

Introduction



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Integrating Hebbian and homeostatic plasticity: introduction

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Hebbian plasticity is widely considered to be the mechanism by which information can be coded and retained in neurons in the brain. Homeostatic plasticity moves the neuron back towards its original state following a perturbation, including perturbations produced by Hebbian plasticity. How then does homeostatic plasticity avoid erasing the Hebbian coded information? To understand how plasticity works in the brain, and therefore to understand learning, memory, sensory adaptation, development and recovery from injury, requires development of a theory of plasticity that integrates both forms of plasticity into a whole. In April 2016, a group of computational and experimental neuroscientists met in London at a discussion meeting hosted by the Royal Society to identify the critical questions in the field and to frame the research agenda for the next steps. Here, we provide a brief introduction to the papers arising from the meeting and highlight some of the themes to have emerged from the discussions.

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

1. What are Hebbian and homeostatic plasticity and why might it be important to integrate them?

Hebbian plasticity is widely considered to be the mechanism by which information can be coded and retained in neurons in the brain. Proposed by Donald Hebb in the 1940s (hence Hebbian plasticity) [1], a very large body of experimental evidence has since supported the idea that coincident presynaptic and postsynaptic activity does indeed lead to changes in the gain of the synapse [2]. The detection of coincidence by the brain is crucial for learning about the world because, as the philosopher David Hume wrote in 1740 in *A treatise of human nature*, '... the constant conjunction of objects determines their causation...'. Hebbian plasticity plays an important role in such fundamental properties of the brain as learning, memory, development and recovery from loss of function. Homeostatic plasticity can broadly be defined as neuronal change that tends to return the neuron back towards an initial set point; this could be achieved by a number of mechanisms, including synaptic scaling, changes in inhibition and changes in intrinsic membrane properties. The importance of homeostatic plasticity is that it prevents neurons from becoming saturated in one direction or the other, which would result at one extreme in excitotoxic damage and on the other a comatose state. From a theoretical standpoint, homeostatic plasticity can prevent saturation of synaptic strength, which, should it occur at the maximum end of the range, would reduce the coding ability of the neuron [3]. The two forms of plasticity frequently work in opposite directions. Hebbian plasticity inherently leads to a positive feedback process when activity is increased, where an increase in synaptic gain increases the probability of a further increase in synaptic gain. Homeostatic plasticity, on the other hand, involves negative feedback that moves the neuron back towards its original state following a perturbation, including perturbations produced by

Hebbian plasticity. To understand how plasticity works in the brain, and therefore how learning, memory, sensory adaptation, development and recovery from injury work, requires development of a theory of plasticity that integrates both forms of plasticity into a whole.

2. A brief history of Hebbian and homeostatic plasticity

Hebbian plasticity has dominated thinking about the mechanisms and consequences of synaptic plasticity over the past 25 years. Many aspects of sensory adaptation, neural circuit development, and learning and memory can all be modelled using simple Hebbian plasticity processes where the sign of the plasticity is determined by the timing of pre- and post-synaptic activity [1,4]. An early hindrance to modelling synaptic plasticity in this way arose from the possibility that cells might saturate their synaptic weights, a problem papered over by the introduction of soft-saturation. The Bienenstock–Cooper–Munro (BCM) theory also avoids the problem of saturation at the minimum and maximum end of the ‘synaptic weight’ scale by introduction of a sliding threshold for Hebbian modification of synaptic strength [5]. However, there has never been a clear consensus within the field on what the biological basis of the sliding threshold might be. Nevertheless, this inherently homeostatic mechanism was a herald of biological discoveries to come. The discovery of synaptic scaling was important in showing how homeostatic mechanisms could regulate the net excitatory drive to neurons [6]. Furthermore, if the scaling were multiplicative in nature it might not only maintain synaptic excitability within tolerable limits, but also preserve the relative synaptic weights on the neuron and thereby preserve information coding. The discovery of the dependence of synaptic upscaling on tumour necrosis factor alpha (TNF α) has led to the demonstration of its presence in plasticity processes *in vivo* [7–9], in much the same way as the dependence of long-term potentiation (LTP) on the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor had previously established its role in learning and memory [10–12]. However, the field has struggled to integrate the two plasticity modes and make clear and testable predictions about how they interact. To what degree are Hebbian and homeostatic processes involved in sensory adaptation, development, learning and memory? Where are the sites of Hebbian and homeostatic plasticity in the neuron? What is the time course of homeostatic plasticity that is so vital to maintenance of stability? What are the biological mechanisms by which the neuron senses overall excitability and scales its input accordingly? At a meeting in London in April 2016, computational and experimental neuroscientists came together to identify the critical questions in the field and to frame the research agenda for the next steps.

3. The three position papers

To initiate discussion before we all arrived in London, three position papers were written and made available for the participants to read. The paper by Lisman [2] lays the groundwork for what we understand about Hebbian plasticity. The paper by Turrigiano [3] sets out the nature of homeostatic plasticity and synaptic scaling as well as

reminiscing on the difficult birth of the first paper on this topic! The paper by Zenke & Gerstner [13] analyses the interactions between homeostatic and Hebbian plasticity modes within a computational framework. The Lisman position paper makes clear at the start the scope of the problem with which scientists are faced in understanding plasticity; it is argued that the synapse supports six types of plasticity, three of which might be described as Hebbian (short-term potentiation (STP), LTP and long-term depression (LTD)) and two homeostatic (synaptic scaling- and distance-dependent scaling). The other form of plasticity is late phase LTP, which, it is argued, is not strictly Hebbian [2] and concerns structural changes at the synapse.

The Turrigiano position paper explains the requirement for a homeostatic plasticity mechanism that continually tunes the synapses in the neuronal circuit to maintain neurons at their firing rate set points. The question is raised of whether cells have their own set points or whether the circuit as a whole maintains a set point to which each individual neuron contributes, but from a different set point at any given time. Slomowitz *et al.* [14] originally found evidence that individual cells increased or decreased their firing rate to different values but the ensemble average was maintained at a set point [14]. In contrast, Hengen *et al.* [15] recently showed that cells in visual cortex return to within 15% of their own set points following perturbation even though they start from widely differing initial firing rates. These findings raise the important issue of the scale at which homeostasis takes place. While Hebbian plasticity needs to be synapse-specific to code specific information, homeostatic plasticity could and perhaps does occur over a number of different spatial scales from the synaptic to the cell population level.

In addition to the issue of spatial scale, a further critical question is the temporal scale of interactions between Hebbian and homeostatic plasticity. The third paper by Zenke & Gerstner [13] considers the time course of homeostatic plasticity from a theoretical perspective and whether a rapid homeostatic mechanism is required in addition to the relatively slow forms described in ocular dominance plasticity or barrel cortex plasticity studies. On the one hand, homeostatic plasticity needs to be slower than Hebbian plasticity, because fast homeostasis runs the risk of suppressing necessary activity fluctuations and, moreover, can create an unstable feedback system with consequent oscillations and overshoot of the set point. On the other hand, homeostatic plasticity must be rapid enough to contain the positive feedback inherent in Hebbian modes of plasticity. Zenke & Gerstner [13] set up the argument that multiple rates of homeostasis are required, which of course leads to the question of whether there is evidence for different rates and if so, what mechanisms might underlie each.

4. Multiple mechanisms, multiple terminology

Evidence was presented at the meeting for several forms of homeostatic plasticity with different rates [16], and before going any further, it might be useful to urge caution in using the term homeostatic plasticity without qualification. The term ‘homeostatic’ disguises a multitude of similarly acting but mechanistically distinct processes. As pointed out by Turrigiano [3], using a phenotypic approach to classifying plasticity can lead to difficulties and could result in

talking at cross purposes or conflating two different mechanisms. In discussing plasticity in this article and at the Royal Society discussion meeting, we identified at least four distinct forms of homeostatic plasticity, which might usefully be kept separate until proven otherwise

- (1) firing rate homeostasis (FRH),
- (2) synaptic scaling (multiplicative and non-multiplicative),
- (3) inhibitory feedback (either via inhibitory synapse homeostasis or excitatory drive onto inhibitory cells), and
- (4) plasticity of intrinsic membrane properties.

FRH is a potentially problematic term in that it could be generated by any of the other types of homeostatic plasticity. Firing rate is generally thought to be the parameter that the cell monitors in order to generate an error signal that instigates homeostasis [3], but firing rate could be restored by altering synaptic weights, inhibitory feedback, intrinsic membrane properties or any of these mechanisms in combination. Furthermore, firing rate often refers to the basal firing rate or spontaneous firing rate of the cell, but it can also refer to the evoked response generated by a particular sensory input, or as with Hengen *et al.* [15] to the spontaneous and evoked activity during natural exploration [15]. Here, we have reserved the term FRH for basal firing rate changes rather than for evoked. In a later paper in this issue, Glazewski *et al.* [17] provide evidence that basal firing rate and evoked FRH can change independently of one another in a particular subset of layer 5 neurons (layer 5 regular spiking cells). This argues for a further subdivision of FRH into evoked and spontaneous FRH.

5. A question of scale

There is a reasonable consensus about the scale at which Hebbian plasticity takes place; while induction of LTP, for example, is associative and requires several synapses to be activated simultaneously, single synapses express the plasticity at the level of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and presynaptic release machinery and single pairs of cells can act autonomously to express Hebbian plasticity. Keck *et al.* [16] point out that activity-independent spine fluctuations could temper the runaway increase in synaptic strength that can result from Hebbian mechanisms. Spine sizes are known to fluctuate *in vivo* independently of activity, and the fluctuations are proportional to the size of the synapse. The largest and presumably most efficacious spines are thus likely to suffer the greatest decreases in size. Therefore, this activity-independent process may have an outcome that supports homeostasis.

Lisman and co-workers [18] explore the fine scale of Hebbian plasticity further and summarize evidence that synapses are organized in a modular form that leads to quantal increases or decreases in postsynaptic strength. By analysing data from structural studies at electron microscopy and super-resolution light microscopy levels, they model the relationship between synaptic gain and growth. Importantly, they draw on evidence that the pre- and postsynaptic elements of the synapse are aligned in nanocolumns [19] to argue that the two sides of the synapse grow in register with one another during the late phase of LTP and that there are approximately 10 size states. Costa *et al.* [20] also draw on a large body of literature that plasticity occurs at the pre- and postsynaptic loci, to explain the functional

benefits of such a system. Most computational models currently change synaptic weight postsynaptically only, but here the authors argue that once the presynaptic component is taken into account, several additional features arise, such as more reliable receptive fields, rapid recovery of previously forgotten information and reduced response latencies [20].

How does an almost point localized Hebbian system interact with a homeostatic mechanism? Is homeostasis maintained at the level of the individual synapse, the individual dendrite, the whole neuron, the circuit level, or at all of the above? Toyozumi and co-workers have concluded that stability of neuronal responses can be attained if slow homeostatic and fast Hebbian plasticity operate at different sites [16,21]. At the macroscopic end of this scale, one might imagine that glial cells are ideally placed to coordinate homeostatic plasticity over a wide area of the brain. Evidence that production of TNF α is required for homeostatic plasticity in the visual cortex [8] and in particular that glial TNF α is vital for synaptic scaling in the hippocampal cell culture preparation [7] implies glial cells play an important role in homeostatic plasticity. Interestingly, Papouin *et al.* [22] argue that while glial cells may provide for coordination over a wide distance, they can also act very locally. Astrocytes are capable of producing calcium signals in very restricted compartments within small processes that are in contact with the neuronal synapse. Such small processes had previously been missed owing to the limited resolution of earlier techniques, but have now become apparent. It remains an open question how glial cells might sense increases or decreases in synaptic firing rate and how they then respond with TNF α signalling. On the one hand, it could be performed by sensing extracellular potassium levels which increase with increased activity, or possibly by the small perisomatic processes sampling extracellular transmitter levels. In addition to a possible role in homeostatic plasticity, glial cells are also implicated in Hebbian forms of plasticity [23], which creates a further substrate for integration of Hebbian and homeostatic plasticity.

6. Inhibition, disinhibition and homeostatic mechanisms

While much of the discussion at the meeting centred on excitatory neurons and excitatory plasticity, there was clearly an understanding that inhibitory mechanisms are likely to provide a means of rapid homeostatic response (see [24]). If inhibition is recurrent, then it scales with the feed-forward excitation and acts with only a short delay to restrain excitation homeostatically. However, inhibitory cells also change their synaptic gain in response to longer-term changes in synaptic drive. Parvalbumin cells decrease their firing rate in the visual cortex in response to monocular deprivation, a process that leads to an increase in responsiveness in excitatory cells and an early restoration of binocular cell firing rate [25]. Inhibition also changes dramatically over longer timescales, acting to restore normal levels of response in excitatory neurons [26]. In the somatosensory cortex, rapid disinhibition has also been observed (following whisker-row deprivation) as a decrease in inhibitory post-synaptic currents (IPSCs) onto layer 2/3 excitatory cells [27]. The two systems appear similar across cortical areas and involve parvalbumin positive cells in each case as discussed by Gainey & Feldman [24]. The rapid homeostasis conferred by disinhibition is in contrast to the

slower homeostatic plasticity of excitatory responses found in both visual and somatosensory cortex [24].

Could this be the solution to the question posed by Zenke & Gerstner [13]? Could rapid homeostatic plasticity be conferred by changes in inhibition while slower TNF α -dependent synaptic scaling is only triggered in response once a longer lasting or higher threshold change in excitatory drive is sensed? At present, the theoretical need and the experimental evidence are not perfectly aligned. Rapid inhibition is required to limit excessive excitation caused by Hebbian processes, but at present, we have evidence for rapid disinhibition that allows Hebbian and synaptic scaling processes to increase excitation [24,25]). One further complication arises from the finding that inhibitory changes may be restricted to early development and to the critical period in visual cortex [25,28,29]. However, a possible solution to this complication is that action potential-independent GABA release may be modulated by sensory experience and hence excitatory sensory drive in adult visual cortex [30]. Dark exposure leads to a decrease in miniature (m) IPSC frequency that could allow an increase in Hebbian plasticity to proceed, and this plasticity is not restricted to a critical period. In a separate study reported in this issue, Erchova *et al.* [31] show that the perineuronal net that surrounds inhibitory parvalbumin positive inhibitory neurons is also decreased by dark exposure and leads to a more rapid recovery of binocular function following monocular deprivation.

7. Detecting homeostatic plasticity *in vivo*

How can Hebbian and homeostatic plasticity be detected *in vivo*? The two might easily be mistaken for one another; for example, is the potentiation of open eye responses following monocular deprivation a Hebbian potentiation or a homeostatic rebound from the decrease in activity owing to one eye being closed? Monocular deprivation produces a rapid depression of the closed eye responses in the visual cortex followed by a slower potentiation towards baseline levels, which, because it acts towards restoring the original evoked firing rate for the closed eye input, might be considered homeostatic [8,21]. This view gains support from the finding that the rebound of the closed eye response is absent in TNF α knockout mice [8] and the C57BL/6JOLA^{Hsd} substrain of mice, both of which lack synaptic scaling [9]. Because synaptic scaling is itself a homeostatic mechanism, it would appear that homeostatic synaptic scaling is sufficient to explain the increase in closed eye response. As discussed above (§6), the disinhibitory response of inhibitory interneurons to monocular deprivation also needs to be taken into account in ocular dominance plasticity [24] as it would also tend to act in a homeostatic fashion in its own right and could additionally gate Hebbian plasticity.

Glazewski *et al.* [17] provide evidence that homeostatic plasticity processes occur in the somatosensory cortex. The trick used to isolate a homeostatic component in the absence of Hebbian plasticity is to deprive all the whiskers rather than leaving some spared whiskers, which would lead to a competitive advantage for the more active spared inputs and to Hebbian potentiation (see [32]). Glazewski *et al.* [17] report a slow compensatory potentiation despite continued deprivation, which returns the neuronal responses to baseline following an initial depression. The time course of

homeostatic plasticity is remarkably similar between visual and somatosensory cortex [24], and, crucially, the slow component of homeostatic plasticity is absent in a Harlan strain of mice that lack synaptic scaling (the C57BL/6Ola^{Hsd} mouse) [17]. The similarities and differences between plasticity in the visual and somatosensory systems are thoroughly analysed in two reviews in this issue [24,32].

What leads the neurons back towards a set point and how do they know where they are going? This question has been tackled by Clopath *et al.* [33], who show that two features of the cortical circuit are important for restoring the tuning properties of cells following a perturbation, namely a subnetwork of non-plastic connections and a highly recurrent network of plastic connections between similarly tuned cells. This system also tends to increase the stability of the system at rest, despite the constant turnover in synaptic connections [34].

8. Behavioural consequences of losing homeostatic plasticity

One of the issues that arose at the meeting is the paucity of behavioural studies in animal models that lack certain forms of homeostatic plasticity. While it is possible at present to probe the relationship between synaptic/cellular mechanisms and sensory cortical plasticity, it is not clear what the predictions might be for a loss of synaptic scaling (for example) at the behavioural level. Furthermore, if one were to lose one homeostatic mechanism, it may be possible that another would compensate and therefore prevent a measurable effect. Behavioural studies to date have shown that TNF α and TNF α receptor knockout mice exhibit both a decrease in anxiety-like behaviour [35] (but see [36]) and some impairments in learning and memory, depending on the receptor subtype engaged [35]. However, the relationship between these phenotypes and the synaptic cellular mechanisms involving TNF α remains obscure in a way in which the relationship between (say) NMDA receptor antagonism and disruption of learning and memory is not [11,12]. One of the challenges, therefore, is to design behavioural experiments that will probe specific aspects of the role of synaptic scaling in learning and memory and to design studies at the cellular level that explain the anxiolytic effect of reduced TNF α activity.

In this issue, Konefal and Stellwagen review the action of TNF α in the brain before going on to consider TNF α in the maternal immune activation (MIA) model of neurodevelopment disorders, which include schizophrenia-like and autism-like symptoms and the development of abnormal social responses. They find that TNF α alpha is not required for abnormal social responses in MIA model mice, and suggest that other cytokines act in parallel to TNF α to cause the effects [36]. This study emphasizes once more that TNF α plays a particular role in the brain that is distinct from that of the other cytokines.

9. Remaining questions for the field

One of the goals of our meeting was to identify the critical questions in the field and frame the research agenda for the next important steps. As mentioned at the start of this

introduction, we originally wanted to ask to what degree Hebbian and homeostatic processes are involved in sensory adaptation, neural circuit development, and learning and memory. What are the time courses of homeostatic plasticity mechanisms that are so vital to maintenance of stability? What are the biological mechanisms by which the neuron senses overall excitability and scales its input accordingly? The final paper in this issue, written by Keck *et al.* [16] with input from the discussion session at the meeting and further offline discussion, aims to crystallize some of the key conclusions from both the speakers at the meeting and the participants in the audience. The detailed arguments are laid out in that consensus paper and are not repeated here. Some of the questions that we imagined would be important at the start remained important and unanswered at the end of the meeting, such as the question of the timescale of

homeostatic and Hebbian interactions, but other questions were developed much further, such as the need to understand the spatial scales of synaptic plasticity and homeostatic set points, and how Hebbian and homeostatic mechanisms interact. There was a consensus that in order to pursue the answers to these questions successfully, continued interactions between computational and experimental neuroscientists will be vital.

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