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Keeping Your Brain in Balance: Homeostatic Regulation of Network Function

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Abstract

To perform computations with the efficiency necessary for animal survival, neocortical microcircuits must be capable of reconfiguring in response to experience, while carefully regulating excitatory and inhibitory connectivity to maintain stable function. This dynamic fine-tuning is accomplished through a rich array of cellular homeostatic plasticity mechanisms that stabilize important cellular and network features such as firing rates, information flow, and sensory tuning properties. Further, these functional network properties can be stabilized by different forms of homeostatic plasticity, including mechanisms that target excitatory or inhibitory synapses, or that regulate intrinsic neuronal excitability. Here we discuss which aspects of neocortical circuit function are under homeostatic control, how this homeostasis is realized on the cellular and molecular levels, and the pathological consequences when circuit homeostasis is impaired. A remaining challenge is to elucidate how these diverse homeostatic mechanisms cooperate within complex circuits to enable them to be both flexible and stable.

Contents

INTRODUCTION

With the advent of new tools for monitoring and manipulating identified mammalian neurons, there has been an explosion of interest into how complex microcircuits are wired up to perform specific computations. One extraordinary aspect of most such circuits is their complexity. Within neocortex, a common circuit motif is recurrent excitation, where glutamatergic pyramidal neurons excite each other to amplify signals. Such positive feedback can quickly get out of control and is held in check by a variety of feedback and feedforward inhibitory circuit motifs, mediated by a variety of γ aminobutyric acid–ergic (GABAergic) interneurons that self-organize into convoluted inhibitory and disinhibitory loops (Chiu et al. 2019) (**Figure 1**). Further complicating matters, these loops can be dynamically adjusted through changes in modulatory tone during distinct behavioral states and by experience-dependent adjustment of synaptic weights. Despite this dynamism, excitation must consistently recruit sufficient inhibition to prevent activity from blowing up uncontrollably, but not so much that it dies down prematurely. The idea that excitation and inhibition are carefully balanced—and that disruptions in this balance might contribute to circuit disfunction and thus myriad neurological disorders—has become almost a truism in neuroscience (Nelson & Valakh 2015, Sohal & Rubenstein 2019), yet we still do not fully understand how this balance is achieved and actively maintained within complex and dynamic central circuits.

One solution to this instability problem in neocortical networks is to deploy a set of homeostatic plasticity rules that use negative feedback to actively adjust the excitation-inhibition balance (Turrigiano & Nelson 2004). In theory, stable circuit function can emerge through local rules that allow neurons to sense and adjust their gain. A rich variety of plasticity mechanisms that fit roughly within the conceptual framework of homeostatic plasticity have now been identified (Chen et al. 2022, Gainey & Feldman 2017, Turrigiano 2012, Wefelmeyer et al. 2016), and in some cases, inroads have been made into describing the molecular pathways that mediate them (Chowdhury & Hell 2018, Fernandes & Carvalho 2016).

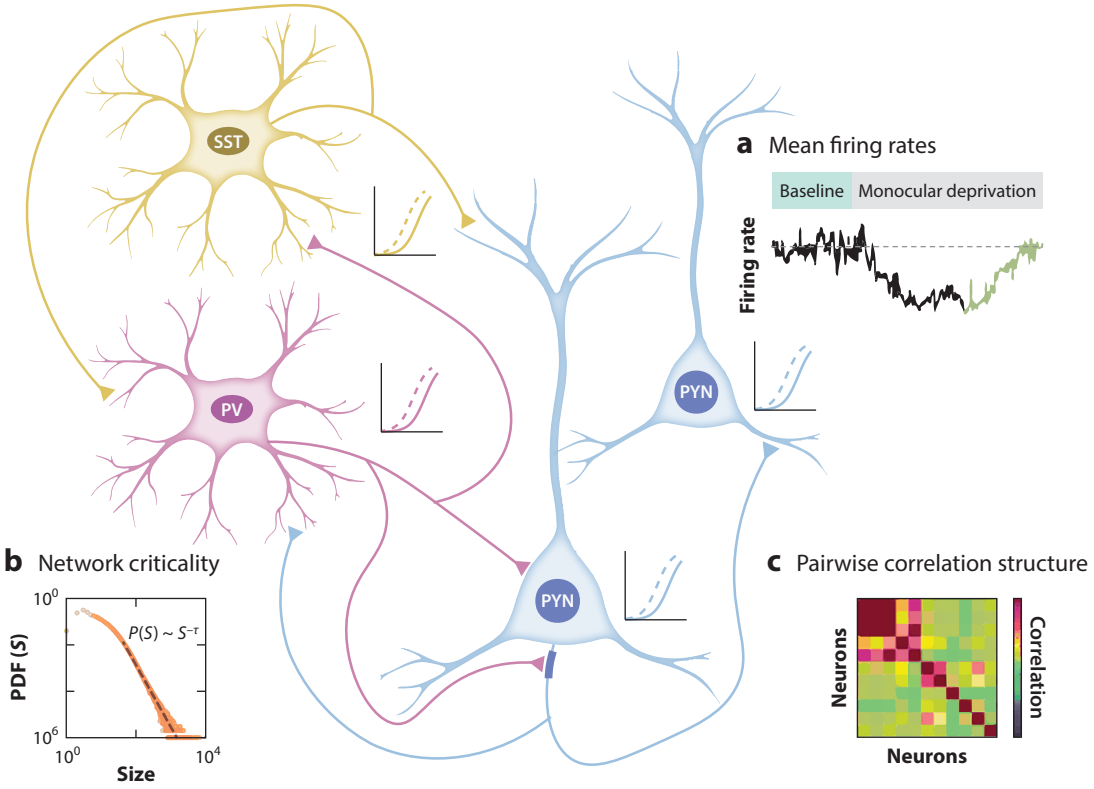

Figure 1

Modularity of cellular homeostatic mechanisms for independent control of distinct network features. The complexity of neocortical microcircuits arises from interconnected common circuit motifs formed by different types of neurons. These motifs include recurrent excitation between PYNs as well as feedback and feedforward inhibition between PYNs, PVs, and SSTs; additional interneuron types are not pictured for simplicity. In a properly functioning circuit, excitation and inhibition are carefully balanced by a set of cellular homeostatic mechanisms to maintain circuit stability and improve network function, and distinct aspects of network function are constrained by different homeostatic mechanisms. Based on the current evidence, network features that are subjected to homeostatic feedback control include (*a*) mean firing rates (or firing rate homeostasis), (*b*) network criticality [illustrated as the probability (*P*) of observing an avalanche of a given number of spikes (*S*), which can be fit by power laws; τ, the exponent generated from the best fit, is depicted as the slope of the *dashed black line*], and (*c*) local correlation structure (illustrated as a correlation matrix, where each grid indicates the correlation value for a given pair of neurons). In particular, there is evidence that homeostatic regulation of excitatory network nodes through synaptic scaling and intrinsic homeostatic plasticity can stabilize mean firing rates and network correlation structure, while the regulation of inhibitory nodes can stabilize the network near a critical regime. Abbreviations: P, probability; PDF, probability distribution function; PV, parvalbumin-positive interneuron; PYN, pyramidal neuron; S, spike; SST, somatostatin-positive interneuron. Illustrations in panels *b* and *c* are adapted, with permission, from data published by Ma et al. (2019) and Wu et al. (2020), respectively. Neuron images created with Biorender.com.

Despite this progress, we are just beginning to understand how homeostasis manifests within highly recurrent and complex microcircuits in vivo. Here we focus on recent in vivo work illuminating which aspects of circuit function are under direct homeostatic control, the cellular and molecular mechanisms that mediate these phenomena, and whether defects in homeostatic plasticity might contribute to the genesis of neurological disorders. Because of space limitations, we focus here on mammalian neocortex, and we direct the reader to recent excellent reviews of important work on homeostasis in other brain regions and organisms (Davis & Müller 2015, Frank et al. 2020, Goel & Dickman 2021, Wenner 2014). While the conceptual framework we outline

here likely generalizes to many neural circuits, we wish to emphasize that different circuits have unique needs and constraints, and homeostatic plasticity is likely to be carefully tuned to match these regional needs.

HOMEOSTATIC PLASTICITY AND NETWORK STABILITY IN VIVO

The last decade has seen exciting advances in our understanding of which circuit features are constrained by homeostatic negative feedback and how this constraint improves circuit function. If we loosely define a variable as being under homeostatic control if it (*a*) is maintained within a confined range and (*b*) returns precisely back to that range when perturbed, then there is now good evidence in neocortex that mean firing rates (Hengen et al. 2013, 2016), sensory tuning curves (Noda et al. 2023, Rose et al. 2016), measures of network criticality (Ma et al. 2019), and the correlation structure of the local network (Wu et al. 2020) are all homeostatically regulated. A fascinating recent development is the emergence of converging experimental and computational evidence that different forms of homeostatic plasticity are instrumental in controlling these distinct aspects of network function (**Figure 1**)—something we touch on at the end of this section.

Firing Rate Homeostasis

One way to help stabilize overall circuit activity is to endow each component neuron with the ability to homeostatically regulate its own firing rate. The first in vitro description of homeostatic synaptic scaling (described in detail in following sections) implicated this mechanism in the slow (over many hours) stabilization of neuronal firing rates (Turrigiano et al. 1998), and many subsequent studies support the idea that mean neuronal firing rates in vitro are indeed under homeostatic control (Burrone et al. 2002, Gonzalez-Islas & Wenner 2006, Slomowitz et al. 2015). Consistent with this idea, imaging studies in intact primary visual cortex (V1) established that network activity is homeostatically restored to baseline during prolonged visual deprivation (Kaneko et al. 2008, Keck et al. 2013, Mrsic-Flogel et al. 2007), but because these approaches did not allow firing rates to be carefully resolved, they left open the question of how precisely the firing of individual neocortical neurons is regulated.

Stability of the firing rate distribution. Recent technological advances have made it possible to record and analyze extracellular spiking in ensembles of neurons continuously over many days in freely behaving animals. These rich data sets allow the characteristics and stability of individual neurons and ensembles to be assessed and the monitoring of homeostatic regulation of circuit properties in real time as it unfolds. One of the most striking features of cortical ensemble activity is the broad distribution of mean firing rates, which spans three to four orders of magnitude and follows a skewed, lognormal distribution (Buzsáki & Mizuseki 2014). Equally striking, the average firing of each regular-spiking (mostly glutamatergic) neuron is constrained to a narrow zone, even across distinct environments and behavioral states, and together, these zones tile this very broad distribution (Dhawale et al. 2017; Hengen et al. 2016; Torrado Pacheco et al. 2019, 2021). Furthermore, when mean firing rates are perturbed by prolonged visual deprivation, this distribution is homeostatically restored (Hengen et al. 2013), suggesting that this broad firing rate distribution plays some critical role(s) within these circuits (Buzsáki & Mizuseki 2014). One speculative possibility is that, because the rate of Hebbian plasticity depends on firing rates (Abbott & Nelson 2000, Lim et al. 2015, Wilmes & Clopath 2023), having a wide range of mean firing rates might allow circuits to reconfigure (or learn) in response to both slow and fast external events.

Homeostatic regulation around individual set points. How might the distribution of mean firing rates be maintained over time in highly plastic circuits? One possibility is that individual

neurons regulate around an individual set point range [a firing rate set point (FRSP)]. Consistent with this idea, during visual deprivation, the firing of individual putative pyramidal neurons first drops and then, over approximately two days, is slowly regulated back to the original baseline (Hengen et al. 2016). Conversely, when the eye is reopened, individual firing rates first overshoot and then again are regulated precisely back (Torrado Pacheco et al. 2021). Similar observations at the population and single-cell levels show that in V1 and primary somatosensory (S1) and auditory (A1) cortices of young animals, sensory deprivation drives a bimodal response in which spontaneous or sensory-driven activity first drops (due to Hebbian mechanisms) and then rebounds to baseline on a slow timescale due to homeostatic plasticity (Espinosa & Stryker 2012, Gainey & Feldman 2017, Kaneko et al. 2008, Keck et al. 2013, Teichert et al. 2017) (**Figure 1*a***).

Homeostasis is likely needed over a range of slow and fast timescales to stabilize circuits against the various perturbations they will encounter. During the early phase (day 1) of sensory deprivation in S1 and V1, there is—paradoxically—very little change in the firing rates of pyramidal neurons. In contrast, firing rates of fast-spiking (FS) inhibitory neurons drop almost immediately and also rebound more quickly (Gainey et al. 2018, Hengen et al. 2013, Kuhlman et al. 2013). Thus the initial stability in pyramidal firing is likely due to disinhibition mediated by a rapid drop in inhibitory firing. On even faster timescales, even very rapid and extreme changes in sensory input have little effect on mean pyramidal neuron firing rates (measured over seconds to minutes) in juvenile V1 (Torrado Pacheco et al. 2019). This suggests that these circuits are tuned so that excitation and inhibition instantaneously adjust to stabilize firing in response to changes in external drive; exactly how this tuning is accomplished and maintained is not fully understood, but mechanisms that locally match excitation and inhibition could contribute (Haider et al. 2006, Iascone et al. 2020, Tao & Poo 2005, Xue et al. 2014). Taken together, these studies show that within neocortical networks there exist strong homeostatic forces that operate on a number of timescales to constrain the mean activity of both networks and individual neurons and regulate the firing of individual neurons around an individual FRSP. An open question is the degree to which these FRSPs are malleable and can be modified either developmentally or by experience.

Homeostatic Maintenance of Higher-Order Network Properties

To function effectively, neocortical circuits must keep firing rates from blowing up or decaying away to nothing, be capable of refining and then maintaining the correlation structure of the local network in response to experience-dependent plasticity, and remain well tuned to detect or influence events in the external world. To achieve all this in a dynamic way most certainly requires that other features of neocortical networks besides firing rates are under direct homeostatic control. A flurry of recent studies have begun to explore this possibility.

Criticality. Neocortical networks are thought to operate in a critical regime where excitation-inhibition balance ensures that each spike in the network evokes (on average) one spike in a downstream partner. Networks that operate near criticality generate internally or externally driven spike trains that exhibit a wide (power law) distribution of temporal and spatial scales (avalanche distribution), thus maximizing the potential for information transfer (Cocchi et al. 2017). While approximations of this balanced state have been observed both in vitro and in vivo (Cocchi et al. 2017), it has been controversial whether this is epiphenomenal or arises through a process of active regulation (Shew & Plenz 2013). Consistent with previous reports from in vitro systems (Beggs & Plenz 2004, Shew et al. 2015), V1 networks recorded chronically in vivo operate close to criticality. More strikingly, within hours of initiating visual deprivation, network dynamics become subcritical but then quickly regulate back to near-criticality (Ma et al. 2019), strongly suggesting that network features that promote criticality are under homeostatic control. Interestingly, the

return to criticality precedes the rebound in pyramidal neuron firing and instead tracks the faster drop and rebound in FS inhibitory activity (Hengen et al. 2013, Ma et al. 2019), suggesting that the restoration of criticality is mediated by homeostatic mechanisms that target inhibitory circuit elements (**Figure 1*b***).

Correlation structure and tuning properties. Local network connectivity is modified by experience to store information and refine functional properties, and this is reflected in the correlation structure of spiking activity. It has been an open question whether homeostatic recovery from major perturbations can preserve or restore this local correlation structure. Analysis of the pairwise correlation structure of ensembles of V1 neurons in freely behaving rats revealed that—although mean firing rates are stable throughout the classical critical period—the pairwise correlations increase and are stronger in the light than in the dark, suggesting that they carry meaningful signals (Torrado Pacheco et al. 2019, Wu et al. 2020). While visual deprivation initially reduces these correlations, they are slowly restored during prolonged deprivation with a time course that mirrors the recovery in pyramidal neuron firing rates (**Figure 1*c***). Interestingly, the sensory tuning properties of individual neocortical neurons, which are strongly influenced by local network connectivity, are also restored after recovery from sensory deprivation (Rose et al. 2016) or loss of neurons (Noda et al. 2023), and homeostatic rules can stabilize tuning in the face of significant representational drift (Rule & O'Leary 2022). Taken together these studies suggest that homeostatic mechanisms operate on the local network to amplify a backbone of maintained (or slowly drifting) network correlations and can thus help to restore function even in the face of network degradation driven by cell loss or other traumatic perturbations.

Homeostatic Plasticity Mechanisms that Control These Network Features

In the following sections we discuss three major cellular forms of homeostatic plasticity that have been implicated in the homeostatic regulation of firing rates, criticality, and correlation structure. These are excitatory synaptic scaling (in which neurons proportionally scale excitatory postsynaptic strength up or down in the right direction to compensate for perturbations in firing), inhibitory homeostatic plasticity (where inhibition is adjusted, often in the opposite direction from excitation), and intrinsic homeostatic plasticity (IHP, where neurons regulate ion channels to adjust excitability).

There is strong evidence that excitatory synaptic scaling and IHP are necessary for firing rate homeostasis, as genetic or pharmacological manipulations that block these forms of plasticity prevent it (Barnes et al. 2015, Kaneko et al. 2008, Tatavarty et al. 2020). Modeling studies suggest that these two forms of plasticity—which target synaptic and intrinsic properties, respectively—can control distinct features of network activity (Cannon & Miller 2016, 2017; Wu et al. 2020) (**Figure 1*a*,*c***). For example, IHP can still restore firing rates when synaptic scaling is absent but cannot restore correlation structure; in contrast, synaptic scaling is well suited to restore network correlation structure because it acts to proportionally scale up excitation and so preserves the differences between synaptic weights that drive these correlations (Wu et al. 2020). Finally, homeostatic adjustment of inhibition through excitatory synaptic scaling onto GABAergic interneurons is effective at restoring criticality (Ma et al. 2019). While the exact network features that can be conserved via a given homeostatic mechanism likely depend on details of network architecture, these studies illustrate that these distinct forms of homeostatic compensation are not functionally redundant and can be harnessed to provide dynamic control over a wide range of network features.

While closing an eye drives uniform recovery of firing and pairwise correlation structure during the critical period through synaptic scaling and IHP in V1 (Hengen et al. 2013, Lambo &

Turrigiano 2013, Wu et al. 2020), imaging in adult animals following eye removal revealed that only a subset (~50%) of neurons with highly correlated activity underwent homeostatic recovery (Barnes et al. 2015). Further, this recovery was driven by a decrease in inhibition onto pyramidal neurons rather than synaptic scaling up. Interestingly, directly suppressing activity in adult V1 does induce synaptic scaling up (Wen & Turrigiano 2021), and homeostatic recovery in adult A1 also relies on synaptic scaling (Teichert et al. 2017). It is thus likely that the mode of sensory deprivation (e.g., eye closure versus removal) can drive distinct sequences of Hebbian and homeostatic plasticity that lead to different functional outcomes at the network level.

CELLULAR BUILDING BLOCKS OF CIRCUIT HOMEOSTASIS

As discussed above, there is growing evidence that different network features can be stabilized by distinct forms of homeostatic plasticity. The cellular building blocks of homeostatic compensation can be roughly divided into those that target excitatory synapses, inhibitory synapses, or intrinsic neuronal excitability. Further, within each of these broad classes there are functionally and mechanistically distinct subclasses that depend on various aspects of cell identity and operate over a variety of temporal and spatial scales and with different activity requirements for induction (Maffei & Turrigiano 2008, Turrigiano 2011). Many of these appear to be modular in that they can be independently expressed at different nodes within a neural circuit and can be mixed and matched to endow the network with developmentally appropriate compensatory capabilities (Maffei & Turrigiano 2008, Pan-Vazquez et al. 2020, Ranson et al. 2012, Wen & Turrigiano 2021). The resulting enormous complexity has not been fully explored, and it remains unclear exactly how many distinct forms of homeostatic plasticity exist within neocortical circuits. Below we highlight forms of homeostatic plasticity known to operate within intact neocortical circuits in vivo.

Homeostatic Regulation of Excitatory Synapses

Compelling evidence shows that central neurons adjust the strength of excitatory synapses to maintain activity around a homeostatic set point. Given the complexity of neocortical circuits, it is not surprising that mechanisms targeting excitatory synapses operate across a variety of temporal and spatial scales. For example, there are global mechanisms that adjust the entire synapse population of a neuron (e.g., synaptic scaling) and local mechanisms that act on a subset of synapses. Furthermore, homeostatic compensations can occur at either the presynaptic or postsynaptic side of the synapse to adjust distinct aspects of circuit function. Below, we discuss some of the best-studied homeostatic mechanisms that operate on excitatory synapse.

Synaptic scaling. One of the best-studied forms of synaptic homeostatic plasticity is synaptic scaling of excitatory synapses onto excitatory pyramidal neurons (Turrigiano et al. 1998). Synaptic scaling operates in a cell-wide and cell-autonomous manner to slowly scale the postsynaptic strength of glutamatergic synapses in the right direction to compensate for prolonged perturbations to neuronal firing (Turrigiano 2008). Over the past quarter century, synaptic scaling has been demonstrated under many in vitro and in vivo conditions and in response to a variety of activity perturbations (Pozo & Goda 2010, Turrigiano 2012). Most studies that perturb firing over long timescales have observed compensatory changes in the distribution of excitatory postsynaptic weights that are best fit by a multiplicative function (hence scaling) (e.g., Gainey et al. 2009, Keck et al. 2013, Kim & Tsien 2008, Schaukowitch et al. 2017, Stellwagen & Malenka 2006, Teichert et al. 2017, Torrado Pacheco et al. 2021, Turrigiano et al. 1998, Zubov et al. 2022), but deviations from scaling have been observed (e.g., Hanes et al. 2020, Pekala & Wenner 2022). These deviations may reflect measurement error or the simultaneous induction of synaptic

scaling and additional forms of local homeostatic (see below) or Hebbian plasticity. Finally, it is not known whether multiplicative scaling operates at the level of individual synapses or at the level of the distribution of synaptic weights due to the difficulty of following individual synaptic strength over the long periods of time required to induce scaling.

Excitatory synaptic scaling up has been observed in many regions of neocortex and hippocampus following activity manipulations that lower firing in vivo, including sensory deprivation (Desai et al. 2002, Greenhill et al. 2015, Hengen et al. 2013, Keck et al. 2013, Kotak et al. 2005, Teichert et al. 2017) and genetic or pharmacological manipulations (Echegoyen et al. 2007, Wen & Turrigiano 2021, Wu et al. 2021). Not surprisingly, the expression of synaptic scaling depends on cell type, cortical layer, and developmental stage (Chen et al. 2022, Gainey & Feldman 2017, Tien & Kerschensteiner 2018, Turrigiano 2011), indicating that not all neuron types within a circuit need to express it. Scaling up of excitatory synapses contributes to slow upward firing rate homeostasis in V1 during sensory deprivation (Hengen et al. 2013, 2016), the restoration of network activity after scotoma (Keck et al. 2013), the restoration of tuning properties in A1 (Teichert et al. 2017), and the maintenance of breathing networks during hibernation (Zubov et al. 2022). Scaling down is less well studied in vivo, but its induction correlates with downward firing rate homeostasis during eye reopening (Torrado Pacheco et al. 2021) and is necessary for the emergence of memory specificity in insular cortex (Wu et al. 2021).

Local forms of synaptic compensation. For classic synaptic scaling induced by changes in firing, there is good evidence that the unit of computation is the neuron (Goold & Nicoll 2010, Ibata et al. 2008, Turrigiano 2008). In contrast, some compensatory processes act at the level of dendritic branches or even individual synapses, which may enhance information processing capabilities (Barnes et al. 2017, Poirazi et al. 2003, Rabinowitch & Segev 2006). First, there is evidence for local synaptic normalization that redistributes a set total dendritic synaptic weight during long-term potentiation (Bourne & Harris 2011, El-Boustani et al. 2018). Second, homeostatic increases in spine size induced by some forms of visual deprivation occur selectively on dendritic branches that have undergone recent spine loss (Barnes et al. 2017), suggesting that synaptic scaling can be either locally induced or locally gated under some conditions, possibly by similar mechanisms to those that underlie behavior-state gating (Diering et al. 2017, Hengen et al. 2016, Torrado Pacheco et al. 2021). At an even more local level, blockade or potentiation of synaptic transmission at one or a few synapses in culture can lead to compensatory changes in local synaptic strength under some conditions (Dubes et al. 2022, Hou et al. 2008, Letellier et al. 2019, Sutton et al. 2006) but not others (Harms et al. 2005, Ibata et al. 2008). Such ultralocal compensation in central neurons has not been documented in vivo, so its functional significance is still unclear. Finally, distinct synapse types onto the same postsynaptic neuron can be differentially sensitive to homeostatic regulation (Turrigiano 2017). An important future goal is to understand when and how synaptic compensation is spatially restricted.

Homeostatic Regulation of Inhibitory Synapses

The magnitude, timing, and placement of excitation and inhibition a neuron receives will strongly influence its firing properties and thus its role in information processing (Haider & McCormick 2009, Isaacson & Scanziani 2011, Keck et al. 2017b, McFarlan et al. 2023). Conceptually, regulation of pyramidal neuron firing might be best achieved through reciprocal changes at excitatory and inhibitory synapses, and there is a long literature on the activity-dependent regulation of inhibition in sensory cortex (Chen & Nedivi 2013; Gainey & Feldman 2017; Jones 1993; Maffei et al. 2004, 2006; Morales et al. 2002; Sanes & Kotak 2011). In cultured neocortical neurons, the same manipulation (blocking spiking) that induces synaptic scaling up indeed scales inhibitory

postsynaptic strength down and also reduces inhibitory synapse number (Kilman et al. 2002); bidirectional scaling up and down of GABAergic synapses has now been widely reported in both cortical and hippocampal cultures (Ge et al. 2018, Hartman et al. 2006, Peng et al. 2010, Pribiag et al. 2014, Rannals & Kapur 2011, Saliba et al. 2007, Swanwick et al. 2006) as well as in vivo in response to sensory deprivation (House et al. 2011, Takesian et al. 2011, Yang et al. 2011). Most reports on inhibitory scaling document coordinated changes in synapse number and strength (Hartman et al. 2006, Kilman et al. 2002, Peng et al. 2010, Yang et al. 2011).

In the intact developing cortex, inhibitory circuits are especially sensitive to sensory perturbations (Ribic 2020), and proper homeostatic regulation of these circuits likely plays a key role in stabilizing certain higher-order network properties such as criticality (Ma et al. 2019). Inhibitory plasticity often occurs faster than excitatory plasticity, so that dynamic changes in inhibition can precede (and even trigger) changes in excitatory circuitry (Gainey & Feldman 2017; Hengen et al. 2013, 2016; Kuhlman et al. 2013). The direction and magnitude of inhibitory plasticity is tightly coupled to the developmental stage (Karmarkar & Buonomano 2006, Compans & Burrone 2023, Sanes & Kotak 2011); for example, inhibitory plasticity can flip sign at the transition from early to later postnatal development (Lefort et al. 2013; Maffei et al. 2004, 2006). Finally, there is great diversity in cortical GABAergic cell types, which is reflected in diverse wiring patterns within the network (Chiu et al. 2019) as well as in their subcellular targeting of postsynaptic partners. This complexity is mirrored in the cell type specificity of inhibitory plasticity (Maffei et al. 2004, Pan-Vazquez et al. 2020). For example, while elevated network activity during early postnatal development downregulates axo-axonic GABAergic synapses (at a stage when they are depolarizing) from chandelier cells, it upregulates axo-somatic synapses from basket cells (Pan-Vazquez et al. 2020). Presumably, much of this complexity ensures that, at the circuit level, the net effect of inhibitory homeostatic changes is to stabilize network function. These few examples make clear that unraveling the rules for homeostatic plasticity of inhibition, and deciphering its expression and function within complex microcircuits, will require considerable future effort.

Homeostatic Regulation of Intrinsic Excitability

Neuronal excitability is determined not only by the number, strength, and timing of synaptic inputs but also by the input-output function of the neuron: how much current (input) is required to make the neuron fire (output). This is determined by both passive cable properties and the distribution of ionic conductance across the entire neuron (Daoudal & Debanne 2003, Zhang & Linden 2003). One important factor in shaping intrinsic excitability is the identity and membrane distribution of voltage-gated ion channels (Marder & Goaillard 2006). Just like ligand-gated ion channels that mediate synaptic transmissions, voltage-gated ion channels are subject to activity-dependent regulation, and the contribution of intrinsic plasticity to some forms of learning and memory has been well documented (Sehgal et al. 2013, Zhang & Linden 2003). Naturally, neurons also use negative feedback to regulate their intrinsic excitability. This was first demonstrated in invertebrate central pattern generator neurons where outward and inward conductance are actively adjusted to maintain burst firing (Marder & Prinz 2002, Turrigiano et al. 1994), and subsequent work in neocortical and hippocampal neurons found that homeostatic regulation of intrinsic excitability, or IHP, is a common mechanism in the central nervous system (Cudmore et al. 2010, Desai et al. 1999, Karmarkar & Buonomano 2006, Lee et al. 2015, O'Leary et al. 2010) and plays essential roles in circuit homeostasis.

Similar to synaptic homeostatic mechanisms, IHP exhibits great cell type and developmental diversity (Gainey & Feldman 2017, Turrigiano 2011); for example, in V1, IHP can be induced in layer 2/3 pyramidal neurons before and during the critical period (Lambo & Turrigiano 2013,

Maffei & Turrigiano 2008, Wen & Turrigiano 2021) but is absent in adults (Wen & Turrigiano 2021). Interestingly, in S1 and A1, sensory deprivation rapidly reduces intrinsic excitability in FS interneurons, which contributes to the rapid disinhibition of pyramidal neurons during the early phase of sensory deprivation (Gainey et al. 2018, Henton et al. 2023, Li et al. 2014, Takesian et al. 2011). Intrinsic plasticity in FS cells thus does not stabilize their own firing but instead serves to homeostatically regulate downstream pyramidal neuron firing.

Intrinsic plasticity can differentially modify neuronal output by fine-tuning excitability in subcellular compartments. Some examples include changes in dendritic voltage-gated ion channels that locally boost or dampen excitatory postsynaptic potentials to influence spike generation (Campanac et al. 2008, Losonczy et al. 2008, van Welie et al. 2004, Wierenga et al. 2005); conductance changes in the somatic region that alter the resting potential/conductance to make it easier or harder to reach threshold (Chen et al. 2014, Henton et al. 2023, Lombardo et al. 2018); and regulation of the structure and channel composition of the axon initial segment to influence spiking threshold (Grubb & Burrone 2010, Morgan et al. 2019, Zbili et al. 2021). There is one report of action potential broadening induced by activity deprivation (Li et al. 2020a), but other studies have failed to observe this despite robust changes in the input-output function (Trojanowski & Turrigiano 2021, Wen & Turrigiano 2021), suggesting that this is not a common feature of IHP.

Synaptic and intrinsic plasticity can be simultaneously (Echegoyen et al. 2007, Kotak et al. 2005, Lambo & Turrigiano 2013, Wen & Turrigiano 2021, Zbili et al. 2021) or independently engaged (Gainey & Feldman 2017, Karmarkar & Buonomano 2006, Maffei & Turrigiano 2008, Wen & Turrigiano 2021) and may regulate distinct aspects of circuit dynamics (Cannon & Miller 2016, Wu et al. 2020). Because the activity manipulations used to study homeostatic plasticity perturb multiple calcium-dependent signaling pathways in parallel, it remains unclear whether synaptic plasticity and IHP are activated by the same activity sensors.

Other Forms of Compensatory Plasticity

Many other forms of compensatory plasticity that could contribute to network stability have been identified. These include presynaptic homeostatic plasticity (Chipman et al. 2022, Davis & Müller 2015, Nair et al. 2021), heterosynaptic plasticity (Chater & Goda 2021, Oh et al. 2015), and metaplasticity (Keck et al. 2017a, Lee & Kirkwood 2019). Given the intense need for neural circuits to maintain stability on many temporal and spatial scales, it is no doubt strategically advantageous for networks to have a wide palette of mechanisms to deploy as needed.

MOLECULAR MECHANISMS OF HOMEOSTATIC PLASTICITY

To homeostatically regulate excitability, neurons must be able to detect deviations from some activity set point and then set in motion signal transduction cascades to ultimately regulate ion channel abundance and distribution. As the reader can imagine, this requires the participation of myriad signaling pathways, cell biological processes, and molecular players. Here we provide a broad overview of our current understanding of these processes.

Excitatory Synaptic Scaling

There is good evidence that synaptic scaling is induced by changes in a neuron's own firing, triggered by changes in calcium influx through voltage-gated ion channels and modulation of calcium-dependent kinases (Fernandes & Carvalho 2016, Goold & Nicoll 2010, Ibata et al. 2008); ultimately, this results in changes in *N*-methyl-D-aspartate receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) accumulation at synaptic sites to modulate postsynaptic strength (Pérez-Otaño & Ehlers 2005, Turrigiano 2008). Though induced

by changes in firing, scaling can be modulated by activity-dependent release of secreted factors (Barnes et al. 2017, Reimers et al. 2014, Rutherford et al. 1998, Steinmetz & Turrigiano 2010, Stellwagen & Malenka 2006). Furthermore, while classic synaptic scaling induced by changes in firing is independent of NMDAR activation (Turrigiano et al. 1998), suppressed firing in combination with local NMDAR blockade or dendritic hyperpolarization can trigger distinct forms of local homeostatic compensation (Hou et al. 2008, Kavalali & Monteggia 2023, Reese & Kavalali 2015, Sutton et al. 2006) mediated by local translation (Sutton et al. 2006, 2007) or retinoic acid and fragile X mental retardation protein (FMRP)-dependent pathways (Bockaert et al. 2021, Chen et al. 2014). In V1, sensory deprivation paradigms that alter neocortical firing trigger NMDAR-independent synaptic scaling (Barnes et al. 2015; Hengen et al. 2013, 2016; Keck et al. 2013; Torrado Pacheco et al. 2021), while manipulations that have little effect on average firing [such as prolonged dark rearing (Torrado Pacheco et al. 2019)] instead trigger NMDAR-dependent metaplasticity of synaptic strength (Bridi et al. 2018, Rodriguez et al. 2019). Finally, blockade of neurotransmission may override spiking signals and directly trigger compensatory changes in synaptic strength under some conditions (Fong et al. 2015). Presumably, different activity manipulations modulate distinct sources of calcium or other activity-dependent signals and thus activate distinct downstream pathways.

Downstream of altered calcium influx, scaling is accomplished through transcription and translation-dependent changes in trafficking pathways and synaptic scaffolds (Schanzenbächer et al. 2016, 2018; Schaukowitch et al. 2017; Steinmetz et al. 2016; Valakh et al. 2023), as well as through changes in kinase and phosphatase activity that induce wide-spread changes in the phosphoproteome (Desch et al. 2021, Schanzenbächer et al. 2016, Wu et al. 2022). A long list of molecular players has now been implicated in scaling, including transcriptional and epigenetic regulators that can induce (Schaukowitch et al. 2017, Sweatt 2016) or constrain (Valakh et al. 2023) homeostatic changes, cell adhesion molecules (Thalhammer & Cingolani 2014), postsynaptic scaffolding proteins required for AMPAR trafficking (Fernandes & Carvalho 2016, Gainey et al. 2015, Tan et al. 2015, Tatavarty et al. 2020), and complexes involved in protein recycling and degradation (Dörrbaum et al. 2020, Steinmetz et al. 2016). Importantly, excitatory synapses onto GABAergic interneurons can also be homeostatically adjusted (Chang et al. 2010, Gu et al. 2013, Rutherford et al. 1998), and the activity-dependent transcriptional networks activated in interneurons are distinct from those activated in pyramidal neurons to allow for a fine-tuned response (Spiegel et al. 2014). Finally, the molecular players involved in scaling down are in many cases distinct from those involved in scaling up (Chowdhury & Hell 2018, Turrigiano 2012). Altogether, it is still challenging to fit all of this information into a unified mechanistic understanding of synaptic scaling.

Inhibitory Homeostatic Plasticity

Due to the great functional diversity of inhibitory cell types, homeostatic changes at inhibitory synapses are not fully explored, and it seems that not all sources of inhibition are under homeostatic control (Chiu et al. 2018, Maffei et al. 2004, Xue et al. 2014). Inhibitory scaling up and down may also have distinct induction requirements: Upscaling can be cell-autonomously induced by elevated postsynaptic spiking (Peng et al. 2010), whereas downscaling requires the suppression of network activity (Hartman et al. 2006). The calcium dependence of inhibitory scaling has not been directly established, but it can rely on calcium-calmodulin-dependent kinase II (CaMKII) but not IV (CaMKIV) signaling (Battaglia et al. 2018, Joseph & Turrigiano 2017). Like excitatory scaling, inhibitory scaling is modulated by secreted factors, including brain-derived neurotrophic factor (BDNF) and endocannabinoids (Kim & Alger 2010, Peng et al. 2010, Rutherford et al. 1997, Swanwick et al. 2006).

To date, relatively few molecular players have been implicated in inhibitory homeostatic plasticity. These players include presynaptic GABA transporters (Gois et al. 2005, Hartmann et al. 2008), postsynaptic glycosylation of a cell adhesion molecule (Pribiag et al. 2014), the ubiquitination level of the GABA receptor β3 subunit (Saliba et al. 2007), and postsynaptic scaffold proteins (Battaglia et al. 2018, Ge et al. 2018).

Intrinsic Homeostatic Plasticity

Both synaptic scaling and IHP are driven by changes in intracellular calcium (Ibata et al. 2008, Li et al. 2020a) but likely from different calcium sources since they can be independently recruited (Maffei & Turrigiano 2008, Wen & Turrigiano 2021). There is evidence that both depend on CaMKIV signaling in vitro (Joseph & Turrigiano 2017), but conditional knockout of CaMKIV does not prevent IHP induction in vivo, suggesting that there is compensation from other kinase pathways (Trojanowski & Turrigiano 2021). In hippocampal neurons, chronic inactivity reduces extracellular signal–regulated kinase 1/2 (ERK1/2) activation to increase intrinsic excitability (Baculis et al. 2022), while elevated activity reduces intrinsic excitability through a protein kinase A (PKA)-dependent pathway (Wu et al. 2008).

IHP manifests as changes in voltage-gated ion channels in a variety of subcellular membrane compartments, and this is likely accomplished through cell biological processes that are similar to those that regulate ligand-gated ion channel trafficking and membrane accumulation. Which channels are targets of homeostatic regulation depends on cell type, and they can include sodium channels (Desai et al. 1999, Driscoll et al. 2013, Grubb & Burrone 2010), potassium channels (Cudmore et al. 2010, Henton et al. 2023, Lee et al. 2015), and hyperpolarization-activated cyclic nucleotide-gated channels (Campanac et al. 2008, van Welie et al. 2004). Understanding the mechanisms that regulate ion channel accumulation within subcellular compartments to homeostatically tune excitability will be key to understanding when and how synaptic and intrinsic homeostatic mechanisms are jointly recruited.

Activity Set Points

One of the deep remaining mysteries in the field is exactly how homeostatic activity set points are instantiated at the molecular or network level. The presumption is that neurons have a target intracellular calcium concentration, and calcium-dependent processes that regulate, for example, the kinetics of ion channel insertion and removal to achieve this target will drive the neuron to some equilibrium activity state (O'Leary et al. 2014). FRSPs are individually tuned to span a very broad mean rate distribution (Hengen et al. 2013, 2016) due to differences in synaptic and intrinsic properties (Trojanowski et al. 2021), but the molecular differences that underlie this variation are not understood. Interestingly, at the network level, FRSPs can be modified by manipulations that change mitochondrial function and energy metabolism, suggesting interactions between calcium targets and energy homeostasis (Ruggiero et al. 2021, Styr et al. 2019). Finally, whether the conservation of network features such as criticality and correlation structure emerges entirely from the interactions of cell-autonomous activity set points, or whether there exist additional network-level targets and feedback mechanisms, is unknown.

Sleep/Wake and Gating of Homeostatic Plasticity

A fascinating feature of firing rate homeostasis is that it is gated by sleep and wake states. Upward firing rate homeostasis (dependent on synaptic scaling up and IHP) only occurs during active waking states (Hengen et al. 2016) and is dependent on wake-active cholinergic inputs to V1 (Bottorff et al. 2023). In contrast, downward firing rate homeostasis (correlated with scaling down)

only happens during sleep states (Torrado Pacheco et al. 2021) and relies on state-dependent regulation of the immediate early gene product Homer1a and constitutive metabotropic glutamate receptor activity (Diering et al. 2017). The functional consequences of temporally segregating upward and downward homeostasis are not entirely clear, but this segregation might ensure strong unidirectional homeostatic compensation when it is needed most and perhaps allow unopposed Hebbian changes during limited windows of time to enable some temporal features of learning to emerge (Wu et al. 2021). Finally, an interesting possibility is that the same molecular pathways that are important for temporal gating of homeostatic plasticity could also be used to spatially restrict its induction during local forms of homeostatic plasticity.

PATHOLOGICAL CONSEQUENCES WHEN HOMEOSTASIS BREAKS DOWN

Defects in homeostatic plasticity have been described in a wide range of rodent monogenic disease models, including autism spectrum disorders (ASDs) and Alzheimer's disease (Ellingford et al. 2021, Pratt et al. 2011, Radulescu et al. 2023, Ruggiero et al. 2021, Tatavarty et al. 2020), and a number of therapeutic agents (including lithium and ketamine) have been shown to interact with the homeostatic plasticity machinery (Gideons et al. 2017, Suzuki et al. 2021, Tatavarty et al. 2020). These findings have led to widespread speculation that disruptions in the cellular building blocks of homeostatic plasticity could contribute to circuit disfunction in many neurological disorders by impairing the ability of circuits to dynamically adjust their excitability in response to developmental or experience-dependent perturbations.

Perhaps the best evidence for this is in the domain of ASDs/intellectual disability, where several high-confidence genes associated with these human disorders—including *Shank3*, *Mecp2*, *Fmr1*, and *Chd8*—lead to the impairment or absence of one or more of the cellular building blocks of homeostatic plasticity (Ellingford et al. 2021, Nelson & Valakh 2015, Park et al. 2021, Tatavarty et al. 2020). For example, loss of the synaptic scaffold protein Shank3 impairs bidirectional synaptic scaling, IHP, and vision-dependent learning (Kuhnle et al. 2022), and prevents firing rate homeostasis (Tatavarty et al. 2020). Activity-dependent changes in Shank3 phosphorylation can toggle synapses between expression of scaling up and scaling down, presumably by altering signaling within the postsynaptic density (Wu et al. 2022), and homeostatic plasticity can be restored after Shank3 loss through lithium treatment or inhibition of the lithium-sensitive glycogen synthase kinase 3 (GSK3) (Tatavarty et al. 2020), suggesting that some therapeutic effects of lithium could work through the reinstatement of homeostatic plasticity.

Interestingly, in many of these ASD models, baseline and/or sensory evoked activity in sensory cortex is relatively unimpaired (Antoine et al. 2019, Tatavarty et al. 2020), suggesting that when one homeostatic mechanism is missing, others can to some extent fill in (Antoine et al. 2019, Booker et al. 2020). Nonetheless, it seems that the loss of one or more forms of homeostatic plasticity leaves networks vulnerable to perturbations, which manifests as impaired experience-dependent plasticity or learning (Kuhnle et al. 2022, Li et al. 2020b, Tatavarty et al. 2020, Wu et al. 2021). In light of our larger discussion, this work suggests that the features of network homeostasis (firing rates, criticality, correlation structure, or memory specificity) that are dysregulated in a given disease model will depend on exactly which cellular homeostatic mechanisms are disrupted.

DISCLOSURE STATEMENT

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

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LITERATURE CITED

Abbott LF, Nelson SB. 2000. Synaptic plasticity: taming the beast. *Nat. Neurosci.* 3(Suppl.):1178–83

Antoine MW, Langberg T, Schnepel P, Feldman DE. 2019. Increased excitation-inhibition ratio stabilizes synapse and circuit excitability in four autism mouse models. *Neuron* 101(4):648–61.e4

Baculis BC, Kesavan H, Weiss AC, Kim EH, Tracy GC, et al. 2022. Homeostatic regulation of extracellular signal-regulated kinase 1/2 activity and axonal $K_v7.3$ expression by prolonged blockade of hippocampal neuronal activity. *Front. Cell. Neurosci.* 16:838419

Barnes SJ, Franzoni E, Jacobsen RI, Erdelyi F, Szabo G, et al. 2017. Deprivation-induced homeostatic spine scaling in vivo is localized to dendritic branches that have undergone recent spine loss. *Neuron* 96(4):871–82.e5

Barnes SJ, Sammons RP, Jacobsen RI, Mackie J, Keller GB, Keck T. 2015. Subnetwork-specific homeostatic plasticity in mouse visual cortex in vivo. *Neuron* 86(5):1290–303

Battaglia S, Renner M, Russeau M, Côme E, Tyagarajan SK, Lévi S. 2018. Activity-dependent inhibitory synapse scaling is determined by gephyrin phosphorylation and subsequent regulation of $GABA_A$ receptor diffusion. *eNeuro* 5(1):ENEURO.0203-17.2017

Beggs JM, Plenz D. 2004. Neuronal avalanches are diverse and precise activity patterns that are stable for many hours in cortical slice cultures. *J. Neurosci.* 24(22):5216–29

Bockaert J, Perroy J, Ango F. 2021. The complex formed by group I metabotropic glutamate receptor (mGluR) and Homer1a plays a central role in metaplasticity and homeostatic synaptic scaling. *J. Neurosci.* 41(26):5567–78

Booker SA, Simões de Oliveira L, Anstey NJ, Kozic Z, Dando OR, et al. 2020. Input-output relationship of CA1 pyramidal neurons reveals intact homeostatic mechanisms in a mouse model of fragile X syndrome. *Cell Rep.* 32(6):107988

Bottorff J, Padgett S, Turrigiano GG. 2023. Basal forebrain cholinergic activity is necessary for upward firing rate homeostasis in the rodent visual cortex. *PNAS* 121(1):e2317987121

Bourne JN, Harris KM. 2011. Coordination of size and number of excitatory and inhibitory synapses results in a balanced structural plasticity along mature hippocampal CA1 dendrites during LTP. *Hippocampus* 21(4):354–73

Bridi MCD, de Pasquale R, Lantz CL, Gu Y, Borrell A, et al. 2018. Two distinct mechanisms for experience-dependent homeostasis. *Nat. Neurosci.* 21(6):843–50

Burrone J, O'Byrne M, Murthy VN. 2002. Multiple forms of synaptic plasticity triggered by selective suppression of activity in individual neurons. *Nature* 420(6914):414–18

Buzsáki G, Mizuseki K. 2014. The log-dynamic brain: how skewed distributions affect network operations. *Nat. Rev. Neurosci.* 15(4):264–78

Campanac E, Daoudal G, Ankri N, Debanne D. 2008. Downregulation of dendritic I_h in CA1 pyramidal neurons after LTP. *J. Neurosci.* 28(34):8635–43

Cannon J, Miller P. 2016. Synaptic and intrinsic homeostasis cooperate to optimize single neuron response properties and tune integrator circuits. *J. Neurophysiol.* 116(5):2004–22

Cannon J, Miller P. 2017. Stable control of firing rate mean and variance by dual homeostatic mechanisms. *J. Math. Neurosci.* 7(1):1

Chang MC, Park JM, Pelkey KA, Grabenstatter HL, Xu D, et al. 2010. Narp regulates homeostatic scaling of excitatory synapses on parvalbumin-expressing interneurons. *Nat. Neurosci.* 13(9):1090–97

Chater TE, Goda Y. 2021. My Neighbour Hetero—deconstructing the mechanisms underlying heterosynaptic plasticity. *Curr. Opin. Neurobiol.* 67:106–14

Chen JL, Nedivi E. 2013. Highly specific structural plasticity of inhibitory circuits in the adult neocortex. *Neuroscientist* 19(4):384–93

Chen L, Li X, Tjia M, Thapliyal S. 2022. Homeostatic plasticity and excitation-inhibition balance: the good, the bad, and the ugly. *Curr. Opin. Neurobiol.* 75:102553

Chen S, Benninger F, Yaari Y. 2014. Role of small conductance Ca^{2+}-activated K^+ channels in controlling CA1 pyramidal cell excitability. *J. Neurosci.* 34(24):8219–30

Chipman PH, Fetter RD, Panzera LC, Bergerson SJ, Karmelic D, et al. 2022. NMDAR-dependent presynaptic homeostasis in adult hippocampus: synapse growth and cross-modal inhibitory plasticity. *Neuron* 110(20):3302–317.e7

Chiu CQ, Barberis A, Higley MJ. 2019. Preserving the balance: diverse forms of long-term GABAergic synaptic plasticity. *Nat. Rev. Neurosci.* 20(5):272–81

Chiu CQ, Martenson JS, Yamazaki M, Natsume R, Sakimura K, et al. 2018. Input-specific NMDAR-dependent potentiation of dendritic GABAergic inhibition. *Neuron* 97(2):368–77.e3

Chowdhury D, Hell JW. 2018. Homeostatic synaptic scaling: molecular regulators of synaptic AMPA-type glutamate receptors. *F1000Research* 7:234

Cocchi L, Gollo LL, Zalesky A, Breakspear M. 2017. Criticality in the brain: a synthesis of neurobiology, models and cognition. *Prog. Neurobiol.* 158:132–52

Compans B, Burrone J. 2023. Chandelier cells shine a light on the formation of GABAergic synapses. *Curr. Opin. Neurobiol.* 80:102697

Cudmore RH, Fronzaroli-Molinieres L, Giraud P, Debanne D. 2010. Spike-time precision and network synchrony are controlled by the homeostatic regulation of the D-type potassium current. *J. Neurosci.* 30(38):12885–95

Daoudal G, Debanne D. 2003. Long-term plasticity of intrinsic excitability: learning rules and mechanisms. *Learn. Mem.* 10(6):456–65

Davis GW, Müller M. 2015. Homeostatic control of presynaptic neurotransmitter release. *Annu. Rev. Physiol.* 77:251–70

Desai NS, Cudmore RH, Nelson SB, Turrigiano GG. 2002. Critical periods for experience-dependent synaptic scaling in visual cortex. *Nat. Neurosci.* 5(8):783–89

Desai NS, Rutherford LC, Turrigiano GG. 1999. Plasticity in the intrinsic excitability of cortical pyramidal neurons. *Nat. Neurosci.* 2(6):515–20

Desch K, Langer JD, Schuman EM. 2021. Dynamic bi-directional phosphorylation events associated with the reciprocal regulation of synapses during homeostatic up- and down-scaling. *Cell Rep.* 36(8):109583

Dhawale AK, Poddar R, Wolff SB, Normand VA, Kopelowitz E, Ölveczky BP. 2017. Automated long-term recording and analysis of neural activity in behaving animals. *eLife* 6:e27702

Diering GH, Nirujogi RS, Roth RH, Worley PF, Pandey A, Huganir RL. 2017. Homer1a drives homeostatic scaling-down of excitatory synapses during sleep. *Science* 355(6324):511–15

Dörrbaum AR, Alvarez-Castelao B, Nassim-Assir B, Langer JD, Schuman EM. 2020. Proteome dynamics during homeostatic scaling in cultured neurons. *eLife* 9:e52939

Driscoll HE, Muraro NI, He M, Baines RA. 2013. Pumilio-2 regulates translation of $Na_v1.6$ to mediate homeostasis of membrane excitability. *J. Neurosci.* 33(23):9644–54

Dubes S, Soula A, Benquet S, Tessier B, Poujol C, et al. 2022. miR-124-dependent tagging of synapses by synaptopodin enables input-specific homeostatic plasticity. *EMBO. J.* 41(20):e109012

Echegoyen J, Neu A, Graber KD, Soltesz I. 2007. Homeostatic plasticity studied using in vivo hippocampal activity-blockade: synaptic scaling, intrinsic plasticity and age-dependence. *PLOS ONE* 2(8):e700

El-Boustani S, Ip JPK, Breton-Provencher V, Knott GW, Okuno H, et al. 2018. Locally coordinated synaptic plasticity of visual cortex neurons in vivo. *Science* 360(6395):1349–54

Ellingford RA, Panasiuk MJ, De Meritens ER, Shaunak R, Naybour L, et al. 2021. Cell-type-specific synaptic imbalance and disrupted homeostatic plasticity in cortical circuits of ASD-associated *Chd8* haploinsufficient mice. *Mol. Psychiatry* 26(7):3614–24

Espinosa JS, Stryker MP. 2012. Development and plasticity of the primary visual cortex. *Neuron* 75(2):230–49

Fernandes D, Carvalho AL. 2016. Mechanisms of homeostatic plasticity in the excitatory synapse. *J. Neurochem.* 139(6):973–96

Fong M, Newman JP, Potter SM, Wenner P. 2015. Upward synaptic scaling is dependent on neurotransmission rather than spiking. *Nat. Commun.* 6(1):6339

Frank CA, James TD, Müller M. 2020. Homeostatic control of *Drosophila* neuromuscular junction function. *Synapse* 74(1):e22133

Gainey MA, Aman JW, Feldman DE. 2018. Rapid disinhibition by adjustment of PV intrinsic excitability during whisker map plasticity in mouse S1. *J. Neurosci.* 38(20):4749–61

Gainey MA, Feldman DE. 2017. Multiple shared mechanisms for homeostatic plasticity in rodent somatosensory and visual cortex. *Philos. Trans. R. Soc. B* 372(1715):20160157

Gainey MA, Hurvitz-Wolff JR, Lambo ME, Turrigiano GG. 2009. Synaptic scaling requires the GluR2 subunit of the AMPA receptor. *J. Neurosci.* 29(20):6479–89

Gainey MA, Tatavarty V, Nahmani M, Lin H, Turrigiano GG. 2015. Activity-dependent synaptic GRIP1 accumulation drives synaptic scaling up in response to action potential blockade. *PNAS* 112(27):E3590–99

Ge Y, Kang Y, Cassidy RM, Moon K-M, Lewis R, et al. 2018. Clptm1 limits forward trafficking of $GABA_A$ receptors to scale inhibitory synaptic strength. *Neuron* 97(3):596–610.e8

Gideons ES, Lin P-Y, Mahgoub M, Kavalali ET, Monteggia LM. 2017. Chronic lithium treatment elicits its antimanic effects via BDNF-TrkB dependent synaptic downscaling. *eLife* 6:e25480

Goel P, Dickman D. 2021. Synaptic homeostats: latent plasticity revealed at the *Drosophila* neuromuscular junction. *Cell. Mol. Life Sci.* 78(7):3159–79

Gois SD, Schäfer MK-H, Defamie N, Chen C, Ricci A, et al. 2005. Homeostatic scaling of vesicular glutamate and GABA transporter expression in rat neocortical circuits. *J. Neurosci.* 25(31):7121–33

Gonzalez-Islas C, Wenner P. 2006. Spontaneous network activity in the embryonic spinal cord regulates AMPAergic and GABAergic synaptic strength. *Neuron* 49(4):563–75

Goold CP, Nicoll RA. 2010. Single-cell optogenetic excitation drives homeostatic synaptic depression. *Neuron* 68(3):512–28

Greenhill SD, Ranson A, Fox K. 2015. Hebbian and homeostatic plasticity mechanisms in regular spiking and intrinsic bursting cells of cortical layer 5. *Neuron* 88(3):539–52

Grubb MS, Burrone J. 2010. Activity-dependent relocation of the axon initial segment fine-tunes neuronal excitability. *Nature* 465(7301):1070–74

Gu Y, Huang S, Chang MC, Worley P, Kirkwood A, Quinlan EM. 2013. Obligatory role for the immediate early gene NARP in critical period plasticity. *Neuron* 79(2):335–46

Haider B, Duque A, Hasenstaub AR, McCormick DA. 2006. Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. *J. Neurosci.* 26(17):4535–45

Haider B, McCormick DA. 2009. Rapid neocortical dynamics: cellular and network mechanisms. *Neuron* 62(2):171–89

Hanes AL, Koesters AG, Fong M, Altimimi HF, Stellwagen D, et al. 2020. Divergent synaptic scaling of miniature EPSCs following activity blockade in dissociated neuronal cultures. *J. Neurosci.* 40(21):4090–102

Harms KJ, Tovar KR, Craig AM. 2005. Synapse-specific regulation of AMPA receptor subunit composition by activity. *J. Neurosci.* 25(27):6379–88

Hartman KN, Pal SK, Burrone J, Murthy VN. 2006. Activity-dependent regulation of inhibitory synaptic transmission in hippocampal neurons. *Nat. Neurosci.* 9(5):642–49

Hartmann K, Bruehl C, Golovko T, Draguhn A. 2008. Fast homeostatic plasticity of inhibition via activity-dependent vesicular filling. *PLOS ONE* 3(8):e2979

Hengen KB, Lambo ME, Van Hooser SD, Katz DB, Turrigiano GG. 2013. Firing rate homeostasis in visual cortex of freely behaving rodents. *Neuron* 80(2):335–42

Hengen KB, Torrado Pacheco A, McGregor JN, Van Hooser SD, Turrigiano GG. 2016. Neuronal firing rate homeostasis is inhibited by sleep and promoted by wake. *Cell* 165(1):180–91

Henton A, Zhao Y, Tzounopoulos T. 2023. A role for KCNQ channels on cell type-specific plasticity in mouse auditory cortex after peripheral damage. *J. Neurosci.* 43(13):2277–90

Hou Q, Zhang D, Jarzylo L, Huganir RL, Man H-Y. 2008. Homeostatic regulation of AMPA receptor expression at single hippocampal synapses. *PNAS* 105(2):775–80

House DRC, Elstrott J, Koh E, Chung J, Feldman DE. 2011. Parallel regulation of feedforward inhibition and excitation during whisker map plasticity. *Neuron* 72(5):819–31

Iascone DM, Li Y, Sümbül U, Doron M, Chen H, et al. 2020. Whole-neuron synaptic mapping reveals spatially precise excitatory/inhibitory balance limiting dendritic and somatic spiking. *Neuron* 106(4):566–78.e8

Ibata K, Sun Q, Turrigiano GG. 2008. Rapid synaptic scaling induced by changes in postsynaptic firing. *Neuron* 57(6):819–26

Isaacson JS, Scanziani M. 2011. How inhibition shapes cortical activity. *Neuron* 72(2):231–43

Jones EG. 1993. GABAergic neurons and their role in cortical plasticity in primates. *Cereb. Cortex* 3(5):361–72

Joseph A, Turrigiano GG. 2017. All for one but not one for all: Excitatory synaptic scaling and intrinsic excitability are coregulated by CaMKIV, whereas inhibitory synaptic scaling is under independent control. *J. Neurosci.* 37(28):6778–85

Kaneko M, Stellwagen D, Malenka RC, Stryker MP. 2008. Tumor necrosis factor-α mediates one component of competitive, experience-dependent plasticity in developing visual cortex. *Neuron* 58(5):673–80

Karmarkar UR, Buonomano DV. 2006. Different forms of homeostatic plasticity are engaged with distinct temporal profiles. *Eur. J. Neurosci.* 23(6):1575–84

Kavalali ET, Monteggia LM. 2023. Rapid homeostatic plasticity and neuropsychiatric therapeutics. *Neuropsychopharmacology* 48(1):54–60

Keck T, Hübener M, Bonhoeffer T. 2017a. Interactions between synaptic homeostatic mechanisms: an attempt to reconcile BCM theory, synaptic scaling, and changing excitation/inhibition balance. *Curr. Opin. Neurobiol.* 43:87–93

Keck T, Keller GB, Jacobsen RI, Eysel UT, Bonhoeffer T, Hübener M. 2013. Synaptic scaling and homeostatic plasticity in the mouse visual cortex in vivo. *Neuron* 80(2):327–34

Keck T, Toyoizumi T, Chen L, Doiron B, Feldman DE, et al. 2017b. Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions. *Philos. Trans. R. Soc. B* 372(1715):20160158

Kilman V, van Rossum MCW, Turrigiano GG. 2002. Activity deprivation reduces miniature IPSC amplitude by decreasing the number of postsynaptic $GABA_A$ receptors clustered at neocortical synapses. *J. Neurosci.* 22(4):1328–37

Kim J, Alger BE. 2010. Reduction in endocannabinoid tone is a homeostatic mechanism for specific inhibitory synapses. *Nat. Neurosci.* 13(5):592–600

Kim J, Tsien RW. 2008. Synapse-specific adaptations to inactivity in hippocampal circuits achieve homeostatic gain control while dampening network reverberation. *Neuron* 58(6):925–37

Kotak VC, Fujisawa S, Lee FA, Karthikeyan O, Aoki C, Sanes DH. 2005. Hearing loss raises excitability in the auditory cortex. *J. Neurosci.* 25(15):3908–18

Kuhlman SJ, Olivas ND, Tring E, Ikrar T, Xu X, Trachtenberg JT. 2013. A disinhibitory microcircuit initiates critical-period plasticity in the visual cortex. *Nature* 501(7468):543–46

Kuhnle CG, Grimes M, Suárez Casanova VM, Turrigiano GG, Van Hooser SD. 2022. Juvenile Shank3 KO mice adopt distinct hunting strategies during prey capture learning. *eNeuro* 9(6):ENEURO.0230-22.2022

Lambo ME, Turrigiano GG. 2013. Synaptic and intrinsic homeostatic mechanisms cooperate to increase L2/3 pyramidal neuron excitability during a late phase of critical period plasticity. *J. Neurosci.* 33(20):8810–19

Lee H-K, Kirkwood A. 2019. Mechanisms of homeostatic synaptic plasticity in vivo. *Front. Cell. Neurosci.* 13:520

Lee KY, Royston SE, Vest MO, Ley DJ, Lee S, et al. 2015. *N*-methyl-D-aspartate receptors mediate activity-dependent down-regulation of potassium channel genes during the expression of homeostatic intrinsic plasticity. *Mol. Brain.* 8(1):4

Lefort S, Gray AC, Turrigiano GG. 2013. Long-term inhibitory plasticity in visual cortical layer 4 switches sign at the opening of the critical period. *PNAS* 110(47):E4540–47

Letellier M, Levet F, Thoumine O, Goda Y. 2019. Differential role of pre- and postsynaptic neurons in the activity-dependent control of synaptic strengths across dendrites. *PLOS Biol.* 17(6):e2006223

Li B, Suutari BS, Sun SD, Luo Z, Wei C, et al. 2020a. Neuronal inactivity co-opts LTP machinery to drive potassium channel splicing and homeostatic spike widening. *Cell* 181(7):1547–65.e15

Li J, Jiang RY, Arendt KL, Hsu Y-T, Zhai SR, Chen L. 2020b. Defective memory engram reactivation underlies impaired fear memory recall in fragile X syndrome. *eLife* 9:e61882

Li L, Gainey MA, Goldbeck JE, Feldman DE. 2014. Rapid homeostasis by disinhibition during whisker map plasticity. *PNAS* 111(4):1616–21

Lim S, McKee JL, Woloszyn L, Amit Y, Freedman DJ, et al. 2015. Inferring learning rules from distributions of firing rates in cortical neurons. *Nat. Neurosci.* 18(12):1804–10

Lombardo J, Sun J, Harrington MA. 2018. Rapid activity-dependent modulation of the intrinsic excitability through up-regulation of KCNQ/Kv7 channel function in neonatal spinal motoneurons. *PLOS ONE* 13(3):e0193948

Losonczy A, Makara JK, Magee JC. 2008. Compartmentalized dendritic plasticity and input feature storage in neurons. *Nature* 452(7186):436–41

Ma Z, Turrigiano GG, Wessel R, Hengen KB. 2019. Cortical circuit dynamics are homeostatically tuned to criticality in vivo. *Neuron* 104(4):655–64.e4

Maffei A, Nataraj K, Nelson SB, Turrigiano GG. 2006. Potentiation of cortical inhibition by visual deprivation. *Nature* 443(7107):81–84

Maffei A, Nelson SB, Turrigiano GG. 2004. Selective reconfiguration of layer 4 visual cortical circuitry by visual deprivation. *Nat. Neurosci.* 7(12):1353–59

Maffei A, Turrigiano GG. 2008. Multiple modes of network homeostasis in visual cortical layer 2/3. *J. Neurosci.* 28(17):4377–84

Marder E, Goaillard J-M. 2006. Variability, compensation and homeostasis in neuron and network function. *Nat. Rev. Neurosci.* 7(7):563–74

Marder E, Prinz AA. 2002. Modeling stability in neuron and network function: the role of activity in homeostasis. *BioEssays* 24(12):1145–54

McFarlan AR, Chou CYC, Watanabe A, Cherepacha N, Haddad M, et al. 2023. The plasticitome of cortical interneurons. *Nat. Rev. Neurosci.* 24(2):80–97

Morales B, Choi S-Y, Kirkwood A. 2002. Dark rearing alters the development of GABAergic transmission in visual cortex. *J. Neurosci.* 22(18):8084–90

Morgan PJ, Bourboulou R, Filippi C, Koenig-Gambini J, Epsztein J. 2019. Kv1.1 contributes to a rapid homeostatic plasticity of intrinsic excitability in CA1 pyramidal neurons in vivo. *eLife* 8:e49915

Mrsic-Flogel TD, Hofer SB, Ohki K, Reid RC, Bonhoeffer T, Hübener M. 2007. Homeostatic regulation of eye-specific responses in visual cortex during ocular dominance plasticity. *Neuron* 54(6):961–72

Nair AG, Muttathukunnel P, Müller M. 2021. Distinct molecular pathways govern presynaptic homeostatic plasticity. *Cell Rep*. 37(11):110105

Nelson SB, Valakh V. 2015. Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. *Neuron* 87(4):684–98

Noda T, Kienle E, Eppler J-B, Aschauer DF, Kaschube M, et al. 2023. Homeostasis of a representational map in the neocortex. bioRxiv 2023.06.13.544358. **https://doi.org/10.1101/2023.06.13.544358**

Oh WC, Parajuli LK, Zito K. 2015. Heterosynaptic structural plasticity on local dendritic segments of hippocampal CA1 neurons. *Cell Rep*. 10(2):162–69

O'Leary T, van Rossum MCW, Wyllie DJA. 2010. Homeostasis of intrinsic excitability in hippocampal neurones: dynamics and mechanism of the response to chronic depolarization. *J. Physiol.* 588(1):157–70

O'Leary T, Williams AH, Franci A, Marder E. 2014. Cell types, network homeostasis, and pathological compensation from a biologically plausible ion channel expression model. *Neuron* 82(4):809–21

Pan-Vazquez A, Wefelmeyer W, Sabater VG, Neves G, Burrone J. 2020. Activity-dependent plasticity of axo-axonic synapses at the axon initial segment. *Neuron* 106(2):265–76.e6

Park E, Lau AG, Arendt KL, Chen L. 2021. FMRP interacts with RARα in synaptic retinoic acid signaling and homeostatic synaptic plasticity. *Int. J. Mol. Sci.* 22(12):6579

Pekala D, Wenner P. 2022. The uniform and nonuniform nature of slow and rapid scaling in embryonic motoneurons. *J. Neurosci.* 42(7):1224–34

Peng Y-R, Zeng S-Y, Song H-L, Li M-Y, Yamada MK, Yu X. 2010. Postsynaptic spiking homeostatically induces cell-autonomous regulation of inhibitory inputs via retrograde signaling. *J. Neurosci.* 30(48):16220–31

Pérez-Otaño I, Ehlers MD. 2005. Homeostatic plasticity and NMDA receptor trafficking. *Trends Neurosci*. 28(5):229–38

Poirazi P, Brannon T, Mel BW. 2003. Pyramidal neuron as two-layer neural network. *Neuron* 37(6):989–99
Pozo K, Goda Y. 2010. Unraveling mechanisms of homeostatic synaptic plasticity. *Neuron* 66(3):337–51
Pratt KG, Zimmerman EC, Cook DG, Sullivan JM. 2011. Presenilin 1 regulates homeostatic synaptic scaling through Akt signaling. *Nat. Neurosci.* 14(9):1112–14
Pribiag H, Peng H, Shah WA, Stellwagen D, Carbonetto S. 2014. Dystroglycan mediates homeostatic synaptic plasticity at GABAergic synapses. *PNAS* 111(18):6810–15
Rabinowitch I, Segev I. 2006. The interplay between homeostatic synaptic plasticity and functional dendritic compartments. *J. Neurophysiol.* 96(1):276–83
Radulescu CI, Doostdar N, Zabouri N, Melgosa-Ecenarro L, Wang X, et al. 2023. Age-related dysregulation of homeostatic control in neuronal microcircuits. *Nat. Neurosci.* 26:2158–70
Rannals MD, Kapur J. 2011. Homeostatic strengthening of inhibitory synapses is mediated by the accumulation of $GABA_A$ receptors. *J. Neurosci.* 31(48):17701–12
Ranson A, Cheetham CEJ, Fox K, Sengpiel F. 2012. Homeostatic plasticity mechanisms are required for juvenile, but not adult, ocular dominance plasticity. *PNAS* 109(4):1311–16
Reese AL, Kavalali ET. 2015. Spontaneous neurotransmission signals through store-driven Ca^{2+} transients to maintain synaptic homeostasis. *eLife* 4:e09262
Reimers JM, Loweth JA, Wolf ME. 2014. BDNF contributes to both rapid and homeostatic alterations in AMPA receptor surface expression in nucleus accumbens medium spiny neurons. *Eur. J. Neurosci.* 39(7):1159–69
Ribic A. 2020. Stability in the face of change: lifelong experience-dependent plasticity in the sensory cortex. *Front. Cell. Neurosci.* 14:76
Rodriguez G, Mesik L, Gao M, Parkins S, Saha R, Lee H-K. 2019. Disruption of NMDAR function prevents normal experience-dependent homeostatic synaptic plasticity in mouse primary visual cortex. *J. Neurosci.* 39(39):7664–73
Rose T, Jaepel J, Hübener M, Bonhoeffer T. 2016. Cell-specific restoration of stimulus preference after monocular deprivation in the visual cortex. *Science* 352(6291):1319–22
Ruggiero A, Katsenelson M, Slutsky I. 2021. Mitochondria: new players in homeostatic regulation of firing rate set points. *Trends Neurosci*. 44(8):605–18
Rule ME, O'Leary T. 2022. Self-healing codes: how stable neural populations can track continually reconfiguring neural representations. *PNAS* 119(7):e2106692119
Rutherford LC, DeWan A, Lauer HM, Turrigiano GG. 1997. Brain-derived neurotrophic factor mediates the activity-dependent regulation of inhibition in neocortical cultures. *J. Neurosci.* 17(12):4527–35
Rutherford LC, Nelson SB, Turrigiano GG. 1998. BDNF has opposite effects on the quantal amplitude of pyramidal neuron and interneuron excitatory synapses. *Neuron* 21(3):521–30
Saliba RS, Michels G, Jacob TC, Pangalos MN, Moss SJ. 2007. Activity-dependent ubiquitination of $GABA_A$ receptors regulates their accumulation at synaptic sites. *J. Neurosci.* 27(48):13341–51
Sanes DH, Kotak VC. 2011. Developmental plasticity of auditory cortical inhibitory synapses. *Hear. Res.* 279(1):140–48
Schanzenbächer CT, Langer JD, Schuman EM. 2018. Time- and polarity-dependent proteomic changes associated with homeostatic scaling at central synapses. *eLife* 7:e33322
Schanzenbächer CT, Sambandan S, Langer JD, Schuman EM. 2016. Nascent proteome remodeling following homeostatic scaling at hippocampal synapses. *Neuron* 92(2):358–71
Schaukowitch K, Reese AL, Kim S-K, Kilaru G, Joo J-Y, et al. 2017. An intrinsic transcriptional program underlying synaptic scaling during activity suppression. *Cell Rep.* 18(6):1512–26
Sehgal M, Song C, Ehlers VL, Moyer JR. 2013. Learning to learn—intrinsic plasticity as a metaplasticity mechanism for memory formation. *Neurobiol. Learn. Mem.* 105:186–99
Shew WL, Clawson WP, Pobst J, Karimipanah Y, Wright NC, Wessel R. 2015. Adaptation to sensory input tunes visual cortex to criticality. *Nat. Phys.* 11(8):659–63
Shew WL, Plenz D. 2013. The functional benefits of criticality in the cortex. *Neuroscientist* 19(1):88–100
Slomowitz E, Styr B, Vertkin I, Milshtein-Parush H, Nelken I, et al. 2015. Interplay between population firing stability and single neuron dynamics in hippocampal networks. *eLife* 4:e04378
Sohal VS, Rubenstein JLR. 2019. Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. *Mol. Psychiatry* 24(9):1248–57

Spiegel I, Mardinly AR, Gabel HW, Bazinet JE, Couch CH, et al. 2014. Npas4 regulates excitatory-inhibitory balance within neural circuits through cell-type-specific gene programs. *Cell* 157(5):1216–29

Steinmetz CC, Tatavarty V, Sugino K, Shima Y, Joseph A, et al. 2016. Upregulation of μ3A drives homeostatic plasticity by rerouting AMPAR into the recycling endosomal pathway. *Cell Rep*. 16(10):2711–22

Steinmetz CC, Turrigiano GG. 2010. Tumor necrosis factor-α signaling maintains the ability of cortical synapses to express synaptic scaling. *J. Neurosci.* 30(44):14685–90

Stellwagen D, Malenka RC. 2006. Synaptic scaling mediated by glial TNF-α. *Nature* 440(7087):1054–59

Styr B, Gonen N, Zarhin D, Ruggiero A, Atsmon R, et al. 2019. Mitochondrial regulation of the hippocampal firing rate set point and seizure susceptibility. *Neuron* 102(5):1009–24.e8

Sutton MA, Ito HT, Cressy P, Kempf C, Woo JC, Schuman EM. 2006. Miniature neurotransmission stabilizes synaptic function via tonic suppression of local dendritic protein synthesis. *Cell* 125(4):785–99

Sutton MA, Taylor AM, Ito HT, Pham A, Schuman EM. 2007. Postsynaptic decoding of neural activity: eEF2 as a biochemical sensor coupling miniature synaptic transmission to local protein synthesis. *Neuron* 55(4):648–61

Suzuki K, Kim J-W, Nosyreva E, Kavalali ET, Monteggia LM. 2021. Convergence of distinct signaling pathways on synaptic scaling to trigger rapid antidepressant action. *Cell Rep*. 37(5):109918

Swanwick CC, Murthy NR, Kapur J. 2006. Activity-dependent scaling of GABAergic synapse strength is regulated by brain-derived neurotrophic factor. *Mol. Cell. Neurosci.* 31(3):481–92

Sweatt JD. 2016. Dynamic DNA methylation controls glutamate receptor trafficking and synaptic scaling. *J. Neurochem.* 137(3):312–30

Takesian AE, Kotak VC, Sanes DH. 2011. Age-dependent effect of hearing loss on cortical inhibitory synapse function. *J. Neurophysiol.* 107(3):937–47

Tan HL, Queenan BN, Huganir RL. 2015. GRIP1 is required for homeostatic regulation of AMPAR trafficking. *PNAS* 112(32):10026–31

Tao HW, Poo M. 2005. Activity-dependent matching of excitatory and inhibitory inputs during refinement of visual receptive fields. *Neuron* 45(6):829–36

Tatavarty V, Torrado Pacheco A, Groves Kuhnle C, Lin H, Koundinya P, et al. 2020. Autism-associated Shank3 is essential for homeostatic compensation in rodent V1. *Neuron* 106(5):769–77.e4

Teichert M, Liebmann L, Hübner CA, Bolz J. 2017. Homeostatic plasticity and synaptic scaling in the adult mouse auditory cortex. *Sci. Rep.* 7(1):17423

Thalhammer A, Cingolani LA. 2014. Cell adhesion and homeostatic synaptic plasticity. *Neuropharmacology* 78:23–30

Tien N-W, Kerschensteiner D. 2018. Homeostatic plasticity in neural development. *Neural Dev*. 13(1):9

Torrado Pacheco A, Bottorff J, Gao Y, Turrigiano GG. 2021. Sleep promotes downward firing rate homeostasis. *Neuron* 109(3):530–44.e6

Torrado Pacheco A, Tilden EI, Grutzner SM, Lane BJ, Wu Y, et al. 2019. Rapid and active stabilization of visual cortical firing rates across light-dark transitions. *PNAS* 116(36):18068–77

Trojanowski NF, Bottorff J, Turrigiano GG. 2021. Activity labeling in vivo using CaMPARI2 reveals intrinsic and synaptic differences between neurons with high and low firing rate set points. *Neuron* 109(4):663–76.e5

Trojanowski NF, Turrigiano GG. 2021. CaMKIV signaling is not essential for the maintenance of intrinsic or synaptic properties in mouse visual cortex. *eNeuro* 8(4):ENEURO.0135-21.2021

Turrigiano GG. 2008. The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* 135(3):422–35

Turrigiano GG. 2011. Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. *Annu. Rev. Neurosci.* 34:89–103

Turrigiano GG. 2012. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb. Perspect. Biol.* 4(1):a005736

Turrigiano GG. 2017. The dialectic of Hebb and homeostasis. *Philos. Trans. R. Soc. B* 372(1715):20160258

Turrigiano GG, Abbott LF, Marder E. 1994. Activity-dependent changes in the intrinsic properties of cultured neurons. *Science* 264(5161):974–77

Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. 1998. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* 391(6670):892–96

Turrigiano GG, Nelson SB. 2004. Homeostatic plasticity in the developing nervous system. *Nat. Rev. Neurosci.* 5(2):97–107

Valakh V, Wise D, Zhu XA, Sha M, Fok J, et al. 2023. A transcriptional constraint mechanism limits the homeostatic response to activity deprivation in mammalian neocortex. *eLife* 12:e74899

van Welie I, van Hooft JA, Wadman WJ. 2004. Homeostatic scaling of neuronal excitability by synaptic modulation of somatic hyperpolarization-activated Ih channels. *PNAS* 101(14):5123–28

Wefelmeyer W, Puhl CJ, Burrone J. 2016. Homeostatic plasticity of subcellular neuronal structures: from inputs to outputs. *Trends Neurosci.* 39(10):656–67

Wen W, Turrigiano GG. 2021. Developmental regulation of homeostatic plasticity in mouse primary visual cortex. *J. Neurosci.* 41(48):9891–905

Wenner P. 2014. Homeostatic synaptic plasticity in developing spinal networks driven by excitatory GABAergic currents. *Neuropharmacology* 78:55–62

Wierenga CJ, Ibata K, Turrigiano GG. 2005. Postsynaptic expression of homeostatic plasticity at neocortical synapses. *J. Neurosci.* 25(11):2895–905

Wilmes KA, Clopath C. 2023. Dendrites help mitigate the plasticity-stability dilemma. *Sci. Rep.* 13(1):6543

Wu C-H, Ramos R, Katz DB, Turrigiano GG. 2021. Homeostatic synaptic scaling establishes the specificity of an associative memory. *Curr. Biol.* 31(11):2274–85.e5

Wu C-H, Tatavarty V, Jean Beltran PM, Guerrero AA, Keshishian H, et al. 2022. A bidirectional switch in the Shank3 phosphorylation state biases synapses toward up- or downscaling. *eLife* 11:e74277

Wu WW, Chan CS, Surmeier DJ, Disterhoft JF. 2008. Coupling of L-type Ca^{2+} channels to K_V7/KCNQ channels creates a novel, activity-dependent, homeostatic intrinsic plasticity. *J. Neurophysiol.* 100(4):1897–908

Wu YK, Hengen KB, Turrigiano GG, Gjorgjieva J. 2020. Homeostatic mechanisms regulate distinct aspects of cortical circuit dynamics. *PNAS* 117(39):24514–25

Xue M, Atallah BV, Scanziani M. 2014. Equalizing excitation-inhibition ratios across visual cortical neurons. *Nature* 511(7511):596–600

Yang S, Weiner BD, Zhang LS, Cho S-J, Bao S. 2011. Homeostatic plasticity drives tinnitus perception in an animal model. *PNAS* 108(36):14974–79

Zbili M, Rama S, Benitez M-J, Fronzaroli-Molinieres L, Bialowas A, et al. 2021. Homeostatic regulation of axonal Kv1.1 channels accounts for both synaptic and intrinsic modifications in the hippocampal CA3 circuit. *PNAS* 118(47):e2110601118

Zhang W, Linden DJ. 2003. The other side of the engram: experience-driven changes in neuronal intrinsic excitability. *Nat. Rev. Neurosci.* 4(11):885–900

Zubov T, Do Amaral-Silva L, Santin JM. 2022. Inactivity and Ca^{2+} signaling regulate synaptic compensation in motoneurons following hibernation in American bullfrogs. *Sci. Rep.* 12(1):11610