

25. Clesceri, L. S., Greeberg, A. E. & Eaton, A. D. (eds) *Standard Methods for the Examination of Water and Wastewater* 20th edn (American Public Health Association, Washington DC, 1998).
26. Mitchell-Olds, T. & Shaw, R. E. Regression analysis of natural selection: statistical inference and biological interpretation. *Evolution* **41**, 1149–1161 (1987).

Acknowledgements

We thank J. Shurin, M. Willig, M. Vandermeulen, P. Lorch and especially T. Knight for discussions and comments. A. Downing, J. Shurin and T. Leibold helped with the pond survey. This research was supported by the Kellogg Biological Station (Michigan State University), the University of Chicago, the University of California—Davis, the University of Pittsburgh and the NSF.

Competing interests statement

The authors declare that they have no competing financial interests.

Correspondence and requests for materials should be addressed to J.M.C. (e-mail: jchase@pitt.edu).

Correlated binocular activity guides recovery from monocular deprivation

Peter C. Kind^{*†}, Donald E. Mitchell[‡], Bashir Ahmed^{*}, Colin Blakemore^{*}, Tobias Bonhoeffer[§] & Frank Sengpiel^{||}

^{*} University Laboratory of Physiology, Parks Road, Oxford OX1 3PT, UK

[†] Department of Biomedical Sciences, University of Edinburgh, Hugh Robson Building, George Square, Edinburgh EH8 9XD, UK

[‡] Department of Psychology, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J1

[§] Max-Planck-Institut für Neurobiologie, Am Klopferspitz 18a, 82152 München-Martinsried, Germany

^{||} Cardiff School of Biosciences, Museum Avenue, PO Box 911, Cardiff CF10 3US, UK

Monocular deprivation (MD) has much more rapid and severe effects on the ocular dominance of neurons in the primary visual cortex (V1) than does binocular deprivation¹. This finding underlies the widely held hypothesis that the developmental plasticity of ocular dominance reflects competitive interactions for synaptic space between inputs from the two eyes². According to this view, the relative levels of evoked activity in afferents representing the two eyes determine functional changes in response to altered visual experience. However, if the deprived eye of a monocularly deprived kitten is simply reopened, there is substantial physiological and behavioural recovery, leading to the suggestion that absolute activity levels, or some other non-competitive mechanisms, determine the degree of recovery from MD^{3–7}. Here we provide evidence that correlated binocular input is essential for such recovery. Recovery is far less complete if the two eyes are misaligned after a period of MD. This is a powerful demonstration of the importance of cooperative, associative mechanisms in the developing visual cortex.

In normal kittens, artificially induced strabismus, which misaligns the receptive fields of binocular neurons and hence effectively decorrelates the inputs from the two eyes, causes a substantial breakdown of cortical binocularity^{3,8}. We have tested whether strabismus induced immediately after MD prevents physiological and behavioural recovery of the reopened deprived eye. The results demonstrate the role of correlated activity in the recovery process.

Ten kittens were monocularly deprived for 10 days, starting at 5 weeks of age. In five animals, MD was followed by normal binocular experience (MDB). In the other five cats, a convergent strabismus (esotropia) was induced in the nondeprived eye when

the deprived eye was reopened (MDS). In four of these cats, an esotropia of between 10° and 20° persisted throughout the recovery period, as judged from the positions of the corneal reflexes, whereas in one animal (MDS4), the visual axes seemed to become realigned within a few days of the strabismus surgery.

Intrinsic-signal optical imaging of V1 of both hemispheres was performed at least 14 days after the deprived eye had been reopened. In two additional control kittens we performed optical imaging, immediately after a 10-day period of MD, to obtain maps of activation through each eye. In these animals, in agreement with previous results⁹, deprived-eye responses were weak and restricted to small ‘islands’ that occupied, on average, only 14.3% of cortical territory in V1 ipsilateral to the deprived eye and 18.2% of V1 contralateral to the deprived eye (see Fig. 3a).

All five MDB cats exhibited remarkable recovery of responses through the previously deprived eye; the maps were generally indistinguishable from monocular responses in normal cats of similar age. In the ipsilateral hemisphere (Fig. 1a), on average the previously deprived eye dominated 48.2 ± 3.5% (mean ± s.d.) of the cortical surface, compared with 48.8 ± 3.8% in four normal kittens. In the contralateral hemisphere, the deprived eye’s domains occupied 52.6% (±4.2%), compared with 51.2% (±3.8%) in normal kittens.

In contrast, representation of the deprived eye was still much reduced in all four kittens in which inputs from the two eyes were decorrelated because of a persistent strabismus (MDS1–3 and MDS5). In the hemisphere ipsilateral to the deprived eye, responses to stimulation of that eye were often restricted to ‘islands’ (Fig. 1b; for example, animals MDS2 and MDS3). The deprived eye’s territory covered just 36.7% (±3.6%) of the imaged region, significantly less than in the kittens with normal binocular recovery ($P < 0.002$, one-tailed t -test; see Fig. 2). Even if the data were included from the additional animal (MDS4) in which the visual axes became realigned, the mean cortical territory dominated by the deprived eye was 39.4% (±6.8%), significantly smaller than in the five MDB kittens ($P < 0.02$). The results also differed significantly from data for the ipsilateral eye in four kittens of similar age

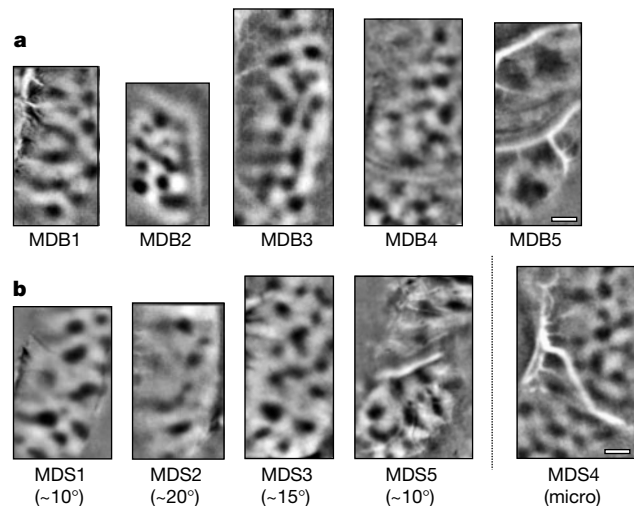


Figure 1 Ocular-dominance maps from left-hemisphere V1 of cats with 10-day MD of the left eye. **a**, Five cats in which MD was followed by concordant binocular vision (MDB); **b**, five cats which were strabismic during the binocular recovery period (MDS). Dark islands represent regions dominated by the left (originally deprived) eye. In all the MDB animals, dark and light areas occupy roughly equal areas (**a**). In the MDS cats (except the microstrabismic cat MDS4 (micro)), dark (left-eye) regions often form relatively isolated patches in a lighter ‘sea’ of cortex dominated by the right (nondeprived) eye (**b**). Blood vessel artefacts appear as light-grey linear and branching patterns (for example, MDS4 and MDB5). Scale bar, 1 mm. In all images the posterior pole is at the bottom.

made strabismic shortly after eye-opening without prior MD ($48.0 \pm 5.8\%$, $P < 0.01$). For the hemisphere contralateral to the deprived eye, the difference between the strabismic group (MDS1–5, $46.0 \pm 3.1\%$) and the binocular recovery group (MDB1–5) was smaller but also significant ($P < 0.02$, one-tailed t -test; see Fig. 2).

The one kitten in which an obvious strabismus persisted for only a few days after surgical induction (MDS4) served as an interesting control: it had undergone exactly the same procedures as the other strabismic animals but had quickly gained roughly aligned binocular input. The amount of cortical territory dominated by the deprived eye in MDS4 was indistinguishable from that in the MDB kittens (50.2% in the ipsilateral hemisphere and 47.0% in the contralateral hemisphere).

No significant correlation was found between the territory dominated by the deprived eye and the duration of the recovery period in either the MDB group ($r = 0.87$, $P > 0.05$) or the MDS group ($r = 0.05$, $P > 0.9$). This indicates that whatever physiological recovery occurred was complete within 2 weeks. But there was a highly significant negative correlation between the angle of squint and the territory dominated by the deprived eye (averaged across both hemispheres) in the MDS animals ($r = -0.98$, $P < 0.005$).

In addition to reducing the amount of territory recaptured by the previously deprived eye, strabismus also affected the recovery of orientation selectivity. Immediately after MD, activity resulting from deprived-eye stimulation was very weak and restricted to small islands that responded to all stimulus orientations⁹ (see Fig. 3a). However, in the five kittens with normal binocular recovery (MDB), deprived-eye responses to different orientations became spatially well segregated, and normal orientation selectivity was regained (Fig. 3b).

Recovery of orientation selectivity through the previously deprived eye was more variable and weaker overall in the strabismic (MDS) kittens. In some cases, deprived-eye domains responded almost equally well to all orientations (Fig. 3c), as in monocularly deprived control animals. Single-cell recordings from one animal (MDS3) established that this finding was not due to the very close proximity of selective neurons with widely differing orientation preferences. Rather, most neurons driven by the deprived eye exhibited very poor orientation selectivity. Their half-width of

tuning at half-height was $47.7 \pm 5.6^\circ$ (mean \pm s.e.m.; $n = 11$), about twice the value for cells in area 17 of normal cats or cats made strabismic without prior MD¹⁰.

We quantified the orientation selectivity of optical responses through each eye by calculating, for each pixel, an orientation selectivity index, OSI (see Methods), and averaging it across all pixels. The mean OSI through the deprived eye, as a percentage of that through the nondeprived eye, indicates the degree of recovery. Again, the difference between the MDB and MDS groups was greater for the hemisphere ipsilateral to the deprived eye. In the binocular recovery group, the orientation selectivity of responses through the deprived eye was $83.0 \pm 11.3\%$ (mean \pm s.d.) of that through the nondeprived eye. In contrast, in the strabismic group it

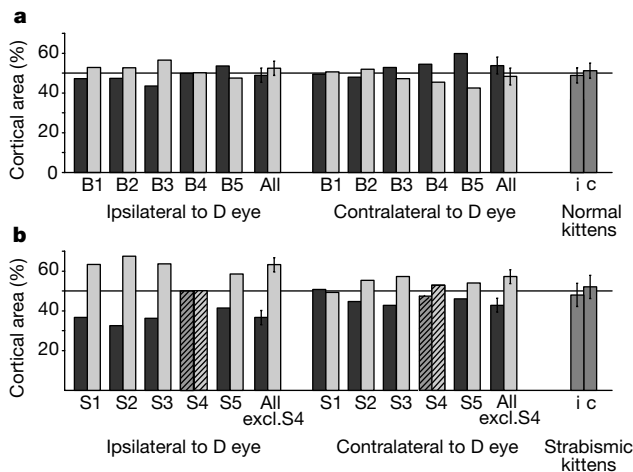


Figure 2 Histograms of cortical surface area dominated by each of the two eyes in MDB cats (a) and in MDS cats (b). Dark bars represent the left, previously deprived eye and light bars the right, non-deprived eye. Data for both hemispheres are displayed separately. In (a), average areas for all five animals are also shown (All), as are results for the ipsilateral (i) and contralateral (c) eyes in four normal kittens. In (b), hatched bars indicate results from kitten MDS4, in which surgical strabismus was transient. Average data from the other four kittens (All excl. S4) are shown, as are results for both eyes in four strabismic kittens.

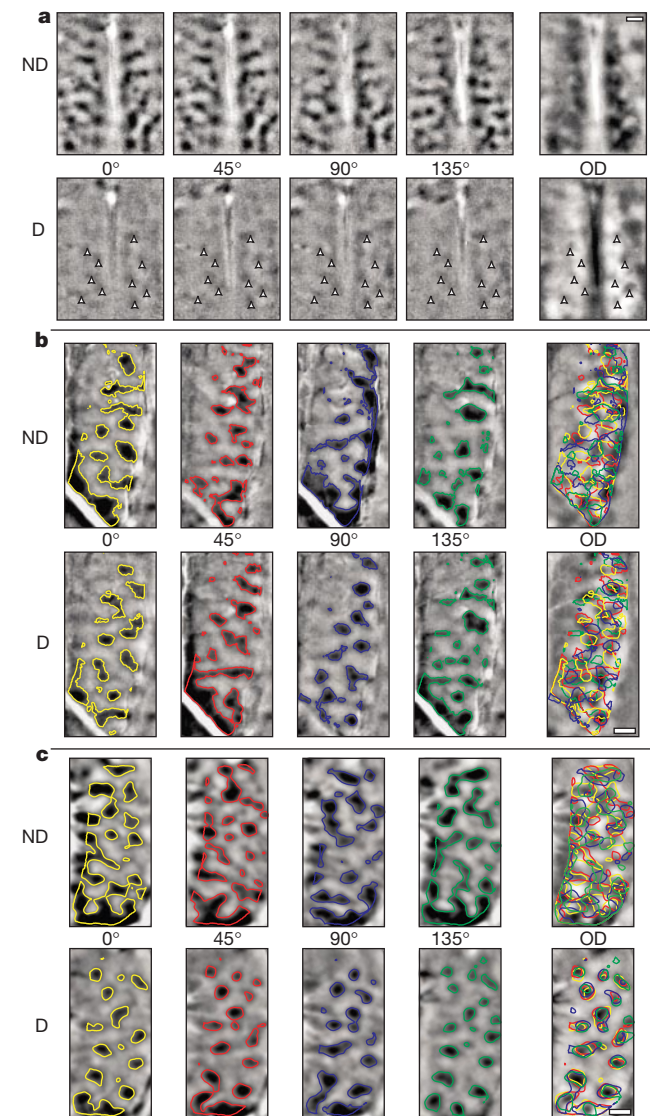


Figure 3 Orientation and ocular-dominance maps for deprived (D) and nondeprived (ND) eyes from a kitten imaged immediately after MD (a), a cat (MDB3) with concordant binocular recovery (b) and a cat (MDS3) with strabismus after MD (c). In a, both hemispheres are shown; in b and c only the left hemisphere is shown. For the control animal (a), arrowheads pointing to small regions still responsive to the deprived eye in the ocular-dominance map have been superimposed on the iso-orientation maps. Iso-amplitude lines in b and c encompass regions of the same minimum signal strength in the four orientation maps. The same lines are then superimposed on the ocular-dominance (OD) maps on the far right. Scale bars, 1 mm; posterior pole is at the bottom.

was only $63.0 \pm 17.4\%$. The difference between the two groups was significant ($P < 0.05$, one-tailed t -test). For the contralateral hemisphere, the relative orientation selectivity through the deprived eye was also greater in the MDB group ($86.6 \pm 6.9\%$) than in the MDS group ($78.1 \pm 18.9\%$) but the difference was not significant. The animal with only transient strabismus (MDS4) showed the greatest recovery of orientation selectivity of all MDS kittens.

Recovery of vision in the deprived eye was tested behaviourally in three littermate pairs of kittens, all subsequently studied by optical imaging. In three MDB kittens, vision through the previously deprived eye recovered faster and attained higher acuity than in three MDS kittens. The MDB kittens began to discriminate gratings of the lowest spatial frequency within 1 or 2 days of the deprived eye being reopened, compared with 3–5 days for MDS animals (Fig. 4). Acuity achieved after 3 weeks was, on average, twice as high in the MDB group (5.44 ± 1.1 cycles deg^{-1} ; mean \pm s.d.) as in the MDS group (2.63 ± 0.13 cycles deg^{-1}). This difference was highly significant ($P < 0.01$, one-tailed t -test). At the same time, acuity in the nondeprived eye did not differ between the two groups (MDB, 7.47 ± 0.37 cycles deg^{-1} ; MDS, 7.03 ± 0.36 cycles deg^{-1} ; $P = 0.11$).

The strabismic animals studied behaviourally included MDS4, whose eyes seemed to become realigned shortly after surgery. Surprisingly, the recovery of acuity in the deprived eye was not superior to that of the other MDS animals, although optical recording revealed substantial re-expansion of the deprived eye's territory. Perhaps realignment of the visual axes was precise enough to provide a correlated input to neurons with relatively large receptive fields, sufficient to account for the optical imaging results, but not to align the smallest receptive fields, which mediate maximal behavioural acuity. The site of the deficit in visual acuity might also be higher in the visual cortical pathway than V1, in agreement with previous reports of reduced visual acuity despite relatively normal neuronal responses in the striate cortex^{11,12}.

Immediately after MD, input from the nondeprived eye dominates the primary visual cortex. However, during a subsequent period of binocular vision there is substantial recovery in the deprived eye. We have now demonstrated that both behavioural and physiological recovery are greatly reduced if the two eyes are misaligned. These results strongly suggest that the correlation of activity between the two eyes promotes recovery through the deprived eye.

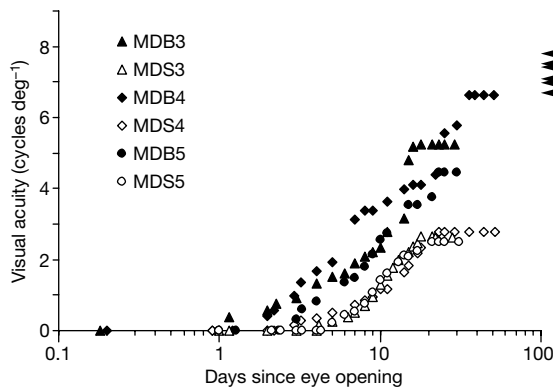


Figure 4 Recovery of visual acuity in the previously deprived eye of three kittens with binocular recovery (MDB, filled symbols) and three kittens with esotropic strabismus (MDS, open symbols) after a period of MD. For littermate pairs of kittens the same type of symbol is used. Grating acuity of the previously deprived eye, obtained with the jumping-stand technique, is plotted against days since the termination of MD. The final acuities of the nondeprived eyes are represented by arrows at the far right. Note that the low acuity through the previously deprived eye cannot reflect a visual deficit associated with squint (strabismic amblyopia), because the esotropia was induced in the nondeprived eye.

If, after MD, the deprived eye is reopened and the other eye is closed (reverse suture), input from the initially deprived eye to the visual cortex recovers completely¹³ (although, interestingly, behavioural recovery is delayed compared with that during simple binocular vision¹⁴). This implies that the absolute level of activity from the initially nondeprived eye alone can drive recovery. The partial recovery in our strabismic animals, compared with that in control kittens examined immediately after MD, might have been due simply to the restoration of activity from the deprived eye. However, some correlated input, sufficient to drive binocular associative mechanisms, might have remained. Surgical strabismus reduces the mobility of the strabismic eye. Hence, during eye movements, the two visual axes would become aligned occasionally, producing correlation of the inputs. Such intermittent correlation would be more frequent for smaller angles of squint. There was indeed a highly significant inverse correlation between the angle of squint and the degree of recovery of input from the deprived eye, as judged by optical imaging, even with angles of deviation above 10° . In fact, intermittent correlation could account for the 20–40% of neurons that maintain binocular input in animals with surgically induced strabismus alone^{8,10}.

At first glance, our findings seem to contradict those of Malach and Van Sluyters¹⁵, who reported that the degree of physiological recovery from MD was similar in kittens with concordant binocular visual input and in those with an induced strabismus in the deprived eye. However, their animals showed only a small strabismic deviation and therefore their greater recovery might, as we suggest for MDS4 in our study, have depended on some degree of correlation of input from the two eyes. Moreover, during the period of MD, Malach and Van Sluyters¹⁵ kept their kittens in complete darkness except for three short (2-h) exposures to light each day. Hence, they were effectively dark-reared for 18 h per day, which might have affected the plasticity of cortical neurons¹⁶.

The need for precise binocular alignment to promote the recovery of input to cortical neurons could account for an otherwise perplexing discrepancy between species. Reopening the deprived eye after MD in monkeys causes little or no physiological recovery unless the nondeprived eye is closed¹⁷—a result that has been taken as evidence for competition. However, the receptive fields in the monkey's foveal representation are so tiny that even a very small misalignment of the visual axes (which frequently occurs after MD^{18–20}) would be likely to compromise the correlation between ocular inputs and hence to prevent recovery.

Our results, together with the effects of reverse suture, therefore argue that both absolute levels of activity⁷ and the degree of correlation of input from the two eyes influence the binocularity of neurons during the postnatal development of the visual cortex. The balance of synaptic input from the two eyes might depend to a large extent on the input from one eye acting as a 'teacher' in an associative learning mechanism for synaptic modification. Many aspects of our findings can be accounted for by the so-called BCM theory of Bienenstock *et al.*²¹, which invokes a changeable 'modification threshold' that depends on integrated synaptic activity. This theory also accounts for the results of many other rearing procedures including MD, reverse suture and dark-rearing^{14,22–25}. □

Methods

Animals

All experimental procedures were performed with the approval of the appropriate British, Canadian and German government authorities. Ten kittens were raised normally until about postnatal day 35 (P35). The left eye was then deprived by lid-suture for 10 d, after which (at P45) it was reopened. For five of the kittens (MDB) the ensuing binocular visual experience was presumably concordant because they had no obvious squint and the projections of their visual axes, determined by direct ophthalmoscopy under paralysis during the optical imaging experiments, were similar to those of normal animals. In the other five animals, esotropia (convergent strabismus) was induced at the time of reopening of the deprived eye by extirpation of the lateral rectus muscle of the other eye (MDS). We chose to make the nondeprived eye strabismic, rather than the deprived eye, so

that any tendency for the induced squint itself to cause a visual impairment (strabismic amblyopia) in the deviating eye would actually reduce the likelihood of the nondeprived eye's continuing to dominate the cortex.

In six kittens (three MDB and three MDS), visual acuity in the previously deprived eye was determined daily by the jumping-stand method^{6,7}. Kittens were trained to discriminate between a vertical and a horizontal grating, the spatial frequency of which was increased in accordance with an ascending method of limits. The nondeprived eye was occluded when the previously deprived eye was tested. The visual acuity of the nondeprived eye was also determined during and after the recovery period, either directly or by measurement of the acuity with both eyes open⁶.

After at least 14 days of recovery, ocular dominance and orientation maps in the primary visual cortex of all ten kittens were obtained by optical imaging of intrinsic signals. For six kittens (three MDB, three MDS), both behavioural tests and optical imaging experiments were performed.

Optical imaging and analysis

Anaesthesia was induced with an intramuscular injection of ketamine (20–40 mg kg⁻¹) and xylazine (2–4 mg kg⁻¹). Animals were intubated and artificially ventilated (50–60% N₂O, 40–50% O₂, 0.9–1.2% halothane). Electrocardiogram, electroencephalogram, end-tidal CO₂ and rectal temperature were monitored continuously. Optical imaging of primary visual cortex was performed as described previously²⁵. Images were captured with either a cooled slow-scan charge-coupled device camera or an enhanced differential imaging system (ORA 2001 or Imager 2001; Optical Imaging Inc.), with the camera focused ~500 μm below the cortical surface. Visual stimuli, produced by a stimulus generator (VSG; Cambridge Research Systems), consisted of high-contrast, sinusoidally modulated gratings (0.2–0.6 cycle deg⁻¹) of four different orientations, drifting at a temporal frequency of 2 Hz, presented to the two eyes separately in randomized sequence, interleaved with trials in which the screen was blank. Single-condition responses (averages of 32–96 trials per eye and orientation) were divided (1) by responses to the blank screen, and (2) by the sum of responses to all four orientations ('cocktail blank')²⁵ to obtain iso-orientation maps. Signal amplitude was displayed on an eight-bit greyscale.

Ocular-dominance maps were obtained by dividing the sum of responses to all four orientations through one eye by the similar sum of responses through the other eye. Resulting maps were high-pass filtered (cutoff 1.3 mm). Within a region of interest that comprised the visually responsive part of the images, excluding blood vessel artefacts, pixels were assigned to the left and right eye, respectively, depending on whether their value was greater or less than 1.

Orientation preference maps were calculated by vectorial addition of four iso-orientation maps, and pseudo-colour coded. Orientation selectivity indices (OSIs) were calculated for responses at each pixel as

$$OSI = \frac{\sqrt{(R_0 - R_{90})^2 + (R_{45} - R_{135})^2}}{R_0 + R_{45} + R_{90} + R_{135}}$$

where R₀, R₄₅, R₉₀ and R₁₃₅ represent the responses in each of the four iso-orientation maps²⁶. OSI represents the magnitude of the orientation preference vector divided by the sum of all responses; it is therefore normalized to values between 0 and 1.

Electrophysiology

In one strabismic animal we determined quantitative orientation–direction tuning curves for 11 single units, recorded with glass-insulated tungsten microelectrodes and discriminated by their spike shapes (Brainware, Oxford, UK). All of these cells were dominated by the previously deprived eye. Responses to drifting gratings (optimum spatial and temporal frequency) of 16 different directions were averaged over five trials of 1.5 s duration. Smooth tuning curves were fitted to the data points on the basis of Fourier analysis²⁷, and preferred orientation and half-width of tuning at half-height were determined from these curves.

Received 9 April 2001; accepted 9 January 2002.

1. 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).
2. Guillery, R. W. In *The Making of the Nervous System* (eds Parnevelas, J. G., Stern, C. J. & Sterling, R. V.) 356–379 (Oxford University Press, Oxford, 1988).
3. Mitchell, D. E. & Timney, B. in *Handbook of Physiology Section I (The Nervous System) Vol. 3 Part 1 (Sensory Processes)* (ed. Darian-Smith, I.) 507–555 (American Physiological Society, Bethesda, 1984).
4. Mitchell, D. E., Cynader, M. & Movshon, J. A. Recovery from the effects of monocular deprivation in kittens. *J. Comp. Neurol.* **176**, 53–64 (1977).
5. Mitchell, D. E. The extent of visual recovery from early monocular or binocular visual deprivation in kittens. *J. Physiol. (Lond.)* **395**, 639–660 (1988).
6. Giffin, F. & Mitchell, D. E. The rate of recovery of vision after early monocular deprivation in kittens. *J. Physiol. (Lond.)* **274**, 511–553 (1978).
7. Mitchell, D. E. & Gingras, G. Visual recovery after monocular deprivation is driven by absolute rather than relative visually-evoked activity levels. *Curr. Biol.* **8**, 1179–1182 (1998).
8. Hubel, D. H. & Wiesel, T. N. Binocular interaction in striate cortex of kittens reared with artificial squint. *J. Neurophysiol.* **28**, 1041–1059 (1965).
9. Crair, M. C., Ruthazer, E. S., Gillespie, D. C. & Stryker, M. P. Relationship between the ocular dominance and orientation maps in visual cortex of monocularly deprived cats. *Neuron* **2**, 307–318 (1997).
10. Sengpiel, F., Blakemore, C., Kind, P. C. & Harrad, R. Interocular suppression in the visual cortex of strabismic cats. *J. Neurosci.* **14**, 6855–6871 (1994).
11. Kiorpes, L., Kiper, D. C., O'Keefe, L. P., Cavanaugh, J. R. & Movshon, J. A. Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *J. Neurosci.* **18**, 6411–6424 (1998).

12. Murphy, K. M. & Mitchell, D. E. Bilateral amblyopia following a short period of reverse occlusion in kittens. *Nature* **323**, 536–538 (1986).
13. Blakemore, C. & Van Sluyters, R. C. Reversal of the physiological effects of monocular deprivation in the kitten: further evidence for a sensitive period. *J. Physiol. (Lond.)* **237**, 195–216 (1974).
14. 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).
15. Malach, R. & Van Sluyters, R. C. Strabismus does not prevent recovery from monocular deprivation: a challenge for simple Hebbian models of synaptic modification. *Vis. Neurosci.* **3**, 267–273 (1989).
16. Kirkwood, A., Lee, H.-K. & Bear, M. F. Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex by age and experience. *Nature* **375**, 328–331 (1995).
17. Blakemore, C., Vital-Durand, F. & Garey, L. J. Recovery from monocular deprivation in the monkey. I. Recovery of physiological effects in the visual cortex. *Proc. R. Soc. Lond. B* **213**, 399–423 (1981).
18. Blake, R., Crawford, M. L. & Hirsch, H. V. Consequences of alternating monocular deprivation on eye alignment and convergence in cats. *Invest. Ophthalmol.* **13**, 121–126 (1974).
19. Movshon, J. A. Reversal of the behavioural effects of monocular deprivation in the kitten. *J. Physiol. (Lond.)* **261**, 175–187 (1976).
20. Quick, M. W., Tigges, M., Gammon, J. A. & Boothe, R. G. Early abnormal visual experience induces strabismus in infant monkeys. *Invest. Ophthalmol. Vis. Sci.* **30**, 1012–1017 (1989).
21. 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).
22. 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).
23. 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).
24. Kind, P. C. Cortical plasticity: is it time for a change? *Curr. Biol.* **9**, R640–R643 (1999).
25. Bonhoeffer, T. & Grinvald, A. in *Brain Mapping: The Methods* (eds Toga, A. W. & Mazziotta, J. C.) 55–97 (Academic, London, 1996).
26. Bonhoeffer, T., Kim, D. S., Maloney, D., Shoham, D. & Grinvald, A. Optical imaging of the layout of functional domains in area 17 and across the area 17/18 border in cat visual cortex. *Eur. J. Neurosci.* **7**, 1973–1988 (1995).
27. Wörgötter, F. & Eysel, U. T. Quantitative determination of orientational and directional components in the response of visual cortical cells to moving stimuli. *Biol. Cybern.* **57**, 349–355 (1987).

Acknowledgements

We thank M. Bear and H. Shouval for their helpful discussions, and I. Kehrner and M. Jones for technical assistance. This work was supported by the Wellcome Trust (P.C.K.), the Medical Research Council (C.B., F.S., B.A.), Max-Planck-Gesellschaft (T.B., F.S.), the Canadian Institutes of Health Research (D.E.M.) and the Oxford McDonnell Centre for Cognitive Neuroscience (C.B., B.A.).

Competing interests statement

The authors declare that they have no competing financial interests.

Correspondence and requests for materials should be addressed to P.C.K. (e-mail: pkind@ed.ac.uk).

Spike-timing-dependent synaptic modification induced by natural spike trains

Robert C. Froemke & Yang Dan

Division of Neurobiology, Department of Molecular and Cell Biology, University of California, Berkeley, California 94720, USA

The strength of the connection between two neurons can be modified by activity, in a way that depends on the timing of neuronal firing on either side of the synapse^{1–10}. This spike-timing-dependent plasticity (STDP) has been studied by systematically varying the intervals between pre- and postsynaptic spikes. Here we studied how STDP operates in the context of more natural spike trains. We found that in visual cortical slices the contribution of each pre-/postsynaptic spike pair to synaptic modification depends not only on the interval between the pair, but also on the timing of preceding spikes. The efficacy of each spike in synaptic modification was suppressed by the preceding spike in the same neuron, occurring within several tens of