

Initial recovery of vision after early monocular deprivation in kittens is faster when both eyes are open

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A comparison was made of the speed of visual recovery in the deprived eye of kittens after a 6-day period of monocular deprivation imposed at 5–9 weeks of age in two postdeprivation conditions. In one condition, binocular recovery (BR), both eyes were open, whereas in the other condition, reverse lid-suture (RLS), the formerly nondeprived eye was closed to force the animal to use the originally deprived eye. In littermate pairs, BR kittens began to recover form vision 12 to 30 h before those subjected to RLS. The vision of the deprived eye of the BR animals remained superior to that of their RLS littermates for 4–8 days. Although this finding is difficult to reconcile with competitive mechanisms of synaptic plasticity, it supports a prediction of an alternative model of synaptic plasticity [Bienenstock, E. L., Cooper, L. N. & Munro, P. W. (1982) *J. Neurosci.* 2, 32–48] for slower initial recovery with RLS because of the time required to reset the modification threshold.

The shifts of ocular dominance toward the nondeprived eye in the visual cortex of kittens and infant monkeys after monocular form deprivation (MD) represents the paramount demonstration of developmental plasticity in the brain. On the basis of the much larger physiological effects of monocular as opposed to binocular eyelid suture, Wiesel and Hubel (1) proposed the now popular viewpoint that the overall balance of ocular dominance in the visual cortex results from a competitive interaction between afferents from the two eyes during certain critical periods in early postnatal life. Formal definition of binocular competition (2) stated that during development afferents from the two eyes compete for a limiting diffusible factor (e.g., a neurotrophin) and/or synaptic space on postsynaptic neurons. Models based on binocular competition can account for most of the classic observations on ocular dominance plasticity associated with periods of early deprivation, as well as the normal development of ocular dominance columns (3, 4). However, not all experimental findings can be readily accommodated by mechanisms based on binocular competition. A striking case in point is the substantial recovery of both ocular dominance in the visual cortex of cats and of the vision of the deprived eye in cats and humans after MD in the situation (binocular recovery, BR) where both eyes are open during the recovery period (5–8). The challenge to models based on binocular competition stems from the fact that restoration of normal visual input to the deprived eye without concurrent manipulation of the visual input to the nondeprived eye does little or nothing to reduce the very substantial competitive advantage of this eye. Past measurements of the speed of recovery of visual acuity of the deprived eye after MD during BR suggest that it may rival that observed with reverse lid-suture (RLS), where the formerly nondeprived eye is deprived to provide a competitive advantage to the formerly deprived eye (5, 7, 9).

The present study examined this point more carefully in littermate pairs of kittens in these two recovery situations, after a short (6-day) period of MD imposed at 5–9 weeks of age. We now report the surprising result that the initial recovery of vision

in the deprived eye is faster with BR and, moreover, the visual acuity remains superior to that of the kittens subjected to RLS for 4–8 days. Although this result appears counterintuitive in terms of traditional models based on binocular competition for synaptic space, it is consistent with predictions (10) of an alternative model (the BCM model) of synaptic plasticity proposed by Bienenstock, Cooper, and Munro (11).

Methods

Animals and Rearing Procedures. The study was conducted on four littermate pairs of kittens that were born and raised in a closed laboratory colony. All animals received a 6-day period of MD at either 36 (C842R, C844B), 56 (C808B, C809R), 60 (C826R, C827B), or 64 (C841B, C843R) days of age. The surgical and behavioral testing procedures described below were in accordance with the standards and regulations established by the Canadian Council on Animal Care.

At the ages specified, the left eye of each kitten was deprived of patterned visual input by eyelid suture under gaseous halothane anesthesia using previously described surgical procedures (12). After 6 days, the eyelids of the deprived eye were opened, under gaseous halothane as before. For one member of each littermate pair, the eyelids of the right (formerly nondeprived) eye were sutured closed at the same time while its littermate had both eyes open throughout the recovery period. The suffix R and B adjacent to the animal number designate, respectively, kittens that were subjected to RLS and those that had both eyes open during recovery. On the 6th day of recovery, one animal (C826R) developed a slight corneal clouding that disappeared in 2 days, during which it received aggressive treatment with an ophthalmic antibiotic (gentamicin sulfate 0.3%, five times per day). Behavioral testing was discontinued during treatment.

Behavioral Testing. Training on the behavioral task was begun at about 4 weeks of age. The methods for testing the visual acuity were made by use of a jumping stand (Fig. 1A) and procedures described in detail elsewhere (9, 12). The one departure from past procedures was to employ a discrimination rather than a detection task in which the kittens were rewarded for choosing a vertical square-wave grating as opposed to an adjacent horizontal grating of the same spatial frequency and mean luminance. To permit monocular tests of vision, an opaque contact lens occluder that had a curvature matched to the average corneal curvature of kittens of the same age (13) was placed over the nondeprived eye. A drop of ophthalmic local anaesthetic (Alcaine 1%) was placed in the occluded eye to alleviate potential discomfort.

Abbreviations: MD, monocular deprivation; BR, binocular recovery; RLS, reverse lid-suture; BCM, Bienenstock, Cooper, and Munro; MAR, minimum angle of resolution.

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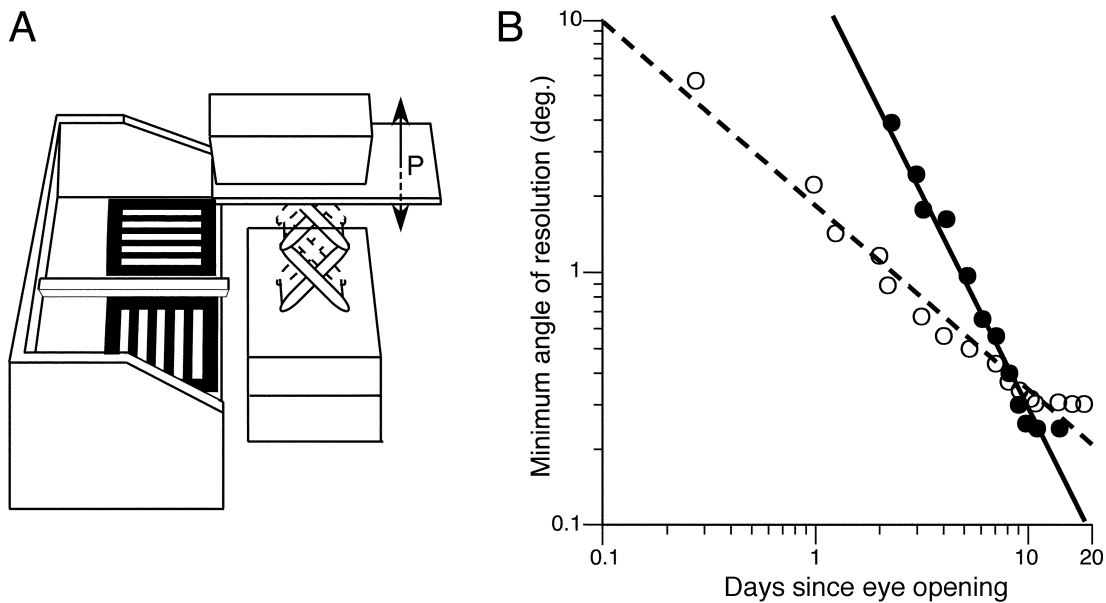


Fig. 1. (A) A sketch (not to scale) of the jumping stand used to measure visual acuity. Kittens were trained to jump from a platform (P) to a vertical grating that was separated by a divider from an adjacent horizontal grating of the same period. See text for details. (B) The MAR of the deprived eye of C844B (○) and C842R (●) as a function of recovery time. The lines through the data represent the best-fitting power functions to the MAR values excluding all data obtained following attainment of the lowest MAR value after approximately 10 days.

To improve the accuracy with which acuity can be specified, the spatial frequency of the gratings were altered in very small steps equated on a logarithmic scale (as many as 12 to the octave). Possibly because the use of such small steps avoids generalization problems, kittens maintain high levels of performance with stimuli within their passband but exhibit a rapid reduction in the proportion of correct responses over only one or two steps near its boundary.

The stimuli were square wave gratings having overall dimensions of 19 cm square (surrounded on all sides by a black border 4 cm wide), a Michelson contrast of 1.0, and a mean luminance of 55 cd/m². Each session began with assessment of the animal's performance with gratings of 32 mm period or having a spatial frequency at least 3 octaves above threshold. The criterion number of correct trials required at each spatial frequency began at one and increased regularly to a minimum of five within an octave of the previous threshold. At any point in the session, when the animal made an incorrect response, it had to achieve a criterion of at least 5 consecutive correct responses or a minimum of 7 out of 10 trials before the spatial frequency was increased. The threshold was defined as the highest spatial frequency for which the animal achieved criterion levels of performance (at least 7 out of 10 correct, but typically 5 out of 5). Psychometric functions were very sharp so that the acuity on any session could be specified very precisely (e.g., figure 1 of ref. 12).

The initial tests of the vision of the deprived eye of each littermate pair were made about 3 h after the eyelids were opened. During the first few days, the vision of the deprived eye of each littermate pair was tested at least twice each day, one kitten immediately after the other, but thereafter tests were conducted daily. In addition to the tests of the vision of the deprived eye, tests of the binocular visual acuity of the animals in the BR condition were made every 3 or 4 days to monitor the vision of the nondeprived eye. All kittens appeared to be blind (defined as an inability to find a closed door on the jumping stand from an adjacent hole 40 cm deep) when first tested through their deprived eye. The jumping platform was set level with the divider that separated the two stimuli so that the animal could

either step onto the closed door or reach for it or the divider with its paw. The vision of the deprived eye was defined as blind if the kitten appeared unable to step onto the closed side except by touching it with its paw or face first. Once the animal appeared to find the closed door (that was changed from the left to right between trials according to a pseudorandom sequence) without touching it first, the jumping platform was raised so as to force the animal to jump. The ability to make 10 consecutive jumps to the door was taken to indicate the ability to make a luminance discrimination. The open door was then closed and covered with a horizontal grating of the same period as the vertical grating on the adjacent door as a test of form discrimination. If the animal achieved criterion on this discrimination, formal testing of acuity was made as described above.

Results

For each littermate pair, the deprived eye of the BR kitten was the first to demonstrate form-vision, and for at least 4 days, this eye possessed better visual acuity than did its RLS sibling. These points are quantified in Table 1, which lists the first test occasion (measured in hours from termination of the period of MD) for which each animal achieved an acuity of 0.25 cycles/deg or better with its deprived eye, and the number of days for which the acuity of the deprived eye of the animals in the BR condition was superior to that of their RLS littermates. A paired sample Student's *t* test conducted on these recovery times for the four littermate pairs revealed that the animals in the BR condition recovered significantly faster than their respective littermates ($P = 0.01$).

The different rates with which vision improved in the two recovery conditions are highlighted by plots of the data on logarithmic scales, with the vision of the deprived eye expressed in terms of the minimum angle of resolution (MAR), the reciprocal of the visual acuity. Earlier (14) it was found that for BR the improvement in the MAR with time was approximately linear when both quantities were plotted on logarithmic scales. Data from the littermate pair (C844B, C842R) that were deprived at 5 weeks, are displayed in Fig. 1B. Results are only shown for the first 2 weeks of recovery, after which changes in

Table 1. Comparison of the speed of improvement of vision of the deprived eye in two conditions of recovery, BR and RLS, for four littermate pairs

Littermate comparison	MD at, days of age	Time to achieve 0.25 cycles/deg, h		Time for which acuity in BR is superior to RLS, days
		BR	RLS	
C844B/C842R	36	23.5	54	8
C808B/C809R	56	7	20	4
C827B/C826R	60	8.5	29	>5
C841B/C843R	64	4.5	23	5

The first index of recovery represents the first tested occasion on which the animal achieved an acuity of 0.25 cycles/deg, and the second is the number of days for which the animal in the BR condition manifested superior acuity with its deprived eye than that of its littermate with RLS.

the MAR were small. The data for both animals over the first 10–12 days followed an approximately linear relationship when plotted on logarithmic scales, implying that the two variables (MAR and recovery time) were related by a power function. Both power functions fitted using linear regression to the data had *R* values of 0.97 but differ in their exponents (slopes). For C844B, the exponent was -0.725 , but that for its reverse occluded littermate (C842R) was higher (-1.69). Thus, although it took longer for form vision to first reappear in the deprived eye of the reverse occluded kitten, the faster rate of the ensuing recovery meant that it overtook the vision recovered in the deprived eye of its littermate after 8 days. Moreover, as in earlier data (5, 7), the acuity of the animal with RLS leveled off at a better level (lower MAR) than did the acuity of the deprived eye of the animal with both eyes open.

Data from the other three littermate comparisons that received a 6-day period of MD at 8 or 9 weeks of age are displayed in Fig. 2. The MAR of the deprived eye of each animal in the BR condition was superior to that of its respective sibling for at least 4 days (see Table 1). The change in the vision of the deprived eye of the three animals in the BR condition could also be well fitted by power functions (not shown). The respective exponents and *R* values of functions fitted to the data for these animals were as follows: C808B ($-0.479, r = 0.98$), C827B ($-0.667, r = 0.95$), and C841B ($-0.584, r = 0.98$). The vision of the RLS animals started

out worse than their siblings but thereafter improved at a faster rate (more negative slope). Although the data for the reverse occluded animals could also be fitted with a power function, the correlation coefficients were not as high as those for their siblings. Indeed, the data from the reverse occluded kittens suggest that the recovery during the first day may occur at a slower rate than in the ensuing days. The respective exponents and *R* values for the latter animals were as follows: C809R ($-1.115, r = 0.97$), C826R ($-1.303, r = 0.93$), and C843R ($-0.869, r = 0.90$), values that were substantially different from their littermates. The regression lines fitted to the individual data for each littermate pair differed significantly (15) [$P < 0.001$ for two pairs but $P < 0.005$ for C841B/C843R]. Moreover, a more conservative paired sample Student's *t* test performed between the mean slopes in the two recovery conditions revealed that they were significantly different ($P < 0.05$).

In common with earlier data (5, 7), RLS animals after 11–20 days of recovery attained grating acuities in their deprived eyes that approached those of normal animals of the same age. In contrast, the acuity of the deprived eye of their BR littermates at the same time was poorer than that of the respective fellow eye by as much as 59% (C808B).

Discussion

We have demonstrated that the initial recovery of vision in the deprived eye after MD was faster in animals receiving binocular vision than their RLS littermates, a result that is counterintuitive to traditional models of competition. The visual advantage conferred on the animals in the BR condition lasted for 4–8 days, but thereafter the vision of the RLS animals was superior. The eventual superiority of RLS over BR for both the vision of the initially deprived eye and for recovery of cortical ocular dominance was evident in earlier studies (5, 7). Moreover, despite the lower frequency of tests of vision, the two animals in the earlier studies that received binocular vision during recovery, namely 45B and 60B, achieved an acuity of 0.25 cycles/deg in their deprived eye 1.5 to 3 days earlier than did their reverse occluded littermates, 45R and 60R, respectively. Although the eventual superiority of RLS for both the vision of the deprived eye and for restoration of cortical ocular dominance was stated as being consistent with competitive mechanisms of synaptic plasticity, the substantial recovery observed with BR was hypothesized to reflect an additional noncompetitive mechanism (5, 7). Simulations (10) of the BCM model of synaptic plasticity reveal faster recovery of functional properties through the deprived eye in the BR condition than with RLS provided the

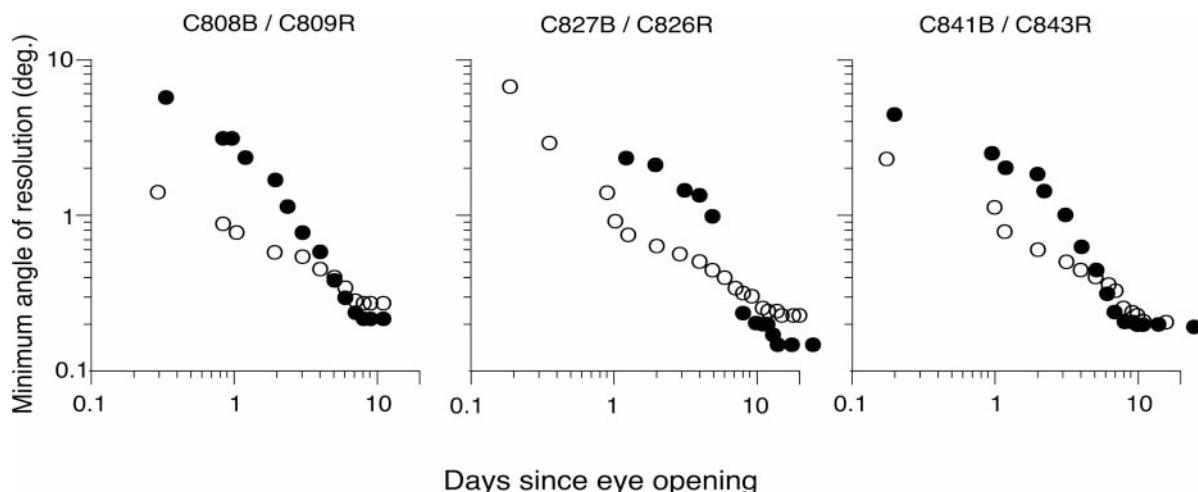


Fig. 2. The MAR of the deprived eye as a function of recovery time for three other littermate comparisons of BR (○) and RLS (●).

noise in both the deprived and nondeprived eyes is sufficiently large.

Theoretical Framework. In this study, recovery was monitored by longitudinal measurements of the visual acuity of the deprived eye, which beg questions about the identity of the particular synapses involved and how such measures might be related to changes in synaptic efficacy. Identification of the neurons that underlie a particular perceptual experience represents a major challenge to sensory neuroscience (16). A common approach to this issue has been to search for a correlation between neuronal and perceptual events. In this context, it is instructive to note the earlier demonstration (7) of a close correlation between the rate of change of ocular dominance of cells in area 17 during RLS and the speed of recovery of the visual acuity of the deprived eye. So although the precise nature of the relationship between measures of visual acuity and changes of ocular dominance in area 17 has not yet been defined, it is apparent that improvements in visual acuity are linked to changes of ocular dominance among populations of cells in area 17. Thus the faster recovery of the vision of the deprived eye with BR as opposed to RLS cannot be ignored with respect to the implications for the existence of mechanisms of synaptic plasticity other than ones based on binocular competition.

Cells in area 17 and beyond vary in ocular dominance and, even after periods of MD lasting 6 days, a small proportion of cells may remain excitable only through the deprived eye. However, this small population of cells demonstrably could not mediate vision in this eye on the jumping stand, so we assume that the subsequent recovery of vision reflects changes in the much larger population of cells that were binocular before the period of MD.

The BCM Model. In contrast to competition-based models that incorporate a heterosynaptic learning rule (4, 17–20), the BCM model uses a homosynaptic learning rule according to which a change in synaptic strength in one set of inputs upon a cell may occur without alteration in the other set. Moreover, this model states that total synaptic weight does not have to remain stable; instead stabilization of synaptic weight is accomplished by a sliding “modification threshold” that varies depending on the average postsynaptic activity over time. Synaptic strengthening, possibly attributable to a process similar to long-term potentiation, occurs at a synapse when presynaptic activity causes postsynaptic activity to exceed the modification threshold; conversely, if this threshold is not reached, then synaptic weakening is induced by a process such as long-term depression at the active synapses (Fig. 3). The theory predicts that inputs from the two eyes can interact, through changes in the average activity of the postsynaptic cell, but do so in the temporal rather than the spatial domain. An important feature of the homosynaptic learning rule is that each synapse on a cell can experience both positive and negative changes in efficacy independent of changes in neighboring synapses. Mathematically stated, the BCM theory proposes that $dm_{j(t)}/dt = \phi[c(t), \theta_m(t)]d_j(t)$, i.e., the synaptic weight of the j th synapse at time t , $m_{j(t)}$, changes in time as a nonlinear function, ϕ , of the postsynaptic activity of the cell $[c(t)]$ and the modification threshold $[\theta_m(t)]$, which itself is a function of the time-averaged postsynaptic activity of the cell, and as a linear function of the presynaptic activity $d_j(t)$.

Predictions of the BCM Theory for Recovery from MD. Attempts to link psychophysical measures of visual acuity to responses of neurons in area 17 suggest a complex relationship, with general agreement that acuity may depend more on the stimulus selectivity of cells (such as their spatial resolution) than on the absolute number of such cells (e.g., refs. 5 and 21–23). In terms of conventional ocular dominance assays, the BCM model

predicts different outcomes for binocular cells versus cells driven almost exclusively by the deprived eye before and after the period of MD. The latter cells would experience a severe reduction in postsynaptic activity during the period of MD and hence their modification threshold (θ_m) would be very low. For these cells, recovery of synaptic connections with the deprived eye would occur at the same rate in both recovery conditions because they never made synaptic connections with the nondeprived eye. However, as illustrated in schematic form in Fig. 3, the predictions of the BCM model for binocular cells, which comprise the vast majority of cells in cat area 17, are quite different for the two recovery conditions.

The situation at the beginning of recovery is illustrated at t_0 and later stages are denoted as t_1 , etc. For the condition of BR, presynaptic activity through the left eye would occur simultaneously with activity through the nondeprived eye. The combined postsynaptic activity would exceed the modification threshold, leading to immediate strengthening of the synapses from the deprived eye. In essence, during BR the nondeprived eye facilitates deprived eye synapses. This recovery can be modeled by associative long-term potentiation (19), a specialized form of a homosynaptic learning rule. By contrast, during the initial stages of RLS, the presynaptic activity arising from either eye would produce very low postsynaptic activity because the now-deprived eye’s image would be blurred through the newly closed eyelid and the efficacy of synapses with the initially deprived eye would be low. Because the modification threshold reflects the time-average postsynaptic response of the cell, it would initially be much higher than the postsynaptic activity arising from presynaptic activity in either eye; therefore, synapses with the initially nondeprived eye would weaken. In turn, the reduction in the total postsynaptic activity would lead to gradual lowering of θ_m . Only when θ_m declines to a much lower value, shown at t_2 , would it lie below the level of postsynaptic activity arising from stimulation of the initially deprived eye, thereby permitting strengthening of the synapses with this eye. Furthermore, the resulting enhancement of the area of the region of synaptic strengthening (Fig. 3*B*), and concurrent depression of the region of synaptic weakening, leads to the expectation that once it begins, the rate of recovery during RLS may be faster than that which occurs during BR (the precise rate of recovery will depend on the exact model parameters). Thus qualitatively, the BCM model predicts that initially recovery would be observed only in BR; however, once vision begins to recover in the situation of RLS, it should proceed at a faster rate.

The prediction of a slower rate of recovery in RLS animals arises from the reduced postsynaptic activity that follows closure of the nondeprived eye that requires θ_m to reset to a low level before recovery can begin. But in the animals with both eyes open, provided the activity between the deprived and nondeprived synapses is correlated, the activity of the deprived eye adds to that of the nondeprived eye to exceed θ_m , thereby permitting initiation of recovery of deprived eye synapses immediately. In agreement with the prediction for RLS, chronic recording methods (24) reveal that during RLS, visually induced activity is lost from the initially nondeprived eye before any such activity is observed through the originally deprived eye. Thus, recovery of deprived eye inputs appears to occur after the weakening of the non-deprived eye inputs. Our data indicate that the modification threshold takes 12–30 h to reset (depending on the age at which MD was initiated), because recovery of form vision (i.e., time to reach 0.25 cycles/deg; Table 1) was delayed by this time in the RLS relative to the BR conditions. These values are comparable to the value of 24 h derived by Clothiaux *et al.* (10) from the data of Mioche and Singer (24) on kittens that received RLS following MD of 1–7 days at 3–4 weeks of age.

Our data suggest a unitary mechanism for the differing results of BR after early MD in cats and monkeys. In contrast to cats and

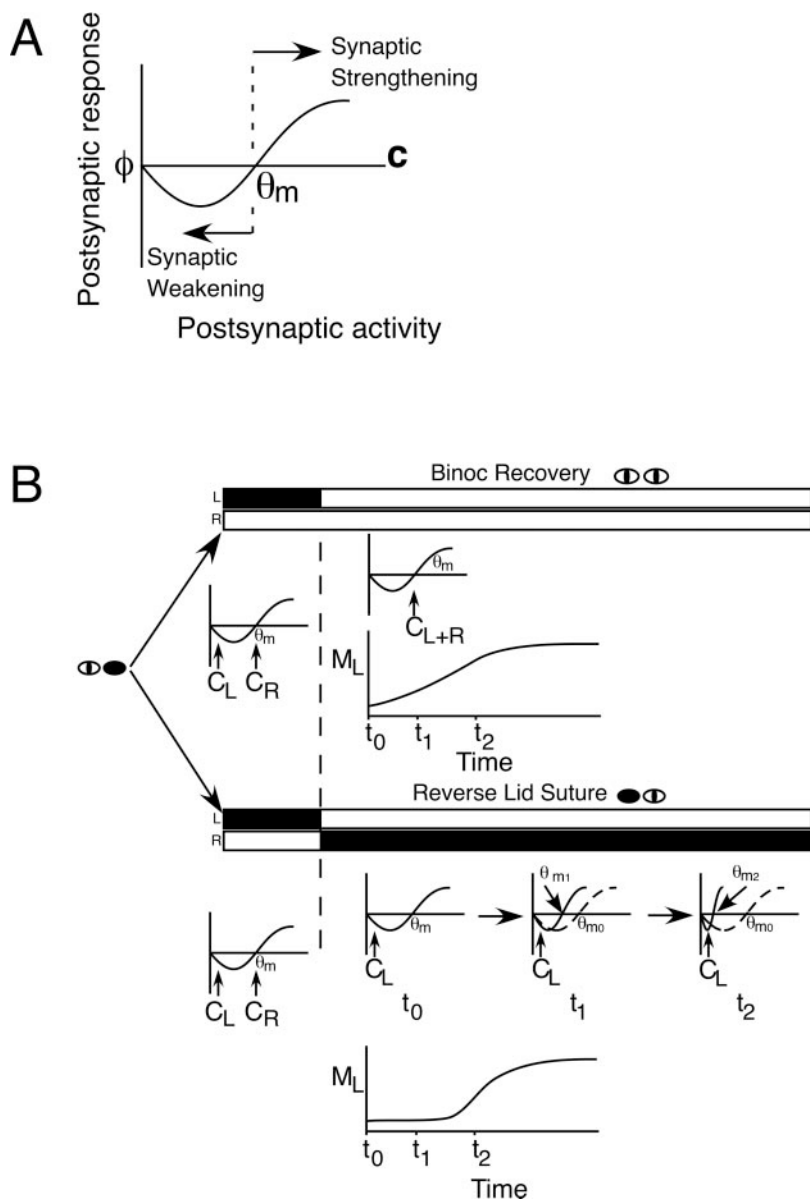


Fig. 3. (A) The BCM model. The synaptic weight of a particular synapse changes in time as a linear function of the presynaptic activity and a nonlinear function (ϕ), of the postsynaptic activity (c) and the modification threshold (θ_m) that is a function of the time-averaged postsynaptic activity of the cell. According to the BCM model, synaptic strengthening of a synapse occurs when presynaptic activity is sufficient to cause depolarization of the postsynaptic cell above the modification threshold, whereas levels of depolarization below this threshold leads to synaptic weakening. See *Methods* for further details. (B) The predicted changes with time in the synaptic weights (M_L) with the deprived (left) eye for the two recovery conditions. C_L and C_R represent the level of postsynaptic activity attributable to stimulation of, respectively, either the left (deprived) or right eye. In the situation of BR, C_{L+R} represents the postsynaptic activity resulting from simultaneous stimulation of both eyes. For the RLS condition, the original modification threshold at time t_0 is designated as θ_{m0} , whereas θ_{m1} and θ_{m2} refer to its level at t_1 and t_2 , respectively. The ϕ function for the RLS condition is indicated at three points in time by the filled line; the dashed line depicts this function at time t_0 . Data from our experiments suggest that resetting of the modification threshold requires 12–30 h depending on the state of developmental plasticity (i.e., the age of the kitten when monocularly deprived).

humans (8), the deprived eye of monkeys undergoes little recovery from deprivation without concurrent closure of the nondeprived eye (25, 26). However, in the monkey experiments, cells were recorded from the representation of the foveal region of area 17 where the receptive fields are very small. Therefore, even a very slight misalignment of the two eyes, which may follow MD (27, 28), would functionally decorrelate the inputs from the two eyes. Such uncorrelated eye input could prevent recovery because inputs from the nondeprived eye would keep θ_m high, and the deprived eye inputs could not be strengthened. In support of such a mechanism, preliminary results in cats show that visual recovery after MD is greatly reduced if the input from the two eyes is uncorrelated by inducing an artificial convergent strabismus in the nondeprived eye (P.C.K., D.E.M., A. Ahmed, C. Blakemore, T. Bonhoeffer, and F. Sengpiel, unpublished work).

The results of this study add to a growing body of evidence supporting the operation of homosynaptic mechanisms of developmental plasticity in the mammalian visual system (24, 29, 30). Experimental support for the BCM model has also been found for other rearing conditions including MD

(30), RLS (24; P.C.K., D.E.M., A. Ahmed, C. Blakemore, T. Bonhoeffer, and F. Sengpiel, unpublished work) and dark-rearing (29). However, it does not necessarily follow that homosynaptic learning rules underlie all of the events that follow MD or those that occur after its termination. Indeed, Kind (20) proposes the operation of a number of learning rules in ocular dominance plasticity. Homosynaptic learning rules (10) or rules based on heterosynaptic competition (19) could underlie the rapid changes in synaptic efficacy associated with short periods of MD or the unmasking of inputs from the deprived eye following application of GABA receptor blockers (31). However, the anatomical changes (32, 33) that rely on axonal growth and retraction almost certainly involve yet another form of plasticity that could be termed “heterocellular” where competition occurs between neurons as opposed to synapses on the same neuron.

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1. Wiesel, T. N. & Hubel, D. H. (1965) *J. Neurophysiol.* **28**, 1029–1040.
2. Guillery, R. W. (1988) in *The Making of the Nervous System*, eds. Parnevelas, J. G., Stern, C. J. & Sterling, R.V. (Oxford Univ. Press, Oxford), pp. 356–379.
3. Hubel, D. H., Wiesel, T. N. & LeVay, S. (1977) *Philos. Trans. R. Soc. London B* **278**, 377–409.
4. Miller, K. D., Keller, J. B. & Stryker, M. P. (1989) *Science* **245**, 605–615.
5. Mitchell, D. E., Cynader, M. & Movshon, J. A. (1977) *J. Comp. Neurol.* **176**, 53–64.
6. Olson, C. R. & Freeman, R. D. (1978) *J. Neurophysiol.* **41**, 65–74.
7. Giffin, F. & Mitchell, D. E. (1978) *J. Physiol. (London)* **274**, 511–537.
8. Jacobson, S. G., Mohindra, I. & Held, R. (1983) *Doc. Ophthalmologica* **55**, 199–211.
9. Mitchell, D. E. (1988) *J. Physiol. (London)* **395**, 639–660.
10. Clothiaux, E. E., Bear, M. F. & Cooper, L. N. (1991) *J. Neurophysiol.* **66**, 1785–1804.
11. Bienenstock, E. L., Cooper, L. N. & Munro, P. W. (1982) *J. Neurosci.* **2**, 32–48.
12. Murphy, K. M. & Mitchell, D. E. (1987) *J. Neurosci.* **7**, 1526–1536.
13. Freeman, R. D. (1980) *Invest. Ophthalmol. Vis. Sci.* **19**, 306–308.
14. Mitchell, D. E. & Gingras, G. (1998) *Curr. Biol.* **8**, 1179–1182.
15. Weisberg, S. (1985) *Applied Linear Regression* (Wiley, New York), 2nd Ed., pp. 179–184.
16. Albright, T. (1991) *Curr. Biol.* **1**, 391–393.
17. Von der Malsburg, C. (1973) *Kybernetik* **14**, 85–100.
18. Oja, E. (1982) *J. Math. Biol.* **15**, 267–273.
19. Linden, D. J. (1994) *Neuron* **12**, 457–472.
20. Kind, P. C. (1999) *Curr. Biol.* **9**, R640–R643.
21. Murphy, K. M. & Mitchell, D. E. (1986) *Nature (London)* **323**, 536–538.
22. Kiorpes, L., Kiper, D. C., O’Keefe, L. P., Cavanaugh, J. R. & Movshon, J. A. (1998) *J. Neurosci.* **18**, 6411–6424.
23. Blakemore, C. (1988) in *Strabismus and Amblyopia*, eds. Lennerstrand, G., von Noorden, G. K. & Campos, E. C. (Plenum, New York), pp. 219–234.
24. Mioche, L. & Singer, W. (1989) *J. Neurophysiol.* **62**, 185–197.
25. Baker, F. H., Grigg, P. & Von Noorden, G. K. (1974) *Brain Res.* **66**, 185–208.
26. Blakemore, C., Vital-Durand, F. & Garey, L. J. (1981) *Proc. R. Soc. London B* **213**, 399–423.
27. Cynader, M. (1979) *Invest. Ophthalmol. Vis. Sci.* **18**, 726–741.
28. Quick, M. W., Tigges, M., Gammon, J. A. & Boothe, R. G. (1989) *Invest. Ophthalmol. Vis. Sci.* **30**, 1012–1017.
29. Kirkwood, A., Rioult, M. G. & Bear, M. F. (1996) *Nature (London)* **381**, 526–528.
30. Rittenhouse, C. D., Shouval, H. Z., Paradiso, M. A. & Bear, M. F. (1999) *Nature (London)* **397**, 347–350.
31. Sillito, A. M., Kemp, J. A. & Blakemore, C. (1981) *Nature (London)* **291**, 318–320.
32. Antonini, A. & Stryker, M. P. (1993) *Science* **260**, 1819–1821.
33. Trachtenberg, J. T. & Stryker, M. P. (2001) *J. Neurosci.* **21**, 3476–3482.