OPINION

The BCM theory of synapse modification at 30: interaction of theory with experiment

Leon N Cooper and Mark F. Bear

Abstract | Thirty years have passed since the publication of Elie Bienenstock, Leon Cooper and Paul Munro's 'Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex', known as the BCM theory of synaptic plasticity. This theory has guided experimentalists to discover some fundamental properties of synaptic plasticity and has provided a mathematical structure that bridges molecular mechanisms and systems-level consequences of learning and memory storage.

It is now widely appreciated that synapses in the cerebral cortex are bidirectionally modified by sensory experience; that homeostatic mechanisms exist to ensure that activity in the cortical network stays within a useful dynamic range; that a manifestation of such synaptic plasticity at the cellular level is the gain and/or loss of responsiveness to particular sensory stimuli; and that the manifestations of such plasticity at the systems and behavioural levels are learning and memory storage. These tenets of modern neuroscience were once, not long ago, theoretical ideas. In 1982, Elie Bienenstock, Leon Cooper and Paul Munro proposed a theory of cortical synapse modification that incorporated these ideas to account for experimental observations of experience-dependent acquisition and modification of neuronal response selectivity in the visual cortex[1]. This proposal, known as the BCM theory, has been successful in explaining the development of visual cortical response properties in different visual environments and has suggested experiments that have uncovered new phenomena, such as homosynaptic long-term depression (LTD) and metaplasticity. The theory has provided a framework in which new questions could be posed and new discoveries could be put into an appropriate place in an overall structure.

The influence of the BCM theory on experimental studies over the past three decades provides a concrete example of the fruitful interaction of theory and experiment in neuroscience (BOX 1). We believe that it is appropriate at this anniversary to evaluate what the theory has done to advance the understanding of synaptic plasticity, learning and memory.

Origins of the BCM theory

It was realized in the early 1970s that networks of neurons can form distributed representations of the world that are 'associative' (that is, recollection of one memory can lead to the recollection of another memory that is linked to the former by experience) and 'content addressable' (that is, memories are accessed by content rather than by a physical address in the neuronal network). Such representations are resistant to the loss of individual neurons and synapses and thus provide a candidate substrate for memory storage in the animal brain. But how can these representations be constructed in networks of neurons? That is, how can the strengths of the vast numbers of synapses that make up neuronal networks be adjusted to obtain a map that corresponds to a particular memory?

Early models of the process of synaptic modification were based on the relative rates of neuronal firing at different synapses[2–4]. Perhaps the simplest of these models was that synaptic modification (and hence learning) follows the famous Hebbian rule that "when an axon in cell A is near enough to excite cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency in firing B is increased" (REF. 5). In other words, neurons that fire together, wire together[6,7].

It was, however, immediately clear that Hebbian learning could only be part of the explanation of synaptic modification, as synapses following this rule would grow in strength without bound. Thus, one early question was how could such learning be stabilized? Furthermore, although information regarding the presynaptic input is locally available at the synapse, the integrated response of the postsynaptic cell to the inputs from all of its dendrites is not. Thus, it was unclear how the information required for Hebbian learning could be made available at synapses. In order for the information required for Hebbian modification to be available locally, it was conjectured that it must be propagated 'backwards' (by depolarization or through spikes travelling in the opposite direction to the usual flow of signals) from the cell body to each of the synapses[8] (FIG. 1). Although such conjectures seemed attractive when they were proposed in the early 1970s, they were criticized because, at that time, there was little evidence for experience-dependent synaptic modification of any kind. It therefore became important to determine whether such synaptic modification takes place and, if so, what form it takes. Furthermore, it was crucial to understand its cellular and molecular basis and thus the cellular and molecular basis for learning and memory storage.

An avenue to attack these questions was provided by the experimental observation that many cortical neurons are selective for particular features of a stimulus. A compelling demonstration of this concept was provided by the 'edge detectors' described by Hubel and Wiesel in the primary visual cortex (V1) of kittens[9]. By the mid 1970s, years of experimentation in the visual cortex had led to two (sometimes controversial) conclusions. First, in animals reared in normal visual environments, most visual cortical neurons are selective for particular stimulus orientations and are binocular and, second, these properties are modified by the visual experience of the animal[10,11]. A robust example of experience-dependent plasticity occurs in monocular deprivation, in which relatively brief monocular eyelid closure leads to a modification, called an ocular dominance shift, whereby cortical responses to stimuli presented to the deprived eye are depressed or disappear (FIG. 2). Thus, it seemed that the relationship between the input and the output of visual cortex neurons could be altered by visual experience. The next question was: could these experience-dependent changes in input–output properties of neurons be attributed to synaptic modification and, if so, what form of modification could explain these observations?

Box 1 | **The role of theory in science**

Can theory be useful in neuroscience? We know that theory is very useful in the physical sciences and no one doubts the value of hypothesis-driven experiments in the biological sciences. It is when the connection between hypothesis and conclusion requires many steps that mathematical theories show their value. The biological sciences, we are sometimes told, are data-driven and too complex to allow for the effective use of mathematical theories. However, consider pre-Copernican astronomy. Ptolemaic astronomers introduced a variety of devices (including equants, deferents and, most famously, circles moving on circles called epicycles) to account for the positions of the planets against the fixed stars. By the time of Copernicus, astronomers were using up to 80 epicycles to fit vast quantities of data gathered over thousands of years of observation. Could the mediaeval astronomer have foreseen that the complexities of the planetary motions would all follow as a consequence of two postulates, namely Newton's second law of motion and Newton's law of gravitation? Of course success in the physical sciences is no guarantee that theory can succeed in neuroscience. However, it does suggest that large amounts of data do not preclude the possibility or usefulness of theory. Rather, we might say that such quantities of data make theory necessary if we are ever to order and understand them. Experiment winnows the possible hypotheses and theory narrows and focuses the experimental alternatives.

What is a good theory? The usefulness of a theory lies in its concreteness and in the precision with which questions can be formulated. A successful approach is to find the minimum number of assumptions that imply as logical consequences the qualitative features of the system that we are trying to describe. As Einstein is reputed to have said: "Make things as simple as possible, but no simpler." Of course there are risks in this approach. We may simplify too much or in the wrong way so that we leave out something essential or we may choose to ignore some facets of the data that distinguished scientists have spent their lifetimes elucidating. Nonetheless, the theoretician must first limit the domain of the investigation: that is, introduce a set of assumptions specific enough to give consequences that can be compared with observation. We must be able to see our way from assumptions to conclusions. The next step is experimental: to assess the validity of the underlying assumptions if possible and to test predicted consequences.

A 'correct' theory is not necessarily a good theory. For example, in analysing a system as complicated as a neuron, we must not try to include everything too soon. Theories involving vast numbers of neurons or large numbers of parameters can lead to systems of equations that defy analysis. Their fault is not that what they contain is incorrect, but that they contain too much.

A theory is not a legal document and, in spite of occasional suggestions to the contrary, no scientist is in communication with the Almighty. Theoretical analysis is an ongoing attempt to create a structure — changing it when necessary — that finally arrives at consequences consistent with our experience. Indeed, one characteristic of a good theory is that one can modify the structure and know what the consequences will be. From the point of view of an experimentalist, a good theory provides a structure in to which seemingly incongruous data can be incorporated and that suggests new experiments to assess the validity of this structure. A good theory helps the experimentalist to decide which questions are the most important.

Theoretical modelling can place ideas of synaptic modification in concrete forms. Hebbian synaptic modification (FIG. 1b) can be written as:

$$\Delta m_j \propto \varphi_i^{Hebb}(c)\, d_j \qquad (1)$$

where m is the synaptic strength, φ^{Hebb} is the Hebbian modification function, c is the firing rate of the postsynaptic neuron, d is the input firing rate, j identifies the presynaptic input and i identifies the postsynaptic neuron. As shown in FIG. 1b, φ^{Hebb} is equal to c. According to this equation, the change in synaptic strength (weight) at the j^{th} synapse is proportional to the product of the firing rates of the j^{th} presynaptic axon and the i^{th} postsynaptic neuron onto which it synapses. However, this equation yields no selectivity (that is, the responses of the neuron will not be limited to a subset of input patterns, as is observed experimentally) and needs stabilization; otherwise, as mentioned above, the synaptic strengths would grow indefinitely.

A first attempt at solving these problems is called the CLO theory, named after the authors Cooper, Liberman and Oja who proposed it[4]. This theory combined Hebbian learning with 'anti-Hebbian' learning (that is, a decrease in m_j when the postsynaptic response is below a particular threshold). This theory can be written as:

$$\frac{dm_j}{dt} = \varphi^{CLO}(c)\, d_j \qquad (2)$$

where φ^{CLO} is the CLO modification function as shown in FIG. 1c.

According to this theory, there is a threshold level of postsynaptic response (termed the modification threshold (θ_m)) at which the polarity of synaptic modification reverses from negative to positive. When $c > \theta_m$, the synaptic weights of active inputs increase, whereas when $c < \theta_m$, the synaptic weights of active inputs decrease. This theory yields some selectivity because synaptic weights can evolve so that the neuron eventually responds only to some inputs (those that initially yielded a response where $c > \theta_m$) and not to others (those that yielded a response where $c < \theta_m$). However, this theory is not stable because setting the threshold too low causes synaptic strength to grow without bound (as in Hebbian learning), and setting the threshold too high causes all synapses to weaken to zero.

The BCM theory added a sliding modification threshold — that is, an adjustable θ_m — to the CLO theory (FIG. 1d). As the value of θ_m automatically adjusts as a function of the average activity of the postsynaptic neuron, the BCM theory overcame the limitations of the CLO theory and yielded both selectivity and stability. A later theoretical innovation by Intrator and Cooper that redefined the movement of θ_m further improved the stability of the BCM theory[12].

In addition to the sliding modification threshold, the BCM theory requires bidirectional synaptic modification: that is, both increases and decreases in synaptic strength. The solutions of the BCM equations converge towards a set of synaptic weights (also known as the fixed points of the theory) that depend on the quality and structure of the visual environment. In a 'patterned' environment (for example, an ordinary visual environment that is crisply imaged on the retina), only selective fixed points are stable. In other words, the synaptic weights move towards stable values such that the neuron responds only to some of the experienced input patterns and therefore shows the property of stimulus selectivity.

It was demonstrated that the BCM theory was in qualitative agreement with experimental results. In a patterned environment, neurons developed stable stimulus selectivity, whereas in a noisy environment (as might occur, for example, when image formation on the retina is degraded by eyelid closure), neurons either did not develop or did not retain selectivity[13]. Furthermore, a large number of simulations have been performed over the years to test the consequences of the theory in various natural image visual environments[14–17]. These simulations have also produced results that agree both qualitatively and quantitatively with experimental findings (FIG. 3).

Testing the assumptions

In the classic monocular deprivation paradigm, neurons in the visual cortex tend to disconnect from neurons in the deprived eye[10,11,18,19]. Intuition suggests that this is a simple case of 'use it or lose it' — that is, the absence of activity in the deprived retina causes the thalamic inputs serving this eye to wither in the cortex. However, the BCM theory proposes instead that the loss of responsiveness and loss of connectivity is actively driven by the residual activity in the deprived eye (represented by the symbol *d*) when this activity consistently and repeatedly fails to correlate with a strong integrated postsynaptic response — that is, when $c < \theta_m$. Thus, poorly correlated activity is worse than no activity at all. Testing this assumption has led to several interesting new experimental observations (see REFS 20–24 for examples), which have in turn led to additional theoretical work.

One theoretically motivated[13,15] experiment was the comparison of the consequences of monocular eyelid closure[18,25,26] or simple blurring of images on the retina[27] with those of temporary anaesthetic-induced inactivation of one retina with tetrodotoxin (TTX). Counterintuitively, but consistent with the BCM theory, the data from this experiment showed that retina inactivation actually protects the deprived synapses from depression. This observation has been made in both kittens[25] and mice[18,26], and in all cases monocular inactivation causes far less visual response depression than monocular eyelid closure, suggesting that response depression is triggered by activity (not inactivity) in the retino–geniculo–cortical pathway.

The interpretation of this result depends on the seemingly reasonable assumption that in the inactivated case, activity in the lateral geniculate nucleus (LGN), which relays activity from the retina to the cortex, is reduced or silenced compared with the eyelid closure case. However, a study that tested this assumption yielded surprising results[28]. The activity of LGN neurons in awake animals was recorded during normal vision, when the eyelid was sealed shut or when TTX was injected into the eye. Consistent with prior assumptions, eyelid closure had no effect on mean LGN firing rates but de-correlated the activity of the neurons. Unexpectedly, however, monocular inactivation also did not reduce mean activity in the LGN. Instead, it caused an increase in correlated firing in cells within the LGN, which was due to the onset of synchronous bursting activity. These results do not challenge the notion that de-correlated activity in the LGN is a trigger for synaptic weakening in the cortex, but they force a substantial revision of how monocular inactivation experiments are interpreted. Instead of silencing cortical inputs, it seems that intraocular TTX imposes a regime of spontaneous hypersynchrony that may protect cortical synapses from weakening (FIG. 4).

These observations inspired a recent analysis of the effect of input correlations during deprivation experiments, which revealed that large correlations in neuronal activity in the LGN can slow the loss of cortical responsiveness to the deprived eye[29]. Further experimental work to quantitatively determine the correlations in firing within the LGN under different viewing conditions would permit a more detailed comparison of theory and experiment.

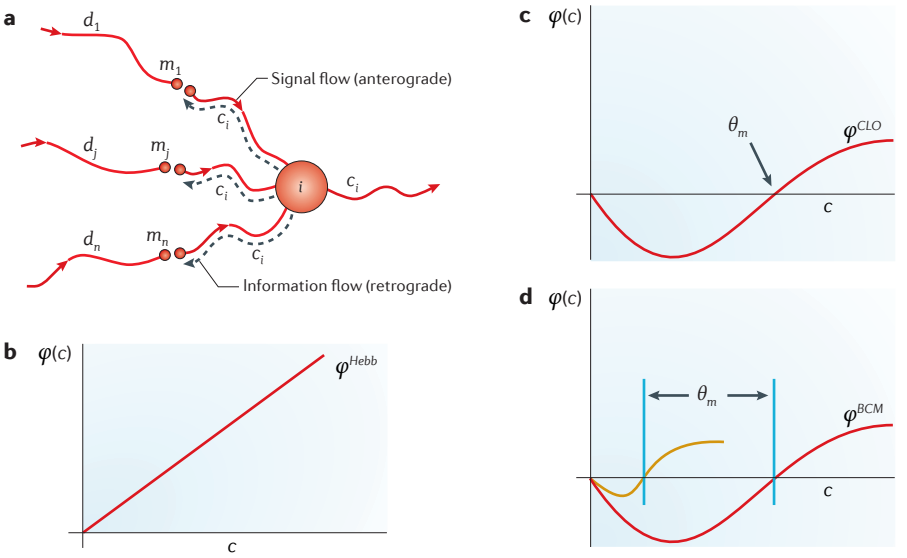

Figure 1 | **Information transfer in cortical cells and theories of synaptic modification. a** | In order for the information required for Hebbian synaptic modification to be available locally at each of the synapses on a postsynaptic cell (*i*), information about the integrated postsynaptic firing rate (c_i) must be propagated backwards or retrogradely (by depolarization or spiking in the direction opposite to the usual anterograde signal flow) from the cell body to each of the synapses. m_j refers to the j^{th} synapse and d_j is the incoming firing rate at this synapse[8]. The existence of 'back spiking' (dashed lines) that could carry the information required for Hebbian modification was later confirmed experimentally and shown to be associated with changes in synaptic strength. **b–d** | These figures show various theories of synaptic modification, wherein the strength of synaptic modification is determined by the product of the input activity (*d*) and the φ function of the concurrent level of integrated response (*c*) in a postsynaptic neuron. **b** | Simple Hebbian modification assumes that active synapses grow stronger at a rate proportional to the concurrent integrated postsynaptic response; therefore, the value of φ increases monotonically with *c*. **c** | The CLO (Cooper, Liberman and Oja) theory combined Hebbian and what has been called 'anti-Hebbian' learning to obtain a more general rule that can yield selective responses[4]. When a pattern of input activity evokes a postsynaptic response greater than what is called the modification threshold (θ_m), the active synapses potentiate. When a pattern evokes a response less than θ_m, the active synapses depress. This property can lead to neurons that respond to some but not all patterns; that is, to selective responses. **d** | The BCM (Bienenstock, Cooper and Munro) theory[1,12] incorporates a sliding modification threshold that adjusts as a function of the history of average activity in the postsynaptic neuron. This graph shows the shape of φ at two different values of θ_m. The orange curve shows how synapses modify after a period of postsynaptic inactivity, and the red curve shows how synapses modify after a period of heightened postsynaptic activity. Part **a** is reproduced, with permission, from REF. 8 © (1973) Elsevier.

Understanding how LGN activity triggers (or fails to trigger) changes in the cortex is of great interest because of its clinical relevance to amblyopia, a leading cause of visual impairment worldwide that can arise from poor image formation in one eye during early childhood. Although the optics of the affected eye can be corrected, there can nevertheless be life-long visual disability owing to weakening of synaptic transmission between the LGN and the visual cortex. It is interesting to consider the possibility that changes in how LGN neurons respond to deprivation could contribute to the developmental regulation of visual cortical plasticity.

New phenomena

One of the most interesting functions a theory can perform is to suggest experiments that reveal new phenomena. Consideration of the

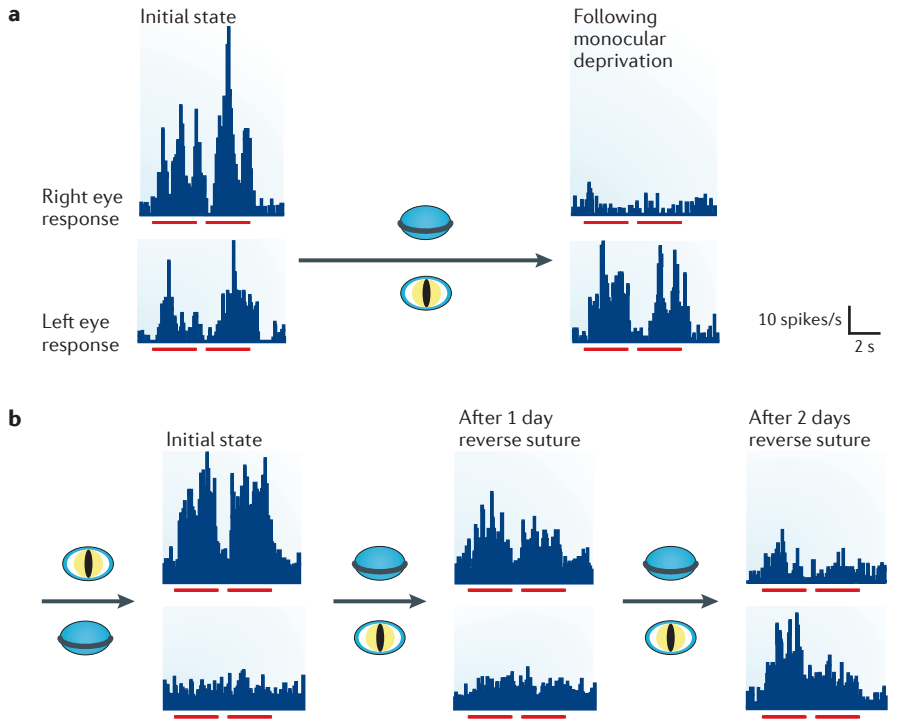

Figure 2 | **Ocular dominance plasticity in the kitten visual cortex. a** | Chronic recording of a neuron in the kitten visual cortex. Histograms show action potentials in response to visual stimulation presented at the times indicated by the horizontal red bars. This animal was reared normally and then subjected to brief monocular deprivation by closure of the right eyelid. The neuron, which was initially binocularly responsive, rapidly lost responses to the deprived eye. **b** | In this case, recordings in a visual cortex neuron began after a period of deprivation of the left eye, so the initial response is monocular. In the manipulation called 'reverse suture', the initially open eye is closed and the previously deprived eye is opened. The newly closed right eye rapidly loses strength even though the neuron is not activated by the other eye. The newly opened eye gains strength slowly after a delay of a day or two. Parts **a** and **b** are reproduced, with permission, from REF. 11 © (1989) American Physiological Society.

BCM theory led to the search for and ultimately the establishment of the phenomena known as homosynaptic LTD, bidirectional synaptic plasticity and metaplasticity[30].

One early challenge to the simple use-it or lose-it model was the discovery by Hubel and Wiesel that eyelid closure has robust cortical effects only when the other eye is open and viewing the world; that is, the consequences of binocular deprivation are mild compared with the consequences of monocular deprivation[31]. This observation spawned the important concept of binocular competition, which is conventionally explained using a model in which strong activation of cortical neurons by the non-deprived eye leads to the production of a 'punishment' signal that causes the demise of inactive cortical synapses associated with the deprived eye[32–34]. However, this explanation for binocular competition is hard to reconcile with the results of a manipulation called 'reverse suture' in which the previously closed eyelid is opened after a period of monocular deprivation and the eyelids of the previously open eye are sutured closed. This manipulation leads to a situation in the cortex in which the strong input pathway is not receiving visual stimulation and the input pathway that is receiving visual stimulation is not strong. Thus, cortical activity immediately falls to a low level[11] and so, presumably, would the hypothetical punishment signal. Nonetheless, the synaptic inputs from the newly deprived eye depress rapidly (at a rate comparable to monocular deprivation), and there is a lag of several days before the synapses serving the previously deprived eye recover strength (FIG. 2). These results were not compatible with the conventional view of binocular competition circa 1985. The BCM theory, with its assumptions about how synapses undergo depression and the inclusion of a slowly adjusting modification threshold, had no difficultly explaining these results. As described below, in the BCM theory, binocular competition occurs because the activity-dependent modification threshold, θ_m, has different values during binocular deprivation and monocular deprivation. This elegant explanation of the reverse suture experiment provided motivation to search for experimental evidence for the assumptions of the theory.

An essential postulate of the BCM theory is the existence of synaptic depression at activated synapses if the postsynaptic cell is not sufficiently depolarized. By 1990, it was well established that long-term potentiation (LTP) occurs at activated synapses in the hippocampus when the postsynaptic cell is strongly depolarized, which was usually accomplished experimentally by synchronously stimulating a large population of synapses at high frequencies[35,36]. To satisfy the synaptic weakening requirement of the BCM theory, Dudek and Bear[37] explored the consequences of reducing stimulation frequency and intensity[37], and this work culminated in the low-frequency stimulation (LFS) protocols that are in widespread use today for inducing *de novo* LTD. Before this experimental advance, which is celebrating its twentieth anniversary, there was widespread scepticism about the existence and significance of any form of homosynaptic LTD[38–41] (BOX 2). However, once there was a reliable and reproducible method to induce it, the study of LTD flourished. This work has led to numerous insights, not only into the fundamental cell biology of synaptic modification[42,43] but also into the pathophysiology of neurological and psychiatric diseases[44].

By systematically varying the stimulation frequency, it was possible to experimentally verify the φ function of the BCM theory: LTD was induced by tetanic stimulation over a range of low frequencies, LTP was induced by stimulation at a range of high frequencies and there was an intermediate stimulation frequency that caused no net change, which was equivalent to θ_m (FIG. 5). Moreover, it was shown that induction of LTD, like LTP, required activation of NMDA-type glutamate receptors (NMDARs). This finding suggests that the amount of calcium flowing through voltage-dependent NMDARs controls the direction and magnitude of synaptic plasticity, a concept that had been suggested previously[45,46] and that was later supported experimentally[47–50]. Additional studies showed that the same synapses could support LTD and LTP, and thus were bidirectionally modifiable[37,47,51,52].

As these and many subsequent studies of LTD and LTP relied on changes in the stimulation frequency to vary the level of NMDAR activation, it is sometimes referred to as 'frequency-dependent plasticity' (to distinguish it from spike-timing-dependent

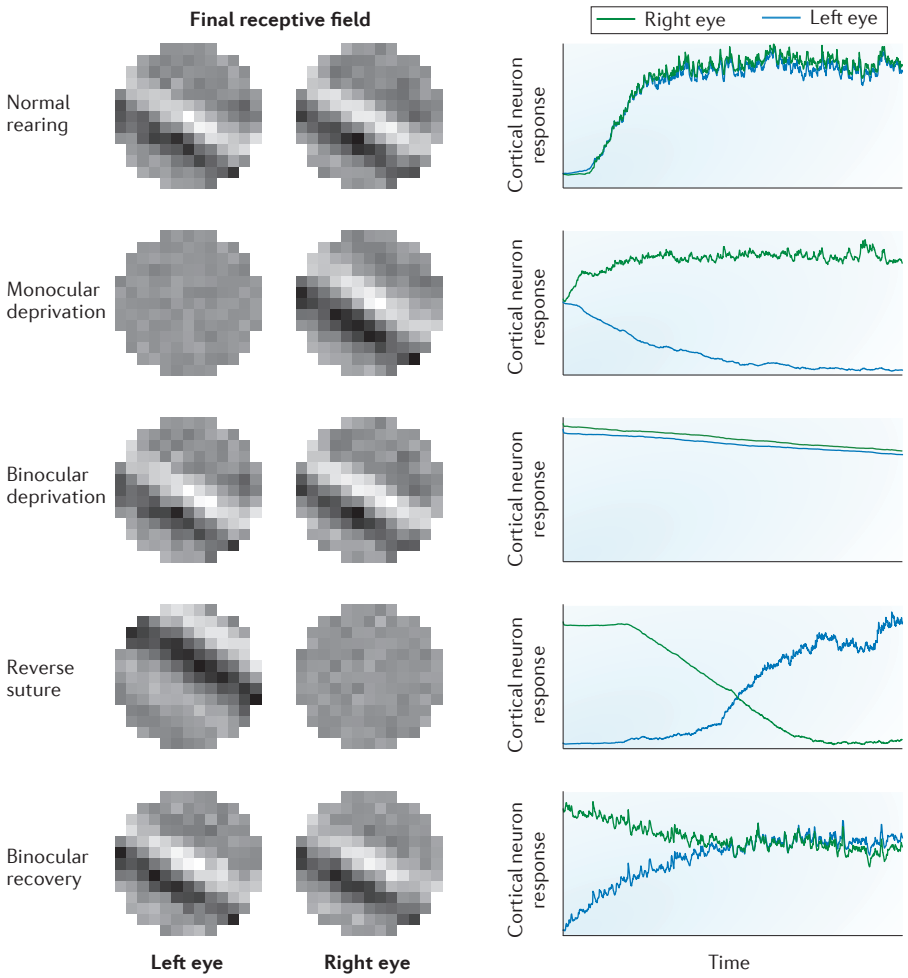

Figure 3 | **Results of BCM simulations in environments using noisy natural images.** The left column of figures shows, for each example, a matrix of the synaptic weights of the inputs from the two retinas onto a single cortical neuron, yielding the neuron's receptive field (that is, the region of the retina to which the neuron responds). Each pixel represents a point in space over the retina and the intensity of the shading corresponds to the synaptic strength from that retinal input (in which white is a strong synapse and black is a weak synapse). The right column shows how the maximal response of the neuron to oriented stimuli changes as a function of time. Left eye responses are shown in blue, whereas right eye responses are shown in green. In normal rearing simulations, both eyes are presented with natural scenes. The neuron acquires stable binocular responses and receptive fields that are selective for stimulus orientation. In monocular deprivation simulations following normal rearing, the left eye is presented with noise and the right with natural scenes. The neuron rapidly loses responsiveness to the deprived eye. In binocular deprivation simulations following normal rearing, both eyes are presented with noise. The neuron retains responsiveness to both eyes, but it is important to note that if the binocular deprivation simulation is run for long enough, selectivity will be lost. In reverse suture simulations following monocular deprivation, the eye initially presented with noise is now presented with natural scenes, and the other eye is presented with noise. Responses to the newly deprived eye are rapidly lost and responses to the formerly deprived eye recover after a delay, explained in part by the time required for θ_m to adjust. In binocular recovery simulations following monocular deprivation, both eyes are presented with natural scenes. The neuron rapidly recovers binocular responsiveness. These simulation results show that the BCM (Bienenstock, Cooper and Munro) theory is in agreement with experimental observations[14,187].

plasticity (STDP), which is discussed below). However, this characterization is overly simplistic. The key variable that governs the polarity of synaptic modification is the postsynaptic membrane voltage at the moment that glutamate binds the NMDAR[53]. Thus, the φ function at synapses in the CA1 region of the hippocampus can be observed with stimulation of variable duration and frequency when the postsynaptic voltage is directly manipulated with current injection[54–56] and when the number of active NMDARs is controlled pharmacologically[49,57].

Experimental verification of the φ function was obtained first in the hippocampus and then reproduced in the visual cortex[58]. The similar qualities of LTD and LTP in these structures (and in various species) suggested the possibility that excitatory synapse modification throughout the cortex might be well described by the BCM theory[53], and indeed the φ function has been experimentally verified in many cortical areas, even including the human inferotemporal cortex[59]. Not surprisingly, the subsequent and ongoing study of synaptic plasticity has led to the discovery of additional forms of LTD and LTP that go well beyond the initial theoretical postulates[60,61]. Nevertheless, the general principles of bidirectional synaptic plasticity that were first revealed by LTD and LTP studies in the CA1 region of hippocampus appear to apply broadly and contribute to many functions[42]. In addition to serving as a guide to discover these principles, the BCM theory has provided a bridge that links elementary forms of synapse modification to their systems-level consequences, such as receptive field plasticity, learning and memory (for additional discussion, see REFS 53,62,63).

LTD and amblyopia

Understanding the diverse mechanisms of homosynaptic LTD has led to significant and therapeutically important insights into the synaptic basis of diseases, including addiction[64], Parkinson's disease[65], Alzheimer's disease[66], fragile X syndrome[67] and autism[68]. However, the original goal of studying this form of plasticity was to understand amblyopia. After two decades of intense study, we can now safely conclude (in mice at least) that the mechanisms of NMDAR-dependent LTD are indeed primarily responsible for the initial loss of visual responsiveness in the visual cortex after monocular deprivation[69–71].

One rapid consequence of monocular deprivation is depression of transmission specifically at thalamocortical synapses — the excitatory synapses that bring information from the LGN into the cortex. The magnitude of this change is sufficient to account entirely for the full ocular dominance shift as measured by the ratio of deprived to non-deprived eye cortical responses[72]. After only 3 days of monocular deprivation there are also clear structural changes in thalamocortical synapses[26] that eventually culminate in the large-scale retraction of axons[73]. These changes do not occur if cortical NMDARs are blocked[74–78]. Connecting NMDAR-dependent deprived-eye depression and LTD has been challenging and often controversial, but it is now

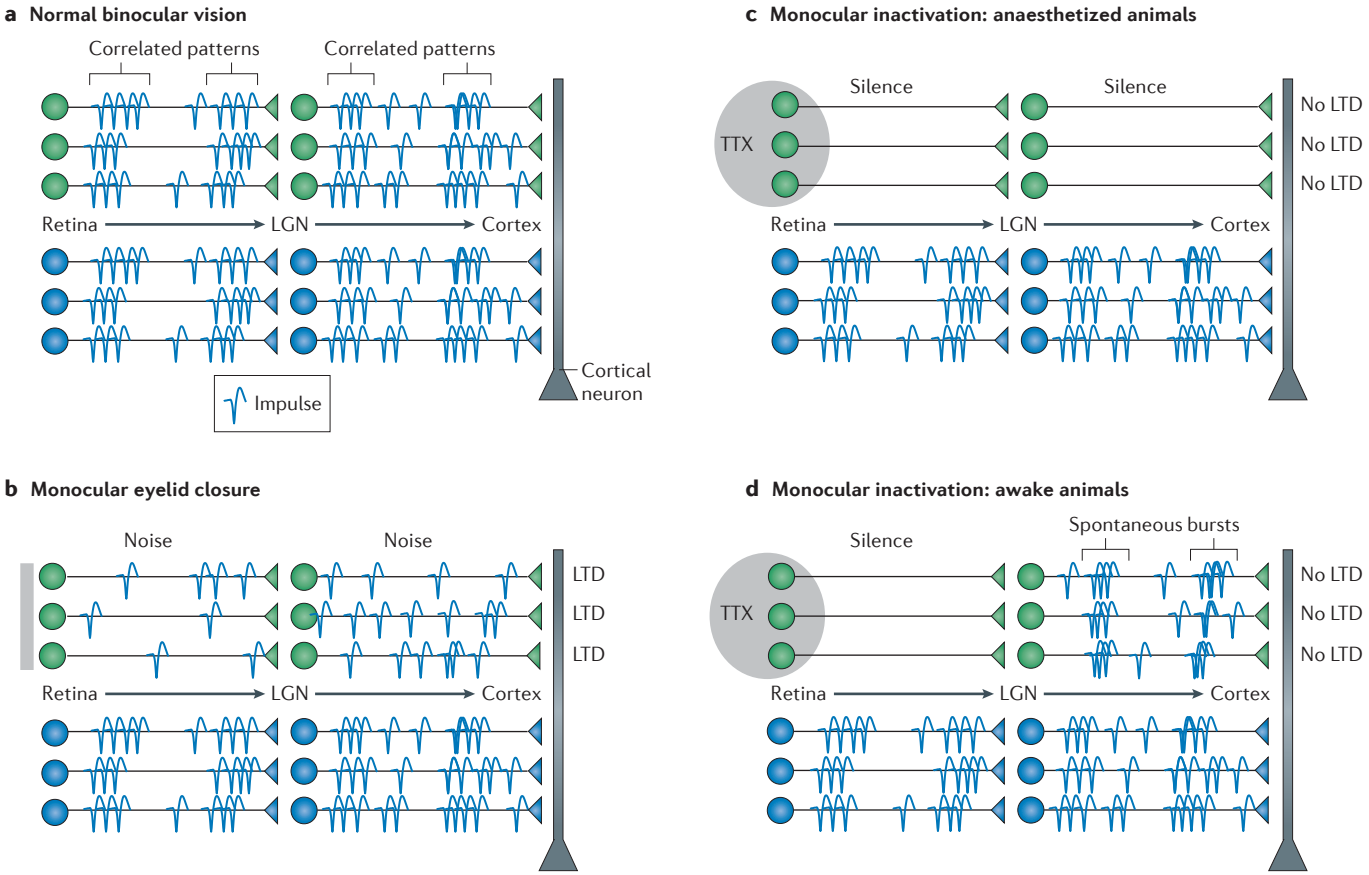

Figure 4 | **Activity patterns that trigger ocular dominance plasticity.** The cartoons depict cortical neurons receiving retinal inputs from right (green) and left (blue) eyes via the lateral geniculate nucleus (LGN). **a** | Normal binocular connections are maintained by patterns of input from the two eyes that are temporally well correlated. **b** | During monocular eyelid closure, the structured activity in one input (green) is replaced by uncorrelated noise. This activity triggers long-term depression (LTD) at LGN–cortical synapses. **c**,**d** | An experimental test of the requirement for noise to trigger LTD was to inject the eye with tetrodotoxin (TTX), which silences the retina. It was observed that inputs from the injected eye continue to drive strong cortical responses after the TTX wears off, showing that silencing the retina protects synapses from the deleterious effects of eyelid closure[18,25]. On the basis of LGN recordings in anaesthetized animals[25,188], the original interpretation of this experiment was based on the assumption that silencing the retino–geniculate input also silences the LGN–cortex inputs (**c**). However, recent experiments performed on awake animals have shown that silencing the retina causes the LGN to fire spontaneously in synchronous bursts[28], which is similar to what occurs naturally during slow-wave sleep[189] (**d**). This regime of highly correlated activity in the awake animal may protect cortical synapses from weakening[29].

established that monocular deprivation induces LTD in the visual cortex[69,70], that the mechanisms of LTD are required for the effect of monocular deprivation[71,79,80] and that LTD can be accompanied by structural plasticity[81]. An interesting complication has been the discovery of different forms of LTD in different layers of the mouse visual cortex. In layer 4, LTD is mediated by NMDAR-triggered AMPA-type glutamate receptor (AMPAR) internalization[70], and inhibition of this mechanism prevents deprived-eye response depression[71,80]. In layer 3, however, LTD is mediated by an NMDAR-dependent mechanism that also requires signalling via the CB1 endocannabinoid receptor and is expressed presynaptically[70]. If CB1 receptors are blocked, there is no deprived-eye response depression in layer 3 (REF. 79).

As new methods have been developed to study the visual cortex, it has been shown that deprivation can change synaptic transmission and neuronal excitability in myriads of ways in different intracortical circuits[61,82,83]. Much work remains to be done in order to understand how each mechanism contributes to the functional consequences of deprivation. However, LTD of excitatory synapses as postulated in the BCM theory is an excellent first approximation of the primary cause of visual impairment after monocular deprivation. Unstructured retinal noise from an eye with poor image formation results in LGN activity that fails to consistently correlate with a strong postsynaptic response in the visual cortex; consequently, NMDARs are weakly activated, AMPARs are internalized (in layer 4) and neurons stop responding to stimulation of the deprived eye. Blocking retinal noise, inhibiting cortical NMDAR activation or preventing expression of NMDAR-dependent LTD protects the visual cortex from the deleterious effects of deprivation[71,80,84].

The physiological relevance of homosynaptic LTD has sometimes been questioned because the experimental induction paradigms (repetitive electrical stimulation[37,47,52,85] or pharmacological activation of glutamate receptors[86–89]) do not mimic the natural patterns of activity in the brain[62]. The same critique can be levelled without exception against every synaptic plasticity paradigm that involves repetitive electrical stimulation of pre- and/or postsynaptic neurons. The justification for these approaches is of course that one hopes they will reveal the mechanisms that serve naturally occurring synaptic modification. In the case of

LTD, it has now been established that the mechanisms revealed by LFS and related induction paradigms also occur *in vivo* and contribute to many forms of experience-dependent modification[44,60,90–93], including ocular dominance plasticity[69,71]. This end — a deep understanding of how synapses lose strength under physiological and pathophysiological conditions — justifies the means used to study LTD over the past 20 years.

The sliding modification threshold

The BCM sliding modification threshold provides another excellent demonstration of the fruitful interplay between experiment and theory. As described above, the sliding modification threshold was introduced in part to provide stabilization. Evidence for a sliding threshold has now been obtained in several brain regions (see REFS 94–101 for example), and it appears to be as widespread as LTD and LTP (FIG. 5).

In the visual cortex, the presence of this sliding threshold immediately helps to explain the differences that are obtained in monocular and binocular deprivation experiments and the results of the reverse suture experiment described above[13,30,102,103]. The sliding threshold is nicely demonstrated by experiments performed in the mouse visual cortex over the past few years[57,104]. In the mouse, binocular responses in the visual cortex are normally dominated by the contralateral eye; thus, monocular deprivation of the contralateral eye in the mouse is similar to the reverse suture approach that has been used in kittens (FIG. 2). The first effect of closing the contralateral eye is a rapid synaptic depression via the mechanism of LTD[18,70,71,80]. After 3 days of monocular deprivation, the cortical response to stimulation of the deprived eye decreases by ~50%, but little change occurs in the cortical response to stimulation of the non-deprived ipsilateral eye. Remarkably, however, over the next several days the response to ipsilateral eye stimulation doubles, compensating for the loss of contralateral eye responsiveness[18,105]. Note that experience through the non-deprived ipsilateral eye has not changed during this time but the consequences apparently have — it now drives response potentiation to maximally use cortical resources made available by the loss of another input[105] (FIG. 6).

The general notion that the rules of synaptic modification vary depending on the recent history of synaptic or cellular activity has come to be called metaplasticity[106], and the BCM sliding threshold was the first instantiation of the concept. The idea is that θ_m, which today we might call an LTP threshold, is set by the recent history of integrated postsynaptic activity. To maintain homeostasis in the face of a changing environment, weakly active neurons seek to 'turn up the volume' on synaptic input by reducing this threshold, whereas hyperactive neurons seek to 'turn down the volume' by raising this threshold (which promotes LTD instead of LTP). According to the BCM theory, the value of θ_m is reduced in the mouse visual cortex during contralateral eyelid closure[17]. This adjustment permits the experience-dependent potentiation of the initially weak inputs from the ipsilateral eye.

This explanation of the choreography of synaptic modification during monocular deprivation differs from that provided by the concept of synaptic scaling, in which

Box 2 | The discovery of homosynaptic long-term depression

Homosynaptic long-term depression (LTD) is now viewed as an inevitable property of synapses. However, it was not always so, and certainly not at the time of its discovery[41]. The reasons for this scepticism were threefold: it was difficult to pinpoint experimental conditions in which LTD could be elicited reliably and distinguished from a pathological change; some reports of LTD proved difficult to reproduce; and there was little conviction (certainly outside the community of theoreticians) that homosynaptic LTD is useful or needed to account for synaptic memory storage or plasticity in the visual cortex.

The existence of homosynaptic LTD was suggested by early observations that electrical stimulation of the cortex or hippocampus sometimes depressed evoked responses[168–171]. However, it was difficult to make the connection between cause and effect. For example, 15 Hz stimulation of the perforant path was reported to be more likely to elicit depression in the dentate gyrus than was 400 Hz stimulation; but this 'LTD' was observed in only 5 out of 16 animals, was transient and always coincided with a spreading depression observed on the electroencephalogram[152]. Similarly, when stimulation was paired with intracellular depolarization of cortical neurons, LTD was observed in 2 out of 28 attempts[169]. In another study, the cortex was stimulated at high frequency in the presence of bicuculline methiodide (BMI) to suppress inhibition. A depressed response was observed in 11 out of 23 neurons, but the same tetanus caused long-term potentiation (LTP) in 8 cells and no change was observed in the remainder[171]. By 1980, it had been shown that hippocampal LTP could be erased by low-frequency stimulation (LFS) at 1 Hz[172–174]. However, to be effective, this stimulation had to be delivered within minutes of LTP induction; the same stimulation had no effect on control pathways. As a similar disruption of LTP could be caused by nonspecific manipulations like temporary anoxia[175], it was believed that the phenomenon of de-potentiation is more relevant to memory consolidation than it is to memory formation or LTD. Without insight into how it could be induced *de novo* in a synapse-specific way, LTD could be easily dismissed as an artefact or an epiphenomenon.

A stronger case could be made at that time for heterosynaptic LTD, which is a generalized loss of synaptic efficacy of unstimulated inputs when the postsynaptic neuron is activated strongly by other inputs[137,176–178] or by antidromic stimulation[179,180]. However, heterosynaptic LTD was robust only at perforant path–dentate gyrus synapses *in vivo*; it was not reliably observed in other brain regions or in slice preparations[181]. Furthermore, this type of change seemed better suited for homeostatic renormalization of synaptic weights than for information storage. Another type of LTD of the parallel fibre–Purkinje cell synapse had been described[182], but this phenomenon depended on co-activation of climbing fibres and was peculiar to the cerebellum[183].

Systematic attempts to establish conditions required for homosynaptic LTD in the hippocampus[184] and visual cortex[163] were described around 1990. It was reported that simultaneous 5 Hz synaptic stimulation and postsynaptic hyperpolarization of CA1 pyramidal neurons could induce LTD by a mechanism that did not require NMDA-type glutamate receptors. However, other laboratories were unable to replicate the findings[38]. In the visual cortex, another NMDA receptor-independent form of LTD was reported, but in this case the necessary condition was 50 Hz stimulation plus postsynaptic depolarization. Unfortunately this phenomenon was difficult to reproduce in the visual cortex and did not generalize to the hippocampus[185].

Seeing is believing, but often to see, one has to believe. The strong theoretical motivation of the BCM (Bienenstock, Cooper and Munro) theory led Dudek and Bear to persist in an attempt to demonstrate homosynaptic LTD when others with less conviction might have moved on[30]. Soon after their initial success in demonstrating this form of plasticity[30,37,51], follow-on studies firmly established the phenomenon, including some that revealed the intracellular trigger for LTD in CA1 (REFS 47,48,186), and others that showed that homosynaptic LTD exists in the visual cortex of two evolutionarily divergent species[58,85]. Additionally, it was shown that homosynaptic LTD and bidirectional synaptic plasticity occur in the adult hippocampus *in vivo*[52]. Thus, in addition to describing a novel form of synaptic plasticity, Dudek and Bear showed that belief in homosynaptic LTD was not misplaced. Today, it is appreciated that homosynaptic LTD of various types is widely expressed in the CNS[44,60,93].

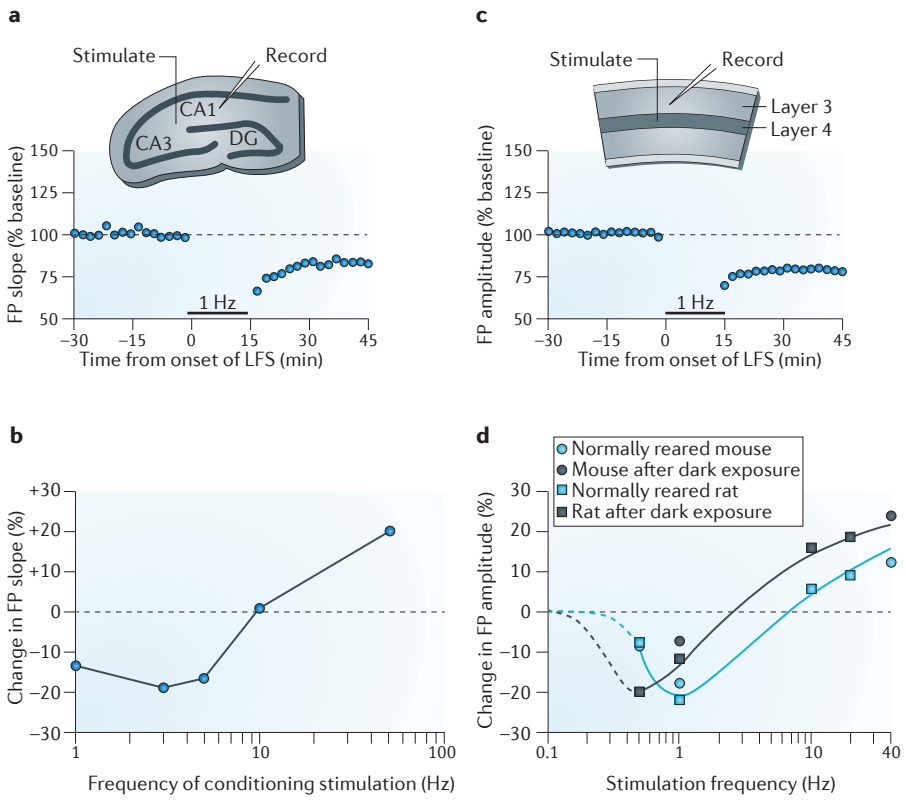

Figure 5 | **Experimental verification of the φ function and the sliding modification threshold.** **a** | Homosynaptic long-term depression (LTD) induced in the CA1 region of hippocampus by low-frequency stimulation (LFS) at 1 Hz[37]. This protocol was used to test the BCM (Bienenstock, Cooper and Munro) assumption that synapses depress when presynaptic activity consistently fails to correlate with strong postsynaptic responses. **b** | By varying stimulation frequency (and thereby the magnitude of the postsynaptic response), it was possible to experimentally demonstrate a synaptic modification function consistent with the assumptions of the BCM theory[53]. When a pattern of input activity evokes a postsynaptic response greater than a critical value corresponding to θ_m, the active synapses potentiate. When a pattern evokes a response less than θ_m, the active synapses depress. **c** | Homosynaptic LTD induced in visual cortex by 1 Hz stimulation[85]. **d** | Stimulation frequency–response functions derived from the visual cortex of normally reared mice and rats are compared to those derived from dark-exposed animals. Curves are semi-schematic and have been fitted to data from REF. 94 and REF. 104. Dashed regions are extrapolated from existing data and remain to be confirmed experimentally. These experiments confirm the BCM assumption of the existence of a sliding modification threshold. The long-term potentiation threshold is reduced in the visual cortex after total light deprivation. DG, dentate gyrus; FP, field potential.

there is a neuron-wide normalization of synaptic weights when activity is increased or decreased[107]. Synaptic scaling is a fascinating and widespread phenomenon, but it does not appear to account for non-deprived-eye potentiation after monocular deprivation. The simple reason is that a comparable increase in ipsilateral eye response fails to occur during binocular deprivation, even when binocular deprivation follows 3 days of contralateral eyelid closure[17,84]. This result indicates that the ipsilateral eye potentiation is driven by experience through the ipsilateral eye and is not a passive consequence of reduced cortical activity. Consistent with this view, the ipsilateral eye potentiation that follows contralateral eye depression requires activation of NMDARs, whereas synaptic scaling does not[108–110] (FIG. 6)

Experiments that were motivated by the BCM theory in visual cortex slices from rats[94,111] and mice[57] showed that lowering cortical activity by brief (≤2 days) binocular deprivation is indeed sufficient to lower the LTP threshold and shift the LTD–LTP frequency–response curves[57,94,111] (FIG. 5). This effect of deprivation is rapidly reversed by restoring vision. The simplest mechanism that can account for a sliding LTP threshold involves activity-dependent regulation of the calcium signals that trigger LTD and LTP[45,112–115]. We now understand that the shifts in the threshold are due to a change in the sensitivity of cortical neurons to NMDAR activation[57], and one underlying mechanism is the activity-dependent regulation of the ratio of NR2A to NR2B subunits in NMDARs[99,114,116,117]. The NR2A/NR2B ratio controls both the biophysical properties and the intracellular protein interactions of these receptors[118–120]. The net result of the shift from NR2A to NR2B is a change in the type of stimulation required to induce LTD and LTP. Light deprivation[121–123] and closure of the contralateral eyelid[124] lowers the NR2A/NR2B ratio in the visual cortex, whereas light exposure increases it. Although there is more to the sliding threshold than this single mechanism[125–133], experiments with mice in which this ratio was manipulated genetically indicate that changes in the NMDAR subunit composition in the visual cortex are causally related to both the shift in LTP threshold[104] and the propensity for non-deprived-eye potentiation after monocular deprivation[110].

The cell biology of the activity-dependent shift in NR2A/NR2B ratio remains to be elucidated in detail. When animals are exposed to light after a period of darkness, NR2A levels rise rapidly (within 2 hours of the onset light exposure) in the visual cortex, and this rise coincides with an increase in the NR2A/NR2B ratio of synaptic NMDARs[121]. This experience-dependent increase in the NR2A/NR2B ratio requires activation of both NMDARs and metabotropic glutamate receptor 5 (REF. 134). Conversely, evidence from cultured cortical neurons indicates that reduced activation of NR2B-containing NMDARs causes an increase in the synthesis of NR2B via an increase in mRNA translation (rather than via an increase in mRNA transcription)[124].

Recent *in vitro* studies in the hippocampus have shown that the NR2A/NR2B ratio (and, as a consequence, the LTP threshold) can be adjusted on a synapse-by-synapse basis depending on the history of local synaptic glutamate release[117,135,136]. These observations diverge from the BCM proposal that the modification threshold has the same value at all synapses on a given neuron and is set by the history of integrated postsynaptic spiking activity. This distinction is important because to account for properties such as binocular competition in the visual cortex, it is necessary that the threshold is set and adjusted on a cell-wide basis. *In vivo* studies in the hippocampus have revealed cell-wide shifts in the LTP threshold that support the theoretical assumptions[96], and it will be important in future studies to unravel the individual and combined contributions of various

molecular mechanisms to the BCM sliding threshold and synaptic homeostasis.

These examples provide excellent demonstrations of the interaction between theoretical, mathematical and logical ideas with experiment. A theoretical proposal that was devised to account for observations in the visual cortex *in vivo* contributed to the metaplasticity concept and culminated in a much deeper understanding of the mechanisms of synaptic plasticity and how they are regulated. Additionally, the theory has provided a structure in which the cellular- and systems-level consequences of various mechanisms can be explored and understood.

Cortical recovery of function

The BCM theory is relevant to the clinically important question of how vision can recover from the deleterious effects of monocular deprivation. If synapses carrying information from the deprived eye are physically present (that is, they have not been completely eliminated) and if the cortex is at an age at which it is modifiable, then the BCM theory suggests that restoring well-correlated activity in the strong (non-deprived) and weak (deprived) eyes should lead to recovery from amblyopia. The process is analogous to associative LTP in the hippocampus[36,137–139]. Weak synapses will potentiate as long as their activity correlates with integrated postsynaptic activity driven by the strong eye that exceeds the modification threshold[13]. The key theoretical requirement is that patterns of activity in the two eyes are well correlated. This hypothesis was explicitly tested by examining recovery from monocular deprivation in kittens with well-aligned binocular optics and in animals with experimentally induced optical misalignment. As predicted, good recovery occurred only in animals that had well-aligned eyes[102].

A strategy that is used to promote recovery from amblyopia in the clinic entails patching the strong eye[140]. According to the BCM theory, this procedure (like reverse suture) works because the modification threshold adjusts when the cortex becomes quiet in the absence of input from the strong eye, again setting up a condition in which the activity of weak synapses correlates with integrated postsynaptic activity that is greater than θ_m. However, recovery during reverse suture (or patching) is predicted to be slow, in part owing to the time it takes for θ_m to adjust. This theoretical prediction has also been tested, and the experiments confirmed that recovery is

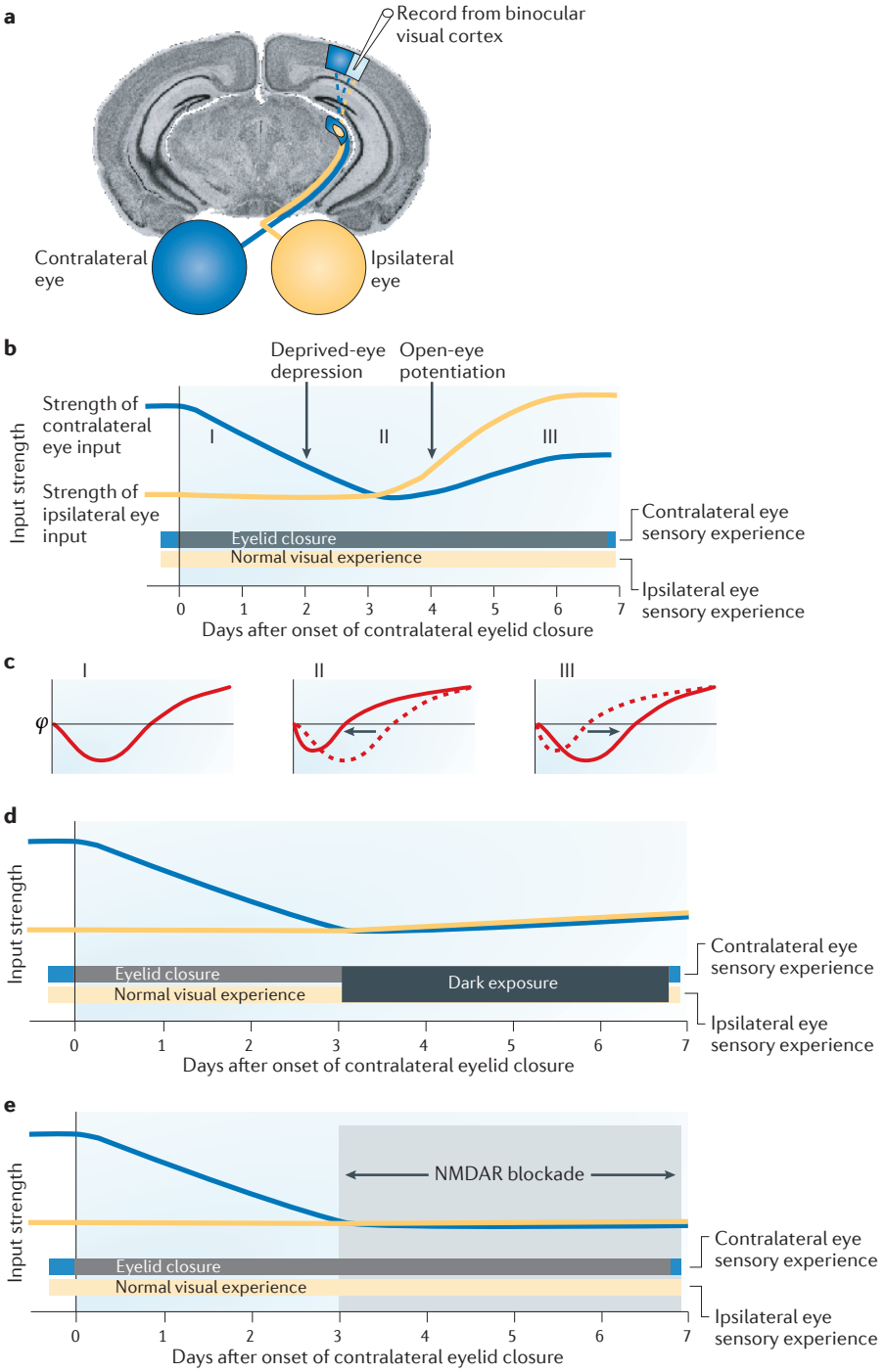

Figure 6 | **Choreography of the ocular dominance shift in the mouse visual cortex. a** | Schematic of the visual pathway from retina to cortex in the mouse. **b** | Schematic of changes in the strength of visual responses caused by deprivation of the contralateral eye[18,190,191]. Note that before deprivation, the response to contralateral eye stimulation is approximately twice as large as the response to ipsilateral eye stimulation. During the first 3 days of monocular deprivation, ocular dominance is shifted by loss of deprived eye responsiveness. Over subsequent days, there is a large compensatory increase in the response to the non-deprived, ipsilateral eye (I, II and III refer to time points before, during and after the full expression of the ocular dominance shift, respectively). **c** | According to the BCM (Bienenstock, Cooper and Munro) theory, this open-eye potentiation is enabled by the adjustment of the modification threshold after the first 3 days of deprivation. The shapes of the φ function at different values of θ_m before (I), during (II) and after (III) the ocular dominance shift are shown. **d** | Full expression of ipsilateral eye potentiation requires visual experience through the ipsilateral eye, showing that it is not merely a passive consequence of cortical inactivity[17]. **e** | Ipsilateral eye potentiation is prevented by blockade of NMDA-type glutamate receptors (NMDARs)[108–110].

faster when monocular deprivation is followed by binocular experience than when the strong eye is patched[103]. The fact that the simple restoration of balanced binocular vision is not always successful in humans is probably explained by the small size of receptive fields in the primate visual system, which necessitates a level of precision in interocular alignment that is difficult to achieve following amblyopia.

The BCM theory makes no explicit statements about why plasticity is more robust in young animals than in adults. The conventional view based on the work of Hubel and Wiesel[141] has been that plasticity is restricted to a critical period of early development, thus explaining why recovery from amblyopia is extremely limited in adults. However, recent research has led to the appreciation that the adult visual cortex retains great potential for synaptic plasticity (for examples, see REFS 108,142) that potentially could be harnessed to promote recovery of function[125]. On the basis of what is known about metaplasticity in the visual cortex and the BCM theory, one might predict that the optimal conditions to promote recovery from amblyopia in adults would be to first lower the value of θ_m and then restore well-correlated visual experience to both eyes. Resetting θ_m could be accomplished, for example, by total light deprivation for several days. Indeed, experiments in adult rats have shown that substantial recovery from the effects of monocular deprivation is possible when binocular vision follows a period of complete darkness[143]. In part, this recovery appears to be accounted for by potentiation of thalamocortical synaptic transmission[144]. The BCM sliding threshold inspired the design of these experiments and provided a framework in which they can be interpreted. The same logic could be applied to promote recovery of function in multiple modalities after deprivation, injury or disease[125].

Beyond the BCM theory

BCM may be regarded as a lowest-order phenomenological theory that operates at a similar level to the ideal gas equation, which has been modified by deeper analysis to include factors such as the finite size of molecules and intermolecular forces. One would expect a similar evolution for the BCM theory, and indeed this is well underway[145].

As described above, LTD and LTP can be induced by varying the stimulation frequency while holding the number of stimulated presynaptic inputs constant. However, bidirectional modifications can also be induced by holding the presynaptic stimulation frequency constant and varying the number of coactive afferents[146], the postsynaptic voltage[55,147] or the level of NMDAR activation[49], as well as by varying the precise timing of pre- and postsynaptic action potentials (STDP[148,149]). There is also considerable variation in the qualities of plasticity at different types of excitatory synapse, even within the visual cortex[70,150].

Are there unifying mechanistic principles that can account for these different methods of inducing plasticity at different synapses? One can begin to answer this question by asking whether the same synapses can express STDP and rate-based (BCM) plasticity using common principles, and attempts to do so have been made[29,151–156]. Attempts have also been made to explain different forms of synaptic plasticity from shared fundamental cellular and molecular mechanisms[157–160]. For example, it had been proposed and demonstrated experimentally that a moderate increase of the calcium concentration above baseline levels produces LTD, whereas a larger increase in concentration produces LTP[46,49,50,161–165]. A calcium control hypothesis that was derived from lower-level molecular models of synaptic modification has been shown to be capable of accounting for the plasticity induced using the various protocols mentioned above[159]. According to this hypothesis, synaptic modification is governed by a single calcium-dependent function that depresses synapses at low amounts of calcium influx and potentiates synapses at larger values. This model can account for plasticity induced by pairing (voltage clamp), STDP or varying presynaptic frequency and thus can lead us from a fundamental physiological mechanism to the BCM theory and experience-dependent plasticity of visual cortical receptive fields.

It is interesting to note that this particular model requires the additional assumption that in neurons expressing STDP, the back-propagating action potential in the dendrites must be broader than the action potential observed in the soma. This assumption is required to account for the observed LTD that occurs when the postsynaptic spike precedes the presynaptic release of glutamate and provides yet another example of the value of theory, as the functional significance of dendritic action potential morphology might be unappreciated without it. Testing these assumptions and the dependence of STDP upon them requires detailed and rigorous experimental examination, but available data indicate that back-propagating action potentials are indeed wider than those found in soma[166,167].

Conclusion

The function of theory in the physical sciences has long been to provide a framework in which further questions could be posed, experiments designed and new phenomena discovered and put in an appropriate place in the overall theoretical structure. We believe that the BCM theory provides a good example of what a theory can do in neuroscience. As we have described, this theory has suggested experiments to confirm both its postulates and some of its consequences, and these experiments in turn have resulted in the discovery of important new phenomena. The interaction between the BCM theory and experiment has thus been fruitful and now, three decades after its introduction, we are at a level of sophistication and refinement that would have been impossible to imagine at the beginning.

If 30 years seems like a long time, we might recall that it took over 2,000 years to progress from early Greek concepts of the motion of the planets to the view we hold today (BOX 1). One hopes the complete elucidation of the nature and basis of cortical synaptic plasticity will be achieved in somewhat less time.

Leon N Cooper is at the Institute for Brain and Neural Systems, Department of Physics, Brown University, Providence, Rhode Island 02912, USA.

Mark F. Bear is at the Howard Hughes Medical Institute, and at the Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA.

e-mails: leon_cooper@brown.edu; mbear@mit.edu

doi:10.1038/nrn3353

1. Bienenstock, E. L., Cooper, L. N. & Munro, P. W. Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J. Neurosci.* **2**, 32–48 (1982).
2. von der Malsburg, C. Self-organization of orientation sensitive cells in the striate cortex. *Kybernetik* **14**, 85–100 (1973).
3. Nass, M. M. & Cooper, L. N. A theory for the development of feature detecting cells in visual cortex. *Biol. Cybern.* **19**, 1–18 (1975).
4. Cooper, L. N., Liberman, F. & Oja, E. A theory for the acquisition and loss of neuron specificity in visual cortex. *Biol. Cybern.* **33**, 9–28 (1979).
5. Hebb, D. O. *The Organization of Behavior: A Neuropsychological Theory* (Wiley, 1949).
6. Lowel, S. & Singer, W. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science* **255**, 209–212 (1992).
7. Shatz, C. J. The developing brain. *Sci. Am.* **267**, 60–67 (1992).
8. Cooper, L. N. in *Proceedings of the Nobel Symposium on Collective Properties of Physical Systems* (eds Lundqvist, B., Lundqvist, S. & Runnstrom-Reio, V.) 252–264 (Aspen Garden: Nobel, 1973).

9. Hubel, D. H. & Wiesel, T. N. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J. Physiol.* **160**, 106–154 (1962).
10. Wiesel, T. N. & Hubel, D. H. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.* **26**, 1003–1017 (1963).
11. Mioche, L. & Singer, W. Chronic recordings from single sites of kitten striate cortex during experience-dependent modifications of receptive-field properties. *J. Neurophysiol.* **62**, 185–197 (1989).
12. Intrator, N. & Cooper, L. N. Objective function formulation of the BCM theory of visual cortical plasticity: statistical connections, stability conditions. *Neural Networks* **5**, 3–17 (1992).
13. Clothiaux, E. E., Bear, M. F. & Cooper, L. N. Synaptic plasticity in visual cortex: comparison of theory with experiment. *J. Neurophysiol.* **66**, 1785–1804 (1991).
14. Blais, B. S., Intrator, N., Shouval, H. Z. & Cooper, L. N. Receptive field formation in natural scene environments. comparison of single-cell learning rules. *Neural Comput.* **10**, 1797–1813 (1998).
15. Blais, B. S., Shouval, H. Z. & Cooper, L. N. The role of presynaptic activity in monocular deprivation: comparison of homosynaptic and heterosynaptic mechanisms. *Proc. Natl Acad. Sci. USA* **96**, 1083–1087 (1999).
16. Blais, B., Cooper, L. N. & Shouval, H. Formation of direction selectivity in natural scene environments. *Neural Comput.* **12**, 1057–1066 (2000).
17. Blais, B. S. *et al.* Recovery from monocular deprivation using binocular deprivation. *J. Neurophysiol.* **100**, 2217–2224 (2008).
18. Frenkel, M. Y. & Bear, M. F. How monocular deprivation shifts ocular dominance in visual cortex of young mice. *Neuron* **44**, 917–923 (2004).
19. Katz, L. C. & Shatz, C. J. Synaptic activity and the construction of cortical circuits. *Science* **274**, 1133–1138 (1996).
20. Ramoa, A. S., Paradiso, M. A. & Freeman, R. D. Blockade of intracortical inhibition in kitten striate cortex: effects on receptive field properties and associated loss of ocular dominance plasticity. *Exp. Brain Res.* **73**, 285–296 (1988).
21. Cruikshank, S. J. & Weinberger, N. M. Receptive-field plasticity in the adult auditory cortex induced by Hebbian covariance. *J. Neurosci.* **16**, 861–875 (1996).
22. Fregnac, Y. & Shulz, D. E. Activity-dependent regulation of receptive field properties of cat area 17 by supervised Hebbian learning. *J. Neurobiol.* **41**, 69–82 (1999).
23. Abraham, W. C., Logan, B., Wolff, A. & Benuskova, L. "Heterosynaptic" LTD in the dentate gyrus of anesthetized rat requires homosynaptic activity. *J. Neurophysiol.* **98**, 1048–1051 (2007).
24. Newman, E. L. & Norman, K. A. Moderate excitation leads to weakening of perceptual representations. *Cereb. Cortex* **20**, 2760–2770 (2010).
25. Rittenhouse, C. D., Shouval, H. Z., Paradiso, M. A. & Bear, M. F. Monocular deprivation induces homosynaptic long-term depression in visual cortex. *Nature* **397**, 347–350 (1999).
26. Coleman, J. E. *et al.* Rapid structural remodeling of thalamocortical synapses parallels experience-dependent functional plasticity in mouse primary visual cortex. *J. Neurosci.* **30**, 9670–9682 (2010).
27. Rittenhouse, C. D. *et al.* Stimulus for rapid ocular dominance plasticity in visual cortex. *J. Neurophysiol.* **95**, 2947–2950 (2006).
28. Linden, M. L., Heynen, A. J., Haslinger, R. H. & Bear, M. F. Thalamic activity that drives visual cortical plasticity. *Nature Neurosci.* **12**, 390–392 (2009).
29. Blais, B. S., Cooper, L. N. & Shouval, H. Z. Effect of correlated lateral geniculate nucleus firing rates on predictions for monocular eye closure versus monocular retinal inactivation. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **80**, 061915 (2009).
30. Bear, M. F. Bidirectional synaptic plasticity: from theory to reality. *Phil. Trans. R. Soc. Lond. B.* **358**, 649–655 (2003).
31. Wiesel, T. N. & Hubel, D. H. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J. Neurophysiol.* **28**, 1029–1040 (1965).
32. Stent, G. S. A physiological mechanism for Hebb's postulate of learning. *Proc. Natl Acad. Sci. USA* **70**, 997–1001 (1973).
33. Oja, E. A. A simplified neuron model as a principal component analyzer. *J. Math. Biol.* **15**, 267–273 (1982).
34. Kind, P. C. Cortical plasticity: is it time for a change? *Curr. Biol.* **9**, R640–R643 (1999).
35. McNaughton, B. L., Douglas, R. M. & Goddard, G. V. Synaptic enhancement in fascia dentata: cooperativity among coactive afferents. *Brain Res.* **157**, 277–293 (1978).
36. Kelso, S. R., Ganong, A. H. & Brown, T. H. Hebbian synapses in hippocampus. *Proc. Natl Acad. Sci. USA* **83**, 5326–5330 (1986).
37. Dudek, S. M. & Bear, M. F. Homosynaptic long-term depression in area CA1 of hippocampus and effects of *N*-methyl-D-aspartate receptor blockade. *Proc. Natl Acad. Sci. USA* **89**, 4363–4367 (1992).
38. Stevens, C. F. Neurobiology. A depression long awaited. *Nature* **347**, 16 (1990).
39. Stevens, C. F. Going down the way you came up. *Curr. Biol.* **3**, 891–892 (1993).
40. Stevens, C. F. Strengths and weaknesses in memory. *Nature* **381**, 471–472 (1996).
41. Ezzell, C. Neuroscientists manic about long-term depression studies. *J. NIH Res.* **5**, 27–29 (1993).
42. Malenka, R. C. & Bear, M. F. LTP and LTD: an embarrassment of riches. *Neuron* **44**, 5–21 (2004).
43. O'Connor, D. H., Wittenberg, G. M. & Wang, S. S. Graded bidirectional synaptic plasticity is composed of switch-like unitary events. *Proc. Natl Acad. Sci. USA* **102**, 9679–9684 (2005).
44. Luscher, C. & Huber, K. M. Group 1 mGluR-dependent synaptic long-term depression: mechanisms and implications for circuitry and disease. *Neuron* **65**, 445–459 (2010).
45. Bear, M. F., Cooper, L. N. & Ebner, F. F. A physiological basis for a theory of synapse modification. *Science* **237**, 42–48 (1987).
46. Lisman, J. A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory. *Proc. Natl Acad. Sci. USA* **86**, 9574–9578 (1989).
47. Mulkey, R. M. & Malenka, R. C. Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron* **9**, 967–975 (1992).
48. Mulkey, R. M., Endo, S., Shenolikar, S. & Malenka, R. C. Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. *Nature* **369**, 486–488 (1994).
49. Cummings, J. A., Mulkey, R. M., Nicoll, R. A. & Malenka, R. C. Ca^{2+} signaling requirements for long-term depression in the hippocampus. *Neuron* **16**, 825–833 (1996).
50. Yang, S. N., Tang, Y. G. & Zucker, R. S. Selective induction of LTP and LTD by postsynaptic $[Ca^{2+}]i$ elevation. *J. Neurophysiol.* **81**, 781–787 (1999).
51. Dudek, S. M. & Bear, M. F. Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. *J. Neurosci.* **13**, 2910–2918 (1993).
52. Heynen, A. J., Abraham, W. C. & Bear, M. F. Bidirectional modification of CA1 synapses in the adult hippocampus *in vivo*. *Nature* **381**, 163–166 (1996).
53. Bear, M. F. A synaptic basis for memory storage in the cerebral cortex. *Proc. Natl Acad. Sci. USA* **93**, 13453–13459 (1996).
54. Debanne, D. & Thompson, S. M. Associative long-term depression in the hippocampus *in vitro*. *Hippocampus* **6**, 9–16 (1996).
55. Ngezahayo, A., Schachner, M. & Artola, A. Synaptic activity modulates the induction of bidirectional synaptic changes in adult mouse hippocampus. *J. Neurosci.* **20**, 2451–2458 (2000).
56. Huang, S. *et al.* Pull-push neuromodulation of LTP and LTD enables bidirectional experience-induced synaptic scaling in visual cortex. *Neuron* **73**, 497–510 (2012).
57. Philpot, B. D., Espinosa, J. S. & Bear, M. F. Evidence for altered NMDA receptor function as a basis for metaplasticity in visual cortex. *J. Neurosci.* **23**, 5583–5588 (2003).
58. Kirkwood, A., Dudek, S. M., Gold, J. T., Aizenman, C. D. & Bear, M. F. Common forms of synaptic plasticity in the hippocampus and neocortex *in vitro*. *Science* **260**, 1518–1521 (1993).
59. Chen, W. R. *et al.* Long-term modifications of synaptic efficacy in the human inferior and middle temporal cortex. *Proc. Natl Acad. Sci. USA* **93**, 8011–8015 (1996).
60. Massey, P. V. & Bashir, Z. I. Long-term depression: multiple forms and implications for brain function. *Trends Neurosci.* **30**, 176–184 (2007).
61. Nelson, S. B. & Turrigiano, G. G. Strength through diversity. *Neuron* **60**, 477–482 (2008).
62. Bear, M. F. in *Mechanistic Relationships Between Development and Learning* (eds Carew, T. J., Menzel, R. & Shatz, C. J.) 205–225 (John Wiley and Sons, 1998).
63. Heynen, A. J., Quinlan, E. M., Bae, D. C. & Bear, M. F. Bidirectional, activity-dependent regulation of glutamate receptors in the adult hippocampus *in vivo*. *Neuron* **28**, 527–536 (2000).
64. Kauer, J. A. & Malenka, R. C. Synaptic plasticity and addiction. *Nature Rev. Neurosci.* **8**, 844–858 (2007).
65. Bagetta, V., Ghiglieri, V., Sgobio, C., Calabresi, P. & Picconi, B. Synaptic dysfunction in Parkinson's disease. *Biochem. Soc. Trans.* **38**, 493–497 (2010).
66. Koffie, R. M., Hyman, B. T. & Spires-Jones, T. L. Alzheimer's disease: synapses gone cold. *Mol. Neurodegener.* **6**, 63 (2011).
67. Krueger, D. D. & Bear, M. F. Toward fulfilling the promise of molecular medicine in fragile X syndrome. *Annu. Rev. Med.* **62**, 411–429 (2011).
68. Auerbach, B. D., Osterweil, E. K. & Bear, M. F. Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature* **480**, 63–68 (2011).
69. Heynen, A. J. *et al.* Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. *Nature Neurosci.* **6**, 854–862 (2003).
70. Crozier, R. A., Wang, Y., Liu, C. H. & Bear, M. F. Deprivation-induced synaptic depression by distinct mechanisms in different layers of mouse visual cortex. *Proc. Natl Acad. Sci. USA* **104**, 1383–1388 (2007).
71. Yoon, B. J., Smith, G. B., Heynen, A. J., Neve, R. L. & Bear, M. F. Essential role for a long-term depression mechanism in ocular dominance plasticity. *Proc. Natl Acad. Sci. USA* **106**, 9860–9865 (2009).
72. Khibnik, L. A., Cho, K. K. & Bear, M. F. Relative contribution of feedforward excitatory connections to expression of ocular dominance plasticity in layer 4 of visual cortex. *Neuron* **66**, 493–500 (2010).
73. Hubel, D. H., Wiesel, T. N. & LeVay, S. Plasticity of ocular dominance columns in monkey striate cortex. *Phil. Trans. R. Soc. Lond. B* **278**, 377–409 (1977).
74. Kleinschmidt, A., Bear, M. F. & Singer, W. Blockade of "NMDA" receptors disrupts experience-dependent plasticity of kitten striate cortex. *Science* **238**, 355–358 (1987).
75. Bear, M. F., Kleinschmidt, A., Gu, Q. A. & Singer, W. Disruption of experience-dependent synaptic modifications in striate cortex by infusion of an NMDA receptor antagonist. *J. Neurosci.* **10**, 909–925 (1990).
76. Bear, M. F. & Colman, H. Binocular competition in the control of geniculate cell size depends upon visual cortical *N*-methyl-D-aspartate receptor activation. *Proc. Natl Acad. Sci. USA* **87**, 9246–9249 (1990).
77. Roberts, E. B., Meredith, M. A. & Ramoa, A. S. Suppression of NMDA receptor function using antisense DNA block ocular dominance plasticity while preserving visual responses. *J. Neurophysiol.* **80**, 1021–1032 (1998).
78. Daw, N. W. *et al.* Injection of MK-801 affects ocular dominance shifts more than visual activity. *J. Neurophysiol.* **81**, 204–215 (1999).
79. Liu, C. H., Heynen, A. J., Shuler, M. G. & Bear, M. F. Cannabinoid receptor blockade reveals parallel plasticity mechanisms in different layers of mouse visual cortex. *Neuron* **58**, 340–345 (2008).
80. Yang, K. *et al.* The regulatory role of long-term depression in juvenile and adult mouse ocular dominance plasticity. *Sci. Rep.* **1**, 203 (2011).
81. Bastrikova, N., Gardner, G. A., Reece, J. M., Jeromin, A. & Dudek, S. M. Synapse elimination accompanies functional plasticity in hippocampal neurons. *Proc. Natl Acad. Sci. USA* **105**, 3123–3127 (2008).
82. Maffei, A., Nelson, S. B. & Turrigiano, G. G. Selective reconfiguration of layer 4 visual cortical circuitry by visual deprivation. *Nature Neurosci.* **7**, 1353–1359 (2004).
83. Maffei, A., Nataraj, K., Nelson, S. B. & Turrigiano, G. G. Potentiation of cortical inhibition by visual deprivation. *Nature* **443**, 81–84 (2006).
84. Smith, G. B., Heynen, A. J. & Bear, M. F. Bidirectional synaptic mechanisms of ocular dominance plasticity in visual cortex. *Phil. Trans. R. Soc. B* **364**, 357–367 (2009).
85. Kirkwood, A. & Bear, M. F. Homosynaptic long-term depression in the visual cortex. *J. Neurosci.* **14**, 3404–3412 (1994).
86. Carroll, R. C., Lissin, D. V., von Zastrow, M., Nicoll, R. A. & Malenka, R. C. Rapid redistribution of glutamate receptors contributes to long-term depression in hippocampal cultures. *Nature Neurosci.* **2**, 454–460 (1999).
87. Lee, H. K., Kameyama, K., Huganir, R. L. & Bear, M. F. NMDA induces long-term synaptic depression and dephosphorylation of the GluR1 subunit of AMPA receptors in hippocampus. *Neuron* **21**, 1151–1162 (1998).

88. Fitzjohn, S. M. *et al.* A characterisation of long-term depression induced by metabotropic glutamate receptor activation in the rat hippocampus *in vitro*. *J. Physiol.* **537**, 421–430 (2001).
89. Huber, K. M., Roder, J. C. & Bear, M. F. Chemical induction of mGluR5- and protein synthesis-dependent long-term depression in hippocampal area CA1. *J. Neurophysiol.* **86**, 321–325 (2001).
90. Griffiths, S. *et al.* Expression of long-term depression underlies visual recognition memory. *Neuron* **58**, 186–194 (2008).
91. Kemp, A. & Manahan-Vaughan, D. Hippocampal long-term depression: master or minion in declarative memory processes? *Trends Neurosci.* **30**, 111–118 (2007).
92. Allen, C. B., Celikel, T. & Feldman, D. E. Long-term depression induced by sensory deprivation during cortical map plasticity *in vivo*. *Nature Neurosci.* **6**, 291–299 (2003).
93. Collingridge, G. L., Peineau, S., Howland, J. G. & Wang, Y. T. Long-term depression in the CNS. *Nature Rev. Neurosci.* **11**, 459–473 (2010).
94. Kirkwood, A., Rioult, M. C. & Bear, M. F. Experience-dependent modification of synaptic plasticity in visual cortex. *Nature* **381**, 526–528 (1996).
95. Holland, L. L. & Wagner, J. J. Primed facilitation of homosynaptic long-term depression and depotentiation in rat hippocampus. *J. Neurosci.* **18**, 887–894 (1998).
96. Abraham, W. C., Mason-Parker, S. E., Bear, M. F., Webb, S. & Tate, W. P. Heterosynaptic metaplasticity in the hippocampus *in vivo*: a BCM-like modifiable threshold for LTP. *Proc. Natl Acad. Sci. USA* **98**, 10924–10929 (2001).
97. Hamada, M. *et al.* Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. *J. Physiol.* **586**, 3927–3947 (2008).
98. Benuskova, L., Diamond, M. E. & Ebner, F. F. Dynamic synaptic modification threshold: computational model of experience-dependent plasticity in adult rat barrel cortex. *Proc. Natl Acad. Sci. USA* **91**, 4791–4795 (1994).
99. Xu, Z. *et al.* Metaplastic regulation of long-term potentiation/long-term depression threshold by activity-dependent changes of NR2A/NR2B ratio. *J. Neurosci.* **29**, 8764–8773 (2009).
100. Bliem, B., Mueller-Dahlbaus, J. F. M., Dinse, H. R. & Ziemann, U. Homeostatic metaplasticity in human somatosensory cortex. *J. Cogn. Neurosci.* **20**, 1517–1528 (2008).
101. Dunfield, D. & Haas, K. Metaplasticity governs natural experience-driven plasticity of nascent embryonic brain circuits. *Neuron* **64**, 240–250 (2009).
102. Kind, P. C. *et al.* Correlated binocular activity guides recovery from monocular deprivation. *Nature* **416**, 430–433 (2002).
103. Mitchell, D. E., Gingras, G. & Kind, P. C. Initial recovery of vision after early monocular deprivation in kittens is faster when both eyes are open. *Proc. Natl Acad. Sci. USA* **98**, 11662–11667 (2001).
104. Philpot, B. D., Cho, K. K. & Bear, M. F. Obligatory role of NR2A for metaplasticity in visual cortex. *Neuron* **53**, 495–502 (2007).
105. Iny, K., Heynen, A. J., Sklar, E. & Bear, M. F. Bidirectional modifications of visual acuity induced by monocular deprivation in juvenile and adult rats. *J. Neurosci.* **26**, 7368–7374 (2006).
106. Abraham, W. C. & Bear, M. F. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* **19**, 126–130 (1996).
107. Turrigiano, G. G. & Nelson, S. B. Homeostatic plasticity in the developing nervous system. *Nature Rev. Neurosci.* **5**, 97–107 (2004).
108. Sawtell, N. B. *et al.* NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron* **38**, 977–985 (2003).
109. Sato, M. & Stryker, M. P. Distinctive features of adult ocular dominance plasticity. *J. Neurosci.* **28**, 10278–10286 (2008).
110. Cho, K. K., Khibnik, L., Philpot, B. D. & Bear, M. F. The ratio of NR2A/B NMDA receptor subunits determines the qualities of ocular dominance plasticity in visual cortex. *Proc. Natl Acad. Sci. USA* **106**, 5377–5382 (2009).
111. Kuo, M. C. & Dringenberg, H. C. Short-term (2 to 5 h) dark exposure lowers long-term potentiation (LTP) induction threshold in rat primary visual cortex. *Brain Res.* **1276**, 58–66 (2009).
112. Feldman, D., Sherin, J. E., Press, W. A. & Bear, M. F. *N*-methyl-D-aspartate-evoked calcium uptake by kitten visual cortex maintained *in vitro*. *Exp. Brain Res.* **80**, 252–259 (1990).
113. Gold, J. I. & Bear, M. F. A model of dendritic spine Ca^{2+} concentration exploring possible bases for a sliding synaptic modification threshold. *Proc. Natl Acad. Sci. USA* **91**, 3941–3945 (1994).
114. Sobczyk, A. & Svoboda, K. Activity-dependent plasticity of the NMDA-receptor fractional Ca^{2+} current. *Neuron* **53**, 17–24 (2007).
115. Kalantzis, G. & Shouval, H. Z. Structural plasticity can produce metaplasticity. *PLoS ONE* **4**, e8062 (2009).
116. Philpot, B. D., Sekhar, A. K., Shouval, H. Z. & Bear, M. F. Visual experience and deprivation bidirectionally modify the composition and function of NMDA receptors in visual cortex. *Neuron* **29**, 157–169 (2001).
117. Lee, M. C., Yasuda, R. & Ehlers, M. D. Metaplasticity at single glutamatergic synapses. *Neuron* **66**, 859–870 (2010).
118. Cull-Candy, S. G. & Leszkiewicz, D. N. Role of distinct NMDA receptor subtypes at central synapses. *Sci. STKE* **2004**, re16, (2004).
119. Sobczyk, A., Scheuss, V. & Svoboda, K. NMDA receptor subunit-dependent $[Ca^{2+}]$ signaling in individual hippocampal dendritic spines. *J. Neurosci.* **25**, 6037–6046 (2005).
120. Barria, A. & Malinow, R. NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. *Neuron* **48**, 289–301 (2005).
121. Quinlan, E. M., Philpot, B. D., Huganir, R. L. & Bear, M. F. Rapid, experience-dependent expression of synaptic NMDA receptors in visual cortex *in vivo*. *Nature Neurosci.* **2**, 352–357 (1999).
122. Quinlan, E. M., Olstein, D. H. & Bear, M. F. Bidirectional, experience-dependent regulation of *N*-methyl-D-aspartate receptor subunit composition in the rat visual cortex during postnatal development. *Proc. Natl Acad. Sci. USA* **96**, 12876–12880 (1999).
123. Corson, J. *et al.* Sensory activity differentially modulates *N*-methyl-D-aspartate receptor subunits 2A and 2B in cortical layers. *Neuroscience* **163**, 920–932 (2009).
124. Chen, W. S. & Bear, M. F. Activity-dependent regulation of NR2B translation contributes to metaplasticity in mouse visual cortex. *Neuropharmacology* **52**, 200–214 (2007).
125. Cho, K. K. & Bear, M. F. Promoting neurological recovery of function via metaplasticity. *Future Neurol.* **5**, 21–26 (2010).
126. Steele, P. M. & Mauk, M. D. Inhibitory control of LTP and LTD: stability of synapse strength. *J. Neurophysiol.* **81**, 1559–1566 (1999).
127. Deisseroth, K., Bito, H., Schulman, H. & Tsien, R. W. Synaptic plasticity: a molecular mechanism for metaplasticity. *Curr. Biol.* **5**, 1334–1338 (1995).
128. Zhang, L. *et al.* Hippocampal synaptic metaplasticity requires inhibitory autophosphorylation of Ca^{2+}/calmodulin-dependent kinase II. *J. Neurosci.* **25**, 7697–7707 (2005).
129. Hardingham, N., Wright, N., Dachtler, J. & Fox, K. Sensory deprivation unmasks a PKA-dependent synaptic plasticity mechanism that operates in parallel with CaMKII. *Neuron* **60**, 861–874 (2008).
130. Narayanan, R. & Johnston, D. The h current is a candidate mechanism for regulating the sliding modification threshold in a BCM-like synaptic learning rule. *J. Neurophysiol.* **104**, 1020–1033 (2010).
131. Huh, G. S. *et al.* Functional requirement for class I MHC in CNS development and plasticity. *Science* **290**, 2155–2159 (2000).
132. Huber, K. M., Sawtell, N. B. & Bear, M. F. Brain-derived neurotrophic factor alters the synaptic modification threshold in visual cortex. *Neuropharmacology* **37**, 571–579 (1998).
133. Mayford, M., Wang, J., Kandel, E. R. & O'Dell, T. J. CaMKII regulates the frequency-response function of hippocampal synapses for the production of both LTD and LTP. *Cell* **81**, 891–904 (1995).
134. Matta, J. A., Ashby, M. C., Sanz-Clemente, A., Roche, K. W. & Isaac, J. T. mGluR5 and NMDA receptors drive the experience- and activity-dependent NMDA receptor NR2B to NR2A subunit switch. *Neuron* **70**, 339–351 (2011).
135. Philpot, B. D. & Zukin, R. S. Synapse-specific metaplasticity: to be silenced is not to silence 2B. *Neuron* **66**, 814–816 (2010).
136. Bellone, C. & Nicoll, R. A. Rapid bidirectional switching of synaptic NMDA receptors. *Neuron* **55**, 779–785 (2007).
137. Levy, W. B. & Steward, O. Synapses as associative memory elements in the hippocampal formation. *Brain Res.* **175**, 233–245 (1979).
138. Wigstrom, H. & Gustafsson, B. Postsynaptic control of hippocampal long-term potentiation. *J. Physiol.* **81**, 228–236 (1986).
139. Barrionuevo, G. & Brown, T. H. Associative long-term potentiation in hippocampal slices. *Proc. Natl Acad. Sci. USA* **80**, 7347–7351 (1983).
140. Stewart, C. E., Moseley, M. J. & Fielder, A. R. Amblyopia therapy: an update. *Strabismus* **19**, 91–98 (2011).
141. Hubel, D. H. & Wiesel, T. N. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* **206**, 419–436 (1970).
142. Hofer, S. B., Mrsic-Flogel, T. D., Bonhoeffer, T. & Hubener, M. Lifelong learning: ocular dominance plasticity in mouse visual cortex. *Curr. Opin. Neurobiol.* **16**, 451–459 (2006).
143. He, H. Y., Ray, B., Dennis, K. & Quinlan, E. M. Experience-dependent recovery of vision following chronic deprivation amblyopia. *Nature Neurosci.* **10**, 1134–1136 (2007).
144. Montey, K. L. & Quinlan, E. M. Recovery from chronic monocular deprivation following reactivation of thalamocortical plasticity by dark exposure. *Nature Commun.* **2**, 317 (2011).
145. Shouval, H. Z. What is the appropriate description level for synaptic plasticity? *Proc. Natl Acad. Sci. USA* **108**, 19103–19104 (2011).
146. Kerr, D. S. & Abraham, W. C. Cooperative interactions among afferents govern the induction of homosynaptic long-term depression in the hippocampus. *Proc. Natl Acad. Sci. USA* **92**, 11637–11641 (1995).
147. Debanne, D., Gahwiler, B. H. & Thompson, S. M. Asynchronous pre- and postsynaptic activity induces associative long-term depression in area CA1 of the rat hippocampus *in vitro*. *Proc. Natl Acad. Sci. USA* **91**, 1148–1152 (1994).
148. Markram, H., Lubke, J., Frotscher, M. & Sakmann, B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275**, 213–215 (1997).
149. Feldman, D. E. Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. *Neuron* **27**, 45–56 (2000).
150. Daw, N., Rao, Y., Wang, X. F., Fischer, Q. & Yang, Y. LTP and LTD vary with layer in rodent visual cortex. *Vision Res.* **44**, 3377–3380 (2004).
151. Pfister, J. P. & Gerstner, W. Triplets of spikes in a model of spike timing-dependent plasticity. *J. Neurosci.* **26**, 9673–9682 (2006).
152. Izhikevich, E. M. & Desai, N. S. Relating STDP to BCM. *Neural Comput.* **15**, 1511–1523 (2003).
153. Gjorgjieva, J., Clopath, C., Audet, J. & Pfister, J. P. A triplet spike-timing-dependent plasticity model generalizes the Bienenstock–Cooper–Munro rule to higher-order spatiotemporal correlations. *Proc. Natl Acad. Sci. USA* **108**, 19383–19388 (2011).
154. Abarbanel, H. D., Huerta, R. & Rabinovich, M. I. Dynamical model of long-term synaptic plasticity. *Proc. Natl Acad. Sci. USA* **99**, 10132–10137 (2002).
155. Appleby, P. A. & Elliott, T. Synaptic and temporal ensemble interpretation of spike-timing-dependent plasticity. *Neural Comput.* **17**, 2316–2336 (2005).
156. Karmarkar, U. R. & Buonomano, D. V. A model of spike-timing dependent plasticity: one or two coincidence detectors? *J. Neurophysiol.* **88**, 507–513 (2002).
157. Castellani, G. C., Quinlan, E. M., Cooper, L. N. & Shouval, H. Z. A biophysical model of bidirectional synaptic plasticity: dependence on AMPA and NMDA receptors. *Proc. Natl Acad. Sci. USA* **98**, 12772–12777 (2001).
158. Shouval, H. Z., Castellani, G. C., Blais, B. S., Yeung, L. C. & Cooper, L. N. Converging evidence for a simplified biophysical model of synaptic plasticity. *Biol. Cybern.* **87**, 383–391 (2002).
159. Shouval, H. Z., Bear, M. F. & Cooper, L. N. A unified model of NMDA receptor-dependent bidirectional synaptic plasticity. *Proc. Natl Acad. Sci. USA* **99**, 10831–10836 (2002).
160. Rachmuth, G., Shouval, H. Z., Bear, M. F. & Poon, C. S. A biophysically-based neuromorphic model of spike rate- and timing-dependent plasticity. *Proc. Natl Acad. Sci. USA* **108**, e1266–e1274 (2011).
161. Malenka, R. C., Kauer, J. A., Zucker, R. S. & Nicoll, R. A. Postsynaptic calcium is sufficient for potentiation of hippocampal synaptic transmission. *Science* **242**, 81–84 (1988).

162. Lynch, G., Larson, J., Kelso, S., Barrionuevo, G. & Schottler, F. Intracellular injections of EGTA block induction of hippocampal long-term potentiation. *Nature* **305**, 719–721 (1983).
163. Artola, A., Brocher, S. & Singer, W. Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. *Nature* **347**, 69–72 (1990).
164. Cormier, R. J., Greenwood, A. C. & Connor, J. A. Bidirectional synaptic plasticity correlated with the magnitude of dendritic calcium transients above a threshold. *J. Neurophysiol.* **85**, 399–406 (2001).
165. Ismailov, I., Kalikulov, D., Inoue, T. & Friedlander, M. J. The kinetic profile of intracellular calcium predicts long-term potentiation and long-term depression. *J. Neurosci.* **24**, 9847–9861 (2004).
166. Stuart, G. J. & Sakmann, B. Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. *Nature* **367**, 69–72 (1994).
167. Magee, J. C. & Johnston, D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* **275**, 209–213 (1997).
168. Bliss, T. V., Burns, B. D. & Uttley, A. M. Factors affecting the conductivity of pathways in the cerebral cortex. *J. Physiol.* **195**, 339–367 (1968).
169. Bindman, L. J., Murphy, K. P. & Pockett, S. Postsynaptic control of the induction of long-term changes in efficacy of transmission at neocortical synapses in slices of rat brain. *J. Neurophysiol.* **60**, 1053–1065 (1988).
170. Bramham, C. R. & Srebro, B. Induction of long-term depression and potentiation by low- and high-frequency stimulation in the dentate area of the anesthetized rat: magnitude, time course and EEG. *Brain Res.* **405**, 100–107 (1987).
171. Hirsch, J. C. & Crepel, F. Use-dependent changes in synaptic efficacy in rat prefrontal neurons *in vitro*. *J. Physiol.* **427**, 31–49 (1990).
172. Barrionuevo, G., Schottler, F. & Lynch, G. The effects of low frequency stimulation on control and "potentiated" synaptic responses in the hippocampus. *Life Sci.* **27**, 2385–2391 (1980).
173. Staubli, U. & Lynch, G. Stable depression of potentiated synaptic responses in the hippocampus with 1–5 Hz stimulation. *Brain Res.* **513**, 113–118 (1990).
174. Fujii, S., Saito, K., Miyakawa, H., Ito, K. & Kato, H. Reversal of long-term potentiation (depotentiation) induced by tetanus stimulation of the input to CA1 neurons of guinea pig hippocampal slices. *Brain Res.* **555**, 112–122 (1991).
175. Arai, A., Larson, J. & Lynch, G. Anoxia reveals a vulnerable period in the development of long-term potentiation. *Brain Res.* **511**, 353–357 (1990).
176. Lynch, G. S., Dunwiddie, T. & Gribkoff, V. Heterosynaptic depression: a postsynaptic correlate of long-term potentiation. *Nature* **266**, 737–739 (1977).
177. Abraham, W. C. & Goddard, G. V. Asymmetric relationships between homosynaptic long-term potentiation and heterosynaptic long-term depression. *Nature* **305**, 717–719 (1983).
178. Tsumoto, T. & Suda, K. Cross-depression: an electrophysiological manifestation of binocular competition in the developing visual cortex. *Brain Res.* **168**, 190–194 (1979).
179. Dunwiddie, T. & Lynch, G. Long-term potentiation and depression of synaptic responses in the rat hippocampus: localization and frequency dependency. *J. Physiol.* **276**, 353–367 (1978).
180. Wickens, J. R. & Abraham, W. C. The involvement of L-type calcium channels in heterosynaptic long-term depression in the hippocampus. *Neurosci. Lett.* **130**, 128–132 (1991).
181. Bear, M. F. & Abraham, W. C. Long-term depression in hippocampus. *Annu. Rev. Neurosci.* **19**, 437–462 (1996).
182. Ito, M. & Kano, M. Long-lasting depression of parallel fiber-Purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex. *Neurosci. Lett.* **33**, 253–258 (1982).
183. Linden, D. J. & Connor, J. A. Long-term synaptic depression. *Annu. Rev. Neurosci.* **18**, 319–357 (1995).
184. Stanton, P. K. & Sejnowski, T. J. Associative long-term depression in the hippocampus induced by hebbian covariance. *Nature* **339**, 215–218 (1989).
185. Goldman, R. S., Chavez-Noriega, L. E. & Stevens, C. F. Failure to reverse long-term potentiation by coupling sustained presynaptic activity and *N*-methyl-D-aspartate receptor blockade. *Proc. Natl Acad. Sci. USA* **87**, 7165–7169 (1990).
186. Mulkey, R. M., Herron, C. E. & Malenka, R. C. An essential role for protein phosphatases in hippocampal long-term depression. *Science* **261**, 1051–1055 (1993).
187. Cooper, L. N., Intrator, N., Blais, B. & Shouval, H. *Theory of Cortical Plasticity* (World Scientific Publishing, 2004).
188. Stryker, M. P. & Harris, W. A. Binocular impulse blockade prevents the formation of ocular dominance columns in cat visual cortex. *J. Neurosci.* **6**, 2117–2133 (1986).
189. Steriade, M., McCormick, D. A. & Sejnowski, T. J. Thalamocortical oscillations in the sleeping and aroused brain. *Science* **262**, 679–685 (1993).
190. McCurry, C. L. *et al.* Loss of Arc renders the visual cortex impervious to the effects of sensory experience or deprivation. *Nature Neurosci.* **13**, 450–457 (2010).
191. Dolen, G. *et al.* Correction of fragile X syndrome in mice. *Neuron* **56**, 955–962 (2007).

Acknowledgements
The authors thank the many colleagues, both theoretical and experimental, with whom they have worked these many years. Our collaborative research has been supported by the US Office of Naval Research, the Army Research Office, the Air Force Office of Scientific Research, the National Science Foundation, the US National Institutes of Health, the Howard Hughes Medical Institute, the Dana Foundation and the Ittleson Family Foundation.

Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
Mark Bear's homepage: http://bearlab-s1.mit.edu/BearLab/
The Institute for Brain and Neural Systems, Brown University: http://www.brown.edu/research/projects/brain-and-neural-systems/home

ALL LINKS ARE ACTIVE IN THE ONLINE PDF