortical networks during activity-dependent development. Recent experiments have begun to address this by using classic manipulations of visual experience to alter cortical activity *in vivo*, and then recording from slices of visual cortex to measure the resulting changes in intracortical synaptic strength.

One piece of evidence that synaptic scaling occurs *in vivo* comes from a developmental analysis of excitatory synapses onto principal neurons in slices from rodent primary visual cortex. During the second and third postnatal weeks, there is an inverse relationship between the frequency and amplitude of mEPSCs, indicating that as the number of excitatory synapses rises (therefore increasing mEPSC frequency) and visual drive increases, synaptic strength is reduced. This interpretation is supported by experiments showing that raising animals in the dark prevents the developmental decrease in quantal amplitude[87]. A similar inverse relationship between synapse number and quantal amplitude has been seen in cultured hippocampal and cortical neurons[66,88] and at the neuromuscular junction[21], indicating that in many developing networks there is a fundamental trade-off between synapse number and synaptic strength.

Further support for the idea that mEPSC amplitude is scaled up or down as a function of cortical activity is provided by experiments in which activity in MONOCULAR PRIMARY VISUAL CORTEX was lowered through monocular injections of TTX (MONOCULAR DEPRIVATION)[87]. This method selectively reduces the expression of markers of activity in the deprived region of cortex[89–91]. Because much of rodent primary visual cortex is driven exclusively by one eye, monocular deprivation effectively deprives the monocular segment of one hemisphere of visual drive, while leaving the other hemisphere unperturbed. Two days of monocular deprivation increases the amplitude of mEPSCs onto pyramidal neurons in the deprived hemisphere, while leaving the control hemisphere unaffected. Similar to the effects of activity deprivation in culture, mEPSC amplitudes are scaled up multiplicatively by monocular deprivation, and these effects are reversed when activity is allowed to resume[87]. Similar results have now been obtained using monocular lid suture (A. Maffei and G.G.T., unpublished data). These results show that the quantal amplitude of excitatory currents in primary visual cortex can be globally scaled up or down as a function of altered sensory experience, and indicate that homeostatic synaptic scaling is important for the activity-dependent refinement of central circuits.

Many forms of cortical plasticity have critical periods during which sensory experience can alter circuit properties, but outside of which sensory experience has little or no effect. These critical periods can be different for different cortical layers — for example, ocular dominance plasticity in binocular visual cortex[92,93] and whisker deprivation plasticity in somatosensory cortex[94,95] end in layer 4 (the principle input layer to cortex) after the first few weeks of life, but persist in layer 2/3 significantly later in development. Synaptic scaling in visual cortex is also developmentally regulated. In the first three weeks of a rat's life, synaptogenesis in layer 4 is most intense, and eye opening occurs — both of which are likely to generate large changes in drive to layer 4. Two days of monocular deprivation beginning at postnatal day (P)14 (immediately before eye opening) scales up mEPSC amplitudes onto principle neurons (star pyramids) in layer 4, but the same treatment has no effect when begun at P21. By contrast, mEPSCs onto layer 2/3 pyramidal neurons were unaffected by monocular deprivation beginning at P14 (when layer 2/3 is only poorly driven by visual activity)[96], but were scaled up by monocular deprivation beginning at P21. Interestingly, scaling in layer 2/3 is coincident with the opening of the critical period for ocular dominance plasticity in rodent binocular cortex[97]. These data indicate that the sites of homeostatic plasticity migrate to different cortical layers in an age-dependent manner. Why synaptic scaling should end early in layer 4 and persist later in layer 2/3 is not clear, but this seems to be a general rule for many forms of cortical plasticity, although the exact developmental profile depends on how visual experience is manipulated and which aspect of cortical plasticity is measured. It remains to be seen whether synaptic scaling continues to operate in the adult cortex after other forms of plasticity have been turned off or have slowed.

The effects of visual deprivation on visual cortical development and plasticity have been interpreted almost entirely in terms of Hebbian changes[11,40,41,81–84]. For example, the ability to induce LTD with extracellular stimulation (as measured by field potential recordings) is reduced in visual cortical slices after monocular deprivation, and there is a small reduction in the surface expression of AMPARs in whole extracts of primary visual cortex[98]. These data have been interpreted to mean that monocular deprivation produces a generalized LTD of excitatory cortical synapses that occludes further LTD. This is seemingly at odds with the observation that, at the same age, excitatory synapses onto layer 2/3 pyramidal neurons are scaled up by dark rearing and monocular deprivation[87]. This discrepancy might be due to measurement differences; field potential recordings are not sensitive enough to determine the absolute amplitude of synaptic connections, or to identify which classes of synapse are altered by monocular deprivation. Work in culture has indicated that different types of synaptic connection (excitatory to excitatory, excitatory to inhibitory, inhibitory to excitatory) are modified in highly selective ways by activity deprivation[35,59,75,76]. Similarly, reduced sensory drive *in vivo* not only scales up some excitatory synapses, but also reduces cortical inhibition[99,100]. This indicates that sensory deprivation *in vivo*, as in culture, alters the balance between excitation and inhibition through a highly selective set of changes in the strengths of different intracortical synapses. Understanding these changes will require measurements of unitary synaptic strength and dynamics between identified classes of pre- and postsynaptic neurons.

Interestingly, deafening produces changes in the excitation–inhibition balance in the auditory inferior colliculus[101], indicating that such changes might be a general response of primary sensory circuits to sensory deprivation. In visual cortex, these changes in the excitation–inhibition balance could have marked effects on Hebbian plasticity, because the amount of inhibition influences the ease with which LTP and LTD can be induced, and alters the expression of, and critical periods for, competitive plasticity[81,83,102,103]. It seems likely that the ultimate effects of sensory deprivation on cortical circuitry are the result of a complex interplay between Hebbian and homeostatic forms of synaptic plasticity.

Concluding remarks

Homeostatic forms of synaptic plasticity are ubiquitous in the developing nervous system, having now been identified at the neuromuscular junction and in invertebrate, spinal, hippocampal and cortical networks. Intensive study of these important phenomena has revealed a palette of mechanisms that contribute to the maintenance of overall excitability. Nervous systems seem to be remarkably clever at compensating for perturbations in activity or synaptic transmission, and the mechanisms engaged are likely to depend on the perturbation. For example, a deficit in postsynaptic receptor accumulation might lead to increased synapse number or release probability, whereas lowered presnaptic drive might result in increased postsynaptic responsiveness to what input is available. This flexibility might ensure that firing rates are maintained within some functional range, regardless of which parameters of excitability are maladjusted.

The study of homeostatic synaptic plasticity is still in its infancy, and many questions remain about its mechanism and function. One pressing issue is whether synaptic scaling is truly 'global', so that changes in activity (through receptor signalling or postsynaptic depolarization) generate a cell-wide signal that operates on all synapses proportionally. Current experiments cannot distinguish between this and the alternate possibility that each synapse generates a local signal that regulates itself in a homeostatic way, because currently either presynaptic and postsynaptic activity have been lowered or raised together, or the postsynaptic neuron has been clamped to hyperpolarized potentials that render all presynaptic inputs less effective. A local mechanism akin to synapse-specific LTP and LTD (but operating more slowly and in reverse) could explain the observation that in some neurons synapses are scaled up as a function of distance from the soma, perhaps in

response to a decrementing depolarizing signal such as back-propagating action potentials[104–106]. Such a local mechanism would have the unfortunate effect of slowly erasing Hebbian changes in synaptic strength. By contrast, global scaling preserves the relative differences between synaptic weights, so that synapse-specific changes generated through associative mechanisms can coexist with overall normalization of neuronal activity. Global scaling is clearly attractive from a computational standpoint, and as cortical pyramidal neurons seem to lack distance-dependent scaling[107], could be the dominant mechanism in this cell type.

Although much remains to be discovered about the mechanisms and function of homeostatic synaptic plasticity, it seems likely to emerge as an important force that allows the activity-dependent refinement of connectivity to unfold during development without jeopardizing 'la fixité du activité intérieur'.

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Competing interests statement

The authors declare that they have no competing financial interests.

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