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Pattern of ocular dominance columns and cytochrome oxidase activity in a macaque monkey with naturally occurring anisometropic amblyopia

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Abstract

Unilateral eyelid suture, a model for amblyopia induced by congenital cataract, produces shrinkage of the deprived eye's ocular dominance columns in the striate cortex. Loss of geniculocortical projections are thought to account for the poor vision in the amblyopic eye. It is uncertain whether ocular dominance columns become shrunken in other forms of amblyopia. We examined the striate cortex in a pigtailed macaque with natural anisometropia discovered at age 5 months. Amblyopia in the left eye was documented at 1 year by behavioral testing. At age 6 years, the left eye was injected with [^{3}H]proline and the striate cortex was processed for autoradiography and cytochrome oxidase (CO). The ocular dominance columns in layer IVc labelled with [^{3}H]proline were normal. CO staining showed a novel pattern of thin dark bands in layer IV. These bands occupied the core zones at the center of the ocular dominance columns. Their appearance resulted from relative loss of CO activity along the borders of the ocular dominance columns, regions specialized for binocular processing. These findings indicate that not all forms of amblyopia are accompanied by shrinkage of ocular dominance columns. The unusual pattern of CO staining in layer IVc reflected a subtle alteration in metabolic activity which may have resulted from impairment of binocular function in anisometropic amblyopia.

Keywords: Amblyopia, Anisometropia, Ocular dominance columns, Cytochrome oxidase, Stereopsis

Introduction

Wiesel and Hubel (1963) created the first animal model of amblyopia by raising kittens with the lids of one eye closed. This manipulation mimicked form-deprivation amblyopia caused by congenital cataract in human infants. The ocular dominance columns belonging to the sutured eye were shrunken, suggesting that amblyopia resulted from loss of geniculocortical input serving the deprived eye in the striate cortex (Hubel et al., 1977).

Amblyopia also occurs in children with anisometropia, or unequal refractive error in the eyes. In a typical case, one eye is several diopters more hypermetropic than the other eye. The child accommodates enough to focus the less hypermetropic eye, but has no incentive to accommodate further (von Noorden, 1990). The more hypermetropic eye remains constantly out of focus, and hence develops amblyopia. Anisometropic amblyopia has been modelled experimentally in animals by surgical removal of one lens (von Noorden & Crawford, 1977), placement of an external defocussing lens (Eggers & Blakemore, 1978; Smith et al., 1985; Kiorpes et al., 1993), and by unilateral cycloplegia with atropine (Ikeda & Tremain, 1978; Boothe et al., 1982; Harwerth et al., 1983; Kiorpes et al., 1987). The effect of anisometropic amblyopia upon the width of the ocular dominance columns in the striate cortex has not been reported in these studies. It would be interesting to learn whether the ocular dominance columns become shrunken, as in amblyopia caused by early form deprivation.

Laboratory studies of amblyopia have gained further impetus with the discovery of naturally occurring strabismus and anisometropia in monkeys (Kiorpes & Boothe, 1981; Kiorpes, 1989; Kiorpes et al., 1993). Data obtained from these animals are especially valuable, because they are likely to parallel the findings in spontaneous cases of human amblyopia. In macaques, strabismus has been found at a rate of 2% by mass screening of animal colonies (Kiorpes & Boothe, 1981). Strabismus can be detected relatively easily by observing a decentered corneal light reflex in one eye (Hirschberg test). By contrast, screening colonies for anisometropia is more difficult, because affected animals look normal upon external inspection. Monkeys with unequal refractive error can be identified only by performing a refraction by retinoscopy after cycloplegia. Perhaps for this reason, only a single macaque with naturally occurring anisometropic amblyopia has come to attention so far. In a prior study, the contrast sensitivity and vernier acuity of the normal eye and the amblyopic eye were reported (Kiorpes et al., 1993). We now describe the pattern of

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ocular dominance columns and cytochrome oxidase (CO) activity in the striate cortex of this animal.

Methods

This paper concerns a single female pigtailed macaque (*Macaca nemestrina*) called "VZ" born at the Washington Regional Primate Center on 1 December 1988. At age 5 months, she was noted by cycloplegic retinoscopy to have a refraction in diopters of +1.75 sphere in the right eye and +5.50 sphere × −0.50 cylinder at 180 deg in the left eye. No explanation was found for the anisometropia. The ocular media were clear and the eyes were aligned orthotropically by Hirshberg light reflex. She fixated steadily with both eyes; no pattern of alternating fixation was observed. Spatial contrast sensitivity testing at age 1 year revealed amblyopia in the left eye (Kiorpes et al., 1993).

At age 6 years, the ocular dominance columns were labelled by injection of 2 mCi of L-[2,3,4,5-^{3}H]proline into the amblyopic left eye under ketamine HCl anesthesia (20 mg/kg, i.m.) and topical proparacaine HCl anesthesia, following a protocol approved by the UCSF Committee on Animal Research. Prior to injection of the isotope, the animal was examined again to exclude any abnormality which might have resulted in anisometropia. The pupillary reactions and eye movements were normal. The corneal reflex to a penlight was centered in each pupil. Cycloplegic retinoscopy was +1.00 sphere × −0.50 cylinder at 180 deg in the right eye and +3.50 sphere × −0.50 cylinder at 180 deg in the left eye. The hypermetropia noted at age 5 months was reduced. This change was not surprising, because primates tend to lose hypermetropia as they mature (Saunders, 1995). In addition, the degree of anisometropia was diminished, from a spherical equivalent of 3.50 diopters at age 5 months to 2.50 diopters at age 6 years. Keratometry readings in the right and left eyes were equal (49.00 diopters × 180 deg, 49.75 diopters × 90 deg). The ocular fundus in each eye was normal.

Nine days after isotope injection, the monkey was anesthetized with ketamine HCl (20 mg/kg, i.m.) for reexamination of the eyes. No evidence was found for any damage to the left eye from the isotope injection. The animal was then given a lethal dose of sodium pentobarbital into the peritoneal cavity. After death, it was perfused with normal saline followed by 2% paraformaldehyde. The eyes, optic nerves, and brain were removed intact. The axial length of each eye was measured by placing one prong of a caliper on the middle of the cornea and the other prong on the sclera overlying the fovea. The axial lengths were 20.65 mm OD, 19.77 mm OS. These measurements indicate that a shorter axial length of the left eye was responsible for the anisometropia.

The striate cortex was unfolded, flattened, and sectioned at 30 μm on a freezing microtome. Alternate sections were prepared for autoradiography or cytochrome oxidase. The column patterns in the autoradiographs were reconstructed with Photoshop 3.0 (Adobe Systems, Inc., Mountain View, CA). To make the black-and-white drawings, we traced the borders of the dark columns at high magnification on the monitor using the "pencil" function at a 1 pixel width setting. The dark columns were then flood-filled with black, copied, and pasted onto a white background. For quantification, the drawings were analyzed using Mocha software (Jandel Scientific, San Rafael, CA). This program has a thresholding function which can be used to assign pixels to right eye columns (black, level of gray = 1) or left eye columns (white, level of gray = 256). By calibration with the scale marker, pixel numbers are converted automatically to mm^2. Intermediate levels of gray were used to quantitate the unreconstructable areas, blind spots, and monocular crescents. For further description of these methods, see Horton and Hocking, 1996*b*.

Results

The spatial contrast sensitivity was tested in each eye at age 1 year. At low spatial frequencies, the contrast sensitivity in the amblyopic left eye was reduced only slightly (Fig. 1). At higher spatial frequencies, the difference in contrast sensitivity between the two eyes became progressively larger. The overall pattern of contrast sensitivity loss mirrored that found in animals with amblyopia from experimental anisometropia (Kiorpes et al., 1993). It also resembled the pattern in humans with anisometropic amblyopia (Bradley & Freeman, 1981). The vernier acuity was 0.31 min of arc in the normal right eye and 1.09 min of arc in the amblyopic left eye. The level of grating acuity in the left eye was equivalent to a Snellen acuity of about 20/60.

The ocular dominance columns were well labelled throughout the striate cortex of both hemispheres by [^{3}H]proline eye injection (Fig. 2). The column pattern looked extremely similar to mosaics reconstructed previously in other macaque species, like *M. mulatta* and *M. fascicularis* (LeVay et al., 1985; Florence & Kaas, 1992; Horton & Hocking, 1996*b*). The striate cortex was unusually large in this animal (Table 1). It measured 1868 mm^2 on the left side and 1746 mm^2 on the right side, averaging 1807 mm^2. This figure was more than 50% greater than the mean V1 area of 1069–1195 mm^2 in *M. mulatta* (Van Essen et al., 1984; Purves & LaMantia, 1993) and 1072 mm^2 in *M. fascicularis* (Horton & Hocking, 1996*b*).

Along the V1/V2 border, we counted 161 (left V1) and 166 (right V1) pairs of columns (Table 1). This number of column pairs was large compared with *M. fascicularis*. In a recent study of six normal adult *M. fascicularis*, the number of column pairs along the V1/V2 border averaged only 120, with a range from 101 to 154 (Horton & Hocking, 1996*b*). However, given the intrinsic variability in column periodicity found in *M. fascicularis*, and the absence of data from normal *M. nemestrina*, we do not ascribe the

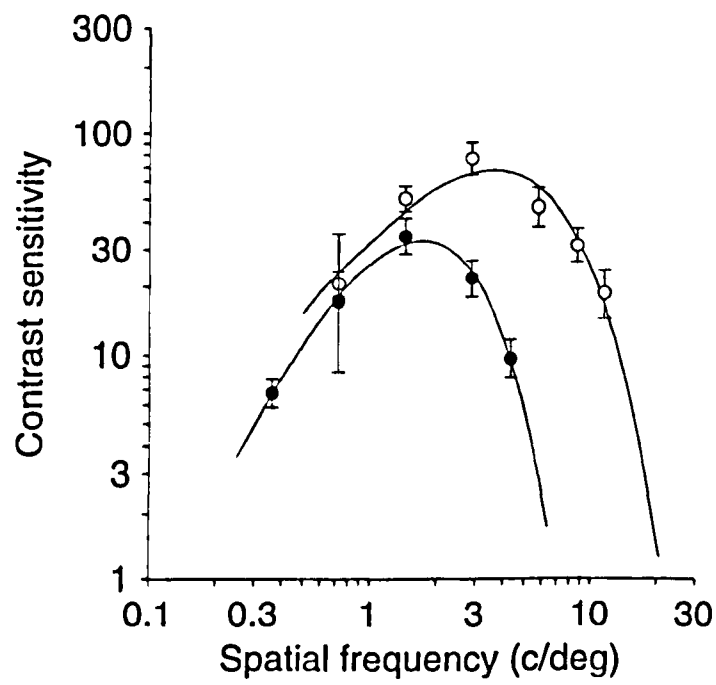


Fig. 1. Spatial contrast-sensitivity function for monkey VZ. Open symbols show data from the normal right eye and solid symbols represent the amblyopic left eye. Testing was done with the optimal correction of the refractive error in each eye. The deficit in contrast sensitivity is most pronounced at higher spatial frequencies. (From Kiorpes et al., 1993).

Table 1. *Measurements of the striate cortex*

	Left Hemisphere	Right Hemisphere
Area V1 (mm^2)	1868	1746
Unreconstructable (mm^2)	152	191
Operculum		
Right eye column area (mm^2)	407	355
	(51.6%)	(49.4%)
Left eye column area (mm^2)	382	364
	(48.4%)	(50.6%)
Periphery		
Right eye column area (mm^2)	473	310
	(57.0%)	(42.1%)
Left eye column area (mm^2)	343	427
	(43.0%)	(57.9%)
Area optic disc (mm^2)	16	17
Area monocular crescent (mm^2)	94	82
V1 perimeter[a] (mm)	168	165
Column pairs along V1/V2 border	161	166
Average column width along V1/V2 border (μm)	522	497

[a]V1 perimeter excludes monocular crescent.

large number of column pairs to an effect of anisometropic amblyopia upon column periodicity.

To determine the mean column width along the V1/V2 border, we divided the perimeter of V1 by the number of columns. This calculation yielded 522 μm (left V1) and 497 μm (right V1), close to the mean values in *M. mulatta* and *M. fascicularis* (LeVay et al., 1985; Horton & Hocking, 1996*b*). The large V1 area (and hence longer perimeter) and large number of column pairs offset each other, resulting in a mean column width near the average for other macaque species.

We were especially interested to learn whether the ocular dominance columns of the amblyopic left eye were shrunken compared with the ocular dominance columns of the normal right eye. Measurements of column areas in V1 of both hemispheres showed no shrinkage of the columns serving the left eye (Table 1). In the opercular cortex, representing ~0–10 deg, the contralateral eye's columns occupied slightly more area (1–2%) than those of the ipsilateral eye. This imbalance should not be ascribed to the animal's history of amblyopia, because it is found in normal macaques. We have found in *M. fascicularis* that the mean ratio of contralateral/ipsilateral column areas is 52:48 in opercular cortex (Horton & Hocking, 1996*b*). Measurement of column areas within the calcarine fissure, representing ~10–60 deg, showed even greater predominance of the contralateral eye (Table 1). This is also a normal finding in macaques, related to the fragmentation of the ipsilateral eye's columns near the monocular crescent representation (LeVay et al., 1985). Other investigators have also noted that the contralateral eye occupies slightly more territory than the ipsilateral eye in V1 of normal monkeys (Florence & Kaas, 1992; Rosa et al., 1992; Tigges et al., 1992).

Alternate sections reacted for CO activity showed a novel pattern in layer IV. There were faint dark bands separated by a pale gap in layer IVb and layer IVc (Fig. 3A). Comparison with an adjacent autoradiograph (Fig. 3B) showed that each dark CO band in layer IV was centered in the middle of an ocular dominance column, but narrower. Hence the dark CO bands were not congruous with the ocular dominance columns, as defined by tritiated proline, but in register with them. To test this relationship further, we examined sample regions at higher magnification, which makes alignment of blood vessels easier. As noted before, the dark CO bands (Fig. 4A) corresponded to the centers of the proline-labelled ocular dominance columns (Fig. 4B). The pale CO gaps straddled the borders between ocular dominance columns. In layers II,III, we observed normal staining of CO patches. There was no loss of activity in patches serving the amblyopic left eye. Each row of patches was in perfect register with a wide dark CO band in layer IVc (Fig. 4C). Given previous studies showing that rows of CO patches fit within the middle of ocular dominance columns (Horton & Hubel, 1981; Horton 1984), this finding provided further evidence that each dark CO band in layer IVc ran down the middle of an ocular dominance column.

Discussion

This pigtailed macaque, the first animal to be studied with naturally occurring anisometropic amblyopia, provided a rare opportunity to examine the striate cortex for structural changes underlying the reduced acuity in the amblyopic eye. The principal finding was that the ocular dominance columns in layer IVc appeared completely normal in autoradiographs. There was no shrinkage of the ocular dominance columns belonging to the amblyopic left eye; the average column widths were similar for the right and left eyes. This result is consistent with a prior report of a human anisometrope, who showed no shrinkage of ocular dominance columns belonging to the amblyopic eye (Horton & Stryker, 1993). By contrast, macaques with form-deprivation amblyopia from early monocular eyelid suture show striking shrinkage of the ocular dominance columns serving the deprived eye (Hubel et al., 1977; LeVay et al., 1980). The absence of column shrinkage in anisometropic amblyopia suggests that form deprivation and optical defocus can have different anatomical correlates in the striate cortex. This conclusion must be tendered cautiously because it is based upon a single animal.

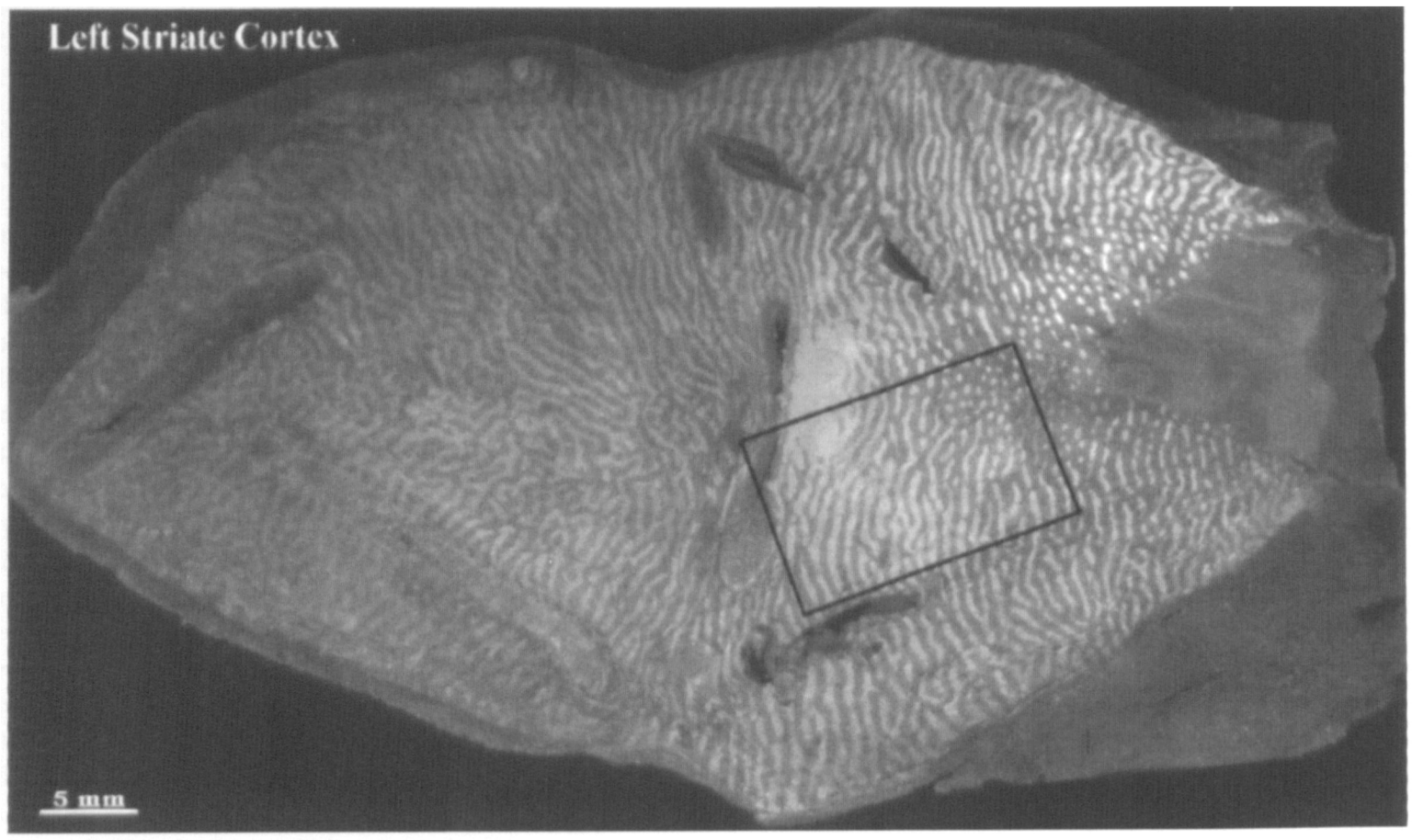
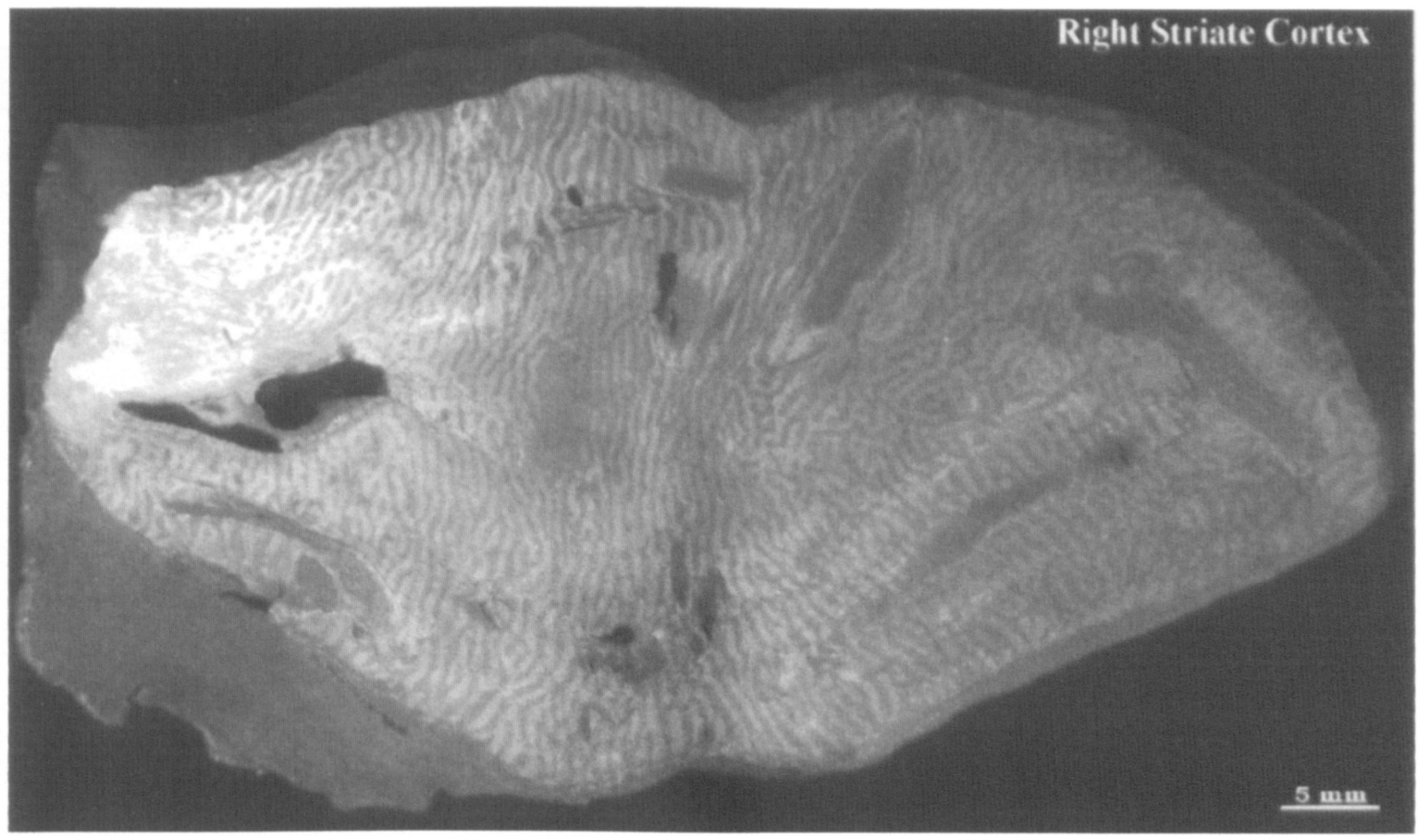
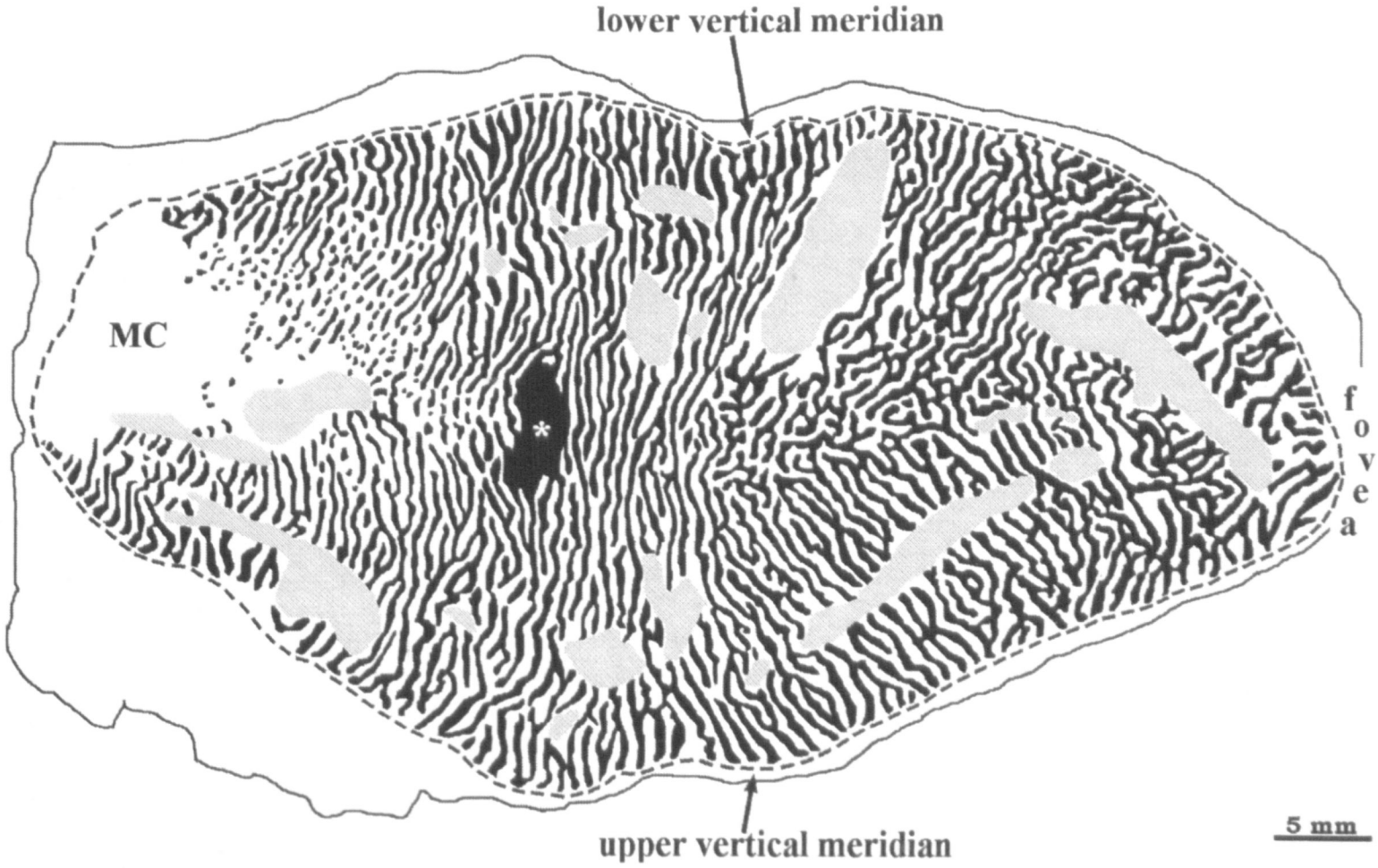


Fig. 2. Montages of ocular dominance columns in the flattened striate cortex from monkey VZ, prepared from autoradiographs through layer IVcβ. In dark field, the [^{3}H]proline-labelled columns of the amblyopic left eye appear light. The regions which could not be reconstructed are shaded in gray in the black-and-white drawings. This animal had a large V1 in each side, with over 160 sets of columns along the V1/V2 border. There was no shrinkage of the light columns serving the amblyopic left eye. The region within the rectangle in the photomontage of left V1 is shown in Fig. 3. MC: monocular crescent, and asterisk: blind spot. (*Figure continues on facing page.*)





In a previous study of anisometropic amblyopia in macaques, Hendrickson et al. (1987) reported moderate shrinkage of deprived eye columns in animals raised with chronic unilateral atropinization. This report differed from the present report in that the amblyopia was produced experimentally in the Hendrickson et al. (1987) study whereas the amblyopia was naturally occurring in the present case. The atropine treatment disturbed focus continuously beginning within the first few postnatal weeks when ocular dominance column organization is malleable; as discussed below, we do not know precisely when the anisometropia developed in monkey VZ. It is important to note that Hendrickson et al. (1987) based their conclusion regarding column shrinkage only on cytochrome oxidase patterns, with no supporting evidence from transneuronal transport or enucleation. As shown previously (Horton, 1984),

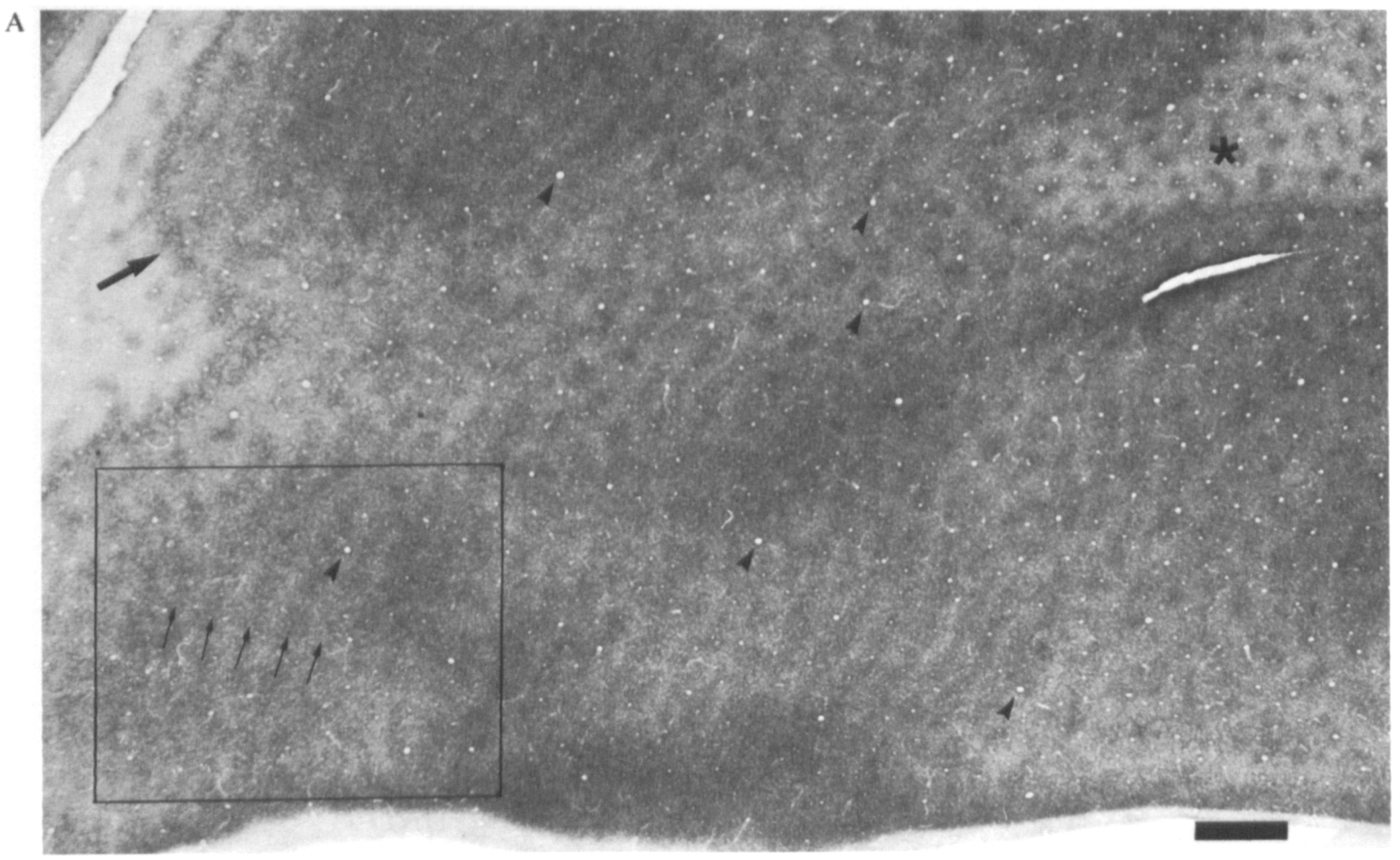
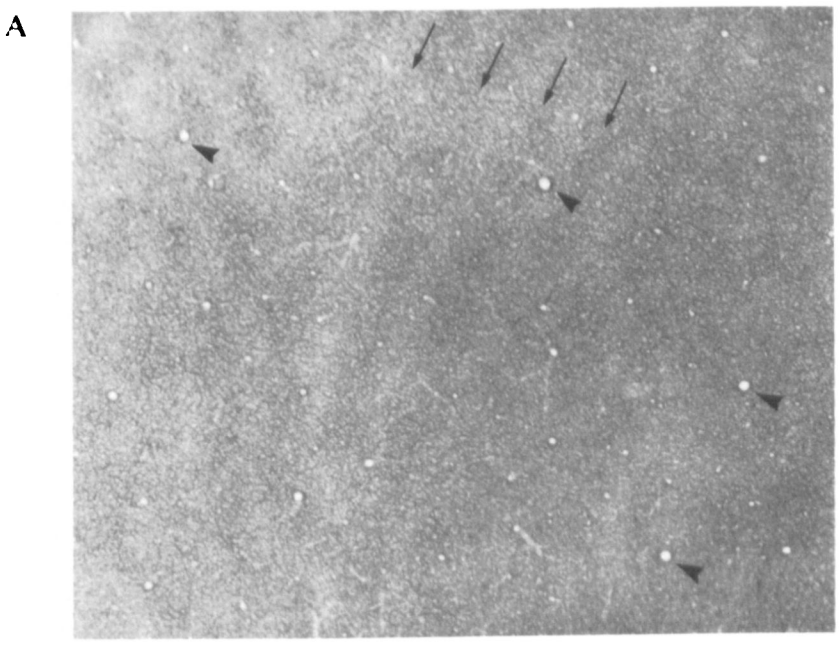


Fig. 3. (A) Section showing CO bands in layer IV (thin arrows). They were most distinct in layer IVcα, but also visible in layer IVcβ and IVb. The asterisk indicates CO patches in layer III and the large arrow shows the "honeycomb" in layer IVa. Arrowheads mark prominent blood vessels used for section alignment. The region within the box is illustrated in Fig. 4. Scale bar 1 mm. (B) Autoradiograph from the rectangle in Fig. 2, cut one section deeper, showing the ocular dominance columns in layer IVc. Each dark CO band in (A) fits in the middle of an ocular dominance column (arrows). There is relative loss of CO activity along the borders between ocular dominance columns, resulting in a pattern of dark bands corresponding to the centers of the ocular dominance columns.

cytochrome oxidase stripes align with the ocular dominance columns but are not necessarily equivalent in extent.

There are two likely explanations for the lack of column shrinkage in our animal. In macaques, the critical period for plasticity of geniculocortical projections in layer IVc is over by age 3 months (LeVay et al., 1980). Anisometropia was detected in our monkey at age 5 months, when the first refraction was performed. If anisometropia developed between 3–5 months of age, the ocular dominance columns would no longer have been vulnerable to shrinkage from visual deprivation. Alternatively, anisometropia might have emerged during the first 3 months of life, or even have been congenital. However, retinal blur caused by a few diopters of refractive error during the critical period probably has less drastic effects than eyelid suture. Eyelid suture deprives the retina of formed images (Wiesel & Hubel, 1963), and therefore induces a profound amblyopia in early life. By contrast, optical defocus allows the retina still to receive formed (albeit blurred) images. The degree of visual deprivation may not be sufficient to shrink the ocular dominance columns in the striate cortex, which is consistent with the milder amblyopia. These considerations underscore the notion that both the timing and the severity of the visual insult govern how the anatomy of the striate cortex is affected by visual deprivation. The amblyopia in monkey VZ was either too mild or too late to cause shrinkage of ocular dominance columns. It was, nonetheless, typical of the depth of amblyopia found in clinical surveys, and hence likely to reflect the findings in many cases of human anisometropic amblyopia (Jampolsky et al., 1955; Helveston, 1966; Sen, 1980; Kivlin & Flynn, 1981; Townshend et al., 1993).



Although the ocular dominance columns labelled by [^{3}H]proline appeared normal, the pattern of CO staining in layer IV was abnormal. Faint, dark CO bands, situated in register with rows of patches in layers II,III, occupied the middle of the ocular dominance columns in layer IVb and IVc. CO bands have not been reported previously in layer IVc of the normal adult macaque striate cortex, although faint rows of patches have been seen in layer IVb (Horton, 1984). However, a similar pattern of dark CO bands running down the core zones of ocular dominance columns in layer IVc has been described in the striate cortex of normal neonatal macaques (Horton & Hocking, 1996*a*). This unusual pattern reflects the subdivision of ocular dominance columns into core zones and border strips (see Fig. 37, Horton, 1984). The core zones run down the middle of the ocular dominance columns, are strictly monocular, and fit in register with the CO patches. The border strips are located along the boundaries of the ocular dominance columns and are more binocular. This subdivision of layer IVc has a counterpart in the pattern seen with the Liesegang silver method (LeVay et al., 1975): the core zones stain darkly whereas the border strips appear light. In normal animals, core zones and border strips have equal metabolic activity, so no CO pattern is visible in layer IVc. In neonatal animals, the border strips stain more weakly for CO (Horton & Hocking, 1996*a*), implying less well-developed binocular mechanisms.

After monocular suture in juvenile animals, CO activity is lost in border strips serving both eyes, and within the core zones of the

Fig. 4. (A) Magnified view of the region enclosed by the box in Fig. 3A, showing the dark bands of CO activity in layer IVc (arrows). At higher power, blood vessels (arrowheads) used for section alignment are more visible, but the CO bands are difficult to appreciate. Holding the page at arm's length improves their visibility. (B) Corresponding region from the adjacent autoradiograph showing proline labelled ocular dominance columns in layer IVc. Arrows, placed in precise register with those in (A), show that each dark CO band runs down the middle of an ocular dominance column. Only two blood vessels (arrowheads) can be seen in the autoradiograph. (C) CO section from layer III showing rows of patches. The dark bands in (A) are in register with each row of CO patches (arrows), confirming that they are in register with the center of ocular dominance columns. Scale bar = 1 mm for all three panels.

deprived eye. This combination of reduced CO activity results in a pattern of thin dark stripes alternating with wide pale stripes in layer IVc (Horton, 1984). A similar pattern of thin dark bands alternating with wide pale stripes is found after unilateral deprivation by chronic instillation of atropine or by aphakia (Hendrickson et al., 1987; Tigges et al., 1992). Hendrickson et al. (1987) double-labelled the deprived eye columns using C^{14}-2-deoxyglucose and concluded that the thin dark stripes were aligned with the deprived eye, whereas after monocular suture, they were aligned with the nondeprived eye. This discrepancy in the literature, on the assignment of the thin dark CO stripes to the deprived or nondeprived eye, remains unexplained.

In our monkey with naturally occurring anisometropic amblyopia, the mild decrement in acuity to ~20/60 in the left eye did not reduce CO activity in the core zones of either eye. CO activity in rows of patches in layers II,III was not reduced either. However, a relative fall in CO activity occurred along the border strips serving both eyes. This resulted in dark bands in layer IV corresponding to the monocular core zones of the ocular dominance columns. From this finding, we conclude that anisometropic amblyopia impaired binocular processing in our monkey, thereby reducing CO activity along binocular regions straddling the ocular dominance columns. This inference is consistent with an electrophysiological study showing marked loss of binocular cells in V1 of monkeys raised with daily atropine instillation in one eye to simulate anisometropic amblyopia (Movshon et al., 1987). It is also consistent with the loss of stereofunction reported in humans and monkeys with anisometropic amblyopia (Peters, 1969; Walraven, 1975; Baitch et al., 1991).

The loss of relative CO activity within the border strips might also be explained by an undetected small-angle strabismus, rather than anisometropia. Strabismus would reduce CO activity along the border strips, because cells in these regions require binocular stimulation for optimal response. Many patients with anisometropic amblyopia also have a microtropia, measuring less than 3–4 deg (Helveston & von Noorden, 1967). It has been suggested that microstrabismus, rather than the anisometropia, may be responsible for their amblyopia (Almeder et al., 1990). We could not exclude a strabismus less than 3–4 deg, by relying upon fixation patterns and the corneal light reflex. Therefore, in monkey VZ either microstrabismus or anisometropia could have been responsible for the loss of CO activity in the border strips of layer IVc.

The ocular dominance and CO patterns found in this amblyopic monkey suggest that naturally occurring anisometropic amblyopia and artificially induced deprivation can have different effects upon structure and metabolic activity in the striate cortex. Our results also indicate that amblyopia is not always accompanied by changes in the size of ocular dominance columns. Relatively mild forms of amblyopia, which are clinically more common, may instead be reflected in the physiological properties of cortical neurons (Movshon et al., 1987). Additional studies of naturally occurring amblyopia will be important for understanding the relationship between ocular dominance patterns and amblyopia.

Acknowledgments

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