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Genetic Instructions and Developmental Plasticity in the Kitten's Visual Cortex [and Discussion]

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Genetic instructions and developmental plasticity in the kitten's visual cortex

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[Plate 1]

Two major properties of neurons in the kitten's visual cortex, binocularity and orientation selectivity, are present when the eyes first open, and therefore can be established by genetic instructions alone. However, both of these attributes require visual experience for their maintenance or strengthening; and both can be rapidly modified by unusual kinds of experience. Alternating sequences of cells dominated by one eye, then the other, can be recorded during penetrations through the cortex in binocularly deprived kittens, typical of the 'ocular dominance columns' of the normal adult cat. However, if one eye is deprived by lid-suture, the entire visual cortex becomes strongly dominated by the open eye.

Experiments in which each eye saw separately through a transparent neutral density filter or a translucent diffuser showed that this phenomenon is caused not by the reduction in retinal illumination, but by the abolition of contrast in the deprived eye. A study of the retrograde transport of horseradish peroxidase from the visual cortex to the principal laminae of the lateral geniculate nucleus suggested that monocular deprivation from early in life may lead to a gross reduction in the distribution of afferent fibres from the deprived laminae. Previous experiments have found that if a kitten is exposed only to contours of one orientation, its cortical neurons become modified in their distribution of preferred orientations. This phenomenon was re-confirmed in a new study using a rigorously objective method of analysis.

Introduction

The theme of this Discussion meeting is the correlation between structural and functional changes during the early development and modification of the nervous system. Here I shall review two developmental phenomena that occur in the visual cortex of the kitten. For one of them, evidence is emerging for a structural change that might partly explain the original physiological observations; in the second case I present evidence that a previously described (but recently questioned) physiological finding is valid, but can offer no certain structural explanation. The two topics are, respectively, the effects of monocular deprivation and the consequences of early exposure to contours of one orientation.

Methods

Physiological recording

The general techniques used for recording the activity of single neurones have already been described in detail (Blakemore & Van Sluyters 1975). Kittens were immobilized by intravenous infusion with Flaxedil (gallamine triethiodide: 10 mg kg^{-1} h^{-1}) and anaesthetized by artificial ventilation with about 80 % nitrous oxide. Electrocardiogram, electroencephalogram,

body temperature, expired CO_2, and sometimes arterial blood pressure, were monitored and great care was taken to maintain the physiological condition of the animal.

The corneae were protected with contact lenses and the refractive condition of the eyes was corrected with additional spectacle lenses. In the present experiments, the responses of neurones were studied by moving a variety of patterns, such as spots, bars and edges, across the stage of an overhead projector, which cast an image on a translucent back-projection screen 57 cm in front of the eyes. Each eye was occluded in turn in order to determine the receptive field properties separately in the two eyes.

In virtually every penetration, small electrolytic lesions were placed, at intervals, by passing current (5 μA for 5 s, electrode tip negative) through the electrode. After perfusion, the brain was frozen, sectioned at 40 μm and stained with cresyl violet. The track was then reconstructed by reference to these electrolytic lesions. All these penetrations were confirmed to lie wholly, or almost entirely, within area 17.

The horseradish peroxidase method

In some animals the retrograde transport (Kristensson, Olssen & Sjöstrand 1971; LaVail 1975) of the enzyme horseradish peroxidase, from the visual cortex to the lateral geniculate nucleus, was used to study the distribution of afferent axons to the cortex. A 20% solution of peroxidase (Sigma Type VI or Boehringer Grade 1) in sterile saline was injected by pressure (about 0.5 μl at each point) into the grey matter of the cortex, through a capillary with a broken tip diameter of about 20 μm. After survival of 24 h the animals were perfused and frozen sections of the brain were reacted with diaminobenzidine hydrochloride and hydrogen peroxide, as described by Thorpe & Blakemore (1975).

Results and discussion

Elementary organization in the cortex of visually inexperienced kittens

In the primary visual cortex of normal adult cats, virtually all neurons are orientation selective and most of them can be influenced through either eye (Hubel & Wiesel, 1962). Moreover, the receptive field properties, in particular the preferred orientations, are usually very similar in the two eyes (Hubel & Wiesel 1962; Noda, Creutzfeldt & Freeman 1971; Blakemore, Fiorentini & Maffei 1972).

There is now little doubt that some cortical cells are orientation selective, even by the strictest criteria, in the visual cortex of very young kittens that have not had visual experience with patterned retinal images, although the exactitude of orientation selectivity may rarely be as fine as it is for most cells in the adult (Hubel & Wiesel 1963; Barlow & Pettigrew 1971; Pettigrew 1974; Blakemore & Van Sluyters 1975; Buisseret & Imbert 1976; Sherk & Stryker 1976). Hubel & Wiesel (1963) reported that a microelectrode, penetrating obliquely through the cortex in such an animal, recorded groups of cells with similar orientation preference, with sudden shifts in preferred orientation from one group to the next. This kind of sequential grouping of neurons has been taken as evidence for a system of orientation 'columns' in adult cats (Hubel & Wiesel 1962). Blakemore & Van Sluyters (1975), though they found fewer than a quarter of all cells to be truly orientation selective in animals that had not had previous visual experience, confirmed that there is some tendency for neighbouring orientation selective cells to have similar orientation preference; and Sherk & Stryker (1976) have provided evidence for

sequential shifts in preferred orientation, from region to region. Thus the skeleton, at least, of an orientation columnar 'map' does seem to exist in the genetically pre-specified connectivity of the kitten's cortex. Nevertheless, many authors have reported that experience of patterned retinal images causes a rapid increase in the proportion of orientation selective cells, the 'sharpening' of their orientation selectivity and hence the perfection of the columnar map (Barlow & Pettigrew 1971; Pettigrew 1974; Buisseret & Imbert 1976; Blakemore & Van Sluyters 1975; Cynader, Berman & Hein 1974).

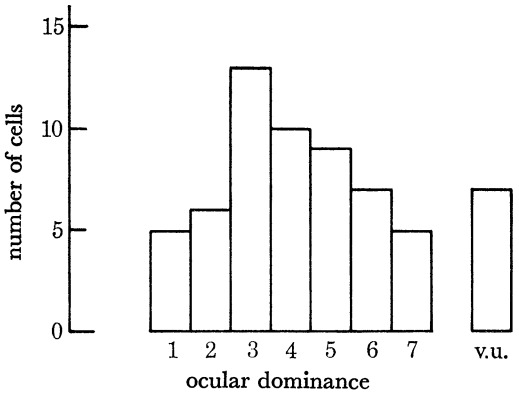

FIGURE 1. This histogram uses the scheme of Hubel & Wiesel (1962) to classify the ocular dominance of 55 visually responsive cortical cells recorded from two very young visually inexperienced kittens, 9 and 19 days old. The scale of ocular dominance runs from complete dominance by the contralateral eye (group 1) to total dominance by the ipsilateral eye (group 7). Cells in the other groups are binocularly driven, ranging from group 2 (contralateral very much stronger than ipsilateral) to group 6 (ipsilateral very much stronger than contralateral). The cells plotted under the column labelled 'v.u.' were visually unresponsive. The distribution in these animals is indistinguishable from that in a normal cat. (Data from Blakemore & Van Sluyters 1975.)

There is even more general agreement that most cortical neurons in kittens at the time of natural eye opening, or even after prolonged binocular deprivation, are binocularly driven (Hubel & Wiesel 1963; Wiesel & Hubel 1965; Pettigrew 1974; Blakemore & Van Sluyters 1975). Figure 1 shows the distribution of ocular dominance, using Hubel & Wiesel's (1962) scheme for classifying cells according to the relative influence of the two eyes, for samples of cortical neurons from two very young kittens, 9 and 19 days old, with no previous visual experience (Blakemore & Van Sluyters 1975). However, the selectivity of these immature cells for the disparity of the retinal images during simultaneous binocular stimulation is far from normal; again, visual experience seems to be required for its perfection (Pettigrew 1974). With no previous visual experience, many binocularly driven neurons also have very different preferred orientations on the two retinae (Blakemore & Van Sluyters 1975); visual experience is needed for the matching of receptive field properties in the two eyes.

The physiological consequences of monocular deprivation

Despite the inherent input from both eyes, the relative strength of the two inputs and the degree of binocular convergence on to individual cells are subject to rapid alteration if normal binocular vision is not preserved early in life. The most straightforward and dramatic of such changes is caused simply by covering one eye, even for a short period, some time during the first few weeks of a kitten's life; such monocular deprivation causes almost all cortical neurones to become completely dominated by the input from the open eye (Wiesel & Hubel 1965;

Hubel & Wiesel 1970). The normal pattern of physiological ocular dominance columns, in which there is regional grouping of cells dominated by one eye or the other, is transformed into a uniform arrangement in which the afferent input from the deprived eye is almost completely silenced.

Covering one eye, usually achieved by suturing together the lids, has two effects on the retinal image: it reduces the mean intensity (by an amount depending on the degree of pigmentation of the lids) and it attenuates, almost abolishes, the contrast. It was not clear from the original experiments whether the dimming or the abolition of pattern was the potent factor.

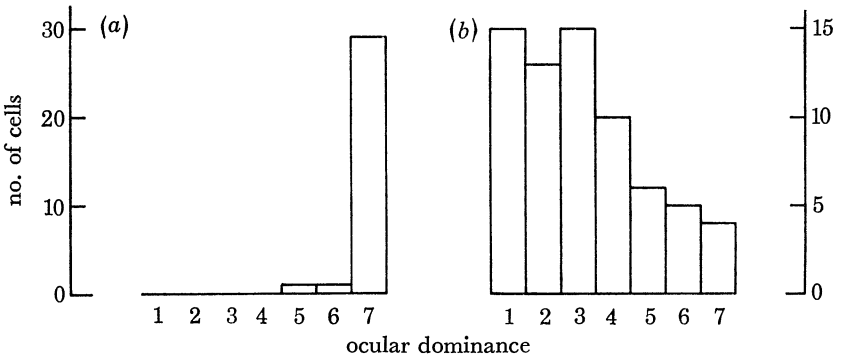

FIGURE 2. Ocular dominance histograms, as in figure 1, for kittens that were housed in the dark and received their only visual experience wearing goggles, through which they saw a normal laboratory environment. (*a*) This animal wore goggles containing an opal diffuser over the left eye (contralateral to the recording site) and a transparent neutral density filter, giving matched mean attenuation of retinal illumination, over the right eye. (*b*) For these two animals, the goggles contained only a 1 log unit neutral density filter over the left (contralateral) eye.

It is now evident, however, that deprivation of patterned retinal images is the crucial component in monocular deprivation. Figure 2 shows two ocular dominance histograms. The first (*a*) is from an animal that received its only visual experience wearing goggles that presented a translucent, opal Perspex diffuser in front of the left (contralateral) eye and, over the right eye, a transparent neutral density filter (0.25 log units), matched in attenuation to the diffuser when transilluminated with omnidirectional light. The effect on the cortex was just as complete as if the contralateral eye had been sutured closed, although both retinae received the same mean illumination. On the other hand, figure 2*b* shows the results from two animals that wore goggles in which the right eye saw normally and the left (contralateral) eye was covered with a transparent 1 log unit neutral density filter. There is perhaps a slight increase in the proportion of monocularly driven cells (28 %, compared with the 10–15 % found in normal cats) but there is certainly no tendency for the contralateral eye (with reduced retinal illumination) to be less well represented. (The reduction of binocularity, which is much more exaggerated if one eye is covered with a 2 log unit filter, may be due to a difference in the *timing* of the inputs or the strength of the discharges from the two eyes, since the retinal latency is likely to be longer and the response weaker in the more dimly illuminated eye: Blakemore 1976.)

Possible morphological consequences of monocular deprivation

In the monkey, similar shifts in ocular dominance are produced by covering one eye (Baker, Grigg & Von Noorden 1974) and they are accompanied by changes in the actual pattern of distribution of afferent fibres in lamina IVc (Hubel, Wiesel & LeVay 1976). In the normal monkey, the axons from the right-eye and left-eye laminae of the lateral geniculate nucleus

terminate in non-overlapping, surface parallel bands (Wiesel, Hubel & Lam 1974), which give rise to the very pronounced ocular dominance clustering of neurons in lamina IV. If one eye is deprived for a long period of time, its bands of axon termination shrink considerably, while the interdigitating stripes for the experienced eye expand.

Thorpe & Blakemore (1975) have used a complementary method to study the termination of afferent axons from the right-eye and left-eye laminae of the lateral geniculate nucleus in monocularly deprived kittens. The enzyme horseradish peroxidase (which is taken up by axon terminals and transported in a retrograde direction to the cell bodies of origin) was injected through a capillary at a large number of points along the whole dorsal aspect of the visual cortex in kittens that had been deprived in the right eye from lid-opening until 2–3 months. After 24 h survival the animals were perfused and the locus of the peroxidase identified by means of the formation of a dense reaction product (LaVail 1975). The widespread injections led to the labelling of cell bodies throughout the antero-posterior extent of the lateral geniculate nucleus, in the medial half of the nucleus (which projects to the exposed dorsal surface of the visual cortex). However, the density of labelling, both in terms of the number of cell bodies containing granules of reaction product and the number of granules per cell, was very much less in the laminae corresponding to the deprived right eye than in the left eye layers.

Figure 3, plate 1, shows dark field photomicrographs of the medial part of the two principal laminae, A and A1, from a single section through the left and the right lateral geniculate nuclei, from an animal deprived in the right eye (which projects to A on the left and A1 on the right). The left-eye laminae are filled with cells containing peroxidase reaction product while there are few such neurons in the other laminae. This result could be explained by reduced activity in the terminals of axons from the deprived laminae, since peroxidase uptake is thought to be coupled to the release of synaptic vesicles (Heuser & Reese 1973). However, the deprived eye was reopened during the period of 24 h survival, which should have ensured a good deal of activity among the cells of the deprived geniculate laminae.

In their first report of this phenomenon Thorpe & Blakemore (1975) suggested that their failure to observe laminar differences in labelling in one animal may have been due to a short period of normal vision before the start of monocular deprivation. However, more recent work has identified a different probable cause for the contamination of the results, namely injection of the white matter and hence direct uptake of peroxidase by damaged axons. In a control experiment, two litter-mate kittens were monocularly deprived from about four weeks. In one the grey matter alone was injected and there was gross laminar asymmetry in geniculate labelling: in the other the white matter was deliberately penetrated and the geniculate laminae were almost equally labelled.

Environmental specification of preferred orientation: an objective demonstration

Since one set of cortical columns – those for ocular dominance – is both innately partially pre-specified yet rapidly modified by visual experience, it might not be surprising to discover that the orientation columnar system, which is only present in a rudimentary form without visual experience, can also be altered by modified visual input. Some time ago, two independent studies suggested that the distribution of preferred orientations of cortical cells can indeed be influenced, rather completely and rapidly by selective visual experience. Hirsch & Spinelli (1970) reared kittens with their sole visual input restricted to horizontal contours in one eye, vertical in the other (achieved by fixing the patterns at the focal length of lenses in goggles

worn by the kittens). Orientation selective neurons in the visual cortex were then usually monocularly driven, with the preferred orientation of each cell closely matching that of the eye providing the excitatory input. More than half of all cells were found to have 'diffuse' receptive fields, but the particular plotting technique used (involving the accumulation of responses to a small spot) also finds such receptive fields in the normal cat: it probably fails to reveal orientation selectivity in neurons of the complex type (Hubel & Wiesel 1962).

Blakemore & Cooper (1970) reared kittens in complete darkness but with occasional binocular exposure inside a cylindrical enclosure, whose walls were covered with stripes of one orientation. Thus the experience of these animals was more or less restricted to contours of one orientation, though it is impossible with this technique to eliminate completely contours of other orientations. And since the kitten is free to move its head, the individual mobility of the animal will certainly have influenced the range of orientations that appeared on its retina. None the less, kittens reared in this striped cylinder were found to have distributions of preferred orientation strongly biased towards the predominant orientation in their environment. Blakemore & Cooper (1970) even suggested that preferred orientation can be actively modified or specified by the visual input, since they found no large regions of silent, non-specific or malresponsive neurones, which would be expected if the result were merely caused by the maintenance of prespecified cells 'tuned' to the experienced orientation and the degenerative failure to mature of unstimulated cells, innately predisposed towards the wrong orientation.

Although the basic phenomenon of environmental modification of preferred orientation has since been confirmed in a large number of laboratories (e.g. Blakemore & Mitchell 1973; Freeman & Pettigrew 1973; Pettigrew & Garey 1974; Cynader, Berman & Hein 1975; Tretter, Cynader & Singer 1975; Turkel, Gijsbers & Pritchard 1975; Spencer 1974), it has recently been brough into question by an unsuccessful attempt to reproduce the results of Blakemore & Cooper (1970). Stryker & Sherk (1975) exposed kittens in a striped cylinder but subsequently found no reliable biasing of preferred orientation. Their experimental procedure, doubtless the most careful so far published, involved a number of refinements to guarantee objectivity. First, the experiments were done 'single-blind': the experimenter did not know whether the particular kitten had been exposed to horizontal or vetrical. Secondly, a computer-controlled visual display plotted each orientational 'tuning curve'. Finally, a regular sampling procedure was used, in which one cell (or unresolved multiple unit activity) was recorded approximately every 100 μm, to avoid collecting the majority of cells from any particular small region. Although some of these refinements of technique had been used separately in other confirmatory studies, no one had previously used them all.

In a lengthy series of experiments on kittens exposed to stripes in Cambridge, there have also been a very small number of failures (although in no case was there a statistically significant bias in an unexpected direction). It therefore seemed possible that negative results after exposing kittens in striped cylinders might be due to the individual variation in spurious exposure, perhaps caused by the animals' mobility. This possibility seems particularly likely, since Stryker & Sherk have themselves very recently confirmed orientational biasing using animals reared by the method of Hirsch & Spinelli (1970), which presumably stabilizes the retinal orientation more efficiently (see note added in proof by Stryker & Sherk 1975). However, they found about half the neurons in these animals to be unresponsive, unusually sluggish or non-specific in their responses. An argument based on degenerative changes in unused neurons would certainly be the most conservative interpretation of these results.

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FIGURE 3. Dark field photomicrographs, taken from a single section, showing the dorso-medial part of the left and right lateral geniculate nuclei. The principal laminae A and A1 are indicated, together with lamina C, which receives input from the contralateral eye, as does lamina A. Somata filled with horseradish peroxidase reaction product appear as light profiles, mainly in lamina A1 on the left and in A and C on the right. These layers receive input from the left eye: this animal had been monocularly deprived by lid-suture of the right eye from the time of natural lid opening. The gross reduction of labelling in the deprived laminae has been observed in a number of animals treated in this way. (Data from Thorpe & Blakemore 1975.) (Magn. × 72.)

(*Facing p.* 430)

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In an attempt to clarify the situation, I have recently concluded a study of orientational modification using a 'single-blind' procedure and a sampling method similar to that used by Stryker & Sherk (1975). Of six animals exposed in striped cylinders, the result was unconvincing in one, quite negative in one other, but positive in the rest. The most objective results come from three further animals exposed to stripes of one orientation in goggles worn by the kittens. In each case the right eye was closed by lid-suture from before the first exposure, to simplify the method of receptive field analysis. Each animal received 30–40 h of exposure, either to horizontal or to vertical contours, between about 3 weeks and 8 weeks of age. During recording, the microelectrode was introduced at the medial edge of the post-lateral gyrus on the right side and was angled obliquely in both the antero-posterior and the medio-lateral planes to ensure that it crossed diagonally through the cortex with respect to the radial palisades of cell bodies. Each penetration extended for at least 5 mm, guaranteeing a wide sample of cortical tissue: cells were samples at regular 100 μm or 200 μm intervals, in a manner similar to that of Stryker & Sherk. However, during the first half of each penetration any other units detected between these regular steps were also studied, in order to compare the results of regular and continuous sampling. Exclusion of these additional cells, recorded between the fixed steps, would not radically have altered the overall results. The experiment was performed 'blind', since the experience of the animal was not discovered until the end of the entire series. But, in order to ensure absolute objectivity without sacrificing the speed and versatility of analysis of preferred orientation by hand, a new method was used, similar to that used by Oyster (1968) in his study of the rabbit retina. A Dove prism was placed in front of the open left eye (the right eye remained closed throughout) and the angle of the prism was changed arbitrarily between neurons. Since a Dove prism mirror-inverts the image and rotates it through twice the angle of the prism itself, it was subsequently a lengthy and tedious calculation to convert between orientation in space and orientation on the retina. For each unit a record was kept of the preferred orientation as plotted on the screen and the angle of the prism. The conversion from the random array of plotted orientations to the true distribution of preferred orientations was not performed until the whole series of recordings was complete.

This procedure allowed the recording of some 40–80 cells in just a few hours. The slower computer-controlled method takes much longer to analyse an adequate sample; but prolonged experiments are, in principle, unsatisfactory, since, in young animals, stimulation received during the experiment may, after a few hours, influence the properties of cortical cells (Pettigrew, Olson & Barlow 1973; Imbert & Buisseret 1975).

The results, confirming previous observations, are illustrated in figure 4. On the left, histograms of the actual orientations of the receptive fields, as plotted on the tangent screen, are shown separately for each animal. Transformation of these data, correcting each time for the effects of the Dove prism, produced the histograms of true preferred orientation on the right. In both sets of histograms the solid arrows show the experienced orientation. Whereas the raw data show no modal tendency whatever, the corrected results are tightly peaked around this orientation (horizontal for two kittens, vertical for the other). Few cells had preferred orientations more than about 45° from the experienced angle. Cells were recorded without difficulty at short intervals throughout every penetration and only 13 neurons out of the 170 studied (7.6 %) had no orientational preference or were visually unresponsive. For most of the orientation selective cells, the narrowness of angular selectivity was within the range found in normal cats and, as in previous experiments (Blakemore & Mitchell 1973; Pettigrew & Garey 1974),

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those cells with preferred orientations very close to the experienced angle were sometimes remarkably selective. In general, however, the responsiveness of neurons was poor and much less reliable than that in normal cats or in kittens exposed to stripes in cylinders; this may be a consequence of the relative deprivation of retinal image movement when the contours are presented in goggles.

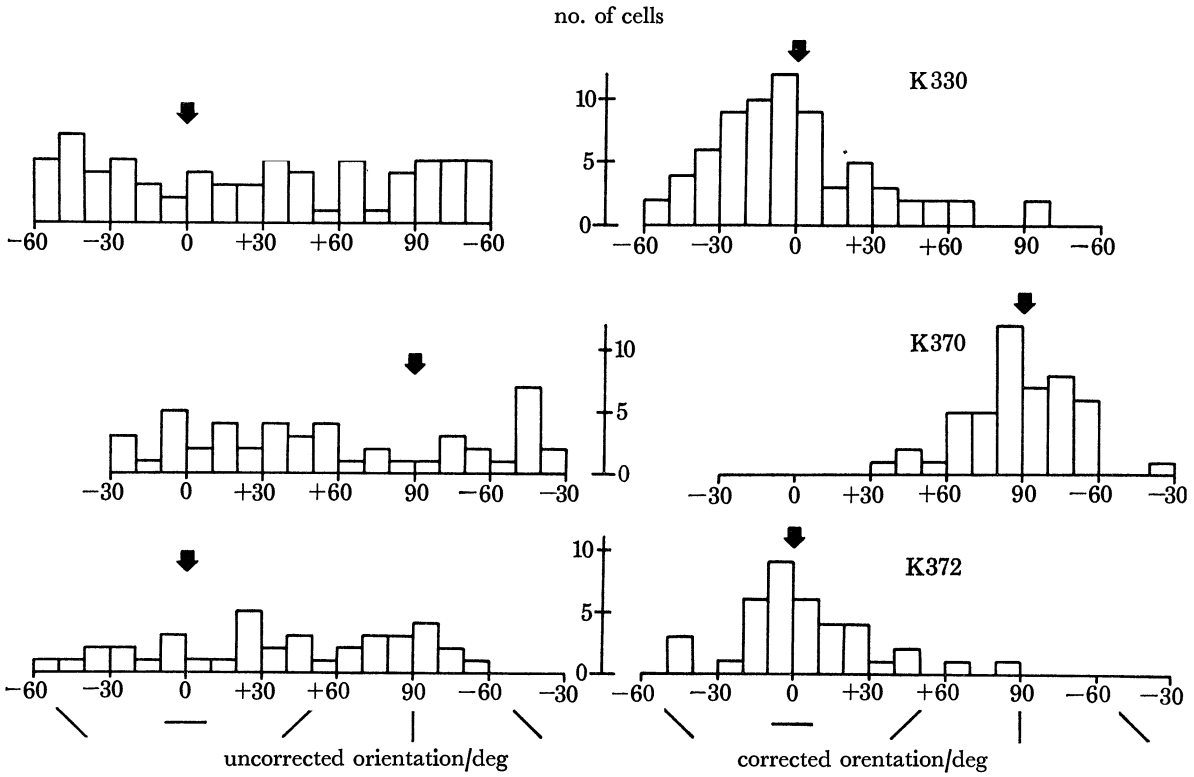

FIGURE 4. Histograms of preferred orientation for samples of cortical neurons with clear orientation preference, from three kittens reared with monocular visual experience of contours of one orientation, analysed by the objective method described in the text. The histograms on the left show the raw orientations as plotted on the tangent screen with a Dove prism in front of the eye, which was varied in angle between units. The histograms on the right replot these data with correction for the settings of the prism. The solid arrows indicate the orientation to which each animal was exposed, horizontal for K330 and K372, vertical for K370.

These positive results after early monocular exposure to stripes in goggles do not, of course, negate the observations of Stryker & Sherk (1975). They show that environmental specification of preferred orientation is a real phenomenon: but the effect is apparently not absolutely reliably produced by exposure in a simple striped chamber. The influence of an experimental environment may depend rather crucially on the quite complete exclusion of extraneous stimuli. In this respect, it seems unlikely that the early visual environment does much more than validate and make more selective the preferred orientations genetically pre-specified. Visual experience is required for the perfection of the orientation columnar map, but its role may normally be simply to impose appropriate orientation preference on the initially unselective cells in each column and, perhaps more important, to ensure that all cells gain well-matched preferred orientations in the two eyes (Blakemore & Van Sluyters 1975).

Some of the experimental work described here was done in collaboration with Drs R. C. Van Sluyters and P. A. Thorpe. I am very grateful to Philip Taylor, Rosalyn Cummings and

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Discussion

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Successful reinsertion of extraocular muscles in the kitten's rotated eye would presumably call for new relations between anatomical location of the retinal image and saccadic eye movement suitable for relocation of that image on the 'fovea'. Is there any evidence for reorganization of (1) retinal-superior colliculus (SC) somatotopic relations and/or (2) juxtaposition of retinal location in the SC with corresponding sites producing appropriate saccades on electrical stimulation in deeper layers of SC?

C. Blakemore. In the eye-rotated cat (Blakemore, Van Sluyters, Peck & Hein 1975), the extraocular muscles do seem to reinsert on the globe, but probably not at their original, displaced insertions. After a long period of recovery the movements of the two eyes (one normal, one rotated) appear roughly conjugate; though when the normal eye is covered the movements of the rotated eye are rather jerky and small in amplitude (Mitchell *et al.* 1976). We are very interested in the possibility of reorganization of the oculomotor system in these animals and are currently studying it. Certainly, M. Cynader, R. C. Van Sluyters and I (unpublished observations) find no evidence for a dramatic change in the retinotopic map from the rotated eye to the superior colliculus, but it is conceivable that some compensatory rearrangement takes place in the efferent organization of the deep layers of the superior colliculus.

Further references

Blakemore, C., Van Sluyters, R. C., Peck, C. K. & Hein, A. 1975 Development of cat visual cortex following rotation of one eye. *Nature, Lond.* **257**, 584–586.
Mitchell, D. E., Giffin, F., Muir, D., Blakemore, C. & Van Sluyters, R. C. 1976 Behavioural compensation of cats after early rotation of one eye. *Expl Brain Res.* **25**, 109–113.

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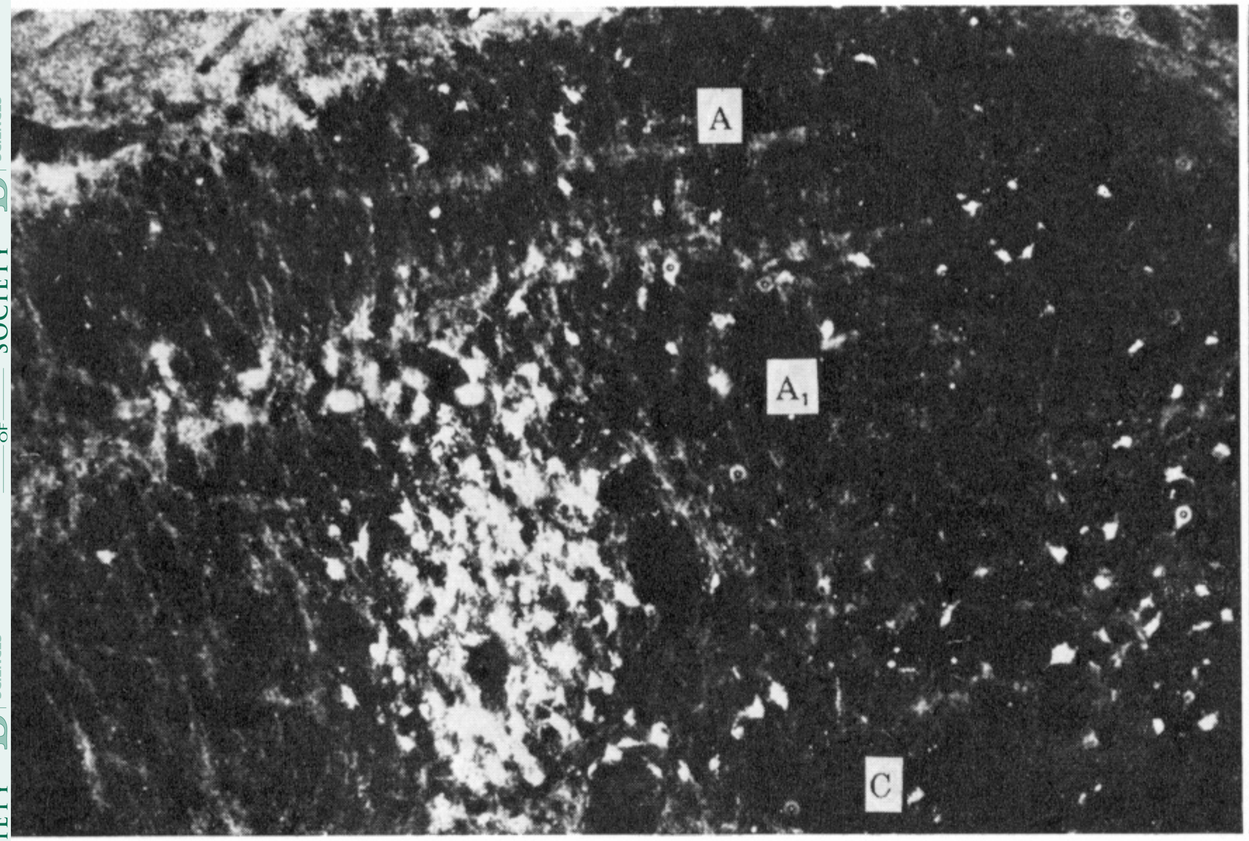

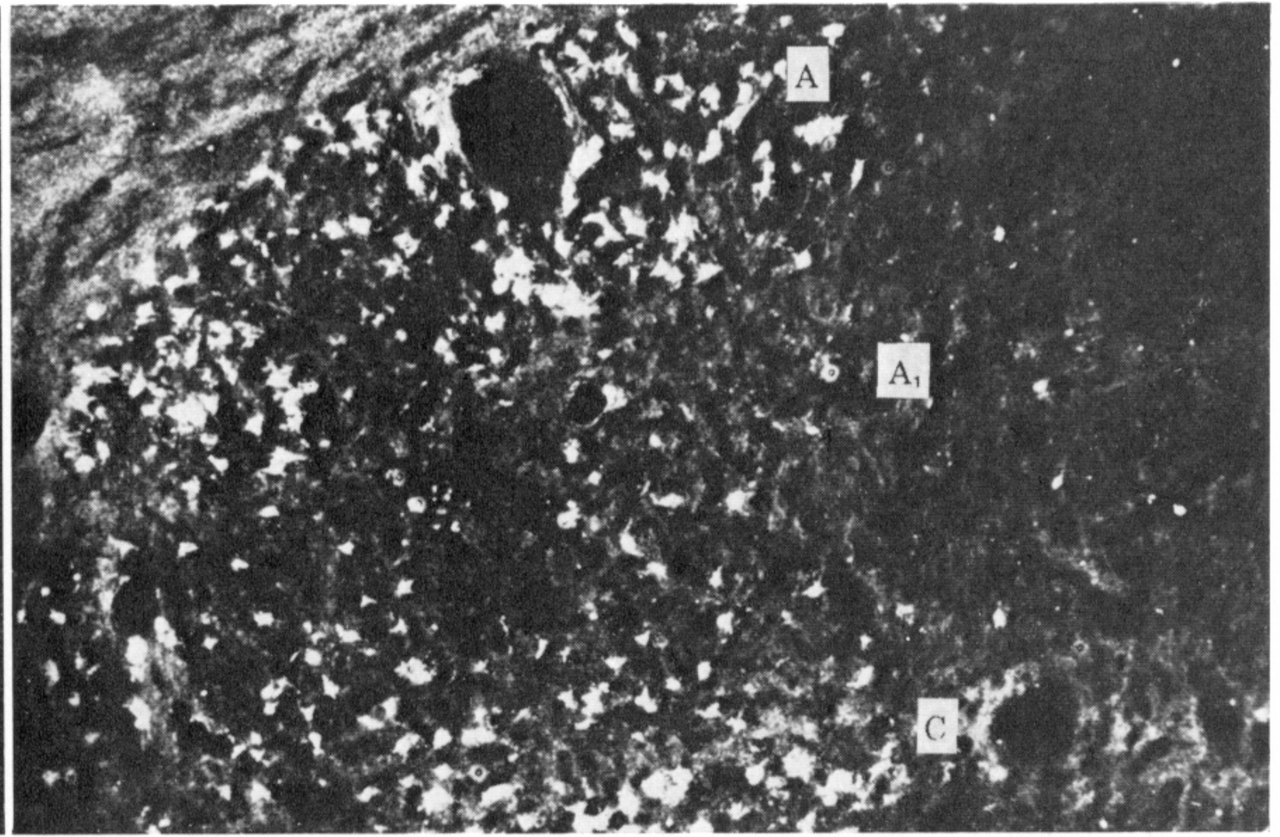

FIGURE 3. Dark field photomicrographs, taken from a single section, showing the dorso-medial part of the left and right lateral geniculate nuclei. The principal laminae A and A1 are indicated, together with lamina C, which receives input from the contralateral eye, as does lamina A. Somata filled with horseradish peroxidase reaction product appear as light profiles, mainly in lamina A1 on the left and in A and C on the right. These layers receive input from the left eye: this animal had been monocularly deprived by lid-suture of the right eye from the time of natural lid opening. The gross reduction of labelling in the deprived laminae has been observed in a number of animals treated in this way. (Data from Thorpe & Blakemore 1975.) (Magn. × 72.)

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