

# Ocular Dominance Column Development: Strabismus Changes the Spacing of Adjacent Columns in Cat Visual Cortex

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To investigate the role of visual experience for the gross layout of ocular dominance (OD) columns in the visual cortex, I compared the respective patterns in normally raised and strabismic cats. OD domains were visualized by (1) trans-neuronal labeling of the afferents from the left or right eye with intraocular  $^3\text{H}$ -proline injections or (2)  $^{14}\text{C}$ -2-deoxyglucose autoradiography after monocular visual stimulation in awake animals. To obtain the complete pattern of OD columns, flat-mount sections were prepared from the unfolded cortical hemispheres. Eliminating correlated activity between the two eyes by making the animals strabismic influenced the gross layout of the OD domains. In area 17, OD domains become more sharply delineated than in normal animals and spaced more widely. Spatial frequency analyses revealed a mean spacing of adjacent columns of 1100–1300  $\mu\text{m}$  in strabismic and of 800–1000  $\mu\text{m}$  in normal cats. In area 18, the spacing of the ocular dominance domains is larger than in area 17 for both normal and strabismic cats (1500–1650  $\mu\text{m}$ ), but little influenced by strabismus. These results indicate that in area 17 decreased correlation of activity between the eyes alters the periodicity of OD columns. In addition, these observations suggest that not only the segregation of afferents into distinct columns but also the final expression of the columnar grid is influenced by visual experience, and in particular by the temporal patterning of neural activity. This is further evidence for the hypothesis that the development of OD columns is governed by activity-dependent self-organizing principles.

**[Key words: area 17, area 18, squint, self-organization, experience dependence, cortical maps]**

When kittens are born, the geniculocortical afferents from the two eyes are overlapping in cortical layer IV, the input layer of primary visual cortex (LeVay and Gilbert, 1976; LeVay et al., 1978). The segregation of these projections into alternating

patches, called “ocular dominance columns,” occurs during early life starting at about 3 weeks of age (LeVay et al., 1978; Shtatz and Stryker, 1978). In the past 20 years, a huge number of investigations demonstrated the influence of afferent activity on the development of the ocular dominance columns by using several different experimental paradigms like monocular and binocular deprivation, impulse blockade, dark rearing, and squint. When neuronal activity is completely blocked in the eyes during a critical period early in development, the patches do not develop at all (Stryker and Harris, 1986; see also Meyer, 1982). When neuronal activity is reduced in the eyes (dark rearing or binocular lid suture) the degree of segregation seems to be reduced as well (Wiesel and Hubel, 1965; Swindale, 1981; Kalil, 1982; Mower et al., 1985). On the other hand, the elimination of correlated activity between the two eyes, as it occurs in strabismus, enhances segregation (Shtatz et al., 1977; Kalil, 1982; Löwel and Singer, 1993b). When neuronal activity is reduced in only one eye (monocular deprivation) projections from this eye occupy much less than their normal share of territory in layer IV, while those from the open eye expand (Wiesel and Hubel, 1965; Hubel et al., 1977; Shtatz and Stryker, 1978; LeVay et al., 1980). It has been concluded from these studies that the formation of ocular dominance columns is driven by activity-dependent competition between the geniculocortical afferents of the two eyes whereby the temporal patterning of neural activity conveys the essential information for the axons to segregate (Stryker and Strickland, 1984). Therefore, many workers in the field interpreted these results as indicating that column formation is the result of a competitive self-organizing process (for review, see Stryker, 1986, 1991; Constantine-Paton, 1983; Constantine-Paton et al., 1990; Goodman and Shtatz, 1993). Whether similar mechanisms are also responsible for the final expression of the columnar pattern, that is, for the spacing of adjacent columns, their width, and location, is less well investigated. If one could demonstrate that these parameters can also be influenced by visual experience one would have compelling evidence that the development of ocular dominance columns is indeed determined by activity-dependent self-organizing principles and not by factors intrinsic to the cortex and independent of properties of the cortical inputs, as recently suggested by Jones et al. (1991).

To investigate the role of visual experience and in particular the temporal patterning of activity for the gross layout of ocular dominance columns, I analyzed these domains in strabismic cats, paying particular attention to the spacing of adjacent domains. For comparison, normally raised control animals were analyzed. All strabismic cats of the present study had a surgically induced divergent squint angle. As a consequence of the misalignment of the optical axes, the activities in the geniculocor-

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Table 1. List of all cats used to visualize ocular dominance columns

Cat	Cortex	Age (weeks)	Weight (gm)	Number of sections	Method	OD spacing ( $\mu$ m)		Length of area 17 (mm)
						Area 17	Area 18	
S1	Right	8	840	58	2-DG	1250		38
	Left			64		1270	1550	39
S2	Right	13	1510	59	2-DG	1220		39
	Left			65		1250	1500	39
S3	Right	8.5	980	60	Proline (+2-DG)	1200		38
S4	Left	9	1000	62	Proline (+2-DG)	1160		37
							1650	
S5	Right	10	940	52	2-DG	1150	1500	34
	Left			53		1180		35
S6	Right	10	1120	56	2-DG	1110		35
	Left			54		1200		
N1	Left	15	1300	54	Proline	960		35
N2	Right	9.5	850	57	2-DG	1020	1600	40
	Left			60		940		40
N3	Right	10.5	1080	59	2-DG	930		40
	Left			62		1000		40
N4	Right	12	1200	65	Proline	770		33
	Left			70		800		33
N5	Right	12	1200	65	Proline	850		32
	Left			58		830	1650	32

Cat, "name" of the animal. Cortex, hemisphere used for the analysis of the OD spacing. Age (in weeks), age of the cats. Weight, body weight (in grams) of the cats. Number of sections, number of cortical flat-mount sections. Method, technique used to visualize ocular dominance columns. OD spacing, spacing of adjacent ocular dominance domains determined by spatial frequency analysis of the autoradiographs. Length of area 17, anterior-posterior extension (in millimeters) of area 17. S, strabismic; N, "normal"; 2-DG, 2-deoxyglucose; OD, ocular dominance column.

tical afferents of the two eyes are no longer correlated and most cells in the visual cortex become responsive exclusively to stimulation of either the right or the left eye (Hubel and Wiesel, 1965). However, these monocularly driven cell populations are capable of subserving normal pattern vision. To avoid double vision, strabismics use only one eye at a time and suppress the signals from the other eye (von Noorden, 1990). Taken together, the amount of neural activity reaching the cortex via the geniculocortical afferents should be similar for normal and squinting cats, whereas the temporal patterning of activity is different.

Some of these results have been reported in abstract form (Löwel and Singer, 1993c,d).

## Materials and Methods

A total of 11 cats were used in this study (see Table 1). All animals had already been subjects of other investigations (Löwel and Singer, 1987, 1992, 1993a,b). In six kittens from four different litters (S1/S2, S3/S4, S5, and S6), divergent strabismus was induced surgically at the age of 2–3 weeks. The remaining five kittens from three different litters (N1, N2/N3, N4/N5) were normally raised (controls). Ocular dominance columns were visualized with two different techniques: (1) anatomically by intraocular  $^3\text{H}$ -proline injections (Grafstein, 1971; Wiesel et al., 1974) and/or (2) functionally with  $^{14}\text{C}$ -2-deoxyglucose after monocular stimulation (Sokoloff et al., 1977). The normally raised cats were awake and freely exploring the laboratory during the monocular 2-DG experiments, and the strabismics were either awake or anesthetized and paralyzed (Löwel and Singer, 1993a,b).

**Surgical procedures and visual stimulation.** For the induction of strabismus, anesthesia was induced with ketamine hydrochloride (10 mg/kg body weight) and xylazine hydrochloride (2.5 mg/kg) intramuscularly, and maintained with ketamine hydrochloride intravenously. In

all six kittens, the medial rectus muscle of the left eye was severed to induce divergent strabismus.

For transneuronal labeling of ocular dominance columns in layer IV, two strabismics and three normally reared cats were anesthetized as above (ketamine/xylazine) and then injected with 2–2.5 mCi of  $^3\text{H}$ -proline (Amersham; injected volume 50  $\mu\text{l}$  in cats N1, N5, S3, and S4, and 25  $\mu\text{l}$  in cat N4) in one eye (the right eye in cats N4, N5, S3, and S4; the left eye in cat N1) (see Table 1).

At the age of 2–3 months, in four strabismic (S1, S2, S3, S4) and two normally raised cats (N2, N3) one eye was occluded and a venous catheter implanted under halothane anesthesia (1–4% halothane in a mixture of 70%  $\text{N}_2\text{O}$ , 30%  $\text{O}_2$ ). After full recovery from anesthesia, 2-deoxy- $\text{D}$ - $^{14}\text{C}$ -glucose (2-DG, Amersham; specific activity, 310 mCi/mmol; 100–120  $\mu\text{Ci/kg}$ ) was injected and the cats were allowed to move freely around in the laboratory for effective monocular stimulation.

The remaining two strabismic cats (S5, S6) were prepared for a "conventional" 2-DG experiment (under anesthesia and paralysis) as described in detail elsewhere (Löwel et al., 1987; Löwel and Singer, 1993a). Therefore, only the essential steps of the preparation are reported. Anesthesia was induced as described above and, after tracheal intubation and cannulation of a femoral vein, was maintained with a mixture of 70%  $\text{N}_2\text{O}$ , 30%  $\text{O}_2$ . The animal's head was fixed in a stereotaxic frame by means of a metal bar cemented to the skull and a muscle relaxant (hexcarbacholinbromide, 10 mg in 45 ml of Ringer, 3 ml/kg/hr) was applied to prevent eye movements. All wound edges were infiltrated with xylocaine. As with standard electrophysiological recordings, the body temperature, ECG, EEG, pulmonary pressure, and  $\text{CO}_2$  content of the expired air were continuously monitored. End-tidal  $\text{CO}_2$  and rectal temperature were kept in the range of 3–4% and 37–38°C, respectively. Both animals were stimulated monocularly through the right eye; therefore, the left (nonstimulated) eye was covered with a black contact lens and an additional black patch. Simultaneously with the onset of light stimulation, the animals received an intravenous injection of 2-deoxy- $\text{D}$ - $^{14}\text{C}$ -glucose (Amersham; specific activity, 310 mCi/mmol; 110–125

$\mu\text{Ci/kg}$ ) at a rate of 25  $\mu\text{Ci/min}$ . Visual stimulation was monocular and consisted of moving square wave gratings that covered the central 20° of the visual field. A 1.5° wide strip along the vertical meridian was stimulated with horizontal contours only, whereas the orientation of the grating in the remaining visual field changed every 5 sec in 45° steps (spatial frequency, 1, 0.5, and 0.15 cycles/degree; velocity, 2 cycles/degree).

**Histological procedures.** After 45 min of visual stimulation, the "2-DG" animals were given a lethal dose of Nembutal injected intravenously. The "proline" animals received a similar overdose of Nembutal after a survival time of 2 weeks (which is needed for the transneuronal transport of the radioactively labeled proline).

The occipital poles of the brains were removed and the visual cortices flat-mounted prior to freezing the tissue on dry ice (Freeman et al., 1987). To provide landmarks for superposition of adjacent sections, three holes were made in the flat-mounts with warm needles. Subsequently, 26- $\mu\text{m}$ -thick serial cryostat sections were cut parallel to the cortical surface. The sections were mounted on glass slides and immediately dried on a hot plate. For  $^{14}\text{C}$ -2-DG autoradiography, they were exposed to x-ray film (Agfa Mamoray M4) for 3–4 weeks. For the visualization of the  $^3\text{H}$ -proline distributions, the sections were postfixed in 4% paraformaldehyde (in the double-labeling experiments, washed to remove all  $^{14}\text{C}$ -2-DG), and then exposed to Ultrofilm (LKB) for 8–12 weeks (Löwel et al., 1988). [To control for the possibility that the  $^3\text{H}$ -proline had contributed to the darkening of the  $^{14}\text{C}$ -2-DG autoradiographs, the sections were exposed a second time, after washout of  $^{14}\text{C}$ -2-DG (now only  $^3\text{H}$  should be contained in the sections), to the x-ray films (sensitive to  $^{14}\text{C}$ ). These controls never revealed any substantial labeling on the  $^{14}\text{C}$  films.]

**Image processing and data analysis.** Although we had unfolded the cortex, single flat-mount sections never covered the full extent of layer IV and therefore did not contain the complete pattern of  $^3\text{H}$ -proline-labeled ocular dominance columns (which are restricted to layer IV). To obtain the complete pattern a photomontage of all label-containing regions was made, using the needle holes as guidelines for the correct superposition of serial sections.

The  $^{14}\text{C}$ -labeled ocular dominance columns extend in columns through all cortical layers (Löwel and Singer, 1992, 1993b). Therefore, single autoradiographs always contain the complete pattern of ocular dominance columns and reconstructions were not necessary.

The mean spacing of columns was determined by spatial frequency analysis. To this end,  $^3\text{H}$ -proline and  $^{14}\text{C}$ -2-DG autoradiographs were analyzed with a digital image processing system (IMAGO II, Compulog). The density distributions of the x-ray films were coded in digital units, ranging from 1 to 256. Average columnar spacing was determined by one-dimensional Fourier analyses along multiple vectors perpendicular to the columnar boundaries. Since ocular dominance domains have a small tendency to be elongated orthogonal to the 17/18 border (Löwel and Singer, 1987; Anderson et al., 1988), most measurements were performed parallel to that border, that is, in an anterior–posterior direction (perpendicular to the long axis of elongated slabs, a direction most probably unaffected by "unfolding" artifacts; see below).

As an indication of the size of area 17, its length was determined by measuring the extension of the area showing (1) ocular dominance domains or (2) "area 17-specific" 2-DG labeling (in the anesthetized cats S5 and S6) on the autoradiographs in an anterior–posterior direction. I did not attempt to determine the surface area of area 17 because flat-mounts may get compressed in a mediolateral direction during unfolding (the gyri and sulci extend predominantly in an anterior–posterior direction so that incomplete unfolding would result in a compression of the autoradiographs in a mediolateral direction).

## Results

### General

In the present study, ocular dominance domains were visualized with two different techniques: (1) anatomically by transneuronal labeling of the geniculocortical input to layer IV of visual cortex after intraocular  $^3\text{H}$ -proline injections and (2) functionally with  $^{14}\text{C}$ -2-DG autoradiography after monocular visual stimulation. Since monocularly activated 2-DG columns are in precise register with the termination zones of the afferents from the activated eye in layer IV (Löwel and Singer, 1992, 1993b) the two techniques give essentially similar results. The only difference

is that proline-labeled ocular dominance domains are restricted to layer IV (LeVay and Gilbert, 1976), whereas the 2-DG labeling extends in a columnar fashion through all cortical layers (Löwel and Singer, 1993b).

### Layout of ocular dominance domains in area 17

As described previously (Löwel and Singer, 1993b), in strabismic the 2-DG and proline patterns display all the features characteristic of ocular dominance domains (Figs. 1, 2; for additional comparison with normally raised cats, see Löwel and Singer, 1987; Anderson et al., 1988): (1) The optic disk representations of the stimulated or injected eye are identifiable in the posterior third of the hemispheres as demarcated oval regions that are solidly labeled ipsilateral to the open or injected eye and unlabeled on the contralateral side. (2) The monocular segment is indicated by uniform labeling at the medial border of the area 17 contralateral to the stimulated or injected eye and by the absence of labeling at comparable eccentricity on the ipsilateral side. (3) The territories of the stimulated or injected eye tend to be larger in the contra- than in the ipsilateral hemispheres.

### "Sharpness" of the segregation of ocular dominance columns in area 17

The reconstructions of the complete pattern of ocular dominance columns in strabismic cats confirm observations of an older study by Shatz et al. (1977): Patches of label representing the ipsi- or contralateral eye were more distinct than in normal cats, most likely due to a decrease in the amount of label distributed between patches (compare Fig. 1A,B). Artificially induced squint therefore appears to decrease the volume of layer IV shared by afferents from the two eyes, which is consistent with the electrophysiological observations of reduced binocularity in these animals (Hubel and Wiesel, 1965).

### Spacing of ocular dominance columns in area 17

In addition to the reported differences between the patterns of ocular dominance columns of strabismic and normally raised cats, the spacing of adjacent domains is also altered in squinting cats. To illustrate this observation, complete reconstructions of ocular dominance domains in all six strabismic cats and in four of the five normally raised control animals are shown here (compare Figs. 1A, 4A–F with Figs. 1B, 2, 3A–F).

To quantify this difference in spacing, the spectral content of the pattern of ocular dominance columns was analyzed by one-dimensional Fourier analyses along vectors perpendicular to the columnar boundaries. Although ocular dominance columns in both strabismic and normal cats are rather patchy, numerous elongated slabs and short bands are also present (see, e.g., the ocular dominance domains adjacent to the optic disk representations in Fig. 1A,B or in general the pattern of ocular dominance columns of the strabismic cat in Fig. 1B). Vectors were therefore oriented perpendicular to the long axis of these slabs. Since ocular dominance columns have a small tendency to elongate orthogonal to the 17/18 border (Löwel and Singer, 1987; Anderson et al., 1988), measurements were performed predominantly in an anterior–posterior direction. Figure 5 shows that the resulting one-dimensional Fourier spectra for the normal cats peak at values between 770  $\mu\text{m}$  and 1020  $\mu\text{m}$  (mean value,  $900 \pm 85 \mu\text{m}$ ), while those of the strabismics range between 1110  $\mu\text{m}$  and 1270  $\mu\text{m}$  (mean value,  $1199 \pm 48 \mu\text{m}$ ; see also Table 1). Figure 6 shows that the two distributions are not only

A



*Figure 1.* Overall pattern of the ocular dominance columns in the visual cortex of the normally raised cat N4 (*A*) and the strabismic cat S3 (*B*, *C*): photographic reconstruction of the  $^3\text{H}$ -proline-labeled columns in layer IV ipsilateral to the injected eye (*A*, *B*) and a graphical reconstruction (by hand-drawing successive sections) of the pattern in *B* (*C*). The optic disk representations appear in the posterior third of area 17 as oval and

B



solidly labeled regions (*downward to the left*). Note the sharp delineation of labeled (*dark gray*) and unlabeled (*light gray*) territories, which is more pronounced in the strabismic animal. Note in addition that the periodicity of the ocular dominance columns is wider in the strabismic animal. *ant*, anterior; *lat*, lateral. Scale bar, 2 mm.

C

ant  
↑  
→ lat



Figure 1. Continued.



different but essentially nonoverlapping: none of the strabismic cats had a spacing of ocular dominance columns in the range of normally raised animals and vice versa.

The values obtained for the normally raised cats are in good agreement with other reports in the literature (Fig. 6): Shatz et al. (1977) measured distances of 1 mm; LeVay et al. (1978), 850  $\mu$ m; and Diao et al. (1990),  $0.8 \pm 0.2$  mm (the measurements of Löwel and Singer, 1987, are contained in the present report). Taken together, in area 17 of strabismic cats ocular dominance domains are on average spaced 1.3 times more widely than in animals with normal visual experience.

To exclude that those differences in spacing were due to differences in age or weight of the animals, I related spacing to these variables. As Figure 7, *A* and *B* indicates, there does not seem to be a systematic relationship between these variables. Interestingly, however, the largest columnar spacing of all cats (1270  $\mu$ m) was obtained in the youngest and lightest cat that was one of the squinting animals (8 weeks, 840 gm). In addition, the strabismic cats of the present study were on average younger (mean value,  $9.8 \pm 1.6$  weeks) and lighter ( $1065 \pm 216$  gm) than the normal controls (mean value,  $11.8 \pm 1.9$  weeks;  $1126 \pm 155$  gm; see also Table 1). In addition, the possibility needs to be considered that the cortical flat-mounts of the strabismic cats had been more compressed during flattening than those of the normal animals, leading to larger columnar spacings in the former than in the latter. To test that possibility, the number of flat-mount sections obtained in the normal and strabismic cases was compared. If compression would have been responsible for the differences, then fewer flat-mount sections should have been obtained from the (more compressed?) cortices of the squinting animals. Figure 7*C* shows that this was not the case. The number of flat-mount sections was comparable in strabismic (52–65; mean value,  $58.3 \pm 4.3$ ) and normal cats (54–70; mean value,  $61.1 \pm 4.6$ ). A final control consisted of the assessment of the length of area 17. To this end, the extension of area 17 was determined in an anterior–posterior direction on the autoradiographs (for details, see Materials and Methods). In strabismic cats, values ranged from 34 to 39 mm (mean value,  $37.1 \pm 1.9$  mm), and in the normal cats from 32–40 mm (mean,  $36.1 \pm 3.6$  mm; see Table 1, Fig. 7*D*). These values are in good agreement with another report in the literature: area 17 of the normally raised cats of Anderson et al. (1988) measured 35 mm anteroposteriorly (range, 32–38 mm). Therefore, strabismic and normally raised animals do not differ significantly in the extension of their area 17 and the observed difference in columnar spacing cannot be due to a different length of area 17.

To quantify the relationships between the various variables (age, body weight, number of sections, length of area 17, strabismus or normal) and the spacing of adjacent ocular dominance columns, the correlation matrix of all variables was examined. The correlation coefficient (c.c.) between the visual experience of the animals (strabismic or normal) and columnar spacing was the largest of all correlations (c.c. 0.91), even larger than the coefficient between the age of the animals and their body weight (c.c. 0.86). Therefore, the statement that the spacing of ocular dominance columns is dependent on whether the cats are squinting or not is at least as significant as the statement that cats gain weight with increasing age. Age (c.c.  $-0.44$ ), body weight (c.c.  $-0.16$ ), number of sections (c.c.  $-0.31$ ), and length of area 17 (c.c. 0.50) are much less strongly correlated with columnar spacing than visual experience. The latter correlation coefficients are similar to the one between age of the animals and length of area

17 (c.c.  $-0.38$ ), that is, similar to the statement that area 17 gets smaller with increasing age. Given these comparisons, the only meaningful statements seem to be those with the highest correlation coefficients: (1) that animals get heavier when they get older (c.c. 0.86), which is trivial, and (2) that columnar spacing strongly depends on the visual experience of the animals (c.c. 0.91). Therefore, visual experience (strabismic or normal) is the *only* variable that is significantly correlated with the spacing of adjacent ocular dominance columns (c.c. 0.91).

Columnar spacing is similar in the two hemispheres of the same animal. The intraindividual variability is 2–9% (the respective larger spacings set to 100%), compared to the interindividual variability of 14% in the strabismic and 32% in the normal animals (see Table 1).

#### Ocular dominance domains in area 18

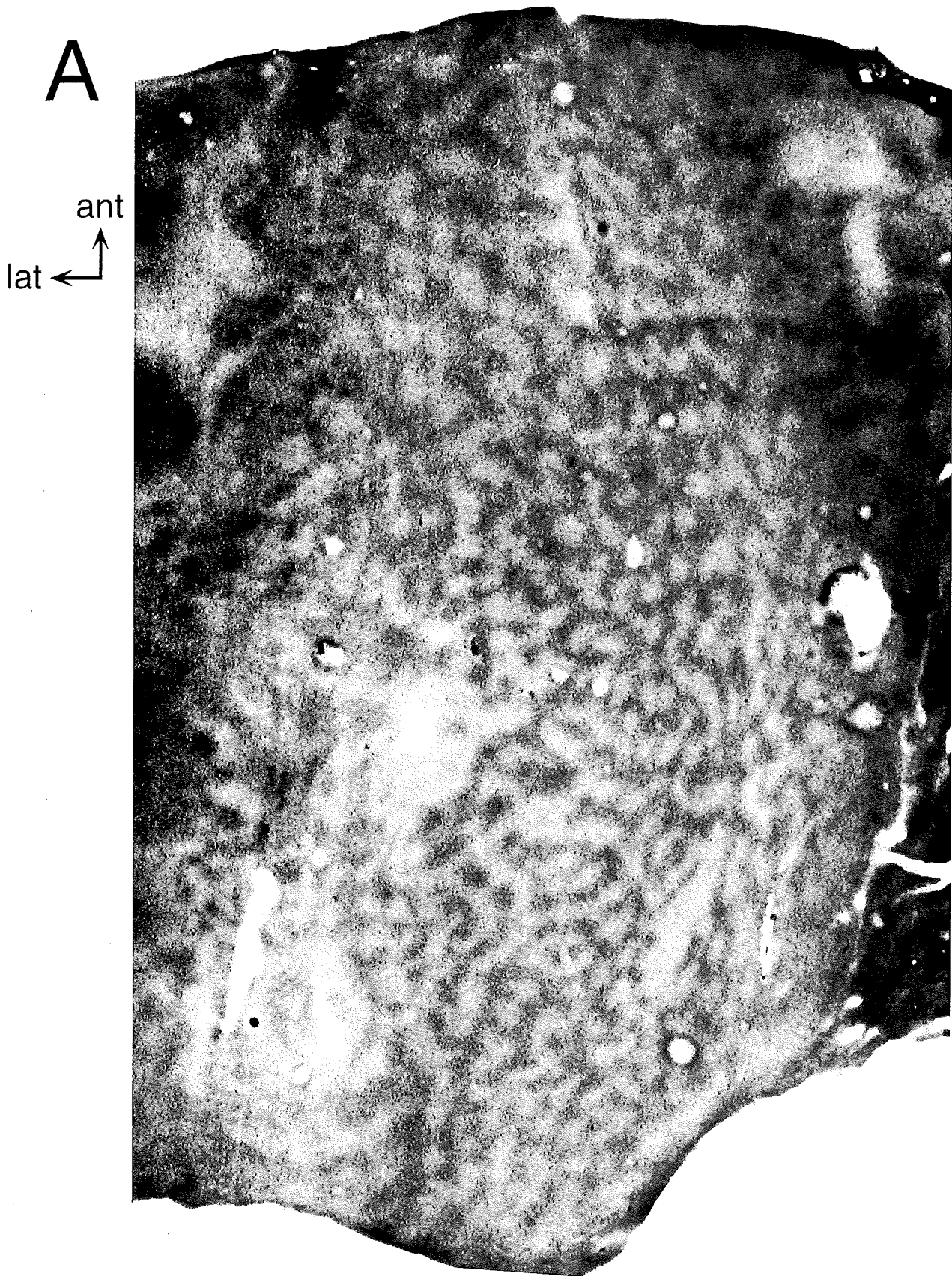
In four strabismic and two normally raised animals, area 18 could be demarcated with sufficient reliability to analyze the proline and 2-DG patterns in this part of the visual cortex. In all squinting animals, well segregated ocular dominance domains were present in area 18 (Fig. 8), both in the proline and 2-DG autoradiographs (compare Fig. 8*A,B*). As in area 17, proline-labeled ocular dominance domains are restricted to layer IV, whereas the 2-DG-labeled domains extend in columns through all cortical layers. These observations indicate that not only the thalamocortical afferents of the two eyes are well segregated in area 18 of squinting cats, as has been described before (Shatz et al., 1977), but that in addition, as in area 17, monocularly induced activity patterns are columnar and in register with the terminal patches in layer IV.

#### Spacing of ocular dominance columns in area 18

Although area 18 is much smaller than area 17 and therefore less accessible to quantitative analyses, columnar spacing was determined by one-dimensional spatial frequency measurements. The respective Fourier spectra of the strabismic cats peak at values between 1500  $\mu$ m and 1650  $\mu$ m (Fig. 9*A*; mean value 1550  $\mu$ m), those of the normals at 1600  $\mu$ m and 1650  $\mu$ m (Fig. 9*B*, mean value 1625  $\mu$ m). Figure 9*C* shows that the two distributions are overlapping, whereby the spacing of adjacent ocular dominance columns is on average slightly smaller in strabismic compared to normal cats. This trend is also present when measurements in the literature are included: According to Shatz et al. (1977), ocular dominance columns have a spacing of about 1600–1800  $\mu$ m in this visual cortical area (measured on the published photoprints); Cynader et al. (1987) give values of 1.86 mm; and Diao et al. (1990) described a spacing of 2.0 mm.

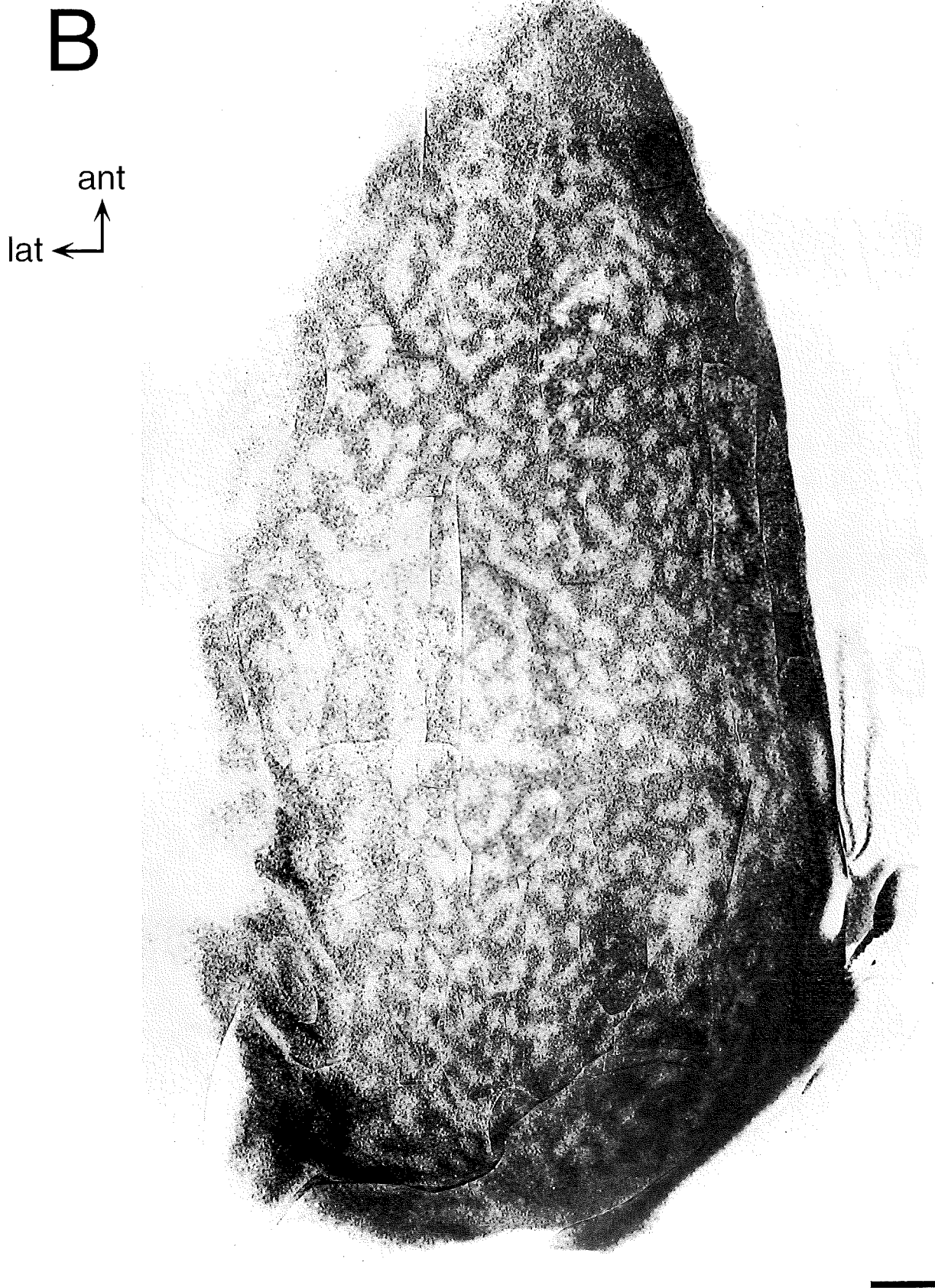
#### Comparison of the spacing of ocular dominance columns in areas 17 and 18

In area 18, ocular dominance columns are more widely spaced compared to area 17 both in strabismic and normally reared cats (Fig. 9*D*; compare also Figs. 6, 9*C*). There are, however, important differences in the ratio of columnar spacings (area 17 vs area 18) between the two experimental groups: in our normally raised animals, ocular dominance domains in area 18 are 1.6–2.0 times larger than in area 17 (Table 1, Fig. 9*D*). These values are in good agreement with numbers given in the literature: Shatz et al. (1977) described that in normal cats, ocular dominance columns in area 18 are “almost doubled” in size

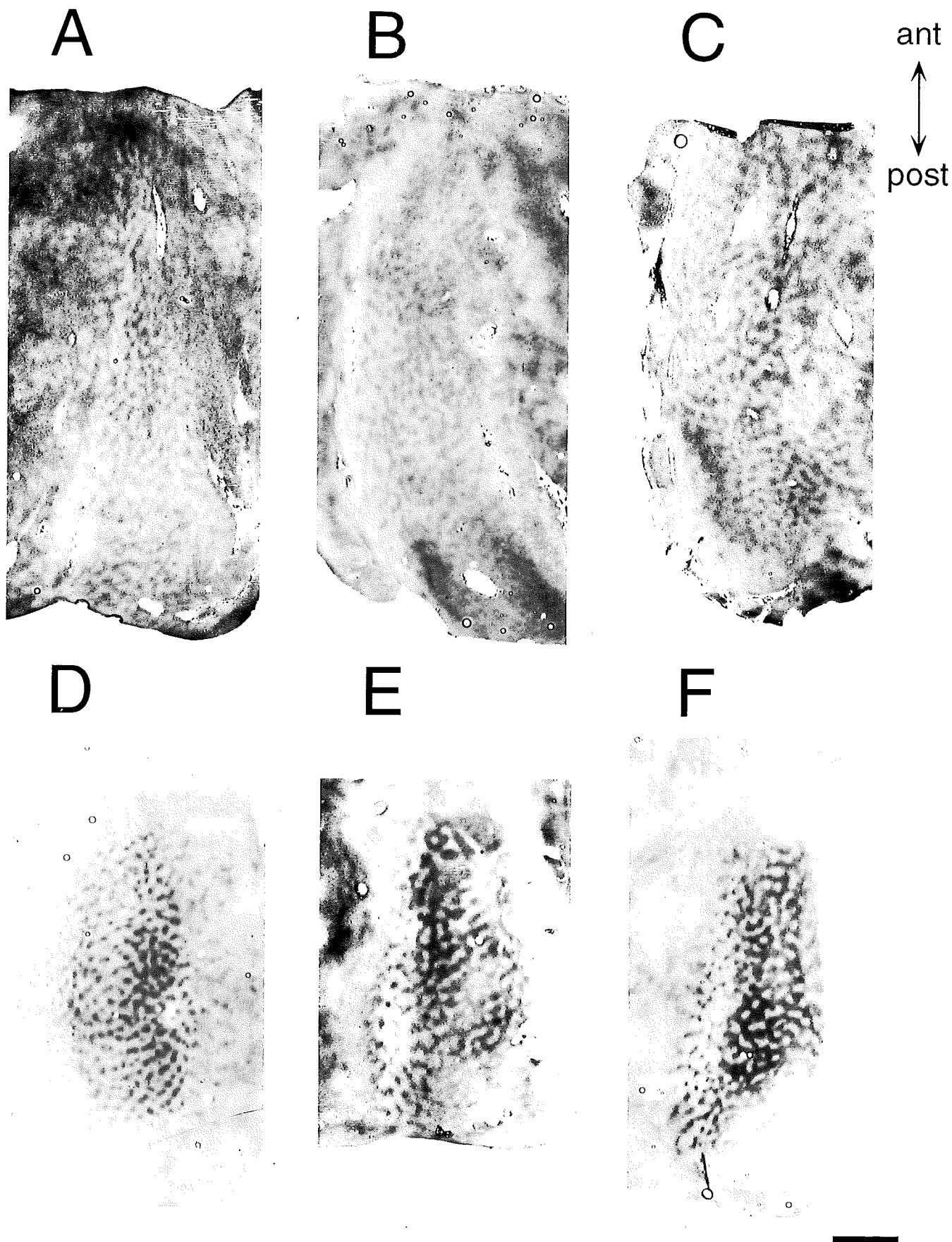


*Figure 2.* The complete pattern of ocular dominance columns in the visual cortex of two other strabismic cats. *A*, Animal S1 had been stimulated through the right eye. 2-DG autoradiograph of a supragranular flat-mount section from the left (contralateral) hemisphere. *B*, Photographic

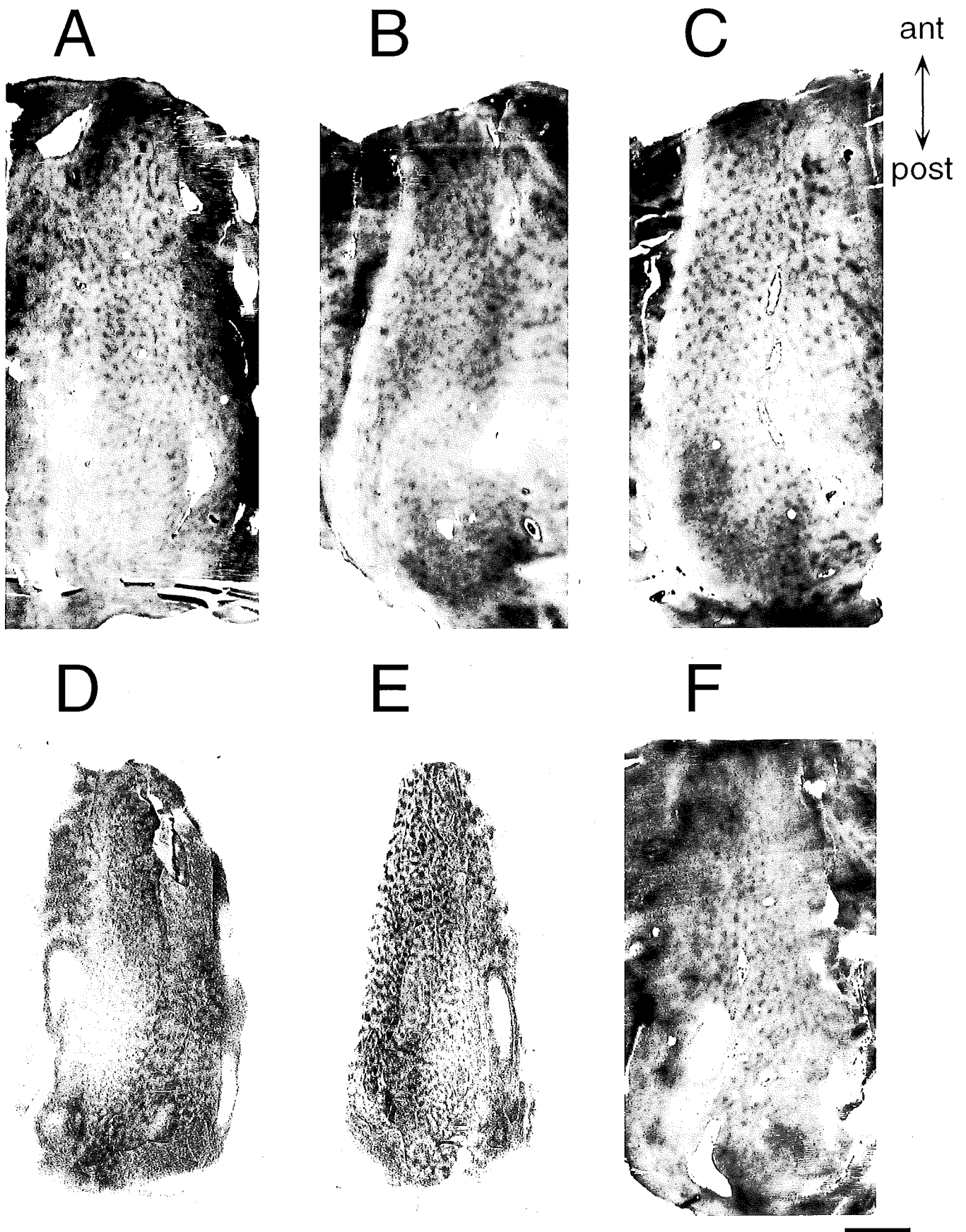




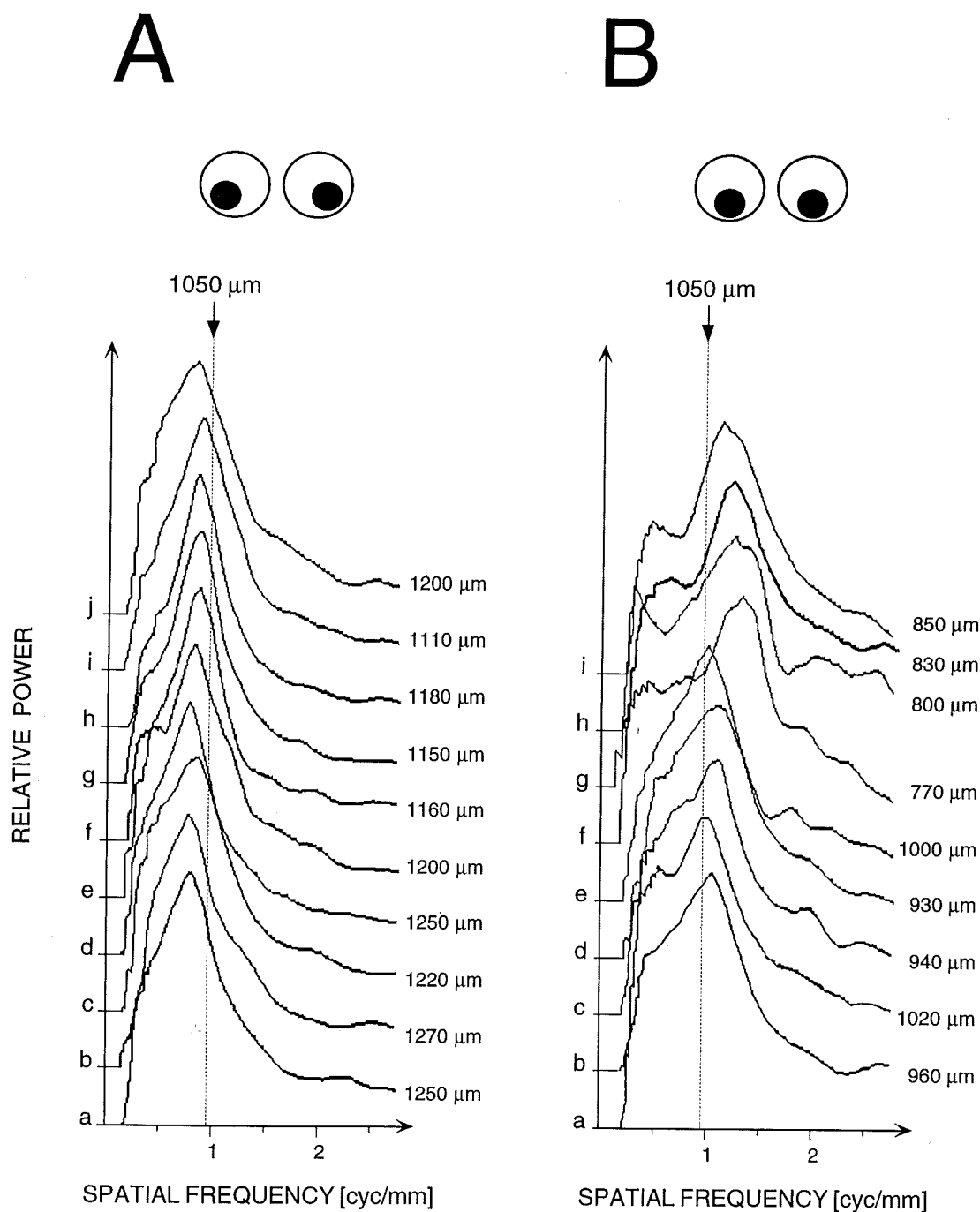
reconstruction of the  $^3\text{H}$ -proline-labeled columns in layer IV contralateral to the injected eye in cat S4. In both cases, the optic disk representations appear in the posterior third of area 17 as oval and only lightly labeled regions. The monocular segments correspond to the heavily labeled regions at the medial border of area 17 (to the *right*). *ant*, anterior; *lat*, lateral. Scale bar, 2 mm.



*Figure 3.* The pattern of ocular dominance columns in the visual cortex of strabismic cats: 2-DG autoradiographs from another six hemispheres in four different animals. *A* and *B*, Left (*A*) and right (*B*) visual cortex of cat S2. *C*, Right hemisphere of cat S1. *D* and *F*, Right (*D*) and left (*F*) hemisphere of cat S5. *E*, Left visual cortex of cat S6. Note that cats S1 and S2 were awake during the monocular 2-DG experiments while cats S5 and S6 were anesthetized and paralyzed, and only the central 20° of the visual field was stimulated visually.



**Figure 4.** The pattern of ocular dominance columns in the visual cortex of normally raised cats:  $^{14}\text{C}$ -2-DG (A–C, F) and  $^3\text{H}$ -proline (D, E) autoradiographs from another six hemispheres in three different animals. A and B, Left (A) and right (B) visual cortex of cat N2. C and F, Left (C) and right (F) hemisphere of cat N3. D and E, Left (D) and right (E) visual cortex of cat N5.

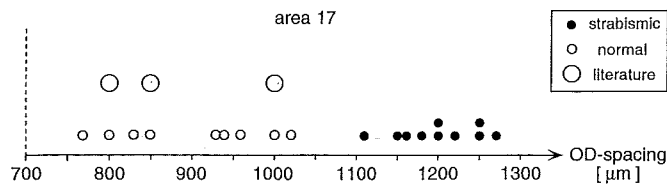


**Figure 5.** Spatial frequency analyses of the patterns of ocular dominance columns in the visual cortex of strabismic (*A*) and normal cats (*B*) (see also Table 1); one-dimensional Fourier analyses of the  $^3\text{H}$ -proline and  $^{14}\text{C}$ -2-DG autoradiographs. The *x*-axes represent the spatial frequency in cycles/millimeter (*cyc/mm*); the respective *y*-axes, the relative power of spectral components (the spectra are stacked to aid comparison). All graphs represent averages along multiple vectors perpendicular to the columnar boundaries. *A*, In the strabismic animals, all spectra (*a–j*) peak left of the dotted line that represents a column-to-column spacing of 1050  $\mu\text{m}$ , thereby exhibiting larger spacings, in particular, the spectra peak at 1250  $\mu\text{m}$  (right cortex) and 1270  $\mu\text{m}$  (left cortex) in cat S1 (*a, b*), at 1220 and 1250  $\mu\text{m}$  in cat S2 (*c, d*), at 1200  $\mu\text{m}$  in cat S3 (*e*), at 1160  $\mu\text{m}$  in cat S4 (*f*), at 1150 and 1180  $\mu\text{m}$  in cat S5 (*g, h*), and at 1110 and 1200  $\mu\text{m}$  in cat S6 (*i, j*). *B*, The spectra of the normal animals peak right of the 1050  $\mu\text{m}$  line (dotted line), thereby exhibiting smaller spacings, in particular, the spectra peak at 960  $\mu\text{m}$  in cat N1 (*a*), at 1020 and 940  $\mu\text{m}$  in cat N2 (*b, c*), at 930 and 1000  $\mu\text{m}$  in cat N3 (*d, e*), at 770 and 800  $\mu\text{m}$  in cat N4 (*f, g*), and at 830 and 850  $\mu\text{m}$  in cat N5 (*h, i*).

compared to area 17 (see also Cynader et al., 1987; Diao et al., 1990). In contrast, in strabimics, the differences in columnar spacing between areas 17 and 18 is much lower: ocular dominance domains in area 18 are only 1.2–1.4 times wider than those in area 17 (Table 1, Fig. 9D).

## Discussion

The main result of the present study is that ocular dominance domains in area 17 of strabismic cats are not only more sharply delineated than in normal animals (Shatz et al., 1977), but that



**Figure 6.** Comparison of the periodicities of the patterns of ocular dominance columns in area 17 of strabismic (●) and normally raised control cats (○). To construct this graph, the peak values of the Fourier spectra in Figure 5A and B were taken. The large open circles represent values published in the literature: Diao et al. (1990), 800  $\mu\text{m}$ ; LeVay et al. (1978), 850  $\mu\text{m}$ ; and Shatz et al. (1977), 1 mm. The x-axis represents the spacing of adjacent ocular dominance columns (OD) in micrometers.

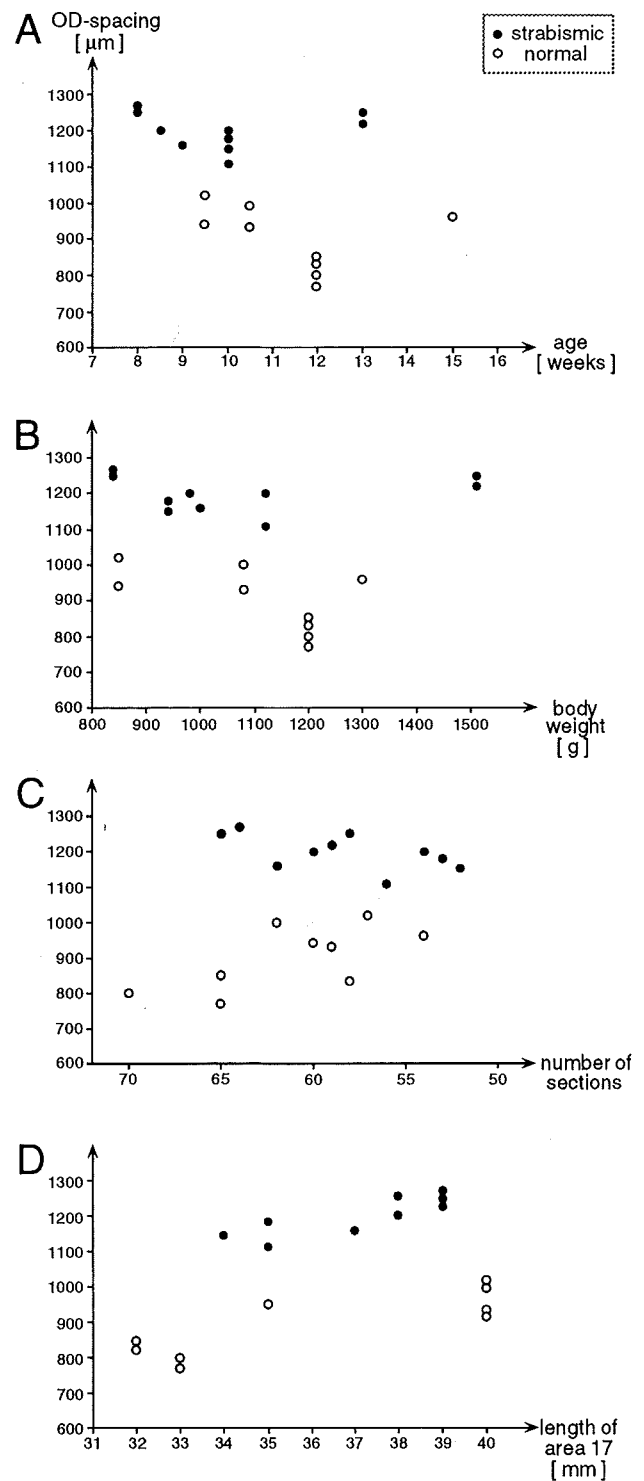
the spacing of adjacent domains is different as well: spatial frequency analyses indicate mean periodicities in the order of 1100–1300  $\mu\text{m}$ . These values are consistently larger than in normal animals in which distances of 800–1000  $\mu\text{m}$  are observed (Shatz et al., 1977; LeVay et al., 1978; Löwel and Singer, 1987; Diao et al., 1990). Since the length of area 17 is the same for animals of both experimental groups, it follows that strabismic cats must have fewer ocular dominance domains compared to normal animals. In cortical area 18, mean spatial frequencies are larger than in area 17 for both normal and strabismic cats and range from 1500–1650  $\mu\text{m}$ . Therefore, in area 18, the spacing of adjacent ocular dominance domains does not seem to be influenced by strabismus.

#### Methodological considerations

Inspection of the ocular dominance columns in area 17 of strabismic cats already shows that the spacing of adjacent domains is larger than in normal animals. Since quantitative analysis of columnar spacings in noisy and irregular patterns such as ocular dominance domains is in general very complicated, emphasis was put on presenting originals (Figs. 1–4). To complement these qualitative observations with quantitative measurements, the spectral content of the patterns of ocular dominance was assessed by one-dimensional Fourier analyses (which has been successfully applied in previous investigations, i.e., Löwel and Singer, 1987; Swindale, 1988). One-dimensional Fourier analysis can be applied to determine columnar spacing because the patterns of ocular dominance columns are not completely patchy but contain numerous elongated slabs or bands (see, e.g., Figs. 1A,B; 2A,B; Löwel and Singer, 1987; Anderson et al., 1988). Since there is a small but consistent tendency for the ocular dominance domains to be elongated roughly orthogonal to the 17/18 border (Löwel and Singer, 1987; Anderson et al., 1988), most of the measurements were performed parallel to that border, that is, in an anterior–posterior direction.

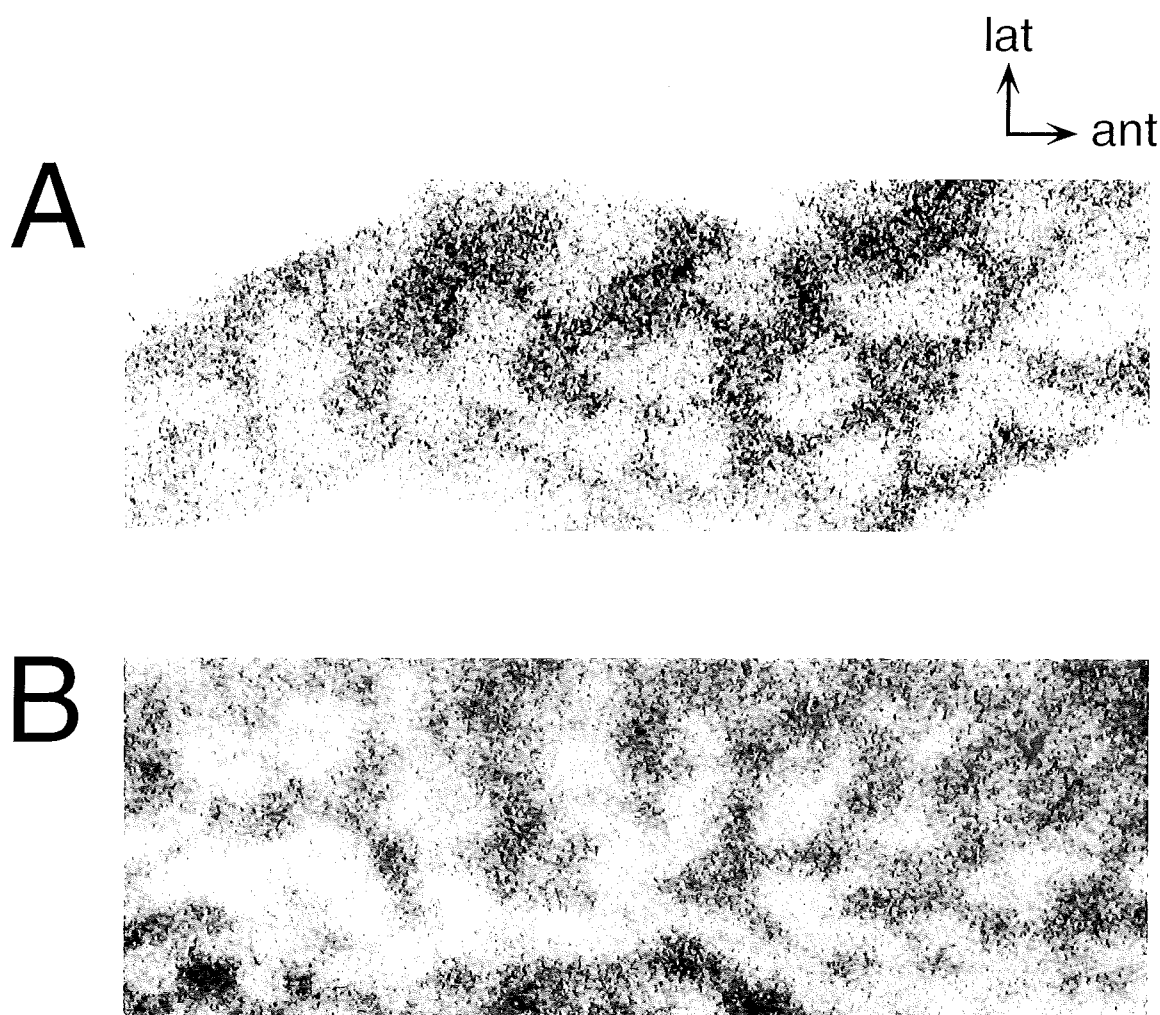
Why did the observation of a different columnar spacing escape the analyses of a number of working groups who already visualized ocular dominance columns in strabismic cats? One possible clue lies in the usage of flat-mount sections in the present study. Differences in spacing may become apparent only if the complete pattern of ocular dominance domains in the entire area 17 (and 18) is analyzed. Differences may not be easily detected if horizontal sections are studied because usually only some of the columns are considered and variability of single column-to-column spacings may be rather high.

Before discussing in detail the difference in spacing, possible artifacts that could influence columnar spacing have to be considered. As already described in the Results, the strabismic and



**Figure 7.** The spacing of adjacent ocular dominance columns (OD) in area 17 of strabismic (●) and normal (○) cats as a function of their age (A), body weight (B), number of flat-mount sections (C), and anterior–posterior extent (“length”) of area 17 (D). Note that the spacing of adjacent ocular dominance columns in strabismic animals is always larger than in the normal animals irrespective of age, body weight, number of flat-mount sections, and length of area 17: the solid circles lie always above the open circles. In addition, both experimental groups (strabismic and normally raised cats) consisted of animals of similar age, body weight, number of sections, and length of area 17.





**Figure 8.** Pattern of ocular dominance columns in area 18 of the strabismic cats S4 (*A*) and S2 (*B*):  $^3\text{H}$ -proline-labeled columns in layer IV (*A*) and  $^{14}\text{C}$ -2-DG-labeled domains in supragranular layer III (*B*) in hemispheres contralateral to the injected, respectively open eye. In both cats, the domains of the noninjected, respectively closed eye are the lightly labeled regions. Scale bar, 1 mm.

control animals were matched for (1) age, (2) body weight, (3) number of flat-mount sections, and (4) length of area 17. Therefore, none of these factors could have contributed to a difference in columnar spacing. In addition, analysis of the correlation coefficients between the different variables demonstrated that visual experience (strabismic or normal) is the *only* variable that is significantly correlated with the spacing of adjacent ocular dominance columns (c.c. 0.91). A further possible source of variability is tissue shrinkage. However, it is unlikely that this is responsible for a change in columnar spacing since all sections were unfixed and processed in the same way. Finally, all possible artifacts would be expected to affect area 18 similarly, but they do not appear to do so in the cases examined.

Taken together, the difference in columnar spacing between strabismic and normal cats cannot be artifactual but must be due to the different visual experience these animals had.

#### *Nature versus nurture: activity dependence of columnar spacing*

The results of the present study show that in area 17, but not in area 18, of strabismic cats, decreased correlation of activity

between the eyes leads to larger ocular dominance domains as in normally raised animals. Therefore, the periodicity of the pattern must be influenced by visual experience, and in particular by the temporal patterning of neural activity. That column formation per se is driven by activity-dependent competition between the afferents serving the two eyes has long been known (Hubel et al., 1977; for review, see Stryker, 1986, 1991; Constantine-Paton et al., 1990; Goodman and Shatz, 1993). In addition, monocular deprivation experiments indicated that one eye's domain could increase at the expense of the other eye's domain (Wiesel and Hubel, 1965; Hubel et al., 1977; Shatz and Stryker, 1978; LeVay et al., 1980). These observations still left open the possibility that the spatial layout of the ocular dominance columns is biochemically built in or genetically fixed. The results of the present study are therefore a direct demonstration that the spatial organization of the columns, in particular the spacing of adjacent domains, also develops in an activity-dependent way and that it cannot be determined alone by factors intrinsic to the cortex and independent of the properties of geniculocortical afferents, as was recently suggested by Jones et al. (1991). In addition, the present observations emphasize the im-

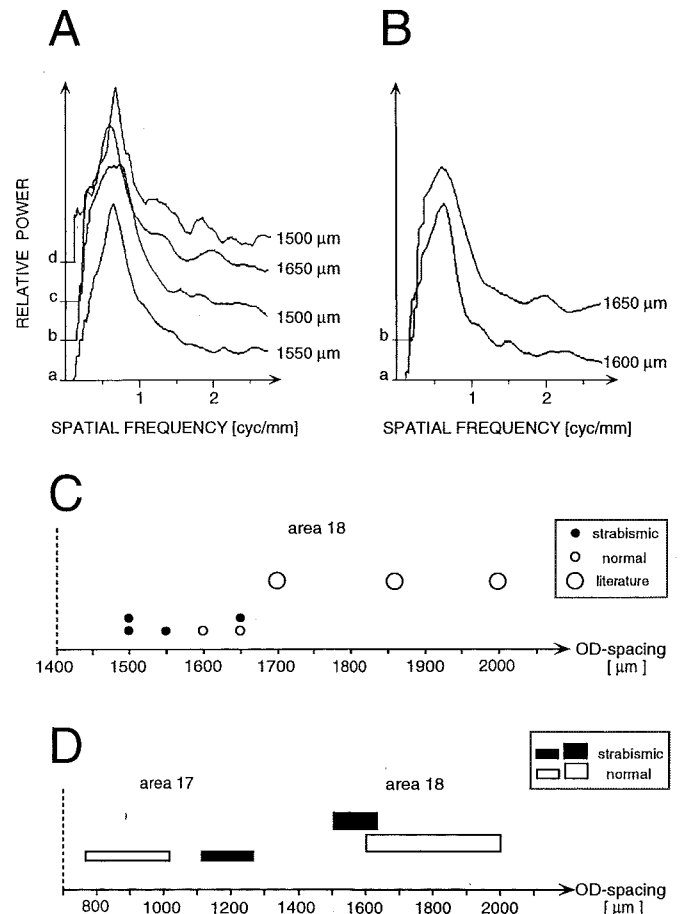
portance of the temporal patterning of neural activity as a crucial factor, not only for the segregation of afferents into distinct columns (Stryker and Strickland, 1984) but also for the final expression of the columnar grid.

### Models of column formation

Most of the numerous models on map formation have dealt with the question of why ocular dominance columns do develop at all (for review, see Constantine-Paton, 1983; Stryker, 1986, 1991; von der Malsburg and Singer, 1988; Clothiaux et al., 1991; Goodman and Shatz, 1993). Since ocular dominance bands can arise in species that normally have none, that is, the famous eye-specific termination bands in tecta of three-eyed frogs (Constantine-Paton and Law, 1978; for reviews, see Constantine-Paton, 1983; Udin and Fawcett, 1988), it was argued that column formation may arise as a by-product of more general mechanisms concerned with map formation (Constantine-Paton, 1983). Stripe formation is now generally interpreted as a compromise between two opposing constraints: a *retinotopic matching* process (during which afferents from the two eyes attempt to connect to postsynaptic neurons as close as possible to their ideal topographic locus in the target structure that limits the size of the same-eye domains) and a *sorting* mechanism for presynaptic proximity (which "forces" afferents from the same eye to remain together in the target zone to build up a domain of like afferents) (LeVay et al., 1975; Constantine-Paton, 1983).

If we now consider the effectiveness of these two opposing constraints in strabismic animals, it appears almost as a logical consequence that ocular dominance domains should be wider in these animals. Since the optical axes of the two eyes in strabismics are not aligned and the images on the two retinas cannot be brought into register, the responses mediated by anatomically corresponding retinal loci (in the two eyes) are no longer correlated. According to Hebb's postulate for associative learning (Hebb, 1949) and its modern extension by Stent (1973) and Changeux and Danchin (1976), synaptic contacts between synchronously active pre- and postsynaptic neurons are selectively strengthened whereas synaptic contacts between asynchronously active pre- and postsynaptic neurons will be weakened. As a consequence, in strabismics, left and right eye afferents will no longer attempt to innervate topographically identical positions in the visual cortex (lacking binocular "clamp"). On the other hand, since neighboring cells within the same retina do have correlated activities (Adrian and Matthews, 1928; Rodieck and Smith, 1966; Arnett, 1978; Maffei and Galli-Resta, 1990; Meister et al., 1991; for review, see Mastronarde, 1989), synapses driven by each eye will try to maximize their association with synchronously active cells (those driven from the *same* eye displaying similar patterns of neural activity) and minimize their association with cells asynchronously activated by the other eye (carrying different patterns of activity). Therefore, the reduced between-eye correlations in strabismics should finally lead to a sharper segregation and to larger stripes, predictions that are consistent with the observations of the present study.

Interestingly, again based on considerations that ocular dominance columns could arise as a "by-product of the mechanisms concerned with map formation," a theoretical model was recently presented which explicitly predicted that "reduced between eye correlations should lead to wider stripes" (Goodhill, 1993). In his model, Goodhill investigated the dependence of the pattern of stripes on the degree of correlation between the eyes. An important aspect of his model is that ocular dominance



**Figure 9.** Quantitative analysis of the spacing of ocular dominance columns in strabismic and normal cats. *A* and *B*, Spatial frequency analyses of the patterns of ocular dominance columns in area 18 of four of the strabismic cats (*A*) and two of the normal control animals (*B*): one-dimensional Fourier analyses of the  $^3\text{H}$ -proline and  $^{14}\text{C}$ -2-DG autoradiographs. The *x*-axes represent the spatial frequency in cycles/millimeter (*cyc/mm*); the respective *y*-axes, the relative power of spectral components (the spectra are stacked to aid comparison). All graphs represent averages along multiple vectors perpendicular to the columnar boundaries. The spectra of the strabismic cats (*A*) peak at 1550  $\mu\text{m}$  in cat S1 (*a*), at 1500  $\mu\text{m}$  in cat S2 (*b*), at 1650  $\mu\text{m}$  in cat S4 (*c*), and at 1500  $\mu\text{m}$  in cat S5 (*d*). The spectra of the normal cats (*B*) peak at 1600  $\mu\text{m}$  in cat N2 (*a*) and at 1650  $\mu\text{m}$  in cat N5 (*b*). *C*, Comparison of the periodicities of the patterns of ocular dominance columns in area 18 of strabismic (●) and normally raised control cats (○). The peak values of the Fourier spectra in *A* and *B* were taken to construct this graph. The large open circles represent values published in the literature: Shatz et al. (1977), 1700  $\mu\text{m}$  (mean of measurements on the published photo-prints); Cynader et al. (1987), 1.86 mm; and Diao et al. (1990), 2000  $\mu\text{m}$ . The *x*-axis represents the spacing of adjacent ocular dominance columns (OD) in micrometers. *D*, Range of the periodicities of the ocular dominance system in areas 17 (thin bars) and 18 (thick bars) of normally raised (open bars) and strabismic (solid bars) cats. Results of the present study and values described in the literature are included (see also *C* and Fig. 6). The *x*-axis represents the spacing of adjacent ocular dominance columns in micrometers. Note that in strabismic cats, the spacing of adjacent domains is larger than in normal cats in area 17 but not in area 18.

segregation can occur even when the two eyes are positively correlated. In all animals with stereoscopic vision, like cat and monkey, at least some amount of positive correlation between the activities of corresponding regions in the two retinas will be present after eye opening during postnatal development. In contrast, many other models about the development of ocular dom-

inance columns explored zero or negative between-eye correlations, which is the natural situation before eye opening and during embryonic development (in animals with stereoscopic vision) or in lateral-eyed animals (i.e., von der Malsburg and Willshaw, 1976; Legéndy, 1978; Swindale, 1980; but see Durbin and Mitchison, 1990; Obermayer et al., 1990). According to Goodhill, neighboring cortical cells have competing tendencies to connect with neighboring cells in the same retina (due to within-eye correlations) and corresponding cells in the other retina (due to between-eye correlations). The stronger the correlation between the two eyes, the more often the latter tendency will win, leading to narrower stripes. In contrast, in strabismic animals, the reduced between-eye correlations should lead to wider stripes (Goodhill, 1983), a prediction that is in accordance with the present observations.

In most other models (i.e., von der Malsburg and Willshaw, 1976; Swindale, 1980), stripe width is set primarily by the extent of the cortical interaction function: longer-range excitation between cortical units leads to wider stripes. However, usually, the degree to which positive between-eye correlations could affect stripe width has not been investigated explicitly. In the recently published and very elaborate Miller et al. model (i.e., Miller, 1990), a model that particularly emphasizes the biological plausibility of its assumptions, the set of parameters contributing to the scale of the stripes is expanded by an "arbor function," describing the spread of afferent arbors and of cortical dendrites (Miller et al., 1989). Therefore, again, cortical interactions determine the width of ocular dominance domains up to a possible limit set by arbor diameters. Opposite-eye anticorrelations, as in strabismus, lead to increased monocular activity in the cortex "without changing the basic periodicity" (Miller and Stryker, 1990). To account for the increased columnar spacing seen in strabismic cats within the framework of these models, one would have to assume either longer-range excitation or a reduction in long-range inhibition in these animals. Experimentally, these possibilities have not been tested yet. Finally, in even other theoretical concepts, such as "elastic net" models (i.e., Durbin and Mitchison, 1990) or "Kohonen"-type models (i.e., Kohonen, 1982, 1984; Obermayer et al., 1990), the form of input correlations again could be important in influencing stripe width. However, again, the effect of strabismus on the size of ocular dominance columns has not yet been tested explicitly in these models. Therefore, and since a detailed discussion of these different models would go beyond the scope of the present report, the interested reader is referred to Goodhill (1991, 1993) and Miller (1990). Taken together, more than one theoretical concept about map formation and the development of ocular dominance columns may in principle account for the present observations. Future experiments are therefore needed to test the various predictions made by different models in order to select those concepts that are more viable than others.

#### *Cooperative development of geniculocortical afferents and long-range tangential connections?*

As discussed earlier, during map formation the sorting mechanism for presynaptic proximity should favor larger "iso"-eye domains in strabismic compared to normal animals. Therefore, the question remains why stripe width increases "only" to values of 1100–1300  $\mu\text{m}$  and not more. In principle, the mapping mechanism as such should not induce any constraints for the size of "iso"-eye domains. However, since an upper limit seems to exist it may help to reveal underlying developmental mechanisms.

Interestingly, the spacing of ocular dominance domains in strabismic cats roughly corresponds to the spacing of iso-orientation columns in normal cats, which are in the range of 1000–1300  $\mu\text{m}$  (Löwel et al., 1987; for a review, see LeVay and Nelson, 1991). In addition, it has been shown recently that long-range tangential connections preferentially connect neurons driven by the same eye in strabismic cats (Löwel and Singer, 1992; see also Tychsen and Burkhalter, 1992). To make that possible, tangential connections and ocular dominance columns must be matched in spatial scale. This in turn indicates that the two systems probably influence each other during development. In this context, it is worth considering the time course of development of the two systems. It is not yet known whether the maturation of the intracortical connections precedes the segregation of geniculocortical afferents into ocular dominance columns or whether both patterns attain adult-like organization in the same postnatal period. If anything, in kitten, patchy intrinsic connections may be present some days earlier than ocular dominance domains: crude patches of tangentially connected neurons are already discernible at postnatal day 10 in kittens (Callaway and Katz, 1990; Luhmann et al., 1990), whereas the segregation of left and right eye afferents starts at about 3 weeks of age (LeVay et al., 1978; Shatz and Stryker, 1978). It is therefore possible that the patchy intrinsic connections and the cortical activity pattern they generate serve as a "template" for the segregating geniculocortical afferents so that the latter become matched in periodicity to the patchy intrinsic connections (which in turn are matched to the orientation column system; see Gilbert and Wiesel, 1989; see also von der Malsburg and Singer, 1988, for a very interesting discussion of developmental interactions of orientation and ocular dominance domains). Alternatively, and probably more likely, is a slightly different scenario: tangential connections and geniculocortical afferents could develop in a cooperative manner. Any changes in the activity of the geniculocortical afferents will influence cortical activity patterns, thereby influencing the pruning of tangential connections. Likewise, changes in tangential connectivity will influence activity correlations in the cortex and thereby affect the stabilization or elimination of afferent synaptic contacts. Finally, in the adult animal, the two systems of connections could evolve into a state of equilibrium, thereby displaying similar spatial periodicities (see also Sirosh and Miikkulainen, 1994).

#### *Spacing of ocular dominance columns in cortical area 18*

As in normally raised cats (Shatz et al., 1977; Cynader et al., 1987; Diao et al., 1990), in area 18 of strabismic animals ocular dominance domains are larger than in area 17. Surprisingly, however, they do not get spaced further than in normal cats. The following two explanations may account for this observation. Either the maximal column-to-column spacing is already reached in the normal cats (so that decreased correlation between the eyes cannot increase the spacing further) or there may be fundamental differences in the development of geniculocortical innervation between these two cortical areas (i.e., Friedlander and Martin, 1989).

From a theoretical point of view, "intracortical connections," thalamocortical "arbors, and perhaps correlations" (Miller et al., 1989) may show a difference between the two regions. It is known that area 18 is innervated predominantly by Y-cell axons, whereas area 17 gets input from both X- and Y-cells. Since Y-cell axon arbors are larger (2 mm) than those of X-cell axons (1.5 mm) (LeVay and Stryker, 1979; Humphrey et al., 1985),

ocular dominance patches in cortical area 18 may develop larger sizes (Miller et al., 1989). In addition, it is possible that stripe width is already at the upper bound allowed by the diameter of afferent arbors so that reduced between-eye correlations do not influence the spatial layout of ocular dominance domains in area 18. Alternatively, the larger ocular dominance columns in area 17 of strabismic cats could also be explained if Y-cell input would dominate this area in these animals. However, no experimental evidence exists in favor of this possibility.

Whereas it is generally believed that the segregation of geniculocortical afferents into ocular dominance columns in area 17 involves retraction of initially expanded and overlapping projections from the left and right eye (Hubel and Wiesel, 1970, 1977; LeVay et al., 1978, 1980; LeVay and Stryker, 1979; Shatz and Luskin, 1986; Antonini and Stryker, 1993), the situation is less clear in cortical area 18. Surprisingly, there are no data in the literature describing the development of ocular dominance columns in area 18, for example, with intraocular injections of tracers such as horseradish peroxidase (HRP) or  $^3\text{H}$ -proline. The only data available are intracellular fillings of Y-axon arborizations in area 18 of kittens and cats (Friedlander and Martin, 1989) and very recently also chronic optical imaging of the functional architecture of kitten area 18 (Bonhoeffer et al., 1993). Friedlander and Martin's investigations demonstrate that in the 4–5-week-old kitten, axonal arbors are smaller than those in the adult, indicating that thalamocortical innervation develops by a moderate expansion, rather than retraction, of the arborizations (Friedlander and Martin, 1989). The optical recording experiments reveal, as early as in 3-week-old kittens, topographically separate functional maps for the right and left eye (Bonhoeffer et al., 1993). In addition, Milleret et al. (1988) reported that the percentage of binocularly activated cortical neurons increases dramatically between 2 and 4 weeks of age. The physiological development of binocularity in area 18 does therefore not seem to mirror that in area 17, which may be taken as an indication of differences in the development of geniculocortical innervation between the two cortical areas (Friedlander and Martin, 1989). It is therefore conceivable that reduced between-eye correlations do not influence the development of the eye-specific domains in area 18 in a similar way as in cortical area 17.

### Conclusions

- (1) In area 17 (but not in area 18) of strabismic cats, decreased correlation between the eyes alters the periodicity of ocular dominance columns: the column-to-column spacing is on average 20–30% larger than in normally raised animals.
- (2) These results indicate that not only the segregation of afferents into distinct columns but also the final expression of the columnar grid is influenced by visual experience and in particular by the temporal patterning of neural activity.
- (3) These findings are further and direct evidence for the hypothesis that the development of ocular dominance columns is governed by activity-dependent self-organizing principles.
- (4) Since strabismus also changes the specificity of horizontal connections in area 17 and since the "sculpting" of the intracortical fibers and the segregation of geniculocortical afferents into ocular dominance columns occurs at the same postnatal period, more complex (and possibly cooperative) interactions between the two developing systems than previously thought are likely to happen.

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