

Theory meets experiment: correlated neural activity helps determine ocular dominance column periodicity

Geoffrey J. Goodhill and Siegrid Löwel

The development of ocular dominance columns in primary visual cortex has attracted much interest from both experimentalists and theoreticians. One key parameter of these columns is their periodicity – it is thus important to understand how this is determined. Novel experimental work demonstrates that the periodicity is influenced by the temporal patterning of afferent activity, as predicted by recent theoretical work.

Trends Neurosci. (1995) 18, 437–439

THE VISUAL CORTEX of the mammalian brain is one of the most prominent structures that has been investigated in the endeavour to understand activity-dependent cortical development. In particular, one of its functional subdivisions, namely the segregated geniculocortical projections of the left and right eye in primary visual cortex called 'ocular dominance (OD) columns', has served as a model system for activity-dependent cortical development. Early in development, these afferent projections overlap in cortical layer IV, and neurones can be driven by inputs from either eye. By the adult state, however (for example, in cats and Old World monkeys), a process of segregation has occurred so that inputs from the two eyes are concentrated in distinct, interdigitated domains, and many cells become dominated by input from one eye. It has been shown experimentally that this segregation is driven by activity-dependent competition between the afferents of the two eyes, whereby the correlations in neural activity convey the information that is necessary for the axons to segregate^{1–3}. This phenomenon has attracted considerable interest from mathematical modellers. There is a large body of data that is consistent with the idea that the changes in synaptic strength that underlie the formation of OD columns obey a Hebbian learning rule⁴. Many theoretical models have been proposed, each based on slightly different mathematical instantiations of the Hebb rule (for a recent review, see Ref. 5).

One key parameter of OD columns is their periodicity (sum of the widths of right- and left-eye columns). What determines this periodicity? Is it an intrinsic factor, or one that is influenced by visual experience? In the paradigm of monocular deprivation, where one eye is kept closed during the critical period for the formation of OD columns (and thus neuronal activity in that eye is reduced), projections from the closed eye occupy much less than their normal share of territory in cortical layer IV, while those of the open eye expand^{6–8}. Although the relative widths of the columns can be changed by such manipulations, no change in overall column periodicity was reported as a result of any of the various rearing conditions that were investigated.

Input activity affects column periodicity

Very recently, studies using the well-known paradigm of raising kittens with artificially induced diver-

gent strabismus have given a new insight. In contrast to normal cats, in strabismic the optical axes of the two eyes are not aligned, and the images on the two retinæ cannot be brought into register. Whereas the amount of activity that reaches the cortex via the geniculocortical afferents should be similar for both normal and strabismic animals, for the latter, the responses that are mediated by anatomically corresponding retinal loci in the two eyes are much less correlated than normal. Strabismic cats thus provide a model system for investigating the effects of input correlations on cortical development. The well-known result in this case is that a much lower degree of cortical binocularity than normal develops: neurones become responsive exclusively to stimulation of either the left or the right eye⁹, and the segregation of the geniculocortical afferents from the two eyes in cortical layer IV is accentuated¹⁰. However, what has only just become apparent, from visualizing the complete pattern of columns across the rugose surface of the cortex, is that raising kittens with a surgically induced divergent squint angle also causes a change in the spacing of adjacent OD columns in the primary visual cortex: the spacing gets wider^{11,12} (Fig. 1). In this study, OD columns were visualized by transneuronal labelling of the afferents from the left or right eye with intraocular injections of [³H]proline or [¹⁴C]2-deoxyglucose (2-DG)-autoradiography after monocular visual stimulation in awake animals. In the strabismic cats, spatial-frequency analysis of the OD patterns on the respective autoradiographs indicated mean periodicities of 1100–1300 μm . These values were consistently larger than in normal animals in which distances of 800–1000 μm are observed^{10,13} (for review, see Ref. 14). These results indicate that in area 17, reduced correlation of activity between the eyes alters the periodicity of OD columns. Therefore, not only the segregation of afferents into distinct columns but also their overall layout is influenced by visual experience, and in particular by the temporal patterning of neural activity. Thus, for the first time, there is evidence that epigenetic factors play a role in determining column periodicity in the mammalian visual cortex.

Theoretical issues

Before OD-column periodicity in theoretical accounts can be addressed, it is important to understand how the

Geoffrey J. Goodhill is at The Salk Institute for Biological Studies, PO Box 85800, San Diego, CA 92186-5800, USA, and Siegrid Löwel is at the Max-Planck-Institut für Hirnforschung, Deutschordenstrasse 46, D-60528 Frankfurt, Germany.

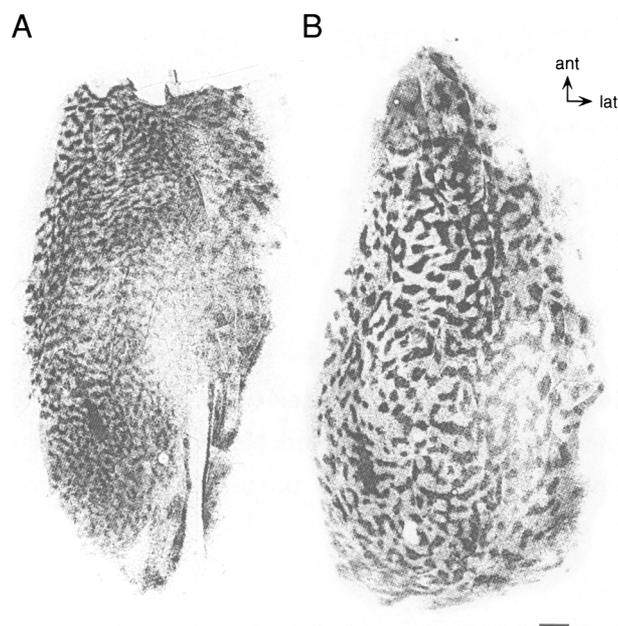


Fig. 1. The effect of strabismus on the pattern of ocular dominance (OD) columns in the primary visual cortex (area 17) of cats. Photographic reconstruction of the [^3H]proline-labelled OD columns in layer IV ipsilateral to the injected eye in a normally raised (A) and a strabismic (B) cat. Note that the spacing of adjacent OD columns is wider in the strabismic compared with the normal cat. In addition, note the sharp delineation of labelled (dark grey) and unlabelled (light grey) territories that is more pronounced in the strabismic animal. In both animals, the optic disk representations appear in the posterior third of area 17 as oval and solidly labelled regions. Abbreviations: ant, anterior; lat, lateral. Scale bar, 2 mm. Modified, with permission, from Ref. 12.

issue of correlations in activity between the eyes has been treated. A popular informal explanation for why cortical cells become monocular during development was proposed by Stent¹⁵. It is phrased in terms of the distinction between normal and strabismic development. For normal development, the explanation holds that inputs in the two eyes are synchronous and, thus, on the basis of a simple Hebbian learning rule, a cell remains binocular. In the strabismic case, inputs are held to be asynchronous, and therefore a cell becomes monocular (assuming that the strength of inputs that are not successful in exciting the cell is decreased steadily). Although this idea has played an important role in furthering discussion of the influence of activity in cortical development, it has two weaknesses as an explanation for the formation of OD columns. First, it fails to explain why there should be any monocular cells in the normal case. Second, synchronous and asynchronous mean 'occurring at the same time' and 'occurring at different times', respectively. Translated into the more precise language of correlations, these mean 'perfectly correlated' and 'perfectly anticorrelated', respectively. Neither of these ever normally hold in reality. Before eye opening, or for perfect strabismus, between-eye correlations are approximately zero. However, in all animals with stereoscopic vision, increasingly strong positive correlations will be present between the activities of corresponding regions in the two retinæ following eye opening.

A variety of different computational mechanisms has been put forward to model the formation of OD columns (for example, Refs 16–25). For some models, results have only been presented for negative between-eye correlations, or the 'prenatal' case of zero correlation. What determines column periodicity in theoretical

models? The most important parameter in many models is the width of the lateral connectivity that is assumed to exist in the cortex: wider interactions lead to a greater column periodicity (analysed in Ref. 20; see also Refs 16 and 18). Generally, these interactions are taken to be fixed (but see Refs 26 and 27). The effect of varying the degree of positive between-eye correlation has been investigated systematically for two models that address both the formation of retinotopy and ocular dominance^{21,24}. For these models, it was found that correlations also had an effect on column periodicity: stronger correlations lead to a smaller column spacing (Fig. 2). It was suggested that the simplest way of testing this result experimentally would be to reduce normal between-eye correlations by raising animals with artificially induced strabismus, and that this should lead to more widely spaced columns²⁴. At the same time as the prediction was made, the above mentioned experiments were performed, and their result was just as predicted by the model.

A qualitative explanation in terms of correlations, which is related to more general arguments regarding the formation of OD columns^{28,29}, can be given as follows. Assume that nearby cortical cells are connected by excitatory lateral connections (as specified in most models). Then these cells will prefer to represent inputs that tend to fire together, that is, are highly correlated. After eye opening, this will be true for both nearby points within an eye, and corresponding points in both eyes. Assuming also that each cortical cell has to make a strict choice as to whether to receive afferent connections from the right or left eye, there will be competing tendencies for nearby cortical cells to represent nearby points in the same eye, and corresponding points in the two eyes. There is a trade-off: the greater the between-eye correlations, the more rapidly the cortex will alternate in representing the left and right eyes, leading to more narrowly spaced OD columns.

If the strict-choice assumption is not made, there is also the possibility for highly correlated points in the two eyes to be brought together on the same cortical cell. In reality, a combination of the two effects appears to occur: there is a higher proportion of binocular cortical cells (concentrated at the column borders) in normal than in strabismic cats^{9,10}.

An alternative way to account for the observed changes in column spacing, owing to strabismus, is to assume that this rearing paradigm changes the extent or shape, or both, of the function that specifies intracortical interactions. More generally, a remaining question is to address the interaction between the influence of input correlations on OD-column periodicity, and that exerted by the extent of local cortical connections. Mathematical analysis of this issue for a more abstract model that has similarities to those in Refs 20 and 21 suggests that column spacing should increase monotonically with both increasing interaction width and decreasing correlation³⁰. To investigate whether this pertains in reality will require new experimental methods to monitor and control the form of lateral interactions.

Monocular deprivation

Occluding one eye clearly affects the strength and spatial extent of both correlations within that eye, and correlations between the two eyes. Thus, a change in column periodicity would also be predicted, in addition to the well-established changes in relative column width^{6–8}.

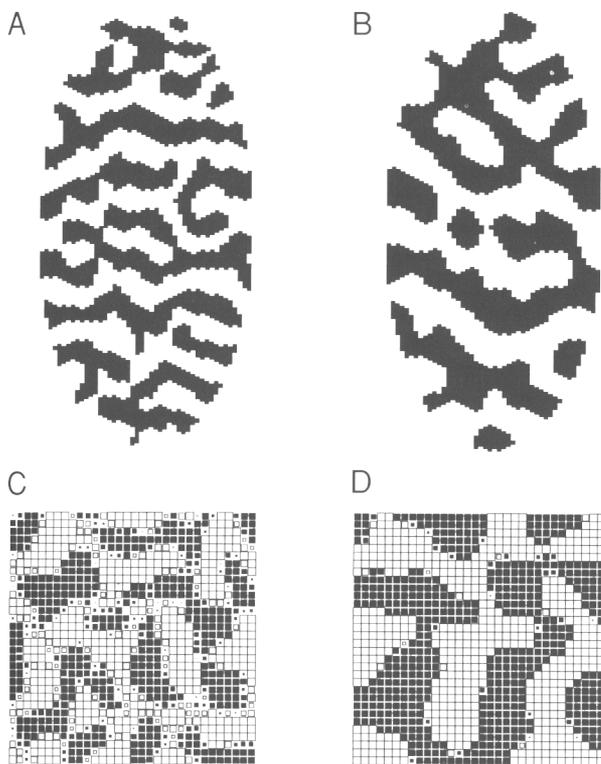


Fig. 2. The effect of varying the strength of between-eye correlations in two models of ocular dominance (OD)-column formation. (A and B) The model from Ref. 21, for two disc-shaped lateral geniculate nucleus (LGN) layers that project to an elliptical cortex. Each square represents a cortical cell. In this model, cortical cells are constrained strongly to be completely monocular in the final state and, thus, squares are coloured simply white or black, depending on which eye dominates. (A) 'Strong' between-eye correlations. (B) 'Weak' between-eye correlations. (C and D) The model from Ref. 24, for two square LGN layers that project to a square cortex. In this model, cortical cells are not constrained as above to be monocular in the final state. The colour of a square represents which eye dominates, and the size of the square represents the degree of dominance so that full-size squares are completely monocular. (C) Strong between-eye correlations (normal case). (D) Zero between-eye correlations (strabismic case). The model reproduces the standard experimental result that fewer binocular cells are found in the strabismic case than in the normal case^{9,10}. Modified, with permission, from Ref. 24.

Preliminary data suggest that this might indeed occur: the sum of the left plus the right eye-column widths showed an overall increase compared with normal cats, despite the relative narrowing of the deprived eye columns³¹ (but see Ref. 32). Since several of the correlation parameters are changed in monocular deprivation, rather than just one as in the strabismic case, it is difficult to extend the qualitative arguments regarding column periodicity presented above to this case. However, this area is ready for investigation in more formal models.

Concluding remarks

The periodicity of OD columns is not completely specified genetically but is susceptible to the influence of the environment – in particular to the temporal patterning of afferent activity. These new experimental and theoretical results provide fresh impetus for increasing collaboration in this domain between experimentalists and theoreticians. One additional prediction that follows is that when the optic nerves of kittens are artificially stimulated asynchronously³³, OD columns that are wider than normal should result. The influence of input correlations on column periodicity might also be relevant to theories of the func-

tional significance of OD columns³⁴, and might also generalize to other columnar systems in the cortex. Furthermore, this work is relevant to the continuing debate over the relative importance of genetic versus epigenetic mechanisms for functional segregation in the cortex^{35–37}.

Note added in proof

Very recent data from the monkey supports the above conclusions. Roe and co-workers have found that rhesus monkeys that are raised with anisometropic amblyopia have more widely spaced OD columns in V1 than normal monkeys³⁸. Since it would be expected that these amblyopic animals would have weaker between-eye correlations than normal animals, this experimental result lends further support to our theoretical arguments.

Selected references

- Constantine-Paton, M., Cline, H.T. and Debski, E. (1990) *Annu. Rev. Neurosci.* 13, 129–154
- Stryker, M.P. (1991) in *Development of the Visual System* (Lam, D.M.-K. and Shatz, C.J., eds), pp. 267–287, MIT Press
- Goodman, C.S. and Shatz, C.J. (1993) *Cell* 72, 77–98
- Hebb, D.O. (1949) *The Organization of Behaviour*, Wiley
- Erwin, E., Obermayer, K. and Schulten, K. (1995) *Neural Comput.* 7, 425–468
- Wiesel, T.N. and Hubel, D.H. (1965) *J. Neurophysiol.* 26, 1003–1017
- Hubel, D.H., Wiesel, T.N. and LeVay, S. (1977) *Philos. Trans. R. Soc. London Ser. B* 278, 377–409
- Shatz, C.J. and Stryker, M.P. (1978) *J. Physiol.* 281, 267–283
- Hubel, D.H. and Wiesel, T.N. (1965) *J. Neurophysiol.* 28, 1041–1059
- Shatz, C.J., Lindström, S. and Wiesel, T.N. (1977) *Brain Res.* 131, 103–116
- Löwel, S. and Singer, W. (1993) *Soc. Neurosci. Abstr.* 19, 867
- Löwel, S. (1994) *J. Neurosci.* 14, 7451–7468
- LeVay, S., Stryker, M.P. and Shatz, C.J. (1978) *J. Comp. Neurol.* 179, 223–244
- LeVay, S. and Nelson, S.B. (1991) in *The Neural Basis of Visual Function* (Leventhal, A.G., ed.), pp. 236–315, Macmillan
- Stent, G.S. (1973) *Proc. Natl Acad. Sci. USA* 70, 997–1001
- von der Malsburg, C. and Willshaw, D.J. (1976) *Exp. Brain Res.* (Suppl. 1), 463–469
- von der Malsburg, C. (1979) *Biol. Cybern.* 32, 49–62
- Swindale, N.V. (1980) *Proc. R. Soc. London Ser. B* 208, 243–264
- Fraser, S.E. (1985) in *Molecular Bases of Neural Development* (Edelman, G.M., Gall, W.E. and Cowan, W.M., eds), pp. 481–507, Wiley
- Miller, K.D., Keller, J.B. and Stryker, M.P. (1989) *Science* 245, 605–615
- Goodhill, G.J. and Willshaw, D.J. (1990) *Network* 1, 41–59
- Cowan, J.D. and Friedman, A.E. (1991) in *Advances in Neural Information Processing Systems* (Touretzky, D.S., ed.), Vol. III, pp. 3–10, Morgan Kaufmann
- Obermayer, K., Blasdel, G.G. and Schulten, K. (1992) *Phys. Rev. A* 45, 7568–7589
- Goodhill, G.J. (1993) *Biol. Cybern.* 69, 109–118
- Berns, G.S., Dayan, P.S. and Sejnowski, T.J. (1993) *Proc. Natl Acad. Sci. USA* 90, 8277–8281
- Montague, P.R., Gally, J.A. and Edelman, G.M. (1991) *Cereb. Cortex* 1, 199–220
- Sirosh, J. and Miikkulainen, R. (1994) *Biol. Cybern.* 71, 65–78
- LeVay, S., Hubel, D.H. and Wiesel, T.N. (1975) *J. Comp. Neurol.* 159, 559–576
- Constantine-Paton, M. (1983) *Trends Neurosci.* 6, 32–36
- Dayan, P.S. (1993) *Neural Comput.* 5, 392–401
- Löwel, S. and Schmidt, K. (1994) in *Sensory Transduction: Proceedings of the 22nd Göttingen Neurobiology Conference* (Elsner, N. and Breer, H., eds), p. 501, Thieme
- Murphy, K.M., Van Sluyters, R.C. and Jones, D.G. (1989) *Invest. Ophthalmol. Visual Sci.* (Suppl.) 30, 30
- Stryker, M.P. and Strickland, S.L. (1984) *Invest. Ophthalmol. Visual Sci.* (Suppl.) 25, 278
- Purves, D., Riddle, D.R. and LaMantia, A.-S. (1992) *Trends Neurosci.* 15, 362–368
- Rakic, P. (1988) *Science* 241, 170–176
- O'Leary, D.D.M. (1989) *Trends Neurosci.* 12, 400–406
- Shatz, C.J. (1992) *Science* 258, 237–238
- Roe, A.W. et al. *Soc. Neurosci. Abstr.* (in press)

Acknowledgements

The authors thank Peter Dayan, Fred Wolf, Kerstin Schmidt, Ken Miller and John Maunsell for inspiring discussions and helpful comments on the manuscript, and Wolf Singer and David Willshaw for their constant support.