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The dialectic of Hebb and homeostasis

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It has become widely accepted that homeostatic and Hebbian plasticity mechanisms work hand in glove to refine neural circuit function. Nonetheless, our understanding of how these fundamentally distinct forms of plasticity compliment (and under some circumstances interfere with) each other remains rudimentary. Here, I describe some of the recent progress of the field, as well as some of the deep puzzles that remain. These include unravelling the spatial and temporal scales of different homeostatic and Hebbian mechanisms, determining which aspects of network function are under homeostatic control, and understanding when and how homeostatic and Hebbian mechanisms must be segregated within neural circuits to prevent interference.

This article is part of the themed issue 'Integrating Hebbian and homeostatic plasticity'.

1. Introduction

It has now been 18 years since the first publication on synaptic scaling [1]. This study demonstrates the existence of a form of synaptic plasticity with fundamentally different characteristics from 'Hebbian' mechanisms such as long-term potentiation (LTP) and long-term depression (LTD), and suggests that synaptic scaling could serve to counteract the destabilizing forces induced by learning or experience-dependent plasticity. Initial reactions to the manuscript were (in retrospect) entertainingly polarized: one reviewer considered the entire theoretical problem to be 'ill-posed', and a second reviewer called our invocation of this stability problem 'a naive theoretical need'. Luckily, the third reviewer saved our bacon by describing the study as a 'stunning, groundbreaking piece of work . . . which opens wide the door to a new viewpoint on synaptic plasticity'.[1] Since the publication of this work, there has been a growing acceptance of the idea that stabilizing plasticity mechanisms are critical for many aspects of proper circuit function, and an explosion of work in what has become an entire field of homeostatic plasticity. This collective effort has uncovered a rich variety of plasticity mechanisms—operating over distinct spatial and temporal scales—that fit roughly within the fold of homeostatic plasticity (see for example volume 78 of *Neuropharmacology*, 2014 on homeostatic plasticity [2]). While the field has come a long way, we still do not fully understand how homeostatic and Hebbian mechanisms cooperate to enable, shape and constrain microcircuit plasticity. Here, I ruminate on some of the progress, as well as the remaining puzzles, in the field. Of necessity, this is not a comprehensive review, and focuses on only a few of the many forms of homeostatic and Hebbian plasticity, and the issues raised by considering how they interact with each other within complex networks.

2. Synaptic scaling and firing rate set points

There are many excellent and thorough reviews on synaptic scaling [3] and homeostatic plasticity in general [2,4–6], so I will not present all the detailed evidence for or against my assertions below—consider this my personal read of the current state of the field. I start with synaptic scaling. In many cell types, there is solid evidence for the existence of a form of synaptic plasticity, synaptic scaling, that operates in a global manner to homeostatically adjust the postsynaptic weights of excitatory synapses [3]. In reduced systems, one can demonstrate that this form of plasticity operates in a global and multiplicative manner, in effect 'scaling' postsynaptic strength up or down [1]. These adjustments likely involve spike-mediated changes in calcium influx and gene expression, and appear to operate largely cell autonomously—by which I mean neurons adjust synaptic weights in response to changes in their own firing. Further, a form of plasticity with these 'phenotypic' characteristics (as well as some of the molecular signatures) of synaptic scaling has been demonstrated *in vivo* in response to a number of sensory or activity-deprivation paradigms [7–11].

What is it about synaptic scaling that qualifies it as 'homeostatic'? It is obviously 'compensatory', in that reduced firing increases excitatory drive, and vice versa. However, the formal definition of a homeostatic system is that it operates in a negative feedback manner, so that when the system deviates from a set point value, an ensuing error signal triggers compensatory mechanisms that bring the system precisely back to this set point. In the case of synaptic scaling, there is considerable evidence that the variable under control is some function of average neuronal firing rate [1,10,12–14]: pharmacological, genetic or sensory manipulations that perturb firing induce synaptic scaling (as well as other homeostatic mechanisms, see below) that cooperate to slowly bring firing precisely back to this firing rate set point. Taken together, the evidence suggests that any force that perturbs firing over a long(-ish) timescale—be it Hebbian changes in the strengths of specific inputs or developmental (or pathological) changes in synapse number—will initiate synaptic scaling, which then slowly modifies synaptic strengths until firing rates are restored. The timescale over which perturbations in firing are sensed and integrated, and the speed of the resulting homeostatic compensation, are still not entirely clear. On a theoretical level, the existence of 'firing rate set points' in neocortical neurons provides a means for circuits to self-tune excitability over long timescales to prevent the development of hypo- or hyperexcitable states [4]. Exactly how big a contribution synaptic scaling makes to this process of firing rate homeostasis (FRH), and how much is achieved through other homeostatic mechanisms, remains unknown.

There is a large literature suggesting that homeostatic mechanisms *in vitro* are largely cell autonomous. For example, you can block or induce synaptic scaling by manipulating the firing or molecular environment of individual neurons, while leaving the rest of the network intact [15–17]. This raises the question of whether FRH is also a cell-autonomous process in which individual neurons regulate their firing around an individual firing rate set point. A recent study that chronically monitored firing rates in cultured cortical neurons concluded that, although the ensemble average firing was preserved during FRH, individual neurons could increase or decrease their firing [13]. In contrast, we recently found that, when we followed the firing of individual neurons over 9 days in V1 of freely behaving rodents during FRH, individual neurons returned quite precisely to an individual set point—on average, firing rates returned to within 15% of their initial value, even though neurons started from widely different mean firing rates [14]. The simplest explanation for this observation is that FRH is largely achieved through a set of cell-autonomous homeostatic mechanisms.

Are other aspects of activity besides mean firing rate conserved during homeostatic plasticity in central nervous system neurons? This remains a largely open question. At the circuit level, coefficient of variation of firing is also restored during FRH, but more complex features of circuit activity have not been analysed [10]. At the subcellular level, there is evidence for dendritic branch-specific conservation of total synaptic strength [18] and presynaptic release probability [19], suggesting the existence of local rules for distributing synaptic weights that perhaps respond to deviations in local dendritic calcium signals. Further, some paradigms for chronically manipulating activity can induce local compensatory adjustments in synaptic strength [20,21]. It is worth considering whether this latter observation undermines the model of synaptic scaling as a global mechanism that scales synaptic weights in response to changes in postsynaptic firing. I would argue, instead, that these global and local mechanisms likely represent fundamentally different forms of plasticity. The preponderance of evidence suggests that these global and local phenomena are induced through distinct mechanisms that allow different aspects of activity to be sensed and translated into synaptic modifications, and are likely to subserve distinct functions within neural circuits.

Put another way, one could argue that if the response to a perturbation in activity is not a global scaling of synapses, then one is (by definition) not studying synaptic scaling. On the other hand, this 'phenotypic' classification approach raises a difficulty, especially for understanding when and where these mechanisms operate *in vivo*: most ways of manipulating activity are likely to simultaneously induce multiple forms of plasticity at excitatory synapses, so the changes one can measure after a given manipulation will be owing to a complex mixture of local and global, Hebbian and homeostatic processes. As a consequence, the lack of purely multiplicative scaling after a given manipulation does not necessarily mean that synaptic scaling has not occurred. As an addendum to this, experimental measures of multiplicative scaling (generally based on miniature excitatory postsynaptic current (mEPSC) amplitude analysis) are relatively insensitive to the possibility that a fraction of synapses are unaffected—so even if scaling is observed, one cannot rule out that some synapse types onto a postsynaptic neuron are immune to synaptic scaling. In fact, it seems quite likely that as more data emerge from *in vivo* systems where cell identity is better preserved than in the culture environment, we will find that synaptic scaling is *synapse-type* specific rather than find globally expressed across all synapse types. What all of this says is that, to confidently assign a synaptic change to any particular form of plasticity, one must use some mixture of induction and expression characteristics (phenotype), and molecular signatures that differentiate between different forms of plasticity. It is rarely possible to do this with complete confidence in the *in vivo* environment.

3. How do multiple forms of homeostatic plasticity cooperate to stabilize firing?

Synaptic scaling is not the only global form of homeostatic plasticity present within cortical microcircuits. Early work in neocortical cultures established that chronic manipulations of activity induce a suite of changes that likely all contribute to the restoration of firing. In pyramidal neurons, this includes changes in intrinsic excitability (induced through changes in voltage-gated current densities and other mechanisms) and homeostatic scaling of inhibitory synapses [22,23]. Further, synapses onto gamma-aminobutyric acid-ergic (GABAergic) neurons (not identified by cell type in these early culture experiments) are regulated differently from synapses onto pyramidal neurons [1,24]. The situation in (for example) a neocortical circuit *in vivo* is obviously even more complex. There is mounting evidence that homeostatic plasticity mechanisms are tuned in various ways to the identity of a neuron type and its function within the circuit [25,26]. For example, visual deprivation during the ‘pre-critical period’ in visual cortex leads to distinct changes at different classes of inhibitory synapse onto layer 4 pyramidal neurons, yet the net effect of all microcircuit changes appears (in the end) to be homeostatic [26]. As a second example, fast-spiking (FS) GABAergic interneurons (FS cells) and pyramidal neurons in the same local circuit undergo FRH at markedly different speeds following sensory deprivation in the visual cortex *in vivo* [10], and something similar has been demonstrated for different types of pyramidal neurons in barrel cortex following whisker deprivation [27].

The observation that pyramidal neurons both *in vitro* and *in vivo* are often simultaneously adjusting excitatory and inhibitory synapses, as well as modulating intrinsic excitability, raises an interesting question about how these homeostatic mechanisms are organized. If each of these mechanisms responds to a different error signal and has an independent set point, then one can easily imagine a situation where they would be in conflict. We currently have little information about the signalling pathways that homeostatically regulate intrinsic excitability and inhibitory scaling, although it is clear that they need not all be induced together *in vivo* [28]. In an analogous manner, it is not entirely clear that network homeostasis can emerge in a complex circuit with many excitatory and inhibitory units independently (and cell autonomously) regulating their own excitability without any network-wide coordinating signal. Further computational and experimental work on these issues would help clarify the requirements for how such multifaceted homeostatic mechanisms should be implemented in recurrent circuits.

4. Are Hebbian and homeostatic mechanisms the only game in town?

Synaptic plasticity is generally considered to be Hebbian if it is associative and input-specific [29]. Thus, correlated firing of pre- and postsynaptic partners will drive potentiation only at synapses between those specific neurons (associative LTP). Input-specific LTD, in which uncorrelated pre- and postsynaptic firing drives synaptic weakening, is also often called ‘Hebbian’. In contrast, the key criterion that a form of plasticity must meet to be considered homeostatic is that it acts to stabilize some parameter around a set point [3,30]. Such a mechanism could, in principle, operate locally or globally, depending on what perturbation is being sensed and what variable is under homeostatic control. The literature supports the idea that there are many forms of plasticity that satisfy either the definitions of Hebbian or the definition of homeostatic plasticity. While homeostatic mechanisms can, in principle, be either global or input-specific, they are not associative. Further, strictly Hebbian forms of plasticity are not homeostatic in the formal sense, as they follow positive feedback rather than follow negative feedback rules [29]. Unlike homeostatic plasticity, Hebbian mechanisms are not inherently stable without additional features such as hard limits to (or saturation of) synaptic strengths, well-tuned spike-timing dependent plasticity (STDP) windows or sliding plasticity thresholds. Thus, although classic CA1 NMDAR-dependent LTP and synaptic scaling (for example) may share some downstream molecular effectors, they are fundamentally different in terms of induction mechanisms and function.

Not every form of synaptic plasticity falls neatly into either the Hebbian or the homeostatic camp. There are, for example, several forms of non-associative plasticity that appear to be competitive, but not necessarily homeostatic. An example of this would be heterosynaptic plasticity, in which LTP of one synapse can produce LTD of nearby neighbouring synapses [31]. In principle, if the amount of heterosynaptic LTD exactly matched the amount of homosynaptic LTP, and if the reverse were also true, such a mechanism could constrain total synaptic strength in a homeostatic manner—but such perfect matching has not been clearly demonstrated. In CA1 hippocampal neurons, total spine synaptic surface area is preserved along dendritic branches after LTP induction, so that enlargement of some spines leads to shrinkage or loss of others [32], suggesting the existence of a competitive mechanism that redistributes a set amount of synaptic resources per unit of dendritic. A second category of plastic mechanisms that fall outside the simple Hebbian/homeostatic framework would be gating mechanisms that turn various forms of plasticity on or off, for example in response to a reinforcement signal or other environmental or internal states (sleep/wake, for example).

5. Can synaptic scaling stabilize Hebbian plasticity?

Synaptic scaling and other homeostatic mechanisms have been suggested to serve two main functions in neural circuits. First, they provide a means by which complicated and highly recurrent networks can self-tune the balance of excitation and inhibition to maintain or restore stable function [4]. There is good evidence for this in primary sensory cortex, where these mechanisms can restore network excitability and individual firing rates even in the face of sensory deprivation paradigms that initially drive a massive depression of firing [10,11,33]. In the rodent V1, this process of rebalancing activity unfolds slowly, over a timescale of hours to days, which is likely fast enough to compensate for most perturbations these networks normally encounter during experience-dependent development. However, this slowness may be a critical issue for another proposed function of synaptic scaling, which is to prevent the positive feedback nature of Hebbian mechanisms from producing runaway potentiation or depression [34]. This problem arises because most homeostatic mechanisms that have been identified within neocortical circuits are slow relative to the rapid changes that can be induced by *in vitro* LTP or LTD protocols, and in theoretical models if the time constants of Hebbian and homeostatic mechanisms are not well-matched then Hebbian positive feedback cannot be kept in check by homeostatic negative feedback [35]. On the other hand, fast homeostatic mechanisms can generate instability at the network level within recurrent circuits [36].

This consideration raises a number of interesting and largely unanswered questions. First, how quickly do Hebbian synaptic changes accumulate during actual learning in real networks? Surprisingly, the answer to this is unclear, as it has not yet been possible to monitor the timecourse of synaptic strength changes during real learning (as opposed to, say, tetanus-induced LTP). While some forms of learning such as conditioned taste aversion are quite fast, others are very slow and unfold over days or weeks—suggesting that the underlying synaptic changes are also occurring slowly. Hebbian mechanisms certainly have the potential to be fast, as demonstrated using very strong associative protocols *in vitro* (tetanic stimulation or strong postsynaptic depolarization paired with synaptic activation) but we still do not know how actual correlations are detected and summed over time to trigger Hebbian plasticity *in vivo*. Nonetheless, it seems likely that under some learning conditions Hebbian changes can happen quickly, so that the speed of homeostatic mechanisms becomes an important concern if they are assigned the task of preventing runaway potentiation.

So this raises the question of just how slow homeostatic mechanisms such as synaptic scaling actually are. *In vitro* measurements where individual synaptic weight changes can be followed using imaging approaches—arguably the most sensitive way to measure rate—suggest that synapses can be globally scaled up or down by about 15–20% during the first hour of activity modulation [15]. This likely represent the maximal rate, because firing is dramatically affected (silenced or strongly increased) during these protocols, and during prolonged block of spiking, synaptic strengths continue to increase progressively with time, but the rate slows down the longer the blockade has been in place [15,37]. It is also worth noting that it has not yet been possible to parametrically modulate firing in a physiological manner and assess the rate and magnitude of synaptic scaling that is induced, so there are many aspects of the function relating changes in firing to synaptic scaling that remain to be explored experimentally.

Recently, we were able to continuously follow firing rates of pyramidal neurons in V1 of freely behaving young (critical period) rats to assess the magnitude and timecourse of perturbations in activity driven by visual deprivation [14]. These data reveal several interesting things. The first is that average firing rates vary widely across pyramidal neurons, but are remarkably stable for an individual neuron over time. There are of course moment-to-moment fluctuations in firing driven by external visual input or internal factors, but these fluctuations occur around a mean rate that is both characteristic of a given cell, and maintained over many days. This stabilization of mean firing rate suggests that any experience-induced changes in synaptic strength that accumulate over time during normal development can be fully compensated by homeostatic mechanisms.

In contrast, a very different picture emerges when visual experience is strongly perturbed through a manipulation such as closure of one eye (monocular deprivation, MD). Under these conditions, there is a biphasic response in V1 (similar in both monocular and binocular portions) [38] in which firing rates are first strongly suppressed after 2 days of MD, but then rebound back to baseline over the ensuing several days despite continued deprivation [10,14]. There is abundant evidence that LTD (along with other mechanisms such as plasticity of inhibition) contributes to the initial depression of firing [28,38–40], whereas synaptic scaling is one major contributor to the delayed restoration of firing [9–11,33]. Interestingly, homeostatic mechanisms restore firing precisely back to each neuron's own baseline firing rate, providing compelling evidence that V1 pyramidal neurons have a cell-autonomous firing rate set point to which they return when firing is perturbed [14]. These data also show (consistent with decades of previous experiments) that initially MD is able to perturb firing away from this set point, implying that, under these conditions, depressive mechanisms such as LTD are initially able to outstrip homeostatic mechanisms and allow the system to become imbalanced.

Why then are homeostatic mechanisms ever able to restore activity? One possibility is that for some reason homeostatic plasticity is delayed in this system and only kicks in once firing rates have been perturbed for long enough (or pass some threshold deviation away from the set point), but once they are activated the magnitude of plasticity is larger than the depressive mechanisms and so 'wins'. There is, however, no evidence for such a delayed homeostatic response *in vitro*. An alternative and (to my mind) more likely answer is that once LTD kicks in and starts to depress firing rates, homeostatic mechanisms also kick in immediately, but the magnitude of synaptic scaling is not sufficient to outweigh the massive LTD induced by the decorrelation of visual input during lid suture. Eventually, LTD induction saturates, and this allows homeostatic plasticity to catch up and restore firing. Either scenario underscores the point that, at least under some extreme circumstances, homeostatic mechanisms can fail to completely compensate for ongoing Hebbian plasticity. This also suggests that—if the development of irrecoverable circuit imbalances is to be prevented during intensive periods of learning—there must be limits on the amount of LTD or LTP that can be induced at synapses. Such limits have been suggested by experimental data and can be implemented either through saturation, or by introducing weight-dependent Hebbian rules in which the magnitude of change is inversely proportional to the existing synaptic weight [29,35,41].

Why build the system this way, with large (or fast) Hebbian mechanism and small (or slow) homeostatic mechanisms? Obviously, homeostatic mechanisms must be slow relative to the fluctuations in firing that carry information [4]. A second issue with having homeostatic and Hebbian mechanisms operate at close to the same timescale is the development of oscillations that prevent the system from reaching steady state [35,36]. A third interesting possibility is that activity may be too constrained under conditions where homeostatic negative feedback can always perfectly compensate for Hebbian plasticity. It may be that windows of time that favour potentiation and/or depression of neuronal firing rates are important for some aspects of memory storage or experience-dependent circuit reconfiguration. Given these problems with fast homeostatic stabilization, it may be that the best way to achieve both a flexible and stable system is to use Hebbian mechanisms that are intrinsically stable owing to synaptic weight limits or other approaches, and then use slower homeostatic mechanisms to maintain circuit excitability and excitation/inhibition

(E/I) balance, introduce competition, and (perhaps) rescale Hebbian mechanisms through metaplastic processes.

While computational approaches to understanding the interplay between Hebbian and homeostatic mechanisms have been enormously useful for outlining a landscape of possible functions, our understanding of where, when and how various learning rules operate in real circuits is still rudimentary enough that it is hard to draw firm conclusions. In the end, understanding what any particular homeostatic mechanism does in any particular circuit requires that we have the means to surgically excise it and determine the consequences for wiring and plasticity. The same is true, of course, for the multitudinous forms of Hebbian plasticity that have been documented at particular excitatory or inhibitory synapses [42]. Even this approach has its limitations in recurrent networks where these various forms of plasticity are likely to be 'bootstrapping' off of each other, and where there may be significant compensation through semi-redundant mechanisms.

6. Interference between Hebbian and homeostatic plasticity mechanisms

Slow and global homeostatic plasticity seems ideally designed to avoid degrading information stored through synapse-specific changes in synaptic strength [4], but there are other potential problems with having both forms of plasticity operating simultaneously in the same neurons. Postsynaptically expressed LTP and synaptic scaling involve changes in the accumulation of synaptic glutamate receptors, so these two forms of plasticity are in some sense competing for control over the number of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) at synapses. Under some conditions, this situation—much like a mismatch in timescales—can cause oscillations in synaptic weights as LTP and synaptic scaling compete with each other to control synaptic strength [35]. In addition to sharing a final common output, these various forms of plasticity also share some elements of the complex signalling networks within neurons that couple changes in activity to the regulation of synaptic strength [5,43]. Such interactions could be either a feature or a bug—for instance, induction of synaptic scaling might affect the magnitude of LTP/LTD in a way that could be usefully 'metaplastic' [44,45]—or alternatively could interfere with information storage by dampening the induction of Hebbian changes. Taken together, these considerations raise the possibility that some forms of Hebbian and homeostatic mechanisms might interfere with each other if they are operating simultaneously at the same synapses.

There are several possible solutions to this problem of interference. One simple solution is to segregate Hebbian and homeostatic mechanisms by cell (or synapse) type within a given circuit. This is an intriguing idea, and there is some evidence that not all circuit elements are subject to homeostatic regulation in all systems [7,25]. However, in a number of other cases, we know that both Hebbian and homeostatic plasticity are occurring at the same set of synapses [9,10], so this is clearly not a general solution to the problem.

A second class of solutions is to have synaptic scaling and LTP target distinct aspects of synaptic function—for example, one might target the number of available binding sites for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at excitatory synapses (through expansion or retraction of postsynaptic density (PSD) area), whereas the other might affect the filling rate of these binding sites. There is little definitive evidence in support of this idea. Both LTP [46] and synaptic scaling [11] are correlated with changes in spine size, suggesting that both affect PSD area. On the other hand, although prolonged activity blockade (3–6 days) is able to expand the size of the PSD [47], this happens on a much slower timescale than the rapid increases in receptor accumulation that can be observed *in vitro* within an hour of activity blockade [15]. Further, there is evidence that scaling down reduces the occupancy of synaptic binding sites for AMPAR, arguing against the idea that scaling down (at least over the first few hours) occurs primarily through an expansion or retraction of PSD area. One interesting observation in support of distinct mechanisms for LTD and scaling down is that while the former is generally thought to involve endocytosis of AMPAR, the later does not [48]. Thus, while it seems plausible that postsynaptic scaling and postsynaptic LTP/LTD target distinct aspects of the synaptic receptor trafficking machinery, the evidence for or against this is still accumulating.

A third class of solution to this interference problem is to *temporally* segregate Hebbian and homeostatic mechanisms, so that they are not happening at the same time. This could be achieved by confining a particular form of plasticity to a specific circadian time or behavioural state. For example, it has been theorized in the 'synaptic homeostasis hypothesis' (SHY) that Hebbian potentiation is induced primarily when animals are awake and actively sampling their environment, whereas homeostatic 'downscaling' is confined to sleep when brain activity is disconnected from external sensory drive [49]. Recently, we tested the idea that homeostatic plasticity might not be a continuous process, but instead might be gated by behavioural state or environmental factors such as light/dark [14]. We recorded continuously from V1 of freely behaving rats during MD, and asked whether the homeostatic restoration of firing that happens between MD2 and MD5 occurs preferentially during sleep or wake states. Surprisingly, we found that FRH is completely suppressed when animals are in either REM or non-REM sleep, and is most strongly induced when animals are in an active waking state. Thus, homeostatic plasticity *in vivo* is strongly gated by sleep/wake state, but rather than occurring during sleep, it is suppressed during sleep and activated only during wake states.

The strongest evidence in neocortical circuits in support of SHY is that the frequency (but not amplitude) of spontaneous synaptic currents was lower after a period of sleep and higher after a period of wake, as were firing rates [50–52]; these data have been interpreted to mean that during wake LTP-like mechanisms potentiate synaptic strength and drive an increase in firing, and during sleep these effects are counteracted by homeostatic mechanisms that downscale synapses and restore excitability [49]. In addition, supposed molecular correlates of Hebbian and homeostatic plasticity vary with sleep and wake [53], but it is not trivial to map these global expression changes onto specific plasticity mechanisms within neocortical circuits. In the same chronic *in vivo* experiments described above, we asked whether we could detect changes in baseline firing rates during sleep or wake, by analysing control data from unperturbed V1. We found that firing rates were remarkably stable across even long periods of waking or sleeping, arguing against the idea that simply being awake in a familiar environment is sufficient to drive enough net potentiation to imbalance V1 circuits, or that sleep inherently drives a reduction in excitability. It was only during an intervention—a lid suture protocol that decorrelates visual input and thus drives strong LTD—that we were able to detect a perturbation in firing, and then its restoration during waking. One really surprising aspect of these data is that most bouts of active waking are quite brief—rats cycle through many brief sleep and wake states during both the light and the dark cycle—but even active waking bouts of approximately 10 min in duration were sufficient to induce measureable FRH. Thus, a process that is transcription-dependent [15,54] and thought to operate slowly (although see discussion of timescales above) can be turned on and off in a matter of minutes in the intact freely behaving animal.

At a mechanistic level, it is entirely unclear how this gating takes place. There is a potentially trivial explanation: sleep-induced changes in the lymphatic system designed to wash away metabolites and toxins [51] might also wash away some extracellular factor that is essential for the induction of homeostatic plasticity. One candidate might be tumor necrosis factor alpha (TNFα), which is clearly essential for the homeostatic recovery of activity during prolonged MD [33,35]; however, our *in vitro* data suggest that synaptic scaling is only impaired by loss of TNFα signalling after many (approx. 24) hours [55], whereas the gating we observe by sleep and wake occurs on a timescale of many minutes [14]. A more interesting possibility is that this gating is an active mechanism that is designed to confine homeostatic mechanisms to active waking states—or conversely to exclude them from sleep states. One obvious possibility is that differences in neuromodulatory tone to V1 during sleeping and waking states are responsible for this gating.

The other fascinating question raised by these data is whether other forms of plasticity that interact with homeostatic mechanisms during prolonged visual deprivation are also segregated by behavioural state—and in particular, whether any of them are confined to sleep. It has been shown, for example, that during rapid ocular dominance plasticity (ODP) in kittens, ODP induced by a few hours of MD can be enhanced by a subsequent few hours of sleep [56–58]; in kittens, this rapid ODP has been ascribed primarily to changes in open-eye potentiation. In rodents, homeostatic mechanisms are thought to make a major contribution to this open-eye potentiation [9,10,33], but in kittens, this process may be primarily driven by an LTP-like mechanism that is enhanced during a consolidation-like process during sleep [58]. This raises the interesting possibility that distinct forms of neocortical plasticity may be temporally segregated into sleep- and wake-dependent processes. If such temporal segregation of different forms of plasticity proves to be a general rule, then it raises an additional set of important constraints when thinking about how Hebbian and homeostatic mechanisms interact, and what kinds of functions they serve during experience-dependent plasticity.

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Endnote

[1] We maintain a small shrine devoted to reviewer 3. In all fairness to reviewers 1 and 2, the manuscript was dramatically improved in response to their critiques.

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