Monocular deprivation effects in the rat visual cortex and lateral geniculate nucleus are prevented by nerve growth factor (NGF). I. Visual cortex

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SUMMARY

The effects of monocular deprivation done during the critical period are usually ascribed to competition between the two sets of monocular thalamic afferents taking place at cortical level. We have suggested that loss in competition for the deprived eye is explained by the lack of a neurotrophic factor, produced in the cortex and dependent on electrical activity. To test this hypothesis we have exogenously supplied nerve growth factor (NGF) to rats monocularly deprived (MD) during the critical period, and studied whether monocular deprivation still affected the functional and anatomical organization of the visual cortex. NGF is produced in the rat visual cortex during the critical period, and its expression, at least in the hippocampus, seems to be regulated by electrical activity. Ocular dominance distribution of area 17 neurons, visual acuity, and Parvalbumin immunoreactivity (Parva-LI) were determined in four sets of animals: normal rats, control untreated monocularly deprived rats, deprived rats treated with cytochrome *c* (to control for non-specific aspects of NGF treatment), and deprived rats treated with NGF. Parva-LI is an excellent marker for the effects of monocular deprivation on the functional organization of the rat visual cortex. We found that exogenous supply of NGF completely prevented the shift in ocular dominance distribution of visual cortical neurons, the loss of visual acuity for the deprived eye, and the strong reduction in Parva-LI induced by monocular deprivation in control rats.

1. INTRODUCTION

In many mammals, normal visual input from both eyes is required for the development and maintenance of cortical binocularity throughout the post-natal development period. The pioneering studies of Wiesel & Hubel (e.g. 1963) demonstrated that binocularity of striate cortical neurons is vulnerable. Closing one eye in a young mammal (kitten, monkey, rat or mouse) causes a dramatic shift in the ocular dominance of cortical neurons away from the closed eye (Wiesel & Hubel 1963; Baker *et al.* 1974; Berardi *et al.* 1991; Dräger 1978). Moreover, the visual acuity of the deprived eye is diminished (Boothe *et al.* 1985; Giffin & Mitchell 1978; Domenici *et al.* 1991).

Anatomically, there is the reduction of the territories occupied in the primary visual cortex by the lateral geniculate nucleus (LGN) afferents driven by the deprived eye, and the complementary expansion of those occupied by the inputs from the non-deprived eye (Shatz & Stryker 1978; LeVay *et al.* 1980). In the LGN, there is a shrinkage of LGN projection cells in the deprived laminae, but only in the part corresponding to the representation of the binocular visual field (Guillery & Stelzner 1970).

These functional and anatomical effects are ascribed to competition between the afferents from the two eyes taking place at cortical level (Wiesel & Hubel 1963; Guillery & Stelzner 1970). At the level of cortical neurons, competition is translated in terms of incoming electrical activity. Sufficient activation of postsynaptic neurons as well as correlation between pre- and postsynaptic activity seem to be essential prerequisites for synapse strengthening (see Shatz (1990) for a review). Strengthening of synaptic contacts could be based on the acquisition of a trophic factor from the target cell (Purves 1985, 1988).

Following this hypothesis, activity in LGN fibres driven by the deprived eye could be insufficient or inappropriate for the production or the uptake of the target-derived neurotrophic factor.

Accordingly we have supplied nerve growth factor (NGF; Levi-Montalcini 1987) exogenously to monocularly deprived rats, and studied whether monocular deprivation still produced its effects. We have found that supply of NGF prevented the effects of monocular deprivation on visual acuity and ocular dominance distribution (Domenici *et al.* 1991; Maffei *et al.* 1993*a*, *b*). The choice of NGF was prompted by the fact that it is present in the visual cortex and its expression, at

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least in the hippocampus, is electrical-activity dependent (Zafra *et al.* 1990; Ernfors *et al.* 1991; Lu *et al.* 1991).

Here we report the functional and anatomical results obtained for the visual cortex. The possibility of exploiting the classical anatomical correlate of monocular deprivation at cortical level, i.e. the shrinkage of deprived ocular dominance columns, was not available, as rat visual cortex lacks clearly defined ocular dominance columns. We therefore took advantage of the recent result obtained in our laboratory (Cellerino *et al.* 1992) showing that Parvalbumin immunoreactivity (Parva-LI) represents a reliable marker for the effects of monocular deprivation on the anatomical organization of the rat visual cortex.

2. METHODS

Long Evans hooded rats (33) were used; 9 rats were normal undeprived, and 20 rats were monocularly deprived for one month by means of eyelid suture (right eye) starting immediately after eye opening (post-natal day 14, P14). This spans the greatest part of the presumed critical period (Rothblat *et al.* 1978; Rothblat & Schwartz 1979; Maffei *et al.* 1993*a*, *b*). In seven rats only monocular deprivation was done, and in seven rats deprivation was combined with intraventricular injection (Kromer 1987; Fischer *et al.* 1991) of beta-NGF (FIDIA Research Laboratories, Abano T., Italy; 1–1.6 μg μl^{-1} in buffered saline, volume injected 2 μl) for the whole deprivation period, according to Domenici *et al.* (1991). In six rats, cytochrome *c*, a molecule used to control for NGF effects, was injected with the same protocol as NGF. In four rats only NGF intraventricular injections were done with the same protocol as for MD + NGF rats.

Eyelid suture and intraventricular injections were done under very brief ether anaesthesia.

Five normal, five MD, five MD + NGF treated rats, and three MD cytochrome *c* treated rats were recorded at the end of the presumed critical period (> P45). Single neuron responses and visual evoked potentials (VEPs) were recorded under urethane anaesthesia (6 $cm^3\ kg^{-1}$, 20% (by volume), intraperitoneal, Sigma) by means of a micropipette, filled with NaCl (3 M), inserted in the binocular portion of the primary visual cortex (binocular area 17, or area OC1B) contralateral to the deprived eye. A blind procedure was used so that experimenters did not know whether animals were untreated, cytochrome *c* treated, or NGF treated.

Details of electrophysiological recordings are given elsewhere (Domenici *et al.* 1991; Maffei *et al.* 1993*a*, *b*). Both eyes were fixed by means of metal rings surrounding the external portion of the eye bulbs (Parnavelas *et al.* 1981), and the cornea was protected with artificial tears. Optic discs were backprojected onto the screen where all receptive fields had been plotted, at the end of the experiments, when pupils were eventually dilated (Lennie & Perry 1981).

For single-cell recordings, location of the receptive field in the visual space, its size and organization, optimal stimulus orientation and direction of movement, ocular dominance class and response type were determined for each cell, according to standard criteria (Hubel & Wiesel 1962; Parnavelas *et al.* 1984). Only cells with receptive fields farther than 30 deg nasal from the optic disc and in the upper visual field (binocular visual field) were included in our sample. In the rat, vertical meridian is estimated to be 55–58 deg from, and horizontal median 30 deg below, the projection of the optic disc. Care was taken that receptive fields were located at comparable eccentricities in the four experimental groups: mean receptive field positions with respect to the vertical meridian were: 12±9 in normal, 10±8 in MD, 10±9 in MD + NGF, and 12±8 in MD + cytochrome *c* rats.

To avoid sampling biases resulting from the organization of area OC1B as far as the ocular dominance is concerned (Thurlow & Cooper 1988), electrode penetrations were angled, and at least two well-spaced penetrations were done for each animal.

Spontaneous discharge was measured by recording for 2–3 min the cell firing rate.

Four normal rats and four undeprived NGF-treated rats were recorded at different stages of development (P19 and P30).

For VEP recordings, the protocol described in Domenici *et al.* (1991) was used.

(*a*) *Anatomy*

The last electrode penetration was marked for subsequent track reconstruction by passing a small current (10 μA for 10 s every 500 μm, and 20 μA continuously passed while slowly withdrawing the electrode).

Animals were deeply anaesthetized with urethane and perfused transcardially with normal saline followed by 4% paraformaldehyde (Riedle, Germany) in 0.1 M phosphate buffer. Brains were dissected, post-fixed (12 h, 4 °C, same fixative) and coronally sliced with a vibratome (60 μm thickness).

For conventional anatomy, sections were stained for cresyl violet. The intraventricular injection site was examined, and track reconstruction was done.

(*b*) *Immunohistochemistry*

Three normal, three MD, three MD + NGF, and three MD + cytochrome *c* rats (all previously recorded) were perfused, their brains post-fixed and sectioned following the same protocol as for Nissl stain. Slices were collected in phosphate buffered saline (PBS) and incubated with monoclonal anti-Parvalbumin (Sigma) 1:20000, 0.1% Triton X-100, 20% normal goat serum in PBS overnight at 4 °C. After washing in PBS, sections were incubated with affinity-purified biotynilated goat anti-mouse (Calbiochem) 1:1000, 5% normal goat serum in PBS for 1 h at room temperature (RT) with gentle agitation. After washing in PBS, sections were incubated with ABC kit (Vector) for 1 h at RT with gentle agitation, and HRP histochemistry was revealed with a standard DAB reaction intensified with nickel ammonium sulphate.

(*c*) *Acetylcholinesterase (AChe) histochemistry*

Three normal and three MD + NGF rats (all previously recorded) were perfused, their brains post-fixed and sectioned following the same protocol as for Nissl stain. AChE pattern was revealed using the protocol of Bear *et al.* (1985).

3. RESULTS

(*a*) *Electrophysiological findings*

Ocular dominance distributions (see figure 1) for single neurons recorded in the binocular portion of the primary visual cortex in (*a*) five normal, (*b*) five MD and (*c*) five MD + NGF rats are reported. At the bottom of each column, the cumulative ocular dominance distribution is shown (filled bars). The figure legend

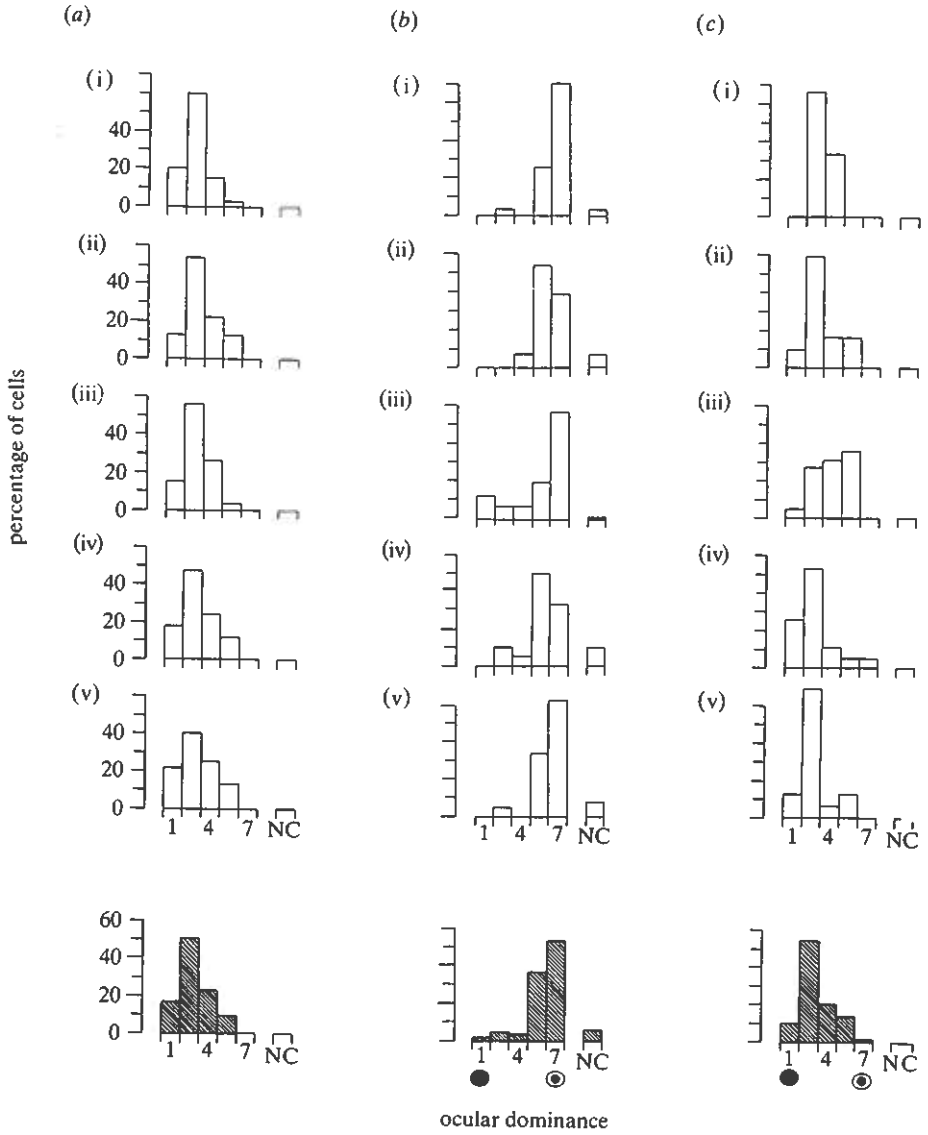

Figure 1. Ocular dominance distribution for visual cortical neurons recorded in the primary visual cortex of (*a*) normal rats, (*b*) monocularly deprived (MD) rats, and (*c*) monocularly deprived rats with intraventricular injections of NGF (MD + NGF). Monocular eyelid closure was done for one month (P14–P45), and recordings were made in the hemisphere contralateral to the deprived eye (eye symbol = open eye, filled symbol = deprived eye). Neurons in ocular dominance class 1 were driven only by stimulation of the contralateral eye; neurons in ocular dominance classes 2–3 were binocular and preferentially driven by the contralateral eye; neurons in ocular dominance class 4 were equally driven by the two eyes; neurons in ocular dominance classes 5–6 were binocular and preferentially driven by the ipsilateral eye; and neurons in ocular dominance class 7 were driven only by the ipsilateral eye. The top five histograms (i–v) in each column are distributions from single animals. The number of cells recorded in each case (*n*) and the visual acuity estimated in each animal for the contralateral eye (deprived eye in MD and MD + NGF rats) (in cycles per degree) are as follows: (*a*) (i) $n = 20$, visual acuity = 0.95; (ii) $n = 32$, 1.0; (iii) $n = 34$, 0.9; (iv) $n = 17$, 1.0; (v) $n = 31$, 1.0; cumulative distribution, $n = 134$; (*b*) (i) $n = 32$; (ii) $n = 30$, 0.35; (iii) $n = 16$, 0.45; (iv) $n = 20$, 0.35; (v) $n = 23$, 0.45; cumulative distribution, $n = 121$; (*c*) (i) $n = 24$, 0.95; (ii) $n = 32$, 0.95; (iii) $n = 19$, 0.8; (iv) $n = 19$, 1.0; (v) $n = 16$, 0.9; cumulative distribution, $n = 110$. Visual acuity was taken as the highest spatial frequency of the visual stimulus (sinusoidal grating) still evoking a VEP signal above noise level. The bottom histogram in each column is the cumulative distribution for the group (filled bars). The category labelled NC contains those neurons that could not be classified by using visual stimuli. A chi-square test, 4 d.f., was used to evaluate the difference between the cumulative ocular dominance distributions. The distribution for MD animals differed significantly both from the distribution in normal rats ($p \ll 0.001$) and in monocularly deprived NGF-treated rats ($p \ll 0.001$). No significant difference was found between the ocular dominance distribution in normal and in MD + NGF rats ($p > 0.05$). Mean visual acuity for MD rats significantly differed from the value of normal and MD + NGF rats (two-tailed *t*-test). Undeprived eyes of MD and MD + NGF rats had normal visual acuity (not shown). Mean ipsilateral index (ratio of cells in classes 5–7 to the total number of responsive cells) and mean binocular index (ratio of classes 2–6 to the total number of responsive cells) for the three groups are: normal rats, 0.091 ± 0.047 and 0.82 ± 0.04; MD, 0.88 ± 0.8 and 0.44 ± 0.06; MD + NGF, 0.15 ± 0.13 and 0.88 ± 0.12. Values for the MD group are significantly different from values in the normal and MD + NGF groups; those for the latter two do not differ.

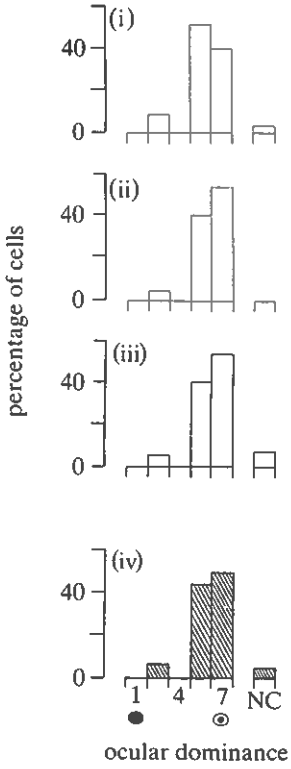

Figure 2. (i–iii) Ocular dominance distribution for single monocularly deprived (MD) rats treated with cytochrome *c*. (i) $n = 24$, visual acuity = 0.45; (ii) $n = 22$, 0.35; (iii) $n = 38$; and (iv) the distribution ($n = 84$). Conventions as for figure 1. Cumulative distribution is significantly different from that in normal and MD + NGF rats, and not significantly different from that in MD rats.

details the visual acuity of the contralateral eye (deprived eye in MD and MD + NGF rats) evaluated in each animal by using VEP recordings.

Ocular dominance distribution in normal rats (figure 1*a*) shows a high proportion of binocular cells (80%), with a bias in favour of the contralateral eye (classes 1 and 2–3); this reflects the predominance of crossed optic nerve fibres in rats (Polyak 1957; mean ipsilateral and binocular indexes in figure 1 legend). Mean visual acuity for this sample of normal rats was 0.97 ± 0.05 cycles deg^{-1}, with all values within the normal range for pigmented rats (Silveira *et al.* 1988; Domenici *et al.* 1991).

In MD rats (figure 1*b*), the proportion of cells driven by the contralateral deprived eye fell dramatically; the ipsilateral, non-deprived eye dominated 90% of cells. Binocularity was also strongly affected: binocular cells amounted to 44% of the total. Mean values for ipsilateral and binocular indexes in MD rats (figure 1 legend) were significantly different from the corresponding values in normal rats. In accordance with previous results (Domenici *et al.* 1991), visual acuities for the deprived contralateral eye were strongly diminished (0.4 ± 0.06 cycles deg^{-1}) with respect to normal values, whereas those for the undeprived eye (0.95 ± 0.05 cycles deg^{-1}; not shown in figure 1) were normal.

Ocular dominance distribution in NGF-treated rats (figure 1*c*) was largely normal: 65% of the cells were dominated by the contralateral deprived eye and 87%

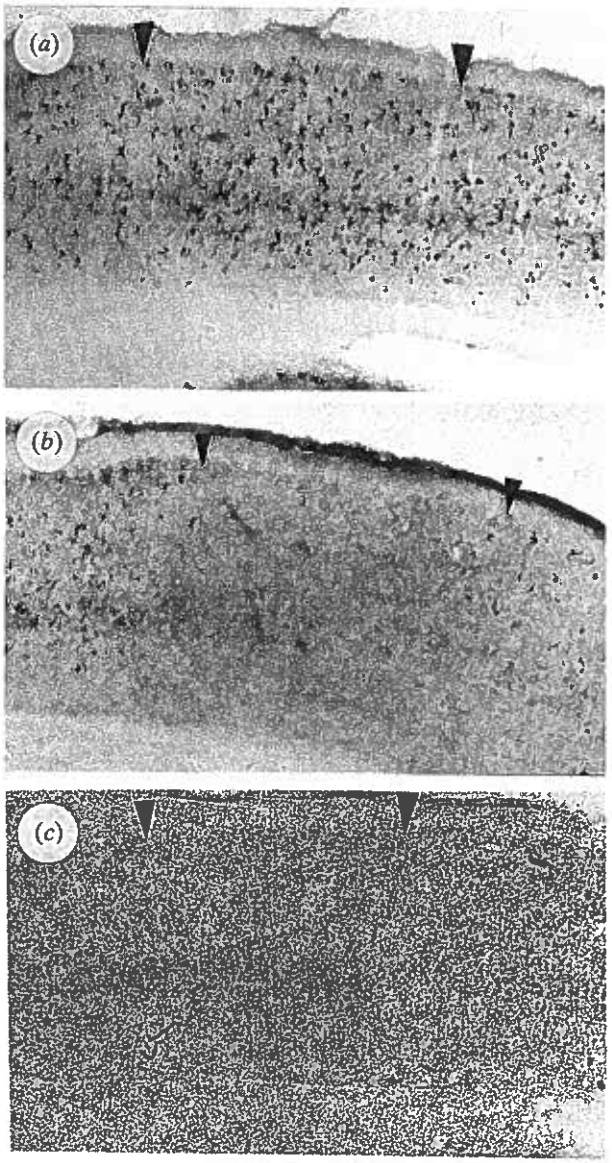

Figure 3. Pattern of Parva-LI in the visual cortex of (*a*) normal, (*b*) MD + cytochrome *c*, and (*c*) MD + NGF rat. Arrows show the borders of the binocular part of the primary visual cortex. Final magnification 200×.

were binocular. NGF counteracted monocular deprivation effects in all NGF-treated rats (mean ipsilateral and binocular indexes in figure 1 legend). Visual acuities for the deprived eye (mean value 0.9 ± 0.08 cycles deg^{-1}) did not differ from those of the undeprived eye (0.92 ± 0.07 cycles deg^{-1}); both were in the normal range, confirming previous results (Domenici *et al.* 1991).

To control for possible non-specific effects of NGF treatment, we determined the ocular dominance distribution and deprived eye visual acuity in three monocularly deprived rats treated with cytochrome *c*. The results are shown in figure 2. It is evident that treatment with cytochrome *c* was ineffective in preventing the effects of monocular deprivation.

(*b*) *Parvalbumin-like immunoreactivity*

Because rat visual cortex lacks an obvious columnar organization, it is more difficult to visualise anatomical effects of monocular deprivation. No clear structural

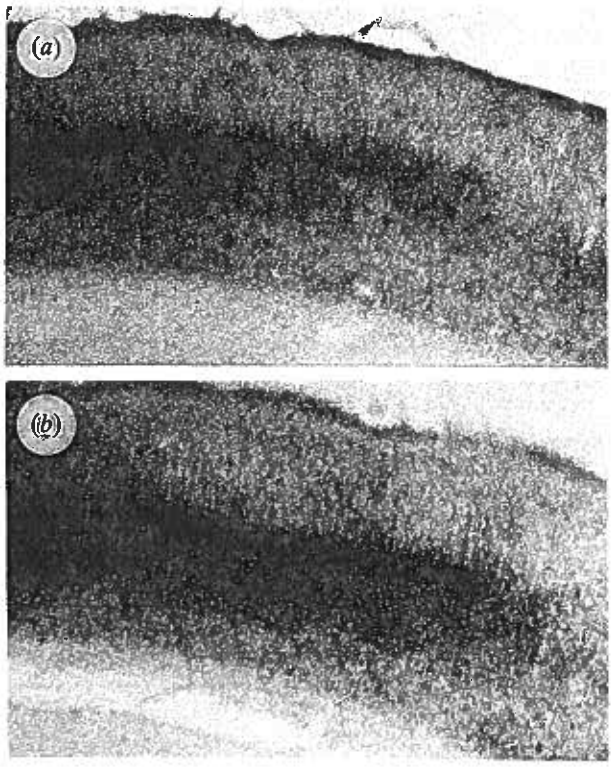

Figure 4. Pattern of AchE in the binocular visual cortex of a normal (right) and an NGF-treated (left) rat. Arrows mark cell bodies positive for AchE. Calibration: 112 μm.

effects of monocular deprivation in rat visual cortex have yet been described. In a recent paper (Cellerino *et al.* 1992), it has been shown that monocular deprivation causes a massive reduction of Parva-LI in the deprived cortex. This effect is restricted to the binocular portion of the visual cortex (contralateral to the deprived eye), and it is absent in dark-reared animals, suggesting that it is due to binocular competition and not visual deprivation per se. The effects of monocular deprivation on Parva-LI were not presented by cytochrome *c* treatment. This can be seen by comparing figure 3*a* and *b* where Parva-LI in the visual cortices of a normal and an MD + cytochrome *c* animal are illustrated. Reduction of Parva-LI was absent in MD + NGF animals (figure 3*c*). Thus, NGF treatment counteracts the striking change in cortical functional anatomy brought about by monocular deprivation.

(*c*) *Controls*

An important point was to assess whether the treatment with NGF had altered the functional and anatomical organization of the visual cortex. In accordance with our previous results (Maffei *et al.* 1993*a*, *b*) no differences in cell responsiveness, spontaneous discharge and receptive field size were noted in NGF-treated rats. Orientation-selective cells were 55% in normal and 52% in MD + NGF rats. Because orientation selectivity of rat visual cortical neurons is very low at the beginning of the critical period (Maffei *et al.* 1993*a*, *b*), the fact that orientation selectivity in NGF-treated rats was normal suggests that the visual cortex had developed normally. This excludes long-term effects of NGF treatment on orientation selectivity, such as those produced by dark rearing. To control for possible transient effects of NGF we recorded from four rats under NGF treatment and four normal rats at two stages of the critical period (P19, and P30; $n = 2$ for each group). Recordings began 1 h after the last NGF injection. In accordance with previous findings, no difference for spontaneous activity or orientational selectivity were found between NGF-treated rats and normal rats of the same age. In addition, we found that the tuning of orientational cells was not affected by NGF. Mean bandwidth at P30 was 80–90 deg both for NGF-treated ($n = 15$) and for normal rats ($n = 15$), a value which is the mean tuning found in normal P45 rats (Maffei *et al.* 1993*a*, *b*) and in MD + NGF rats, recorded at the end of the treatment.

In NGF-treated rats, lamination and thickness of the visual cortex, as assessed by Cresyl Violet, were normal, and so was the extent of its binocular and monocular portions, as assessed by AChE pattern (figure 4). The pattern of AchE is a useful marker of the organization of the rat primary visual cortex (Zilles *et al.* 1987). The similarity of AchE patterns between normal and NGF-treated rats suggests that NGF did not disrupt the organization of the visual cortex. It cannot be taken, however, as conclusive evidence that NGF does not act via the cholinergic system; determination of Chat activity in the visual cortex (Domenici *et al.* 1991) is a more reliable indicator (see Discussion of Domenici *et al.* 1993 (following paper)).

4. DISCUSSION

The findings reported here show that exogenous supply of NGF prevents the ocular dominance shift and the loss in visual acuity induced by monocular deprivation without affecting the functional properties of visual cortical cells. Reduction of Parvalbumin-like immunoreactivity, which illustrates the effects of monocular deprivation on the functional architecture of the rat primary visual cortex, is also prevented by NGF treatment. It seems unlikely that these NGF effects are non-specific (Maffei *et al.* 1993*a*, *b*).

The absence of any gross behavioural effects in animals after intraventricular injections of NGF seems to exclude general pathological alterations. This is supported by behavioural experiments in monocularly deprived NGF-treated kittens: in these animals the behaviour was indistinguishable from that of control kittens, and the visual acuity of the deprived eye was normal (Maffei *et al.* 1993*a*, *b*).

Results in control cytochrome *c* treated rats suggest that NGF effects are not due to treatment per se. Moreover local application of NGF onto one visual cortex prevents the amblyopic effects of monocular deprivation only in the treated hemisphere (Domenici *et al.* 1991). This finding suggests that NGF action occurs within the visual cortex and its afferent systems.

Block of endogenous NGF action by intraventricular transplant of hybridoma cells producing anti-NGF antibodies causes a decrease in the number of binocular cortical neurons and the shrinkage of cell bodies in the LGN (Berardi *et al.* 1992). By contrast, exogenous

supply of NGF prevents the shrinkage of LGN neurons induced by monocular deprivation (see Domenici *et al.* 1993 (following paper)).

Responsiveness, spontaneous activity and orientation selectivity of visual cortical cells were normal in NGF-treated animals, both measured at the end and at different ages during the critical period. This suggests two conclusions: (i) NGF did not alter visual cortical neuron discharge, neither did it interfere with the transmission of visual information, either excitatory or inhibitory; and (ii) NGF did not interfere with the normal development of the visual cortex (Maffei *et al.* 1993*a*, *b*). It may be noted that dark rearing, which is known to delay the development of the visual cortex, affects visual acuity and orientation selectivity of visual cortical cells (Timney *et al.* (1978) for cats; Berardi *et al.* (1992) for rats).

The results with Parva-LI are of particular interest. Monocular deprivation causes a massive reduction of Parva-LI in the binocular portion of the visual cortex contralateral to the deprived eye. This effect is absent in dark-reared animals, suggesting that it is due to binocular competition and not visual deprivation per se (Cellerino *et al.* 1992). Parva-LI reduction could therefore be a marker revealing the loss of the functional input from the deprived eye in the control of cortical space. This would be particularly useful in the rat visual cortex, where no clear ocular dominance columns are present. The finding that NGF treatment prevents the reduction in Parva-LI adds weight to the suggestion, coming from the electrophysiological experiments, that NGF prevents the loss of functional input from the deprived eye.

In conclusion, our data are consistent with the hypothesis that exogenous NGF compensate for a shortage of endogenous NGF, probably due to the effects of the sensory deprivation on the electrical activity in the visual pathways, and that NGF action is exerted primarily on visual neurons. Whether NGF is itself the trophic molecule of LGN fibres or whether it regulates the production of a still unknown molecule remains to be ascertained.

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