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EXOGENOUS SUPPLY OF NERVE GROWTH FACTOR PREVENTS THE EFFECTS OF STRABISMUS IN THE RAT

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Abstract—It has recently been reported that exogenous supply of nerve growth factor prevents the effects of monocular deprivation both in rats and in cats. Here we have extended these experiments to the case of strabismus. Repeated intraventricular injections of nerve growth factor were performed in rats made surgically strabismic early in the critical period. At the end of the critical period the ocular dominance distribution of visual cortical neurons was assessed in strabismic untreated, strabismic nerve growth factor-treated and strabismic Cytochrome C-treated (control) rats by means of extracellular recordings. We found that in rats surgical strabismus causes a consistent loss of binocular neurons. By contrast the treatment with nerve growth factor maintains the normal ocular dominance distribution of neurons in the primary visual cortex.

We conclude that nerve growth factor exogenously supplied prevents the effects induced by surgical strabismus in rats and suggest that nerve growth factor has a role in visual cortical plasticity.

The importance of surgically induced squint experiments in animals stems from the likely relevance of these experiments to human strabismus, to help understand its etiology and possibly suggest therapeutic aids. In mammals with binocular vision a misalignment of the optical axes of the eyes (usually induced by severing a tendinous insertion of an extra ocular muscle) during the critical period causes dramatic changes in cortical physiology. Hubel and Wiesel[13] were the first to report that in neonatal kittens reared for several months with a surgical strabismus the proportion of binocular cells falls from a normal level of around 80% to about 20%. These data have been successively replicated both in kittens[4,12,15,35] and in monkeys.[1,5]

Since the experiments of Hubel and Wiesel the interpretation of the effects of strabismus has been based on the lack of congruence between the two visual inputs. Synchronous activity in the two optic nerves is necessary to maintain binocularity.[34] With an artificial squint, corresponding retinal points see different parts of the visual scene and therefore cortical neurons that would be activated more or less simultaneously by inputs from the two eyes are activated asynchronously. In kittens with an esotropic strabismus the latencies of visual cortical responses to visual stimulation or electrical stimulation of the two optic nerves are different.[4,9,33]

The mechanism underlying the modifiability of visual cortical connections during the critical period are as yet unclear, although several theories have been proposed (for a recent review see Ref. 27). Suppression of the input from one or the other eye may occur at the level of geniculocortical interactions or within the cortical net, for example at the level of inhibitory circuitry.[24] Whatever the site of action, the final result is that many visual cortical synapses are depressed or lost leading to a reduction of binocularly innervated neurons.

The experiments to be reported here originate from previous observations from our laboratory on monocularly deprived rats and cats[2,6,7,22] (monocular deprivation is a useful animal model to study activity-dependent changes in connectivity of the visual cortex). We have shown that exogenous supply of nerve growth factor (NGF) (a well characterized trophic factor at both PNS and CNS levels[20]) prevents the effects of monocular deprivation. It is well known that the visual cortex contains NGF,[21,32] and that its expression is higher during the early stages of postnatal development, later decreasing to adult levels.[10,18] The hypothesis has been raised that during the critical period the strengthening and stabilization of geniculocortical synapses could depend on the physiological level of a target-derived neurotrophic factor, namely NGF, whose production and/or uptake would be activity dependent.

The question we addressed in this paper was whether exogenous supply of NGF could prevent alterations in the visual cortical physiology of rats made surgically strabismic?

EXPERIMENTAL PROCEDURES

Animals and injection procedure

Eighteen Long–Evans (Charles River, Italy) hooded rats were used in this study. Five rats were normal. In 13 rats an esotropic strabismus was surgically induced by cutting the tendinous insertion of the lateral rectus muscle at the scleral

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Abbreviation: BDNF, brain derived neurotrophic factor; NGF, nerve growth factor; P, postnatal day.

insertion, 2 mm from the limbus. In all rats the tenotomy was performed immediately after eye opening (postnatal day 14, P14). The degree of strabismus was of the order of 10–14 prism-dioptres, as measured by pupil reflexes.

Five of the strabismic rats were left untreated; five of them were treated with intraventricular injections of β-NGF, and three rats (control rats) were treated with a solution of Cytochrome C, a molecule with the same isoelectric point as NGF, normally used as a control for NGF.[11] β-NGF (Fidia Research Laboratories, Abano Terme, Italy) and Cytochrome C were prepared in a saline solution at a concentration of 1–1.6 μg/μl. The NGF or Cytochrome C treatment was started at P14 and was repeated every two days for a period of one month (P45). In the rat this corresponds to the whole length of the critical period.[30,31] Injections were made into the lateral ventricle by means of a microsyringe connected to a canula (gauge 27) inserted 1 mm laterally to the median line and 1 mm behind bregma; the volume injected was 2 μl. To check that injections actually reached the lateral ventricle, Pontamine Sky Blue was injected at the same coordinates and was invariably found in the ventricle. Surgery and injections were performed under brief general anaesthesia induced by inhalation of ethane. To control for possible structural alterations caused by repeated injections histology was performed in treated rats using classical staining techniques (Cresyl Violet).

Extracellular unit recordings

At the end of the critical period (P45) the effects of the strabismus in treated and untreated rats were assessed by means of extracellular recordings of single neurons at the level of the binocular region of the primary visual cortex (binocular area 17 or area OC1B). Each rat was anaesthetized with urethane by means of intraperitoneal injections (7 ml/kg, 20% solution, Sigma) and mounted into a sterotaxic apparatus. The angle of strabismus was eliminated by rotating and fixing both eyes by means of metal rings surrounding the bulb and attached to the stereotaxic apparatus. Pupils were left undilated since it proved extremely difficult to provide artificial pupils that would not cause vignetting, as observed by Lennie and Perry.[19] With dilated pupils and without artificial pupils, the quality of the eye optics would be extremely poor and, in addition, glare would probably occur. Given the impossibility to backproject the optic disc with natural pupils (0.5–1 mm in diameter with the luminance we used) at the beginning of each experimental session pupil reflexes and superimposition of binocular receptive fields were assessed to control for correct alignment of the optic axes. At the end of each experimental session the eye alignment and the position of receptive fields within the visual field were controlled by projecting the optic disc of both eyes on a tangential screen (pupils were previously dilated by eye drops of 1% omatropina, Allergan, Italy). Animals were electrocardiographically monitored and their body temperature was maintained around 38°C throughout the experiment. A micropipette filled with NaCl (3 M) was inserted into the binocular portion of the primary visual cortex. Recordings were carried out in the cortex contralateral to the strabismic eye. In three strabismic untreated and three strabismic NGF-treated rats of our sample, recordings were also performed in the cortex ipsilateral to the strabismic eye. To avoid sample biases due to the organization of ocular dominance in area OC1B, the electrode penetrations were angled 55–60° with respect to the cortical surface and at least two well-spaced penetrations were performed for each hemisphere in each rat. Cells were recorded throughout all primary visual cortical layers from a depth of 100 to 1200 μm below the cortical surface. The depth within the cortex was directly read off the micromanipulator. No gross changes in ocular dominance were found with cortical depth.

Visual stimuli were either light bars projected on a reflecting screen or gratings generated by computer on a display (HP 1300A). Both the screen and the display distance from the rat eyes were 20 cm. For each cell the location of the receptive field in visual space, the ocular dominance and the optimal stimulus orientation were evaluated. Only penetrations with all neuronal receptive fields within 30° from the vertical meridian and in the upper visual field (binocular visual field)[14] were considered. The mean eccentricity of receptive fields in our cell sample was 18° from the vertical meridian, without gross differences between normal (mean eccentricity = 17°), strabismic (mean eccentricity = 18°) and strabismic NGF-treated rats (mean eccentricity = 19°). Ocular dominance was assessed with bars of optimal orientation, following the criteria of Hubel and Wiesel: neurons in ocular dominance class 1 were driven only by the contralateral eye; neurons in ocular dominance classes 2 and 3 were binocular and preferentially driven by the contralateral eye; neurons in class 4 were equally driven by the two eyes; neurons in classes 5 and 6 were binocular and preferentially driven by the ipsilateral eye; neurons in class 7 were driven only by the ipsilateral eye. Neurons were classified as orientational if (1) the cell response was maximal for a given orientation (preferred orientation) and (2) it was indistinguishable from the spontaneous activity for stimuli orthogonal to the preferred orientation. Neurons were classified as biased if the cells responded to all tested orientations (vertical, horizontal, $\pm$45°) but with a clear preference for one of them and non-orientational if the responses for the different orientations tested were indistinguishable. Cells unresponsive to visual stimulation were considered as non-classifiable. A blind procedure was adopted in strabismic rats treated either with NGF or Cytochrome C.

In some cells of normal, strabismic and strabismic NGF-treated rats response curves as a function of the stimulus spatial frequency were determined. Eye refraction was optimized by recording visual evoked potentials in response to alternating gratings of various spatial frequencies. Optic lenses of different power were positioned in front of the stimulated eye. The lens that imparted highest visual acuity was considered optimal. Sinusoidal gratings of 40–50% contrast, alternating in contrast at a temporal frequency of 0.5–1 Hz, were generated on a display positioned on the cell's receptive field. The responses (spikes/s) of single cells were recorded and fed into a computer for on-line averaging and Fourier analysis. The cell response evoked by the stimulus could either be at the same temporal frequency as the stimulus (first harmonic) or at twice that frequency (second harmonic) according to the cell's receptive field type. For each spatial frequency the response amplitude was taken as the amplitude of the main harmonic in the Fourier spectrum and the ratio between the amplitude of the response (main harmonic) and the amplitude of the noise was assessed. The noise was estimated by measuring the response when the stimulus was a blank field.

Statistical analysis

The distributions in ocular dominance classes observed in normal, strabismic and strabismic NGF-treated rats were statistically evaluated by chi-square test (four degrees of freedom). The test of significance for binomial distribution[8] was used to evaluate the differences between percentages for orientational selective cells.

RESULTS

The normal ocular dominance distribution for single neurons recorded in the binocular portion of the adult rat primary visual cortex contralateral to the stimulated eye is illustrated in Fig. 1A. The proportion of binocular cells is 77%. The bias in favour of the contralateral eye (classes 1 and 2–3) is evident and reflects the predominance of crossed

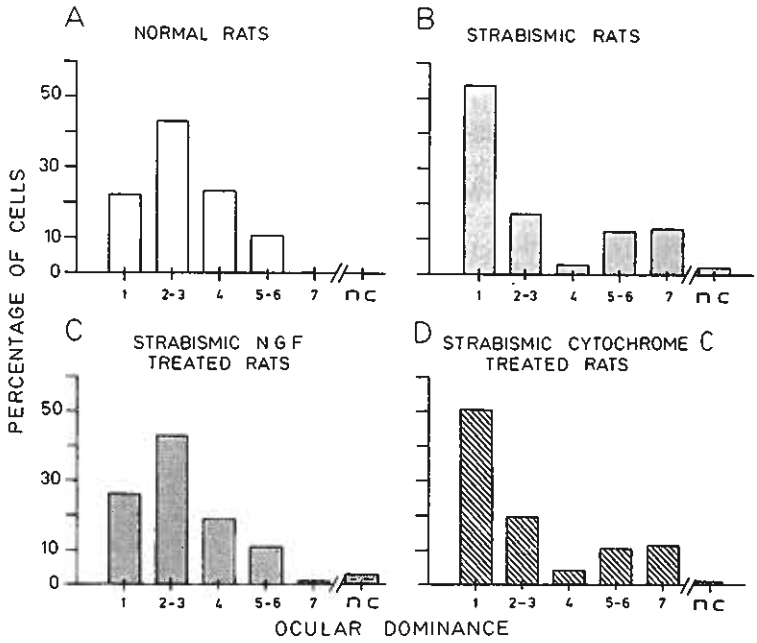

Fig. 1. Ocular dominance distribution of visual cortical neurons recorded in the binocular portion of area 17 (area OC1B) in normal rats (A, 141 cells), strabismic rats (B, 145 cells), strabismic NGF-treated rats (C, 137 cells) and in strabismic Cytochrome C-treated rats (D, 93 cells). In strabismic rats the visual neurons were recorded in the cortex contralateral to the squinting eye. Neurons in ocular class 1 were monocular and driven only by the stimulation of the contralateral eye; neurons of classes 2 and 3 were binocular and preferentially driven by the contralateral eye; neurons of class 4 were binocular and equally driven by the two eyes; neurons of classes 5 and 6 were binocular and preferentially driven by the ipsilateral eye and neurons of class 7 were monocular and driven only by the ipsilateral eye. The category labelled nc contains those neurons that could not be classified using visual stimuli. Differences in ocular dominance distributions assessed in different groups of rats were evaluated by means of chi-square test: strabismic untreated rats vs normal rats, $P < 0.01$; strabismic untreated vs strabismic cytochrome C-treated rats, $P \geqslant 0.05$; normal vs strabismic NGF-treated rats, $P \geqslant 0.05$.

optic nerve fibres.[26] Only 11% of the cells in our sample are dominated by the ipsilateral eye.

Surgical strabismus causes clear changes in the ocular dominance distribution (Fig. 1B). Binocularity is strongly affected, with the proportion of binocular cells decreasing from 77% to 30% of the total.

By contrast the ocular dominance distribution in NGF-treated rats (Fig. 1C) is very similar to normal: 67% of the cells are dominated by the contralateral strabismic eye and 73% are binocular (normal vs strabismic NGF-treated rats, $P > 0.5$).

To control for some non-specific effects of NGF treatment due, for example, to animal handling or anaesthesia, we also recorded three strabismic rats treated with Cytochrome C. The treatment with Cytochrome C was completely ineffective in preventing the effects caused by strabismus (Fig. 1D). The ocular dominance distribution of strabismic Cytochrome C-treated rats is indistinguishable from that of untreated strabismic rats ($P > 0.5$).

In six strabismic rats of our sample we also recorded from the primary visual cortex ipsilateral to the deviated eye (Fig. 2). In three untreated strabismic rats we found a reduction of binocularity similar to that observed in the cortex contralateral to the deviated eye (Fig. 2A). The treatment with NGF (three rats) completely prevented this loss of binocularity (Fig. 2B).

Thus, an exogenous supply of NGF prevents the reduction of binocular neurons induced by the strabismus in both cortices, contralateral and ipsilateral to the squinting eye.

An important point was to assess whether the treatment with NGF had altered other functional properties of visual cortical cells such as the selectivity for the stimulus orientation and spatial frequency.

The selectivity for the stimulus orientation is reported in Table 1 for the same cells for which the ocular dominance had been assessed. The table shows the proportion of non-oriented cells in the total population; no significant differences were found between normal, strabismic untreated and strabismic NGF-treated rats, indicating that at least this gross measure of orientation selectivity is not affected by both strabismus and NGF treatment.

Spatial frequency selectivity of visual cortical cells was assessed in normal (two animals, recorded cells, $N = 10$) and strabismic NGF-treated rats (two animals, recorded cells, $N = 8$). In our limited sample no gross differences between control and NGF-treated rats were observed.

DISCUSSION

Using an electrophysiological approach we found that, in hooded rats, strabismus surgically induced during the critical period results in a significant loss of binocular neurons of the primary visual cortex.

First of all it is necessary to exclude the possibility that this loss of binocular neurons might be caused by a sampling mistake, namely by cell recording in different parts of the visual cortex in normal vs strabismic animals. This possibility is really unlikely since great care was taken in recording neurons with the receptive field in the same part of the binocular visual field.

As far as the ocular dominance distribution is concerned, the binocular region of the rat visual cortex differs from that of cat[4,12,13,15,35] and monkey[1,5] in that there is clear predominance of the contralateral eye. In surgically strabismic rats, the ocular dominance distribution histogram shows that most cells remain dominated by the contralateral eye.

Ocular dominance in strabismic nerve growth factor-treated rats

In strabismic NGF-treated rats both the binocularity and the distribution of visual neurons in ocular dominance classes is the same as that observed in normal rats; this is true both in the cortex contralateral and ipsilateral to the strabismic eye. This effect cannot be attributed to non-specific effects such as those produced by surgery or anaesthesia. In rats used as a control, treatment with Cytochrome C does not prevent the effects produced by surgical strabismus.

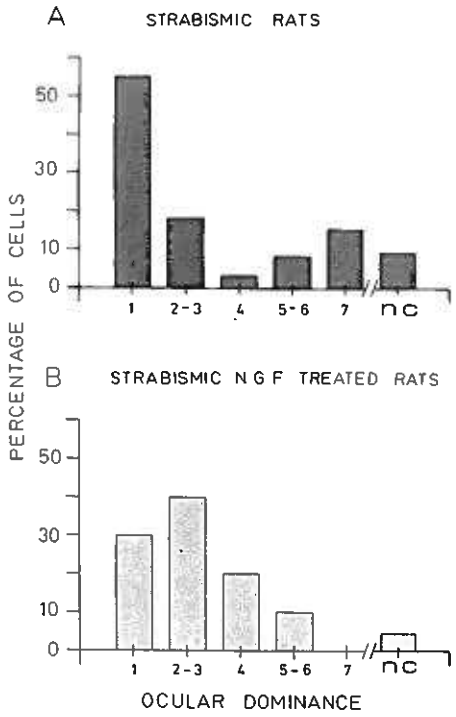

Fig. 2. Ocular dominance distribution for visual cortical neurons recorded in the cortex ipsilateral to the squinting eye in strabismic rats (A, 66 cells) and in strabismic NGF-treated rats (B, 66 cells). Other conventions as in Fig. 1. In the strabismic rats, binocular neurons are reduced, while in the strabismic NGF-treated rats the ocular dominance distribution is similar to normal (normal vs strabismic rats, chi-square test on ocular dominance distribution, $P < 0.01$; normal vs strabismic NGF-treated rats, chi-square test on ocular dominance distribution, $P \gg 0.05$).

Table 1. Neuronal orientation selectivity in normal, strabismic and strabismic nerve growth factor-treated rats

Rat group	Number of rats	Number of cells	Number NO cells	NO percentage (mean ± S.D.)
NOR	5	141	47	33 ± 5
ST	5	145	45	31 ± 3
ST(NGF)	5	137	46	33 ± 7

The visual neurons were classified according to their orientation selectivity. Neurons were classified as non-oriented (NO) if the cell response was of comparable strength on four orientations (vertical, horizontal and ±45°). NOR, normal rats; ST, strabismic rats; ST(NGF), strabismic NGF-treated rats. All differences between groups are not significant (test of significance for binomial distribution,[8] $P \gg 0.05$). In the treated and untreated strabismic rats recordings were carried out in the cortex contralateral to the squinting eye.

Another point to be considered is the possibility that NGF treatment could cause direct or indirect pathological effects in the visual system. The fact that the responses of visual cortical neurons both in terms of orientational and spatial frequency selectivity and spontaneous discharge[6,7] remained relatively normal in NGF-treated rats seems to make this possibility rather unlikely.

The effects observed of exogenous supply of NGF in strabismic rats are not surprising as NGF is a neurotrophic factor physiologically present at the level of CNS (for a review see Ref. 36). In rat neocortex, NGF is expressed in the adult[32] as well as during development.[21] It has recently been reported that the content of NGF in the rat[18] and primate[10] occipital cortex is higher during the first part of postnatal development, later decreasing to adult level.

As far as the NGF receptors are concerned, several papers have described the presence and the distribution of the low affinity form of NGF receptor in many regions of the CNS,[3,25,28,37] the visual system included. The high affinity form of NGF receptor (trk)[16] mediating the biological activity of NGF is also represented at the level of CNS.[17] However, data on the distribution of trk in the visual system are lacking.

At the moment we cannot even be sure that NGF is the neurotrophic factor in question or the only one. NGF is present in the visual cortex but other neurotrophic factors of the NGF family like brain derived neurotrophic factor (BDNF) and neurotrophin-3 are also present.[23] It has been shown that BDNF at high concentration can interact with high affinity NGF receptors and vice versa.[29] The amount of NGF we

have injected is considerable and thus it may well be that it cross-reacts with the receptors of other neurotrophic factors, such as BDNF, mimicking their action.

Nerve growth factor and strabismus

The visual system of mammals is very sensitive during the critical period to manipulations of the visual environment. In particular, binocularity of visual cortical neurons is easily lost if the two visual inputs become imbalanced. The imbalance may consist of alteration of the relative strength of the discharge pattern of one of the two inputs (as in the case of monocular deprivation) or of alteration of temporal simultaneity or correlation of the two inputs (as in the case of natural or artificial strabismus).

Recently we have found that NGF treatment prevents the amblyopic effects of monocular deprivation during the critical period both in rats[2,6,7] and cats.[22] On the basis of these results we have proposed that during development the two monocular inputs compete for the acquisition of a neurotrophic factor whose production, release or uptake are activity dependent. When the inputs from the two eyes are synchronous the response of the cell is likely to be stronger and the release of neurotrophic factor sufficient for strengthening synaptic connections of both visual inputs. When synchronization between the two visual inputs is lost, the production, release or uptake of neurotrophic factor is reduced, competition emerges and as a consequence only the stronger of the two visual inputs is able to maintain or establish its synaptic connections. According to this hypothesis the action of NGF would take place at the level of geniculate afferent–cortical cell connections.

However, reciprocal inhibition between the two eyes has been described and the inhibition exerted by the normal onto the squinting eye is reported in cat to be much stronger than the reciprocal effect.[33] In addition, a pharmacological treatment (bicuculline) blocking inhibitory receptors restores binocular responses in strabismic cats.[24] Thus the hypothesis cannot be excluded that the action of the neurotrophic factor is not, or not only, at the level of geniculocortical connections. It could be primarily within the cortical net at the level of inhibitory interneurons which mediate interocular inhibition.

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REFERENCES

1. Baker F. H., Grigg P. and Von Norden G. K. (1974) Effects of visual deprivation and strabismus on the response of neurons in the visual cortex of the monkey, including studies on the striate and prestriate cortex in normal animals. *Brain Res.* **66,** 185–208.
2. Berardi N., Carmignoto G., Cremisi F., Domenici L., Maffei L., Parisi V. and Pizzorusso T. (1991) NGF prevents the change in ocular dominance distribution induced by monocular deprivation in the rat visual cortex. *J. Physiol.* **434,** 14P.
3. Buck C. R., Martinez H. J., Chao M. S. and Black I. B. (1988) Differential expression of the nerve growth factor receptor gene in multiple brain areas. *Devl Brain Res.* **44,** 259–268.
4. Chino Y. M., Shansky M. S., Jankowski W. L. and Banser F. A. (1983) Effects of rearing kittens with convergent strabismus on development of receptive-field properties in striate cortex neurons. *J. Neurophysiol.* **50,** 265–286.
5. Crawford M. L. J. and Von Norden G. K. (1979) The effects of short-term experimental strabismus on the visual system in *Macaca mulatta*. *Invest. Ophthal. vis. Sci.* **18,** 496–505.
6. Domenici L., Berardi N., Carmignoto G., Vantini G. and Maffei L. (1991) Nerve growth factor (NGF) prevents the amblyopic effects of monocular deprivation. *Proc. natn. Acad. Sci. U.S.A.* **88,** 8811–8815.
7. Domenici L., Berardi N., Carmignoto G., Pizzorusso T., Parisi V. and Maffei L. (1991) Nerve Growth Factor (NGF) prevents the effects of monocular deprivation in the rat. In *The Changing Visual System: Maturation and Aging in The CNS* (eds Bagnoli P. and Hodos W.), Vol. 222, pp. 333–345. Plenum Press, New York.
8. Edwards A. L. (1970) *Experimental Design in Psychological Research*, 3rd ed. H. Watson & Viney, Aylesbury, Bucks.
9. Freeman R. D. and Tsumoto T. (1983) An electrophysiological comparison of convergent and divergent strabismus in the cat: electrical and visual activation of single cortical cells. *J. Neurophysiol.* **49,** 238–253.
10. Hayashi M., Yamashita A. and Shimizu K. (1990) Nerve growth factor in the primate central nervous system: regional distribution and ontogeny. *Neuroscience* **36,** 683–689.
11. Hendry I. A. (1989) *In vivo* administration of Nerve Growth Factor. In *Nerve Growth Factors* (ed. Rush R. A.), IBRO Handbook Series, Vol. 12, pp. 193–229. John Wiley, New York.
12. Holopigian K. and Blake R. (1983) Spatial vision in strabismic cats. *J. Neurophysiol.* **50,** 287–296.
13. Hubel D. H. and Wiesel T. N. (1965) Binocular interaction in striate cortex of kittens reared with artificial squint. *J. Neurophysiol.* **28,** 1041–1059.
14. Hughes A. (1979) A schematic eye for the rat. *Vis. Res.* **19,** 568–588.
15. Kalil R. E., Spear P. D. and Langsetmo A. (1984) Response properties of striate cortex neurons in cats raised with divergent or convergent strabismus. *J. Neurophysiol.* **52,** 514–537.
16. Klein R., Jing S., Venkata Nanduri, O'Rourke E. and Barbacid M. (1991) The trk proto-oncogene encodes a receptor for nerve growth factor. *Cell* **65,** 189–197.
17. Klein R., Parada L. F., Couller F. and Barbacid M. (1989) TrkB a novel tyrosine protein kinase receptor expressed during mouse neural development. *Eur. molec. Biol. Org. J.* **8,** 3701–3709.

18. Large T. H., Bodary S. C., Clegg D. O., Weskamp G., Otten U. and Reichardt L. F. (1986) Nerve growth factor gene expression in the developing rat brain. *Science* **234**, 352–355.
19. Lennie P. and Perry V. H. (1981) Spatial contrast sensitivity of cells in the lateral geniculate nucleus of the rat. *J. Physiol.* **315**, 69–79.
20. Levi-Montalcini R. (1987) The Nerve-Growth Factor 35 years later. *Science* **237**, 1154–1162.
21. Lu B., Buck C. R., Dreyfus C. F. and Black I. B. (1989) Expression of NGF and NGF receptor mRNAs in the developing brain: evidence for local delivery and action of NGF. *Expl. Neurol.* **104**, 191–199.
22. Maffei L., Berardi N., Carmignoto G., Cellerino A., Domenici L., Fiorentini A. and Pizzorusso T. (1992) Role of neurotrophic factors in the plasticity of the mammalian visual system. In *Regeneration and Plasticity in The Visual System: Proceedings of The Retina Research Symposia* (eds Man-Kit Lam D. and Bray G.), Vol. 8. MIT Press (in press).
23. Maisonpierre P. C., Belluscio L., Friedman B., Alderson R. F., Wiegland S. J., Furth M. E., Lindsay R. M. and Yancopoulos G. D. (1990) NT-3, BDNF, and NGF in the developing rat nervous system: parallel as well as reciprocal patterns of expression. *Neuron* **5**, 501–505.
24. Mower G. D., Christen W. G., Burchfiel J. L. and Duffy F. H. (1984) Microiontophoretic bicuculline restores binocular responses to visual cortical neurons in strabismic cats. *Brain Res.* **309**, 168–172.
25. Pioro E. P. and Cuello A. C. (1990) Distribution of nerve growth factor receptor-like immunoreactivity in the adult rat central nervous system. Effect of colchicine and correlation with the cholinergic system—I. Forebrain. *Neuroscience* **34**, 57–87.
26. Polyak P. (1957) *The Vertebrate Visual System.* University of Chicago Press.
27. Rauschecker J. P. (1991) Mechanisms of visual plasticity: Hebb synapses, NMDA receptors and beyond. *Physiol. Rev.* **71**, 587–615.
28. Richardson, P. M., Verge Issa V. M. K. and Riopelle R. J. (1986) Distribution of neuronal receptors for nerve growth factor in the rat. *J. Neurosci.* **6**, 2312–2321.
29. Rodriguez-Tebar A., Dechant G. and Barde Y.-A. (1990) Binding of brain derived neurotrophic factor to the nerve growth factor receptor. *Neuron* **4**, 487–492.
30. Rothblat L. A. and Schwartz M. L. (1979) The effect of monocular deprivation on dendritic spines in visual cortex of young and adult albino rats: evidence for a sensitive period. *Brain Res.* **161**, 156–161.
31. Rothblat L. A., Schwartz M. L. and Kasdan P. M. (1978) Monocular deprivation in the rat: evidence for an age-related defect in visual behavior. *Brain Res.* **158**, 456–460.
32. Shelton D. L. and Reichardt L. (1986) Studies on the expression of the B nerve growth factor (NGF) gene in the central nervous system: level and regional distribution of NGF mRNA suggest that NGF functions as a trophic factor for several distinct populations of neurons. *Proc. natn. Acad. Sci. U.S.A.* **83**, 2714–2718.
33. Singer W., Von Grunau M. W. and Rauschecker J. P. (1980) Functional amblyopia in kittens with unilateral exotropia. I. Electrophysiological assessment. *Expl. Brain Res.* **40**, 294–304.
34. Stryker M. P. and Strickland S. L. (1984) Physiological segration of ocular dominance columns depends on the pattern of afferent electrical activity. *Invest. Ophthal. vis. Sci.* (suppl.) **25**, 278.
35. Van Sluyters R. C. and Levitt F. B. (1980) Experimental strabismus in the kitten. *J. Neurophysiol.* **43**, 686–699.
36. Whittemore S. R. and Seiger A. (1987) The expression, localisation and functional significance of B-nerve growth factor in the central nervous system. *Brain Res. Rev.* **12**, 439–464.
37. Yan Q. and Johnson E. M. (1988) An immunohistochemical study of the nerve growth factor receptor in developing rats. *J. Neurosci.* **8**, 3481–3498.

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