Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions

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Abstract

We summarize here the results presented and subsequent discussion from the meeting on Integrating Hebbian and Homeostatic Plasticity at the Royal Society in April 2016. We first outline the major themes and results presented at the meeting. We next provide a synopsis of the outstanding questions that emerged from the discussion at the end of the meeting and finally suggest potential directions of research that we believe are most promising to develop an understanding of how these two forms of plasticity interact to facilitate functional changes in the brain.

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

1. Introduction

Here we provide an overview of the topics presented at the meeting on Integrating Hebbian and Homeostatic Plasticity at the Royal Society in April 2016. We also summarize the major themes and questions that arose from the subsequent discussions. Firstly, one of the more pleasant and surprising take away messages from the meeting was the overall agreement between the conclusions drawn from the data in numerous preparations, brain areas and approaches to alter activity patterns and levels. We found that there are several general principles that repeatedly emerge across approaches.

One of the more pleasant and surprising take away messages from the meeting was the overall agreement between the conclusions drawn from the data in numerous preparations, brain areas and approaches to alter activity patterns and levels. We found that there are several general principles that repeatedly emerge across approaches.

(1) Stabilizing mechanisms are likely necessary to keep Hebbian changes to the system under control, otherwise activity becomes extreme, either too high or too low.

(2) Multiple mechanisms of both Hebbian and homeostatic plasticity are repeatedly observed across varied experimental and theoretical works.

(3) These mechanisms can stabilize numerous cellular and network parameters—overall firing rate, subthreshold activity and individual synaptic weights.

(4) Hebbian and homeostatic mechanisms have striking similarities observed among different brain regions in vivo and in vitro, suggesting that many of these mechanisms may be common across brain regions.
We review these general principles in turn, and then discuss important future directions to address inconsistencies and missing points in our current understanding.

2. The necessity of stabilizing mechanisms

One question that is frequently raised outside of the homeostatic plasticity field is whether or not these stabilizing mechanisms are actually necessary for proper brain function. This question has been repeatedly addressed by theorists and modellers, and their work typically indicates that without some form of stabilization of firing rates or synaptic weights, network models that can store memory patterns in recurrent synaptic strength become unstable, typically in the direction of activity being too high [1–4]. These runaway increases in activity emerge from the fact that most Hebbian strengthening mechanisms are dependent on coincident firing between the pre- and post-synaptic neurons, and this process involves a positive feedback loop: namely, the more frequent coincident activity in a group of neurons is, the more likely that synapses connecting these neurons are strengthened. These strengthened synapses further increase coincident activity within the group and very quickly, in a positive feedback loop, activity pathologically increases.

3. Mechanisms of homeostatic stabilization

If some form of stability is necessary, what mechanisms may provide this stability and what properties do these mechanisms have? Four major mechanisms were reported at this meeting, although this list is not comprehensive of the possible mechanisms, nor are they mutually exclusive.

(1) Synaptic scaling.

(2) Changes to inhibition through inhibitory cell activity or the strength and number of inhibitory synapses onto excitatory cells.

(3) Constraints and intrinsic fluctuations of spine size dynamics (which likely reflect changes in synaptic strength and thus overlap to some degree with stabilizing mechanisms).

(4) A sliding threshold for long-term potentiation (LTP) and long-term depression (LTD) induction (i.e. metaplasticity or the Bienenstock, Cooper and Munro (BCM) theory).

(a) Synaptic scaling

The first experimental evidence for synaptic scaling [5] demonstrated that in response to a decrease in firing rate, the synaptic weights of the population of the excitatory post-synapses on a cell were increasingly scaled in size by a multiplicative factor, such that the relative weights of the synapses were preserved (and vice-versa in response to an increase in activity). Many studies have confirmed this original result in vitro [6], as well as ex vivo in acute slices prepared from both juvenile and adult animals that had previously undergone in vivo deprivation [7–14]. Synaptic scaling does have layer-specific properties in cortex, where scaling in layer 4 is limited to early development [7], but layer 5 [12,15] and layer 2/3 [10] can scale throughout adulthood. Numerous molecular mechanisms have been implicated in mediating synaptic scaling, including TNF-alpha [15–17], which may be regulated via astrocytic activity and N-methyl-d-aspartate (NMDA) receptor expression [18], retinoic acid [19], among many others (for a review, see [20,21]). Increases in TNF-alpha have been reported to increase and decrease the density of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and gamma aminobutyric acid-A (GABAA) receptors, respectively, in the plasma membrane [17].

(b) Rapid changes to levels of inhibition
In addition to synaptic scaling, which takes several days in vivo, altering the levels of inhibition and generally the balance between excitation and inhibition on a given cell is a frequently observed mechanism used to stabilize activity in the brain. Reducing the levels of inhibition onto excitatory neurons is consistently observed following loss of input in cortex [10,22–27] and has been hypothesized to be a first step in circuit reorganization following input loss [28]. Changes in inhibition can occur via a reduction in the number [12,22,24,26,27,29–33] or strength of inhibitory synapses onto excitatory cells [33], as well as a reduction in the firing rate of the inhibitory neurons following deprivation either temporarily during development [11,34] or for longer time courses in adulthood [29]. Changes in inhibitory tone may be modulated via astrocytes [35] or NMDA receptor input [36]. Changing the activity of inhibitory neurons provides an important homeostatic mechanism by which activity levels can be rapidly (within seconds) adjusted through the increase or the decrease in the firing rate of inhibitory neurons to prevent short-term increases in activity levels that would be associated with pathological activity such as seizures; however, recent work suggests that minimizing changes to inhibition helps maintain temporal coding in the network, which is shaped by the inhibitory circuit [37], so some maintenance of inhibitory tone is likely essential for the circuit. Adjusting synaptic strength or neuronal excitability occurs over much longer time courses of hours [6], which would be much too slow to account for activity peaks that would potentially cause pathological over-excitation.

(c) Changes and fluctuations in spine sizes

Dendritic spines—the location of excitatory synapses—can change in size in response to long-term potentiation (LTP) and long-term depression (LTD) [38,39] or while synaptic scaling occurs [12,40], in a way that likely at least partially reflects changes in synaptic strength. Limits on the sizes of dendritic spines provide yet another mechanism by which stability can be achieved in the brain. Given that spine size has a maximum [39], synapses cannot be strengthened indefinitely [41]. Furthermore, spine size is not only controlled by LTP, LTD and during synaptic scaling, but also by intrinsic fluctuations that happen even in the absence of neural activity [42]. Fluctuations of spine size increase approximately linearly with the initial size and this relationship explains the steady-state distribution of spine sizes with a long tail [42,43]. A simulation study of recurrently connected networks suggests that such fluctuations can stabilize network activity by constitutively restoring the spine size distribution close to the physiological steady-state distribution, while ongoing Hebbian plasticity forms and maintains cell assemblies [44,45]. In addition to changes in the structural size of synapses, the properties and activation of NMDA receptors within a synapse have been implicated in monitoring overall changes to activity levels [46].

4. Parameters of homeostatic balance

In order for these mechanisms to be truly homeostatic, they need to restore cellular and synaptic activity levels back closely to pre-perturbation levels. What characteristics of the circuit are being stabilized by these mechanisms that make this process homeostatic? There is experimental evidence for three balance parameters: firing rate homeostasis, subthreshold activity homeostasis, and synaptic weight homeostasis, and any of these three parameters, when incorporated into the appropriate theoretical model, may stabilize the network to prevent pathological neuronal dynamics or learning [1,3,4,47–58].

First, firing rate homeostasis was initially described with the first experimental evidence of synaptic scaling [5], and altering cellular [59] and network firing rate has consistently evoked a response of the induction of homeostatic mechanisms [5,7,11,12,29,60]. Several studies have now demonstrated that neurons will recover their firing rates in vitro [5,59] and in vivo [11,12,29,60], in parallel with
the induction of homeostatic mechanisms, and that neurons in the developing visual cortex have a firing rate set point to which they return after deprivation [60]. Recent work has also suggested that subthreshold changes in activity levels are sufficient to induce homeostatic mechanisms, specifically synaptic scaling [61], although whether these changes restore subthreshold activity levels remains unexplored.

The sliding threshold proposed in the BCM theory would provide an additional method by which firing rates could be homeostatically modulated [47]. By rapidly and superlinearly increasing the threshold for inducing LTP as background firing rates get higher and decreasing the threshold as background firing rates are lower, synapses would be unlikely to be strengthened if activity rates were too high. This sliding threshold model would provide an internal mechanism by which activity levels never become too high or too low. There is considerable experimental evidence for the existence of such a sliding threshold, including both evidence of structural and functional plasticity, which has been reviewed extensively elsewhere [62]. However, the timescale of the sliding threshold is an important factor for determining the stability [63], and the theoretically predicted supralinear relation of the threshold with background firing rate is awaiting further experimental evidence.

Homeostasis of synaptic weights [64,65] provides an intriguing alternative to homeostatic regulation of firing rate, since constraining synaptic weights would be an effective mechanism for guiding activity-dependent circuit organization. Recent work [66] suggests that overall synaptic weight is conserved on a dendritic branch, thus preventing too much activity that would result from an over strengthening of synapses.

5. Interactions with mechanisms of Hebbian plasticity

Hebbian mechanisms have been largely reviewed elsewhere and are well summarized in one of the position papers in this issue [46]. An important feature of these Hebbian mechanisms in relation to their interaction with homeostatic mechanisms is that their time courses and effects can be wildly different. Hebbian mechanisms are synapse specific and can be implemented over milliseconds (short-term plasticity) to hours (long-term LTP/LTD), whereas synaptic scaling occurs cell-wide and can take a few days to commence in vivo [6,15,16,67]. Hence, there is a considerable disparity between the effects and time courses between these homeostatic and Hebbian mechanisms. Theoretical work suggests that separating the expression mechanisms (e.g. spine size or membrane AMPA density) for these two processes can minimize their interface and prevent oscillatory instability of synaptic weight, which could result from the delay in the negative feedback of the homeostatic plasticity [53]. However, since multiple timescales are involved in both Hebbian and homeostatic mechanisms, further experimental characterization of these disparate time courses is essential going forward [68].

6. Similarities across brain regions in vivo

For both Hebbian and homeostatic mechanisms, there are striking similarities of plasticity responses across numerous regions of cortex and varying plasticity induction paradigms (for a review, see [69]). Starting with homeostatic plasticity, similar mechanisms are invoked following sensory deprivation in both somatosensory [15,26] and visual cortices [7,10–15,22,24,27,60], where decreases in inhibition precede any Hebbian mechanisms and synaptic scaling is reliably induced in a layer-specific manner [7,26,70]. Hebbian mechanisms have correlates in synaptic structural plasticity, in which LTP is correlated with the formation of new spines [71,72], and LTD is associated with the loss of pre-existing spines [73]. The in vivo upregulation of spine dynamics has been observed following sensory deprivation in somatosensory cortex [74–77], olfactory cortex [78,79], auditory cortex [80]
and visual cortex [74,77,81–83], and following learning in motor cortex [84–86] where the memory of the learned motor task depends on the newly formed synapses [87]. The interactions between Hebbian and homeostatic plasticity have largely been described in the visual cortex following monocular deprivation, where it is proposed that the Hebbian process of LTD [88] is followed by an increase in synapse strength [89]. The similarities across somatosensory, motor and visual cortices may suggest that mechanisms of homeostatic and Hebbian plasticity are conserved across brain regions, at least in cortex.

7. Future directions and major questions going forward

While a number of general experimental and theoretical properties emerged from this meeting, a large number of outstanding questions remain to be answered related to how Hebbian and homeostatic plasticity interact to facilitate normal function and circuit plasticity. Here, we outline the major questions that were discussed at the meeting.

(a) Interactions between theoretical and experimental approaches

The field could generally benefit from tighter interactions between theoreticians and experimentalists. One area for potential expansion is in the interaction between theory and experimental approaches that focus on detailed mechanistic work, as well as more general behavioural/in vivo work. Linking results at different levels of investigation, while a general issue in neuroscience, is particularly important to understanding the interaction between homeostatic and Hebbian plasticity. Work in this field has to some degree diverged into two categories. First, systems approaches that include in vivo work done in anaesthetized or behaving animals [11,12,14–16,29,60,67] and theoretical work that models the overall dynamics of the systems [1,3,4,47–55,57,58,90]. These systems studies importantly provide insight into mechanisms that are used in the intact brain and how activity levels are affected by these mechanisms, but have limited control of other secondary inputs from outside of the main pathways studied that may provide compensatory mechanisms. So these experiments often cannot pinpoint the exact inputs and brain states affecting activity levels or the relative changes to the pre- and post-synaptic cells, particularly in behavioural experiments where the animals are free to experience their environment (somewhat) naturally. These limitations make it difficult for the in vivo experiments to provide detailed information—for example, the originating brain area from which inputs are lost following deprivation—to these theoretical studies, where the localization of activity changes (pre- or post-synaptically) and knowledge of the rules for circuit reorganization would be useful. As a result, predictions from theory to in vivo experiments and vice versa thus far are limited to qualitative aspects. The second focus of experiments is at the molecular and cellular experimental level, where numerous molecular mechanisms have been described to play a role in both homeostatic [17,19,21] and Hebbian [91] plasticity, as well as their interactions [92,93]. While new molecular and systems tools make it easier to link these molecular and cellular mechanisms to in vivo experiments, for example, through the use of Cre-dependent expression of target mechanisms, the brain’s redundancy, evidenced by observed compensatory pathways, can make it difficult at times to tease apart the precise roles of individual molecules in the healthy brain. Importantly, the theory and molecular experiments may have greater potential for interaction, which to date has largely unexplored, as theoretical models can predict the time course and spatial scale of action of a molecular cue that would be necessary to facilitate plasticity [94]. Given our knowledge of these potential molecular cues in vivo and in vitro, this is one area where theoretical work could be instructive in linking the systems experiments with the molecular and cellular experiments. Similarly, mechanisms involved in the recovery of individual neurons tuning following sensory deprivation in vivo [11,12,14–16,29,60,67,95] could be explained via theoretical work. Theoretical models using
attractor dynamics or hidden states [96,97] could be implemented to better understand how
interactions between individual cells and the network of cells facilitate the recovery of activity
following deprivation and maintain the same properties of individual cells from prior to deprivation
[95,98]. Overall, better interaction between molecular/cellular and systems level experiments and
theory will be critical to understand the underlying details of the mechanisms of plasticity and how
they are implemented in vivo.

(b) Timescales of homeostatic and Hebbian plasticity interactions

One of the important questions to emerge from this meeting is how the disparate timescales of
homeostatic and Hebbian plasticity could interact to maintain firing rate homeostasis and overall
stability. The main issue emerges from the fact that homeostatic plasticity mechanisms occur over a
very slow time course, hours at their fastest [99], whereas Hebbian plasticity can occur over a period
of seconds to minutes [46]. Given that recurrent excitation and synaptic strengthening can happen
very quickly, the stability mechanisms described by the classic homeostatic mechanisms are not
rapid enough to stop runaway excitation. Theoretical models have described approaches that
facilitate network stability with these disparate time courses [53], but at the same time suggested
the need for a fast downregulating homeostatic mechanism to avoid seizure-like activity [68]. One
possible explanation for this discrepancy between theory and experiment is that a majority of
experiments focus on upregulating homeostatic mechanisms that occur after input loss and a
decrease in activity levels. With the upregulation of activity, a longer time course might be sensible,
given that short-term deceases in activity levels could be for a number of reasons—for example, in
visual cortex, entering a dark room could potentially reduce visual cortical activity. If activity returns
when you enter the light again, having quickly upregulated the strengths of synapses in response to
the dark stimulus would result in too much activity with light stimulation. Hence, upregulating
homeostatic mechanisms may occur over a longer time course to ensure that the reduction of
activity is (semi) permanent before the system compensates for these changes. Additionally, using a
wide dynamic range of activity is optimal for information coding in the brain [100]. Therefore,
adjusting the firing rate set point too quickly would minimize the range of activity patterns and rates
that encode input to a cell and in theory reduce its computational power [53]. As a result,
homeostatic adjustments may be slower when activity levels are not dangerous for toxicity.

These results could suggest the potential for a non-symmetric up- and downregulation, like that
observed for LTP and LTD, where potentiation can occur more reliably and quickly [46]. As for
experimental evidence for homeostatic downregulation, work in cortical cultures indicates that it is
possible [5,20], but approaches for extended increases in activity in vivo remain elusive. The
difficulty of maintaining heightened activity in vivo for extended periods of time, may speak to the
existence of a fast downregulating homeostatic mechanism that has yet to be experimentally
observed. The relevant timescales for both homeostatic and Hebbian plasticity mechanisms remain
an unanswered question and a critical one for understanding their interactions.

(c) Spatial scales of synaptic plasticity and homeostatic set points

Similar to the issue of timescales, understanding the spatial scales of both homeostatic and Hebbian
mechanisms are critical for considering their interactions. Homeostatic mechanisms can be
implemented at the level of individual synapses [101], dendritic branches [66,102–105], single cells
[5,59] and the network [29], but obviously the interactions between these spatial scales will play an
important role in overall firing rate homeostasis. For example, if the activity at all individual synapses
is homeostatically regulated, then activity in dendritic branches, single cells and the network would
be affected (and somewhat regulated) by that local regulation. The spatial scale of plasticity
implementation is another area where molecular and cellular experiments may match up well with theory. Many of the more local implementations (individual synapses, dendritic branches and volume surrounding glial cells) of plasticity mechanisms may be governed by second messengers and molecules acting in these local environments. Thus, examining the relevant spatial scales in theoretical models [106] may offer predictions for the spatial and temporal characteristics of molecules that would potentially facilitate some of the activity effects observed in these models and in the in vivo data.

Understanding the spatial scales of the implementation of plasticity mechanisms may also provide insight into the spatial scales for the set points of activity or synaptic weight to which these homeostatic mechanisms are returning the synapse, branch, cell or network. Whether homeostatic mechanisms are balancing spontaneous firing rate, evoked firing rate, a combination of those two [60], the weight of excitatory synapses [66] or subthreshold activity [61,107] remains unclear. One possibility is that there may be multiple spatial set points and the specific set point is regulated by homeostatic mechanisms implemented at that spatial scale. So balancing neuronal firing rates in the network would occur via network level homeostatic mechanisms, and balancing synaptic weights in a dendrite would occur through dendritic branch-level implementation of homeostatic mechanisms. How and when these different set points and homeostatic mechanisms are implemented at these spatial scales remain unanswered questions and are important for understanding how these plasticity mechanisms occur in vivo.

(d) How do mechanisms interact?

Numerous homeostatic plasticity mechanisms (synaptic scaling, changes to the balance between excitation and inhibition, changes in excitability, spine size fluctuations; [99]) and Hebbian mechanisms (short-term plasticity, short-term potentiation, LTP, LTD [46]) have been described. These mechanisms have largely been studied in isolation and there is limited understanding of how these mechanisms may interact. For example, are multiple homeostatic mechanisms engaged in an individual cell following input loss? If so, do they all have the same threshold of activity change? Previous work [13] indicates that different forms of deprivation induce different homeostatic mechanisms in layer 2/3 of the visual cortex ex vivo, suggesting that the exact nature of changes in activity levels and patterns may influence how and which homeostatic mechanisms are engaged. Additionally, if a cell does engage multiple mechanisms, the order of engagement and further interactions between mechanisms remains unresolved. Multiple studies suggest that the reduction of inhibition levels occurs immediately after sensory deprivation [11,23–26,32], but the consequences for subsequent homeostatic or Hebbian mechanisms is not clear. Consequently, it is an important future topic to explore how individual mechanisms, as well as their interactions, affect behaviour. For example, at a mechanistic level, while TNF-alpha knockout mice show clear abnormalities in sensory responses [15,16], it is yet to be explored if this affects behaviours requiring sensory acuity. At a more general level, it is intriguing to explore the interaction between different mechanisms, as they can compensate for each other [108] and their combination can achieve a non-trivial functional outcome.

In addition to the interactions among the homeostatic mechanisms themselves, the relationship between the Hebbian and homeostatic mechanisms is not particularly well understood. Following monocular deprivation, circuit reorganization is proposed to occur via LTD [88], followed by the homeostatic mechanism of either synaptic scaling [89] or changing the sliding threshold to favour LTP [62], but whether homeostatic mechanisms are only engaged after the cell has induced Hebbian plasticity past some threshold (as may be the case with monocular deprivation) or if these homeostatic mechanisms are constantly at work to never allow activity to get too far out of range is
unclear. One issue in the field is that given the sensitivity of the currently used experimental approaches, one needs to induce a strong change in activity or a significant loss of input in order to be able to measure that homeostatic mechanisms have been engaged. With the advent of new, more sensitive tools to both manipulate activity (light-activated channels) and measure activity (voltage-sensitive dyes), these questions will likely be resolved in the near future. Finally, while numerous molecules have been identified to play a role in mechanisms of both types of plasticity, there is an overlap between these molecular cues [93]. The interactions between the molecular mechanisms of Hebbian and homeostatic plasticity are largely unexplored and are an important question for identifying how these different types of plasticity are induced.

The study of homeostatic plasticity would also be greatly advanced by the development of genetic and pharmacological methods for regulating and preventing it. Hebbian plasticity can be controlled genetically by numerous interventions, from manipulating NMDA receptors through CaM-kinase-II-alpha to scaffolding mechanisms involved in receptor trafficking, and pharmacologically by d,l-2-amino-5-phosphonopentanoic acid (AP5) and 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP). Experimental manipulation of homeostatic scaling has been achieved principally by genetic or pharmacological alteration of TNF-alpha signalling; no selective manipulation is yet known for regulation of inhibition. It will be important for advances in the molecular understanding of homeostatic plasticity mechanisms to lead to additional tools that can be used in vivo and targeted to specific cells. Without such tools, it will be difficult to dissect the interaction of these two forms of plasticity further and make better connections with theoretical studies.

To conclude, the ideas that emerged at this meeting reinforced many of the general concepts that have evolved over the past 15–20 years—the mechanisms of homeostatic plasticity (synaptic scaling, changes in inhibition), the recovery of activity following input loss and the necessity for some form of stability to balance Hebbian changes. Clear directions for future research, together with important experiments going forward include, (i) understanding the relevant timescales for both homeostatic and Hebbian changes and how stability in the circuit can be maintained despite these differences in timescales, (ii) more effectively connecting theory with molecular and systems level experiments, (iii) understanding the spatial scales of both the set points that the cells and networks are trying to achieve and the implementation of plasticity mechanisms, (iv) characterizing the interactions, both spatial and temporal, between mechanisms of homeostatic and Hebbian plasticity, and whether the effector molecules are the same for these two forms of plasticity, (v) understanding the molecular mechanisms for three types of homeostatic plasticity—synaptic scaling, modulation of inhibition and firing rate homeostasis, and (vi) understanding the temporal, spatial and mechanistic dynamics of the understudied synaptic downscaling.

Authors’ contributions

All authors attended the meeting, participated in the discussion and approved the final manuscript. T.K. and T.T. wrote the manuscript.

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We have no competing interests.

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References


66. 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, 354–373. (doi:10.1002/hipo.20768)


