Cortical plasticity: **Is it time for a change?**

Peter C. Kind

Classical studies of plasticity in the visual cortex have been interpreted in terms of heterosynaptic competition between inputs. But an alternative type of 'homosynaptic' plasticity can explain many recent observations and has recently received experimental support. Perhaps both types of plasticity are important.

Address: University Laboratory of Physiology, Oxford University, Parks Road, Oxford 0X1 3PT, UK.
E-mail: peter.kind@physiol.ox.ac.uk

Current Biology 1999, 9:R640–R643
http://biomednet.com/elecref/09609822009R0640

0960-9822/99/$ – see front matter

Wiesel and Hubel first demonstrated that the physiological and anatomical properties of neurons in the primary visual pathways of mammals are dependent on the nature of the animal's early visual experience. They showed that, following an early period of monocular deprivation, by eyelid suture, in cats and primates, neurons in the primary visual cortex became driven almost exclusively by the non-deprived eye — a phenomenon frequently referred to as a shift in 'ocular dominance'. In contrast, binocular deprivation had little effect on cortical binocularity, although it did cause a loss of visual responsiveness. Several researchers later demonstrated that this synaptic uncoupling was not caused simply by degeneration of the inputs from the inactive eye, as the effects of monocular deprivation of one eye could be reversed by a subsequent period of monocular deprivation of the other eye ('reverse-lid suture').

The effects of monocular deprivation and reverse-lid suture only occurred when the treatments were imposed during the first few months of life, leading to the notion of a 'critical' or 'sensitive' period for plasticity. Tracing studies, in which neurons were labelled with dyes, revealed anatomical correlates of these physiological observations. The changes in physiologically identified ocular dominance were found to be mirrored by changes in the pattern of terminations in layer IV of the primary visual cortex of the afferent axons carrying the input from the lateral geniculate nucleus (LGN), the thalamic relay station between retina and cortex. Taken together, these findings suggested that inputs subserving the two eyes compete for synaptic space on visual cortical neurons, and led to the prevailing viewpoint that competitive interactions form the basis for plasticity in the developing visual cortex [1]. Recent evidence from several laboratories, however, has suggested that other, novel mechanisms also play a role in developmental plasticity.

To put these recent papers in context, I shall first briefly review the competition-based theories. Most theories devised to explain ocular dominance plasticity are based on a Hebbian [2] concept of learning; that is, synaptic potentiation will occur if the activities of the presynaptic and postsynaptic neurons are temporally correlated, or more simply stated, 'cells that fire together wire together'. Hebb's theory of synaptic modification was greatly supported by the discovery of long-term potentiation (LTP), the stable enhancement of synaptic potentials following stimulation paradigms in which the presynaptic and postsynaptic neurons are concurrently active beyond some threshold level. LTP is now widely touted as the physiological basis for many forms of learning and memory. Furthermore, although most of the classical work on LTP was done with the hippocampus — which is strongly implicated in spatial learning and memory — LTP can be elicited in a similar manner in the visual cortex of early postnatal animals, leading to the notion that it may also be a synaptic mechanism of developmental plasticity [3].

As ocular dominance plasticity involves morphological changes in the presynaptic terminals, LTP induction must be signalled back to the geniculocortical axons. This transfer of information from the postsynaptic site of LTP induction back to the presynaptic cell has led to the suggestion that there must be some 'retrograde messenger' molecule that carries the signal, at least during the sensitive period for changes in thalamic fibre distribution. In the visual cortex, growth factors — most notably brain-derived nerve growth factor (BDNF) — have been suggested to be the retrograde signal. According to the competition-based theories, inputs from the two eyes would compete for limiting amounts of BDNF. Indeed, exogenous application of BDNF prevents the normal development of ocular dominance columns, as well as the physiological and anatomical effects of monocular deprivation [3].

The initial competition-based theories hypothesized that the induction of LTP in synapses made by axons from the non-deprived eye led to long-term depression (LTD) in synapses made by axons from the deprived eye. Such a mechanism cannot, however, explain plastic changes that occur when the postsynaptic cell is inactive. An example of such changes was reported by Reiter and Stryker [4], who demonstrated that pharmacological blockade of activity in the postsynaptic neuron, combined with monocular deprivation, resulted in a shift in ocular dominance towards the deprived eye. This 'reverse' shift in ocular dominance, however, could be explained by the postsynaptic activity blockade having a relatively greater negative effect on

synapses made by the more active, non-deprived afferents than on those made by the less-active, deprived afferents. This explanation was discounted recently by Hata *et al.* [5], who found that the shift in ocular dominance was mirrored by the normal maturation of the deprived eye geniculocortical arbors and a decrease in size of the non-deprived arbors.

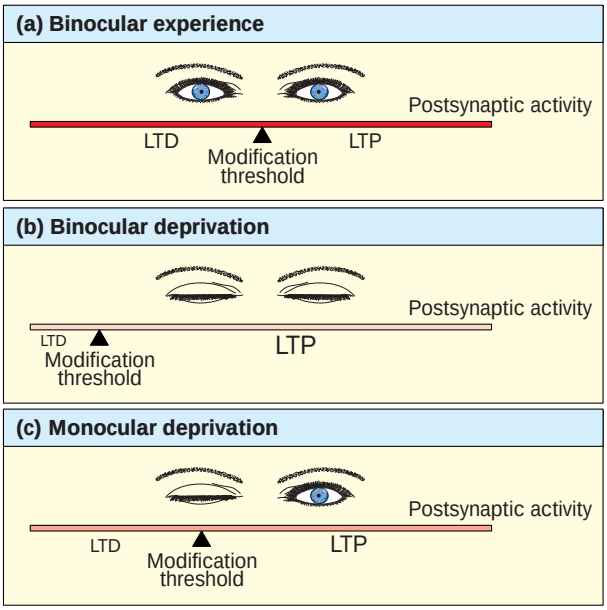
These findings indicate that concordant activity in presynaptic and postsynaptic neurons leads to long-term synaptic strengthening, or LTP, whereas activity in either the presynaptic or postsynaptic neuron alone results in synaptic weakening or LTD. A more complex theory of plasticity is therefore required. One variant invokes a dual threshold for potentiation by a positive retrograde signal: a low threshold in inactive axons, and a higher threshold in active axons. Inactive geniculocortical afferents having a low threshold for the factor would be strengthened when the postsynaptic cell is inactive, provided there is a low-level constitutive release of the factor from inactive neurons. Active presynaptic terminals would be potentiated selectively by the higher concentration, activity-dependent release of the growth factor for which they compete more effectively than inactive terminals. In either case, synaptic strengthening in afferents from one eye would cause synaptic weakening of inputs from the other eye. Alternatively, postsynaptic neurons might release signals — positive when they are active and negative when they are inactive — that only active presynaptic terminals can respond to (for further discussion see [5]).

There is another possible explanation for these various findings which does not invoke competition between synapses for a trophic factor. According to the Bienenstock–Cooper–Munro (BCM) [6,7] model, the observations could reflect homosynaptic plasticity — a type of plasticity in which each synapse behaves independently. The BCM model postulates that the direction, or sign, of a change in synaptic efficacy depends on a modification threshold that changes during development, depending on the average firing rate of the postsynaptic cell (Figure 1). For example, animals reared in complete darkness would have a much lower modification threshold than animals reared in a normal environment. Therefore, neurons are not simply 'plastic' during the sensitive period, with changes dictated by competition for synaptic 'space'; instead their ability to change, and the direction of that change, depends on their history and changes over time.

By the BCM theory, the ocular dominance shift to monocular deprivation occurs because activity in the deprived eye terminals is insufficient to drive the postsynaptic cell above the modification threshold, and these inputs consequently undergo homosynaptic LTD [7]. To test the hypothesis that homosynaptic LTD plays a major role in producing the shifts in ocular dominance to monocular deprivation, Rittenhouse *et al.* [8] compared the effects of monocular deprivation with those of intraocular injections of tetrodotoxin, which blocks sodium channels and thus action potentials. The BCM theory predicts that presynaptic activity is necessary to generate the LTD that causes the ocular dominance shift. Rittenhouse *et al.* [8] found that lid-suture, which does not eliminate spontaneous activity, resulted in a significantly greater shift in ocular dominance than intraocular injection of tetrodotoxin, which blocks most spontaneous activity.

A low level of activity is therefore necessary to induce LTD-type changes and shifts in ocular dominance,

Figure 1



A simplified illustration of the BCM theory of synaptic plasticity in the visual cortex, in which the modification threshold is depicted as the pivot of a seesaw and postsynaptic activity as the platform. The level of postsynaptic activity increases from left to right across the platform, and the average level of postsynaptic activity is illustrated by the depth of red shading of the platform. When the level of postsynaptic activity is below the modification threshold, LTD is induced; when it is above the modification threshold, LTP is induced. The position of the modification threshold changes depending on the average postsynaptic activity and is shown for: (a) binocular experience; (b) binocular deprivation; and (c) monocular deprivation. In the normal situation of binocular experience (a), both LTD and LTP can be elicited and postsynaptic activity is relatively high. The modification threshold would slowly increase as presynaptic afferents increase their efficacy in driving the postsynaptic cell until some equilibrium is reached. During binocular deprivation (b), postsynaptic activity is low, so the modification threshold moves to the left. Thus, the system becomes biased towards LTP induction and the ability to induce LTD is all but eliminated. In contrast, during monocular deprivation (c), the postsynaptic activity is only slightly reduced, because the open eye continues to stimulate the postsynaptic cell.

strongly suggesting that LTD-type changes occur in the visual cortex during the sensitive period. In this regard, the results of Antonini *et al.* [9] are particularly relevant. They found that, following short periods (up to a week) of monocular deprivation, the cortical territory devoted to single thalamocortical axons from the non-deprived eye is comparable to that of normal animals, but the territory devoted to single afferents from the deprived eye is reduced. These 'short' periods of monocular deprivation were sufficient to cause a complete shift in ocular dominance towards the non-deprived eye, despite the lack of expansion of non-deprived eye afferents, suggesting there was no gain in synaptic territory by the non-deprived eye. The decrease in deprived arbor size is consistent with with the BCM theory, which predicts that LTD-induced changes underlie the shift in ocular dominance.

As mentioned above, Hubel and Wiesel's finding that binocular deprivation has much less effect on the properties of cortical neurons than monocular deprivation suggested that plasticity reflected competitive interactions between the two eyes. Can homosynaptic mechanisms of plasticity also explain the effects of binocular deprivation? According to the BCM model, the reduction in postsynaptic activity resulting from dark-rearing would reduce drastically the modification threshold for LTP and all but eliminate the ability to induce LTD. Kirkwood *et al.* [10] confirmed this prediction by demonstrating that visual cortical slices taken from rats that had been raised in complete darkness had much lower levels of LTD, suggesting that the relatively normal features of neurons following binocular deprivation are due to an inability to undergo LTD-type changes. This situation contrasts with monocular deprivation, where activation through the open eye keeps the modification threshold value high. Thus, in the BCM theory, the interactions between the two eyes are mediated by neuron-wide adjustments of the modification threshold.

The homosynaptic model of plasticity also explains the behavioural results of recovery from monocular deprivation that are difficult to interpret by traditional competitive or heterosynaptic models of plasticity. For example, heterosynaptic competition models predict that, following a period of monocular deprivation, the deprived eye should undergo little or no recovery, unless the non-deprived eye is subsequently deprived by reverse-lid suture. According to the BCM theory, however, after the period of monocular deprivation had ended, the deprived eye would show visual recovery, provided that activity in the deprived eye was then correlated with activity in the non-deprived eye. Mitchell and Gingras [11] observed substantial visual recovery during a binocular period following monocular deprivation, supporting the BCM theory. They also observed a delay in the initiation of recovery in animals that were reverse sutured, compared to those that recovered under binocular conditions; following this initial delay, visual recovery occurred at the same rate under either condition, and in a manner that suggested a dependence on the absolute level of activity.

These findings are difficult to explain by a competitive mechanism of plasticity. They can be explained, however, by the BCM theory, which predicts that visual recovery from monocular deprivation during a period of reverse-lid suture would be delayed relative to a period of binocular experience — assuming the two eyes are aligned properly — because, in the latter case, recovery does not depend on the adjustment of the modification threshold. It should be noted, however, that the final extent of recovery was greater in the reverse-lid suture animals, especially when examined physiologically (see below) [1].

Is developmental plasticity in the visual cortex strictly homosynaptic? Just as some aspects of developmental plasticity appear to be explained better by homosynaptic mechanisms, other features seem to be explained better by heterosynaptic or competitive mechanisms. For example, while the behavioural results on recovery from monocular deprivation support the BCM theory, the physiological evidence is less clear. In the monkey, Blakemore *et al.* [12] found little recovery in the proportion of cells driven by the deprived eye during a subsequent binocular period. In the cat, the increase in the proportion of cells driven by the deprived eye was small compared to the behavioural recovery, and increased dramatically with reverse-lid suture. Furthermore, the development of eye-specific patterns in the LGN of ferrets appears to be governed by competitive mechanisms not obviously explained by homosynaptic mechanisms [13].

Other aspects of plasticity that appear to rely on axon growth also seem better explained by a separate type of 'heterocellular' interactions. Horton and Hocking [14] found that, in monkeys, ocular dominance bands are present at birth in layer IV of the visual cortex. However, monocular deprivation causes a large increase in the territory devoted to the non-deprived eye and a corresponding decrease in that devoted to the deprived eye. The inputs from the two eyes must be interacting across ocular dominance band boundaries, in a way that is difficult to explain by homosynaptic (or classical heterosynaptic) mechanisms. For example, according to the BCM theory, the level of postsynaptic activity in layer IV cells of the deprived eye columns would be dramatically reduced (to levels similar to that found in binocularly deprived animals), the modification threshold would reset such that LTD would be dramatically reduced, and no change in ocular dominance would be observed. It appears, therefore, that several forms of plasticity may be concurrently active in the developing visual cortex.

The findings of Antonini and Stryker [9] (see above) that the deprived eye afferents decrease in size prior to the expansion of non-deprived eye afferents suggest that homosynaptic mechanisms may initiate plastic changes, even at the peak of the sensitive period, and that heterosynaptic competition represents a late, structural phase in plasticity. Alternatively, heterosynaptic interactions may be more prevalent early in development, when massive rearrangements in axonal and dendritic structure can be induced to altered visual experience. At any rate, it should not be surprising that more than one type of mechanism may contribute to developmental plasticity. Studies on the hippocampus have revealed numerous forms of LTP and LTD acting through a variety of molecular mechanisms. In the visual cortex, numerous neurotransmitter receptors and second messenger pathways have been shown to play a role in developmental plasticity, so it would be more surprising if the complex changes that occur to altered visual experience were to follow a single set of rules.

References

1. Michell DE, Timney B: Postnatal development of function in the mammalian visual system. In *Handbook of Physiology Section 1: The Nervous System.* Edited by Darian-Smith I. USA: American Physiological Society; 1984:507-555.
2. Daw NW: Mechanisms of plasticity in the visual cortex. *Inv Opth Vis Sci* 1994, 35:4168-4179.
3. Katz LC, Shatz CJ: Synaptic activity and the construction of cortical circuits. *Science* 1996, 274:1133-1138.
4. Reiter HO, Stryker MP: Neural plasticity without postsynaptic action potentials: less-active inputs become dominant when kitten visual cortical cells are pharmacologically inhibited. *Proc Natl Acad Sci* 1988, 85:3623-3627.
5. Hata Y, Tsumoto T, Stryker MF: Selective pruning of more active afferents when cat visual cortex is pharmacologically inhibited. *Neuron* 1999, 22:375-381.
6. Bienenstock AL, Cooper LN, Munro PW: Theory for the development of neuron selectivity: orientation specificity and binocular interaction in the visual cortex. *J Neurosci* 1982, 2:32-48.
7. Bear MF, Cooper LN, Ebner FF: A physiological basis for a theory of synapse modification. *Science* 1987, 237:42-48.
8. Rittenhouse CD, Shouval HZ, Paradiso MA, Bear MF: Monocular deprivation induces homosynaptic long-term depression in visual cortex. *Nature* 1999, 397:347-350.
9. Antonini A, Stryker MP: Rapid remodelling of axonal arbors in the visual cortex. *Science* 1993, 260:1819-1821.
10. Kirkwood A, Lee H-K, Bear MF: Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex by age and experience. *Nature* 1995, 375:328-331.
11. Mitchell DE, Gingras G: Visual recovery after monocular deprivation is driven by absolute, rather than relative, visually evoked activity levels. *Curr Biol* 1998, 8:1179-1182.
12. Blakemore C, Vital-Durand F, Garey LJ: Recovery from monocular deprivation in the monkey. I. Reversal of physiological effects in the visual cortex. *Proc R Soc Lond B Biol Sci* 1981, 213:399-423.
13. Penn AA, Riquelme PA, Feller MB, Shatz CJ: Competition in retinogeniculate patterning driven by spontaneous activity. *Science* 1998, 279:2108-2112.
14. Horton JC, Hocking DR: An adult-like pattern of ocular dominance columns in striate cortex of newborn monkeys prior to visual experience. *J Neurosci* 1996, 16:1791-1807.